

*Bill
with appreciation for your help and
with best regards-*

Bob Conrad

**REVIEW OF MEDICAL FINDINGS IN A MARSHALLESE POPULATION
TWENTY-SIX YEARS AFTER ACCIDENTAL EXPOSURE
TO RADIOACTIVE FALLOUT**

Robert A. Conrad, M.D., et al.

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MEDICAL DEPARTMENT

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REVIEW OF MEDICAL FINDINGS IN A MARSHALLESE POPULATION TWENTY-SIX YEARS AFTER ACCIDENTAL EXPOSURE TO RADIOACTIVE FALLOUT

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January 1980

MEDICAL DEPARTMENT

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DEDICATION

This report is dedicated to Dr. Shields Warren, who died during the past year. The many accolades received by Dr. Warren during his illustrious career need not be reviewed here. He was a leading authority on the pathological effects of ionizing radiation on human beings and was also highly regarded in the field of thyroid pathology. He was the first director of the Division of Biology and Medicine of the Atomic Energy Commission, and he played an important part in the examinations of the atomic bomb survivors in Japan.

Following the fallout accident in the Marshall Islands, we turned repeatedly to Dr. Warren for advice, particularly concerning the pathological aspects of the thyroid lesions. He strongly supported our program and gave generously of his time and talents to help us. He reviewed countless sections of thyroid tissues from the Marshallese and provided valued opinions.

Dr. Warren was a dedicated physician, scientist, and educator. His personal warmth, enthusiasm, sincerity, and encouragement endeared him to all of us. He was a true and loyal friend and we shall sorely miss him.



PREFACE

A 20-year report published 6 years ago (1) covered in detail the medical findings in the Marshallese exposed to radioactive fallout in 1954. The present report updates these findings with emphasis on the data collected during the past 6 years.*

Much of the material presented in the 20-year report will not be repeated. The reader is referred to that report for a review of topics such as the general history of the Marshall Islands, past health status of the Marshallese people, use of the islands from 1946 to 1958 as the Pacific proving grounds for testing nuclear devices, the accidental exposure in 1954 of the people of Rongelap and Utirik Atolls, their evacuation and subsequent return to their homes, organization of the medical teams and surveys, relationship with the Navy and Trust Territory (TT) governing bodies, etc. The findings previously reported in detail will only be summarized in this report.

The Brookhaven National Laboratory (BNL) Medical Program has been limited by its mandate: to observe the people who had been exposed to fallout radiation on Rongelap, Ailingnae, and Utirik Atolls in 1954 and unexposed comparison populations, and to ascertain those diseases in the exposed population that are related to prior exposure to radiation and initiate appropriate treatment for these diseases. However, a number of developments have resulted in expansion of the program. Further thyroid abnormalities developed in the exposed Rongelap people and in several exposed Utirik people. An exposed Rongelap male died of leukemia in 1972. The exposed Rongelap and Ailingnae people who had been placed on thyroid hormone treatment were not adhering strictly to the treatment program; as a result many of those who had had thyroid surgery showed evidence of reduced thyroid function, giving rise to concern that they might develop clinical hypothyroidism unless they complied with the treatment. Another important consideration was the urgent request of the unexposed people living on Rongelap and Utirik (not in the group regularly examined) to be given annual checkups by the BNL medical team. For the above reasons a number of steps have been taken to expand the program. A physician from BNL was stationed in the Marshall Islands in 1972 as resident physician. His principal responsibilities included (a) monitoring the thyroid treatment program, (b) visiting Rongelap, Utirik, and Bikini Atolls for health care purposes every 3 to 4 months, and (c) assisting the TT medical services with the care of Rongelap and Utirik patients at the hospitals at Ebeye and Majuro.

A Marshallese nurse was hired by BNL in 1977 and has been of great assistance to the resident physician. In 1978 a clinical laboratory was established in a trailer at the Ebeye Hospital as a supplement to the hospital laboratory to aid the resident physician in making definitive diagnoses. A medical technician from BNL has been stationed in the islands since 1978.

In 1976 an agreement was formalized between DOE/BNL and the TT which provided for examinations and health care of all Marshallese living on Rongelap and Utirik by the BNL medical team at the time of their visits; for the resident physician to assist TT medical personnel in the care of Rongelap and

*The thyroid section (IX) includes more recent data which became available just before publication of this report.

Utirik patients at the hospitals at Ebeye and Majuro; and for the TT health services to furnish personnel to help with the examinations on Rongelap and Utirik.

In order to determine the possible association of thyroid tumors with radiation exposure in the Utirik group, more data were needed on the incidence of thyroid abnormalities in unexposed Marshallese populations. Thyroid surveys (neck palpations) were conducted in 1973 on 192 people at Likiep Atoll and in 1976 on 162 people at Wotje. In addition, during the past 6 years, nearly all the unexposed Rongelap and Utirik people living on various atolls (more than 900 people) have been included in these examinations.

As part of the expanded medical program certain other diseases not found to be associated with radiation exposure have been given special attention. Diabetes is one of the most common diseases in the Marshall Islands; it is being studied (see Section VII) in the hope that helpful advice will be provided to the Marshall Islands medical service group on its nature and treatment. Intestinal parasitism is widespread in the Marshall Islands. Since 1977 a program of diagnosis and treatment has been carried on at Rongelap and Utirik Atolls (see Section VI). Other special studies (possibly associated with radiation exposure) include those on growth and development in exposed children (see Section IV); on detection of mutant proteins as a possible index of genetic effects in children of exposed parents; and on the frequency of isoleucine substitution in hemoglobin as a possible index of somatic mutation (see Section V.C.2).

Since low levels of residual radiation persist on Rongelap, Utirik, and Bikini, radiological monitoring of personnel on these islands has continued. Urine samples have been radiochemically analyzed on about an annual basis for the radionuclides ^{137}Cs and ^{90}Sr , and more recently for the isotopes of Pu. In addition, gamma spectrographic analysis (whole-body counting) for ^{137}Cs has been done at intervals. These examinations, formerly the responsibility of the BNL medical team, have been carried out since 1975 under the direction of the Safety and Environmental Protection Division of BNL.

The 20-year report (1) outlined a number of problems affecting the medical program in the Marshall Islands. Some of these problems relate to carrying out the examinations, such as the language barrier, cultural differences, scarcity of demographic data, and inadequacy of follow-up medical care in patients seen by the medical team. Criticisms of the BNL medical program, voiced by some, stem largely from lack of understanding of the limited mandate for the program. Other problems relate to the accident, to misconceptions and fears of the people about radiation effects, and to objections to needed continued medical examinations. In the past 5 to 6 years increased efforts to correct misunderstandings among the people have involved expansion of the educational program by discussions at village meetings and special lectures. One member of the team spent several weeks on Rongelap and Utirik for this purpose, and this was greatly appreciated. The necessity of again removing the Bikini people from their home island in 1979 because of unexpectedly high radioactivity levels in the food crops was unfortunate. Misunderstandings have arisen concerning bills for compensation and hospital benefits (travel payments, etc.) for the exposed people. The Burton Bill passed by Congress charges the Department of the Interior with development of a plan for delivery of health care to Marshallese affected by fallout.

With the writing of this report I am ending 26 years of affiliation with this program. During the past year, since my retirement in 1979, I have acted as Consultant to Drs. H. Pratt and E.P. Cronkite, my successors.* This has been a most gratifying and stimulating experience for me and I am happy that we have been able to contribute to the medical evaluation and health care of these people and help expand the knowledge of radiation effects in human beings. In spite of criticism and misunderstandings I am convinced that the Marshallese people have basically maintained strong feelings of friendship and respect for the medical team, and I personally am most grateful to them for this and believe that they know these feelings are mutual.

We have been most fortunate in obtaining the dedicated help of many first-rate physicians and technicians including those from the Trust Territory. My heartfelt thanks to them all. Also the program could not have been carried out without the staunch support of people at Brookhaven National Laboratory, the Departments of Energy and Interior, the Trust Territory, the Army at Kwajalein, and others, to whom I am most grateful.

With the further development of thyroid abnormalities and the possibility that other late effects of radiation may appear, it is imperative that the special medical examinations and health care of these people be continued. I stand ready to help my successors in any way that I can.

The Marshall Islands are entering an era of widespread change, and I sincerely hope that with the greater awareness of the need for improved medical care in the Islands by the new Marshallese Government and the U.S., the future will be brighter for better care of these people.

Robert A. Conard, M.D.

*On June 1, 1981, Dr. William H. Adams (from Texas Tech Academic Health Center, El Paso) came to BNL to take charge of the program.

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The accompanying table lists the individuals, with their affiliations, who have so generously given of their time and talents to participate in medical surveys in the Marshall Islands over the past six years. Without their dedicated efforts, the surveys could not have succeeded, and we are most grateful to all of them.

The senior author would like first to express his gratitude to many people who have assisted in the preparation of this report or who were actively involved in some of the special studies. In the writing and editing of the report, Dr. Donald Paglia was most helpful and is largely responsible for writing Sections I, II, and parts of III and IX. At this Laboratory, Drs. E. P. Cronkite and V. P. Bond have provided valuable advice and support. The assistance of Ms. Margaret Dienes in editing and collating the report, the secretarial assistance of Ms. Bernice Armstrong and Ms. G. Callister, the typing and editing assistance of Ms. Denise G. Warren, and the technical assistance of Messrs. William Scott and Peter Heotis and Ms. Veena Naidu are gratefully acknowledged.

The people who assisted with or wrote sections of the report are mentioned in the appropriate places. In addition, numerous other individuals and many organizations have given tremendous support to the program over the years, and without their help the program could never have succeeded. It will be possible to list only some of these people who have contributed during the past six years. As noted earlier, when the senior author retired in 1979, Dr. Hugh S. Pratt became program chief until he resigned in the summer of 1980. We are indebted to him for his contributions, including improvement of examination protocol, initiation of data processing, and other improvements in the program. Dr. Pratt was succeeded by Dr. Eugene P. Cronkite, the present program director, who has been involved with the program since its inception and during his tenure as Chairman of the Medical Department always strongly supported the program and provided able advice.

We gratefully acknowledge the assistance of a number of Brookhaven physicians who have served as resident physicians in the Marshall Islands, including Drs. Konrad Krotrady, William Grant, Knud D. Knudsen, and Roger S. Rittmaster. Dr. and Mrs. Knudsen were in the islands for two tours, and their dedication to the program and assistance are greatly appreciated. Mr. Peter Heotis and Ms. Jenuk Kabua, a Marshallese nurse, have provided great assistance in the Marshall Islands for the resident physicians. At BNL we would like to acknowledge the valuable assistance of Mr. William Scott in administration, organization, and logistic planning for the surveys. Also, Ms. Veena Naidu and Ms. Susan Wynn have been most helpful to the program directors. The continued support of many others at this Laboratory is gratefully acknowledged: in the Medical Department, Drs. D. C. Borg (Chairman), R. B. Aronson (Deputy Chairman), and others including Drs. H. L. Atkins, L. V. Hankes, R. D. Stoner, J. Iwai, and P. Chandra and Mr. K. P. Mohring (Department Administrator). Among others at BNL, we are most grateful to Dr. V. P. Bond for his support and advice and for the support and assistance of Dr. G. Vineyard, Director, and Messrs. N. P. Rathvon, K. E. Boehm, C. B. Meinhold, D. G. Clareus, and many others. We are particularly grateful to Dr. J. R. Naidu for his

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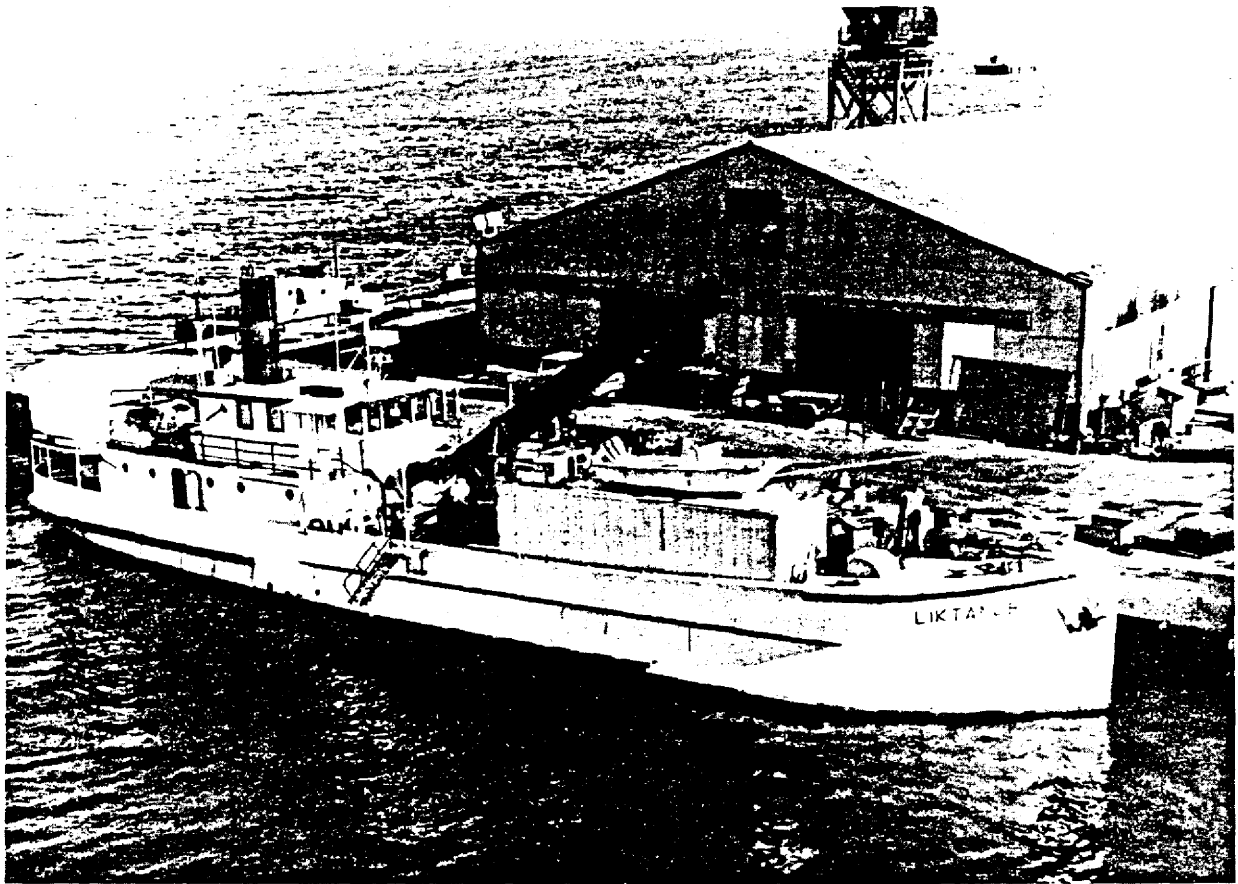
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We appreciate greatly the excellent medical care given the Marshallese patients by the staffs at the Hospital of the Medical Research Center at BNL, the Cleveland Metropolitan General Hospital, and Tripler Army Hospital.

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I. INTRODUCTION

A. Background

In March 1954, an event as unprecedented as it was unfortunate occurred in the Central Pacific. Radioactive debris from a thermonuclear weapon test at Bikini Atoll deviated from predicted trajectories and contaminated several atolls in the northern Marshall Islands. As a result, 239 native inhabitants of these islands along with 28 American servicemen and 23 Japanese fishermen received variably severe exposures to diverse ionizing radiations. Fallout material consisted largely of mixed fission products with small amounts of neutron-induced radionuclides and minimal amounts of fissionable elements, producing a complex spectrum of electromagnetic and particulate radiation. Individuals were exposed to deeply penetrating, whole-body gamma irradiation, to internal radiation emitters assimilated either by inhalation or by ingestion of contaminated water and food, and to direct radiation from material accumulating on body surfaces.

That tragic accident initiated a cascade of events, medical, social and political, which continue in varying forms to this day. Most of these have been discussed in the open medical literature and in periodic reports issued by the medical team headquartered at Brookhaven National Laboratory. This report attempts to summarize some of the principal findings of medical significance that have been observed during the subsequent 26 years with particular emphasis on the last six years.

Because of the unique nature of the incident, medical care of the exposed Marshallese and observation for detection of potential radiation effects have been inextricably bound to complex sociological and political considerations, mentioned in the Preface. The body of the present report, however, will be confined to medical observations on the exposed Marshallese. A 25-year summary of the findings in the Japanese fishermen is presented in Appendix VII. Following the 1954 examinations of the American servicemen, they were returned to the custody of the U.S. Army and have not been examined by the medical team since that time. Expanded presentations of certain aspects of these studies can be found in the 20-year report (1), which is a comprehensive review, and in previous annual reports (2-13), as well as in open literature reports (14-39).

B. The Accident

In the early morning of 1 March 1954, a thermonuclear device code-named Bravo was detonated on a tower at Bikini Atoll as part of the Operation Castle nuclear weapons test series. The energy yield of this experimental device exceeded predictions, and sudden wind structure alterations sent the resultant cloud of radioactive debris unexpectedly eastward rather than over open seas to the north.

Marshallese inhabiting Rongelap, Ailingnae, and Utirik Atolls and a group of American servicemen on Rongerik Atoll were caught within the downwind fallout field for two to three days before they could be evacuated to Kwajalein Atoll by Navy units. In addition, the Japanese fishing vessel,

Fukuryu Maru 5, with 23 crew members, was exposed 80 miles east of Bikini (see Appendix VI).

After extensive decontamination procedures, exposed individuals were observed closely for two months (and at frequent intervals thereafter) by special medical teams assembled at the Kwajalein Naval Base, then were resettled in other islands of the Marshalls group. Medical problems that arose were treated on an individual basis as clinically indicated.

C. Early Clinical Effects

A more detailed summarization of symptoms and clinical findings in the immediate postexposure period is contained in the 20-year report (1).

Nausea occurred within 48 hours in two-thirds of those on Rongelap, the most heavily exposed group, with vomiting and diarrhea in 10%. By contrast, none of those on Utirik (the least exposed group) and only 5% of those on Ailingnae (with intermediate exposures) experienced nausea.

About one-fourth of those on Rongelap and Ailingnae complained of skin irritation and itching; about one-fourth of this group also had eye irritation. These symptoms were quite probably radiation-induced, mostly by direct exposure to high-energy beta emitters, since most of the affected subjects later developed epilation and a few developed conjunctivitis. Some of these symptoms may have been aggravated by the caustic effects of the highly alkaline calcium oxides produced by fireball vaporization of the coral island. Dermal effects were most pronounced on the scalp, neck, dorsa of the feet, axillae, and antecubital fossae. The severity of skin lesions in each group of people appeared to be proportional to the amount of fallout material observed on their atoll. On Rongelap, fallout was described as similar to snowfall, and it actually whitened the hair and adhered to the skin. Partial epilation began within two weeks and eventually affected half of this group. A less dense, powdery mist fell on Ailingnae and Rongerik, and dermal effects there were less evident, epilation beginning in three weeks and affecting <20% of the people. On Utirik, the fallout debris was not visible, and no skin lesions or epilation developed.

Since peripheral blood changes are among the most sensitive and reliable clinical indicators of radiation damage, these were studied closely. Significant hemogram alterations soon became apparent among the more heavily exposed subjects, both on an individual basis and in comparison with mean values for nonexposed Marshallese controls grouped according to sex and five-year age intervals (see Section III). In the Rongelap population, absolute neutrophil counts in all age groups fell 20 to 30% during the second postexposure week and 50% by the fifth week, gradually returning to normal after one year. Lymphocyte counts dropped rapidly to about one-half adult control values by the third day. By two years they were nearly normal. Maximum lymphocyte depressions were even greater (25% of control means) in the younger age groups, who generally exhibited more profound hematologic effects than the adults. Platelet counts reached a low of about one-third control levels during the fourth post-exposure week and eventually required more than two years to return to normal. No significant changes occurred in hematocrit or red blood cell counts.

Similar but less severe hematologic alterations were observed in the group receiving intermediate radiation doses on Ailingnae, whereas the low-exposure group on Utirik did not develop significant alterations of any blood elements except for a slight transient depression of platelets noted only on analysis of the entire population at four weeks post-exposure.

Despite thrombocytopenia and neutropenia in the heavily irradiated group, bleeding tendencies and increased susceptibility to infection were not observed. Even during the nadir of neutropenia, individuals were still able to respond to an outbreak of upper respiratory infections by increasing leukocyte outputs. Clinical sequelae of these hematologic effects were not observed except for one fatal case of acute myeloblastic leukemia in 1972 in a young man who was one year old at the time of exposure. This may well represent a long-term hematologic effect of radiation.

D. Dosimetric Evaluation

1. Early Radiation

A number of caveats should be applied to interpretation of certain data within this and previous reports. These apply principally to radiation dose estimates and dose/effect correlations, especially regarding radiation induction of thyroid neoplasms as discussed in Section IX.C.1.

Since the initial incident created an emergency of unparalleled and unanticipated proportions, data acquisition was necessarily secondary to exigencies of evacuation, decontamination, and care of those affected. Further, the task force was unprepared for gathering extensive dosimetry data or analyzing radiochemical characteristics of the fallout in the actual areas of deposition, since these were quite remote from the areas predicted.

Accurate dosimetry was hindered by a large number of variables:

1. Radiation monitoring teams and equipment were concentrated at a distance in areas of predicted fallout, and no monitoring personnel were in the vicinity of the atolls actually affected.

2. The time of arrival of fallout at each point and its duration could be estimated only by visual observations of the particulate debris, by the recorder of a single low-level gamma detector at the weather station on Rongerik, and by calculations based on meteorological data and fallout prediction models.

3. Actual gamma dose-rate measurements on each island were made by ANPDR/39A survey meters but not until the times of evacuation, 50 to 78 hours after the detonation.

4. Quantitative measurements of short-lived radioisotopes, especially those of iodine (^{133}I , ^{134}I , ^{135}I) were not obtainable.

5. The possibility of chemical fractionation within the cloud and consequent production of localized concentrations of specific radioisotopes was also not measurable.

6. The complex radiation spectra of isotopes comprising mixed fission product fallout produced gamma energy peaks in the regions of 0.1, 0.7, and 1.5 MeV, variably affecting midline depth doses.

7. The distribution of fallout debris on the ground, roofs, trees, and body surfaces produced an exposure geometry unlike any experienced previously

and required upward estimates of midline depth doses (by about 50%) when compared with the same air doses monitoring bilateral narrow-beam radiotherapeutic exposures.

8. Possible effects of location, clothing, shielding, bathing in the lagoon, etc., could not be estimated for each individual; this necessitated assignment of a common whole-body radiation dose estimate to each population.

9. Estimates of internally deposited radioisotopes were based on assays of pooled urine specimens obtained two weeks after the accident and on individual 24-hour urine collections obtained between one and seven weeks after exposure.

Radiation doses thus are not direct measurements but are estimates derived from all sources available at the time and subsequently developed (see Dose Assessment, Appendix II).

Figure 1 presents isopleths of estimated gamma doses three feet in air (neglecting sea water dilution) integrated over the 96-hour period following the Bravo detonation. Despite the relative consistency of dose estimates, the actual values derived are subject to some uncertainty, particularly for doses due to internal deposition, and these uncertainties must be considered when evaluating potential biological effects.

For example, the recent increase in incidence of thyroid neoplasms in the least exposed population (Utirik) raises additional possibilities of chemical fractionation within the rapidly rising, cooling fireball with resultant non-uniform deposition of specific radionuclides as "hot spots" within the fallout pattern, a phenomenon well documented in other nuclear weapon tests (40).

For report purposes, certain dosimetric values have been assigned to island populations (Table 1), but individual doses within each group are obviously subject to broad variation (see Appendix II and Section IX). This is especially pertinent in regard to estimated thyroid doses, since these are a result of a number of imprecisely definable variables. This is exemplified, for example, by the appearance of growth retardation secondary to severe hypothyroidism in some children belonging to a group presumed to have thyroid doses approximating 1150 rads, well below the known level for thyroid ablation.

Table 1. Estimated radiation doses in exposed populations.

Atoll	Number affected*	Estimated whole-body gamma dose (rem)	Estimated thyroid dose (rem) by age at exposure		
			<10 yr	10-18 yr	>18 yr
Rongelap	67	175	810-1800	334-810	335
Ailingnae	19	69	275-450	190	135
Utirik	163	14	60-95	30-60	30

*Includes in utero exposures (3 on Rongelap, 1 on Ailingnae, and 6 on Utirik).

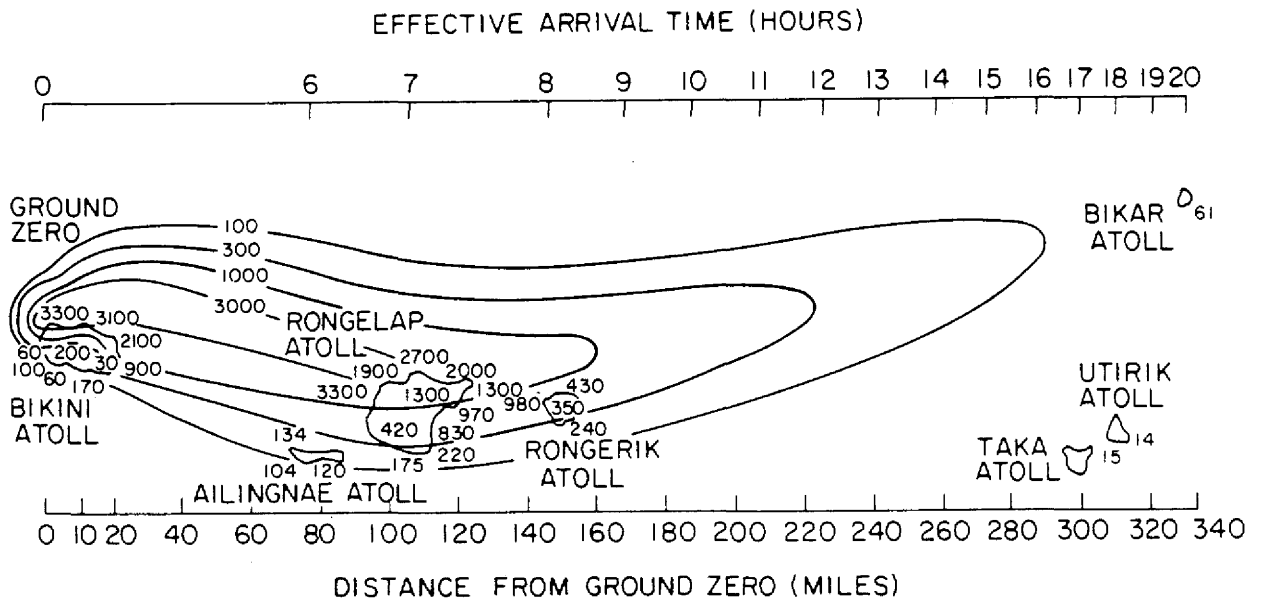


Figure 1. Approximate gamma dose rates (roentgens per hour) at 3 feet above the ground, one day after the detonation. From Glasstone (40).

2. Residual Radiation

To assess potential effects of low-level residual radiation persisting on Rongelap, Utirik, and Bikini, periodic monitoring of the inhabitants of these atolls as well as samples of native flora, fauna, soil, and marine life were performed. These studies are discussed in Section X and Appendix II.

E. Data Evaluation

Reevaluations of dose estimates are planned or under way using more sophisticated technology and computer methods currently available, and it is possible dose estimates may be increased. In the meantime the dose calculations previously developed will continue to be used.

While quantitative variations in dose estimates have an obvious impact on dose/effect correlations, other considerations are equally important in these studies, especially regarding radiation induction of thyroid neoplasms (caveats regarding thyroid dose estimates are discussed in Section IX and Appendix II).

Risk probabilities for development of neoplasms secondary to radiation have classically been derived for malignant tumors of specific organ systems.

This approach may be an oversimplification with the thyroid, however, since thyroid neoplasms may show many morphologic features of malignancy yet behave clinically in a benign fashion. Further, certain thyroid tumors may have identical gross and microscopic morphology, yet exhibit totally different clinical progressions. Thus, the most important prognostic feature in thyroid malignancies is considered by many to be age of onset regardless of pathologic characteristics (41-45).

Accordingly, there is an understandable divergence among pathologists and clinicians in regard to a uniform classification of these lesions. Clearly, the term "cancer" is a misnomer, imprecise and often misleading, and it should be abolished from thyroid nomenclature. Even designations of benign vs malignant must be used circumspectly with proper attention applied to clinical vs pathological connotations, since the correlations may be tenuous at best.

II. GENERAL MEDICAL SURVEYS

A. Background

Following gradual resolution of early radiation effects in exposed Marshallese, a program for their continuing care and observation was instituted under the aegis of the Atomic Energy Commission. A medical team, headquartered at Brookhaven National Laboratory and supplemented by a national corps of consultants, has continued to implement the program under the auspices of the AEC and its descendant agencies (the Energy Research and Development Administration and the Department of Energy) with cooperative support from the Departments of Defense and Interior (Trust Territory of the Pacific Islands).

From its inception, the primary objective of the Marshall Islands program was the early detection and treatment of any medical conditions that might evolve as a consequence of the radiation exposures. Such an objective required a longitudinal prospective follow-up study of exposed individuals along with an appropriate control population. Both scientific and humanitarian considerations dictated establishment of a field capability for administering periodic primary medical care with some mechanism available for secondary and tertiary referral.

In its practical application, several unique problems contributed to the complexity of this program. As noted in the Introduction, the Marshallese were exposed to a highly complex spectrum of radiations under source conditions that were unlike any generally experienced in previous radiotherapeutic, accident, or warfare situations. Dosimetry, therefore, became more a matter of estimation than precision, especially in regard to specific individuals (2). Accurate assessment of risks, morbidity, and mortality was complicated statistically by a number of problems. The sizes of the exposed populations were small. Data on the incidences of various diseases in Micronesia were meager or non-existent, and vital statistics were unreliable because of the lack of accurate record keeping in the islands. It was therefore necessary to include an unexposed comparison population ("control group") in order to evaluate better the findings in the exposed populations. Difficulties associated with these groups are discussed below. In addition to the above problems, geographic, logistic, cultural, and political considerations continually influenced implementation of certain aspects of the program.

In the first decade following the accident, there were few clinical findings that could reasonably be related to radiation (1,13). Cutaneous scarring and depigmentation were the only residue of beta burns, and no evidence of skin malignancy appeared. Exposed Rongelap women may have had an increased incidence of spontaneous abortions, and some children exhibited growth retardation. Peripheral blood elements remained minimally below comparison means for about five years, and some chromosomal defects were detected.

In the second decade, the development of hypothyroidism and thyroid nodules in a significant number of individuals and the occurrence of a fatal case of acute myelogenous leukemia heralded the possible onset of serious late irradiation sequelae. Aspects of these findings have been reported previously (1,33), and some are discussed in greater detail in Section VIII.A. Aside from these problems, the general health of the exposed Marshallese appeared to

be no different from that of the comparison populations. The incidences and types of diseases affecting all groups were similar, and there was no clear evidence of accelerated aging or cataract formation, of decreased longevity, increased mortality, or increased incidence of malignancy (other than thyroid).

B. Methods

1. Procedures

Extended field trips for general examinations were made at least annually, and more frequently during certain periods, following the accident. For major field surveys, the medical team usually consisted of a dozen technological support personnel and four to six physicians, including an expert thyroidologist, a hematologist and a pediatrician when possible, and sometimes a gynecologist and a dentist. During the past six years, a physician and a technologist in full-time residence in Kwajalein have attempted to make quarterly visits to hold general sick call, to conduct follow-up evaluations of continuing problems, and to promote general health care and education among the populace.

Table 1 shows the current locations of various members of the examination group. Many are now congregated at the major population centers: Majuro (the Trust Territory District Center) and Ebeye Island in Kwajalein Atoll. Medical facilities established on these islands by Brookhaven National Laboratory included two large trailers which provided semipermanent quarters for physical, x-ray, and laboratory examinations. Additional support was available from nearby Trust Territory hospitals. The outer islands, including Rongelap and Utirik, necessitated shipborne surveys, since they were essentially inaccessible by air. During the past six years, two chartered vessels were modified to transport the entire medical team and to provide on-board examination facilities and equipment for outer island surveys. These were supplemented by trailers and Butler buildings on some islands.

Table 1. Locations of Marshall Islands groups under study, 1979.

Group	R	U	E	M	K	L	W	Other	Total
Rongelap + Ailinginae exposed	18	-	20	11	1	-	-	5	55
Rongelap unexposed	204	-	360	111	4	-	2	72	753
Utirik exposed	-	54	17	30	-	-	1	10	112
Utirik unexposed	-	264	29	169	-	-	-	16	478
Bikini	4	-	4	159	24	-	6	31	228
Wotje	-	-	-	-	-	-	155	-	155
Likiep	-	-	-	-	-	149	-	-	149
Total	226	318	430	480	29	149	164	134	1930

R = Rongelap; U = Utirik; E = Ebeye; M = Majuro; K = Kili; L = Likiep; W = Wotje.

Medical teams almost always included an equal complement of Micronesians trained as medical practitioners, nurses, health aides, and technologists. These participants were especially valuable in obtaining accurate interval histories, which were primarily directed toward detecting conditions with higher probabilities of radiation association, such as thyroid enlargement or dysfunction or development of neoplasia in other organ system. Family and social histories were also obtained to establish pedigrees, periods of residence on various islands, and smoking and drinking habits, and to supplement demographic data obtained by other means.

Thorough general physical examinations were administered by the medical staff with special attention directed to examination of the thyroid, skin, female breasts, and other sites of potential oncogenesis. Preprinted examination protocol forms ensured uniformity and completeness. Questionable findings were evaluated by consultation with other staff physicians. Positive thyroid findings were always confirmed by a consulting thyroidologist before more extended evaluations and/or surgery were performed in the United States (see Section IX.B).

Patients 40 years of age or older received standard 12-lead electrocardiograms annually (Hewlett-Packard 1500), a 14x17-inch P-A chest x ray bi-annually (or more frequently if indicated by smoking history and/or signs or symptoms of pulmonary pathology), and annual stool examinations for occult blood (Ames Hemocult). Urine was tested for pH, sugar, acetone, blood, and protein with Ames Labstiks. Blood for hematologic and endocrine evaluations was drawn and processed as described in Section III.B. Two-hour postprandial blood sugars were measured annually in known diabetics and periodically in the entire study group, and glucose tolerance tests were periodically administered (see Section VII). Other biochemical assays, such as those for serum enzyme activity and electrolyte and metabolite concentrations, were performed at irregular intervals or as clinically indicated in certain individuals.

Dental examinations have been limited essentially to extractions and fluoride prophylaxis. Periodic ophthalmologic examinations have included slit-lamp inspection for cataracts but not refractions (1).

The pediatric study groups consisted of all children exposed to radiation in March 1954 and a comparison population selected from unexposed Rongelap children in 1957 who were matched as closely as possible for age and sex. Attrition in the control group due to death or emigration was compensated by periodic addition of unexposed individuals. Children born to parents in the adult study groups were also examined routinely as a separate study group. The initial composition of these groups is summarized in Table 2. Rongelap children in each group were examined, generally on an annual basis, by the medical team, which included a pediatrician each year since 1958, except for the four years 1960, 1964, 1967, and 1973. In earlier years, the children on Utirik were not seen as frequently as those on Rongelap, but major efforts to examine them were mounted in 1957, 1959, 1966, 1969, 1972, and each year since 1974, when examinations were performed at least annually on all study groups whether they were residing at Rongelap, Utirik, Majuro, or Ebeye.

Table 2. Composition of initial pediatric study groups.

Age on March 1, 1954	<u>Exposed Rongelap</u>		<u>Exposed Ailingnae</u>		<u>Control Group</u>	
	M	F	M	F	M	F
<u>In utero</u>	3	1	-	-	-	-
0-5 yr	8	7	2	1	9	16
5-10 yr	6	4	3	-	13	7
10-18 yr	5	9	-	-	3	5
Total	22	21	5	1	25	28

When children reached 18 years of age, they were transferred to corresponding adult study groups, so that technically all were adults by 1972. Nonetheless, increasing numbers of children in the island populations, even though not belonging to specific study groups, have been seen by the medical team, making continuing participation by pediatricians important to the field surveys.

2. Control Populations

A group of 115 Marshallese, principally from the village of Rita on Majuro Atoll, was originally selected in 1954 as a control population, since they had background and living conditions similar to those on Rongelap and Utirik. They were matched as nearly as possible by age and sex with each individual in the Rongelap exposed group. Single blood samples from this group provided the primary basis for initial evaluation of hematologic alterations in the exposed Rongelapese. By 1957 attrition by emigration necessitated study of additional unexposed Marshallese to provide statistically valid comparisons. These were selected primarily from blood relatives of the Rongelapese who were away from the atoll at the time of the accident, but were returning to Rongelap with the exposed individuals at the time of repatriation in 1957. The size, age, and sex distribution of this group compared closely with that of the exposed Rongelapese, and its shared genetic heritage was considerably closer than that of the original control group from Majuro. Nonetheless, a number of these individuals were periodically lost to follow-up and were eventually replaced by addition of unexposed Marshallese from other island communities.

During the past decade, an additional comparison population has been examined to evaluate the prevalence of thyroid abnormalities throughout the Marshall Islands. This population was comprised of unexposed Marshallese from Rongelap, Utirik, Likiep, and Wotje Atolls. Though some of these people have been exposed to low levels of residual radiation while residing part time on their home islands, this exposure is not considered to be a significant deterrent to their use since thyroid effects of such exposure, if any are possible, would likely be undetectable (see Appendix I). However, none of the unexposed

groups is a completely valid control group, and the caveats associated with interpretation of the data using these groups are pointed out in Section IX.C.

C. Results

During the past six years, general medical findings in the Rongelap and Utirik populations continued to be comparable and very similar to those noted in previous years. There were no apparent differences between the exposed and unexposed people from either atoll in incidences of specific diseases (other than thyroid abnormalities, described in Section IX).

Subjects in all groups continued to exhibit extensive dental disease -- multiple caries, periodontal inflammation, and early endentulism -- despite repetitive instruction and encouragement in dental hygiene.

Dermatophytic dermatoses and pediculosis, sometimes with secondary infection, remained common, particularly among the children, in whom molluscum contagiosum also occurred with high frequency.

The ophthalmological findings were similar to those reported in the 20-year report (1). These included a high incidence of pingueculae and pterygia, arcus senilis, and senile cataracts. No radiogenic cataracts have been noted. Though some of the cataracts have been associated with diabetes, vascular changes in the fundus associated with this disease were minimal (see Section VII).

The high incidence of diabetes among the adults is discussed in Section VII.

Adults continued to have evidence of hypertension as indicated by systolic pressures >140 mmHg or diastolic >90 mmHg. Virtually every adult studied, regardless of exposure group, registered pressures above these limits at least once during the past six years. Repeated elevations (two or more) were found in 12 of 42 Rongelap exposed adults, 21 of 55 Utirik exposed adults, and 20 of 64 Rongelap controls. This frequency is higher than the 9% incidence reported during the first 20 years (1) and may reflect the advancing age of all groups. Overt clinical evidence of hypertensive heart disease or retinopathy remains scarce.

Evidence of degenerative osteoarthritis in the elderly was uniformly apparent among all groups with equal frequency, and musculo-skeletal complaints such as backaches, lower extremity pain, and decreased flexibility were common.

Pelvic examinations, including Pap smears, resulted in abnormal findings in 7% of the female population examined. Cervical inflammation and trichomonas were commonly seen, and occasionally fungus infections, herpes, and condylomata. The fungal infections were often correlated with diabetes as evidenced by elevated blood sugar levels. Several toxemias of pregnancy were noted. The incidences of the above abnormalities were about the same in the exposed as in the unexposed females.*

Hypertension was practically nonexistent in Marshallese children. Obesity was noted primarily in some girls after they had reached puberty. In

*Dr. Ruth Nicoloff (Permanente Medical Group, Los Angeles) was responsible for interpreting the Pap smears.

earlier surveys, residual findings from a poliomyelitis epidemic were recorded in a few individuals. The liver was palpable in a number of children, but the frequency appeared to be related to young age and not to clinical history or other physical findings.

Complaints noted during dispensary visits followed a general pattern modified primarily by the acuteness of the condition. The most frequent reasons for emergency clinic visits were cough, fever, anorexia, otitis, skin lesions, and diarrhea. Most of the dispensary care involved infants and very young children. Routine examinations of babies born after the return of the Rongelap inhabitants revealed no obvious differences among those born to exposed parents compared with those born to unexposed parents.

The major findings to emerge from the pediatric studies were (1) development of thyroid neoplasia, both benign and malignant, in the exposed children, (2) growth retardation secondary to thyroid injury from radiation in some exposed children on Rongelap, and (3) acute myelogenous leukemia developing in 1972 in a boy exposed at age 1 year on Rongelap who also had a thyroid adenoma resected in 1962. These are discussed in more detail in other sections of this report.

A continued high incidence of intestinal parasitism has been noted. This problem is discussed in Section VI, and recent efforts to treat parasitism on Rongelap and Utirik are described.

Variations in serum electrolytes and other chemistries occurred in random fashion among all groups and were seldom persistent on repeat examination. Statistical evaluations of routine laboratory screening test results, other than hematological, have not been performed.

Table 3 presents a mortality list with possible causes of death. The latter were, in most instances, presumed, since death generally occurred without a physician or health aide in direct attendance, and autopsies were rarely performed because of strong Marshallese cultural resistance to such procedures. Records maintained by local health aides on the outer islands were often marginal in content and accuracy, if not entirely missing, and follow-up questions regarding potential causes of death were often met with uninformative responses, such as death due to old age.

Table 3. Mortality Among Rongelap and Utirik People (as of 1980).

(Possible causes comprise diseases noted in the medical records which might be etiologically related to death. AE = Ailinginae exposed. NC = not confirmed by biopsy or autopsy.)

Year	Subject No. & sex	Age	Possible causes
<u>A. Rongelap exposed</u>			
1956	25 M	46	Heart disease
1957	38 M	78	Heart disease, diabetes
1958	31 M - AE	35	Acute varicella
1959	62 F	60	Ovarian cancer
1962	30 F	60	Cancer of cervix - NC
1962	46 M	84	Heart disease
1962	26 M	21	Accident
1962	56 F	75	Accident
1963	52 F	55	Poliomyelitis, bulbar
1963	57 F	107	"Old age" (?)
1964	43 F - AE	77	Pneumonia, heart disease
1965	28 F - AE	79	Heart disease
1966	29 M - AE	77	Asthma, heart failure
1966	55 M	88	Heart disease
1966	13 F	71	Cancer of uterus - NC
1968	59 F - AE	58	Influenza-pneumonia
1971	50 M - AE	51	Acute asphyxiation, cause unknown
1972	54 M	19	Acute myelogenous leukemia
1972	60 F	74	Heart disease
1974	68 M	64	Cancer, stomach
1977	58 F	82	? Liver disease
1980	82 M	75	ASHD
<u>B. Utirik exposed</u>			
1956	2118 M	24	?
1957	2219 F	57	?
1957	2222 F	63	?
1958	2243 M	50	Drowning
1959	2122 M	87	? CVA
1959	2127 M	73	?
1959	2170 M	46	?
1959	2187 F	61	Pulmonary bronchiectasis, chronic bronchitis
1960	2116 F	27	?
1960	2131 F	35	?
1960	2180 M	76	Asthmatic (?)

Table 3 (cont'd)

Year	Subject No. & sex	Age	Possible causes
1961	2177 M	11	Congenital anomalies (mongoloid ?)
1961	2184 F	67	?
1961	2199 F	49	Pneumonia
1963	2203 F	71	Pneumonia
1964	2163 M	75	ASHD
1964	2190 F	85	Hypertension, arteriosclerosis
1964	2192 F	84	Hypertension
1965	2121 M	68	Arteriosclerosis, paralysis lower limbs (polio ?) (CVA ?)
1965	2154 F	51	Pneumonia ?
1965	2183 M	67	?
1965	2204 F	71	?
1965	2238 F	65	? Pneumonia
1965	2253 M	56	?
1967	2181 F	78	Paralysis (tabes D?, ALS?)
1967	2202 F	72	ASHD, hypertension
1967	2223 F	79	?
1968	2101 M	62	Diabetes
1968	2112 M	70	?
1968	2141 F	67	?
1968	2259 F	36	?
1969	2191 F	90	ASHD
1969	2214 M	80	ASHD?
1970	2175 M	73	ASHD
1970	2211 M	65	ASHD
1971	2246 F	25	?
1971	2258 M	64	?
1972	2178 M	37	Auto accident
1972	2252 M	57	Hypertension
1973	2186 F	67	?
1974	2201 F	68	?
1976	2151 M	21	Suicide
1977	2135 M	54	CVA
1977	2240 M	56	Renal disease
1978	2109 F	70	Diabetes, chronic bronchitis
1978	2169 M	87	ASHD
1979	2198 F	83	Hypertension, ASHD
1980	2146 F	62	Diabetes
<u>C. Rongelap unexposed</u>			
1958	857 M	65	Cerebral thrombosis
1959	854 F	55	Infection in urinary tract, diabetes

Table 3 (cont'd)

Year	Subject No. & sex	Age	Possible causes
1960	933 M	56	Pneumonia, secondary to influenza
1960	927 M	65	Pneumonia, secondary to influenza
1960	861 F	68	Diabetes, cancer of cervix (?)
1962	953 M	48	Status asthmaticus
1962	848 F	41	Neurosyphilis (?)
1963	886 M	54	Asthma (?)
1964	893 F	61	Diabetes
1964	862 M	91	Heart disease
1964	894 F	68	Pneumonia
1966	964 M	90	Probably cardiovascular (?)
1967	967 M	24	Accident
1967	936 F	76	Infection complicating diabetes
1967	853 M	62	Diabetes
1968	860 M	78	Congestive heart failure
1969	852 F	65	Hypertension, diabetes
1970	884 M	76	
1970	916 F	46	Asthma, diabetes
1970	1515 M	50	
1970	918 M	72	Heart disease, diabetes
1970	875 M	53	? (Epileptic)
1971	899 M	76	
1972	947 M	64	Hypertensive heart disease
1972	957 F	64	
1972	858 F	78	Heart disease (?)
1972	961 M	79	Heart disease (?)
1973	856 M	74	Hemiplegia, pneumonia
1973	898 F	75	
1973	1506 M	65	Asthma, heart disease
1974	948 M	66	Heart disease, diabetes
1974	908 F	84	Heart disease, diabetes
1974	978 F	23	Childbirth
1976	1517 M	55	Penicillin reaction
1976	836 M	43	Drowned
1976	897 M	78	ASHD?
1976	910 M	73	Hypertension; ASHD?
1977	878 M	77	Heart disease
1977	855 M	72	Diabetes
1977	929 F	79	ACHD?
1978	1547 F	64	Diabetes, hypertension
1980	859 F	87	Hypertension, ACHD
1980	850 M	69	ACHD?
1980	915 M	83	? Arteriosclerosis
1980	951 F	47	Pneumonitis, diabetes

III. HEMATOLOGIC OBSERVATIONS*

A. Background

Since alterations in leukocyte and platelet counts are among the most sensitive and reliable responses to radiation injury, careful hematologic monitoring of exposed populations was instituted immediately following the accident and has continued subsequently at frequent intervals. All persons were not always available for study during each field trip. Accordingly, surveys were often made on a semiannual or quarterly basis by the medical team or the resident physician at Kwajalein with the objective of performing hematologic evaluations of most exposed individuals at least annually. This allowed values for each person (as well as mean values for each exposure group) to be followed serially in comparison with values for unexposed populations and with each other over the course of time.

The prompt and significant depressions in leukocyte and platelet counts observed in the combined Rongelap and Ailingnae groups immediately after the accident, and the subsequent return to stable plateaus closely approximating control mean values, are shown in Figure 1. The severity of initial depressions in cell counts varied among the three exposed groups, correlating reasonably well with that expected from the best estimates of their degrees of radiation exposure. In the Rongelap group, these effects were moderately severe, and it was thought that an additional increment of 50 to 100 rem probably would have resulted in the sequelae of pancytopenia (infection and hemorrhage) with the statistical possibility of death (2).

The early fluctuations in neutrophil and total leukocyte counts (Figure 1a) apparently followed a burst of leukocytosis during the first few days and might have reflected individual responses to other injuries, such as beta burns, or to transient respiratory infections that occurred during the first month. The response of peripheral lymphocytes (Figure 1b) to the radiation injury was rapid and marked, whereas the platelets fell gradually to reach a nadir in about one month (Figure 1c). Recovery required approximately one year for neutrophils and at least two years for lymphocytes and platelets.

It is notable that the mean peripheral blood counts recorded in Figure 1, especially over the past 6 to 8 years, have shown less annual fluctuations for the combined Rongelap-Ailingnae groups than for the comparison populations. This may reflect the more variable composition of the latter occasioned by gradual attrition of the age- and sex-matched controls available for followup studies and their replacement with individuals from other population groups, primarily unexposed Rongelap residents.

B. Methods

Hematologic measurements for the first few years following the accident were performed on capillary blood from the finger or occasionally from the

*This section was written by Drs. D.E. Paglia (UCLA) and E.P. Cronkite (BNL), with the technical assistance of Mr. W. Scott (BNL).

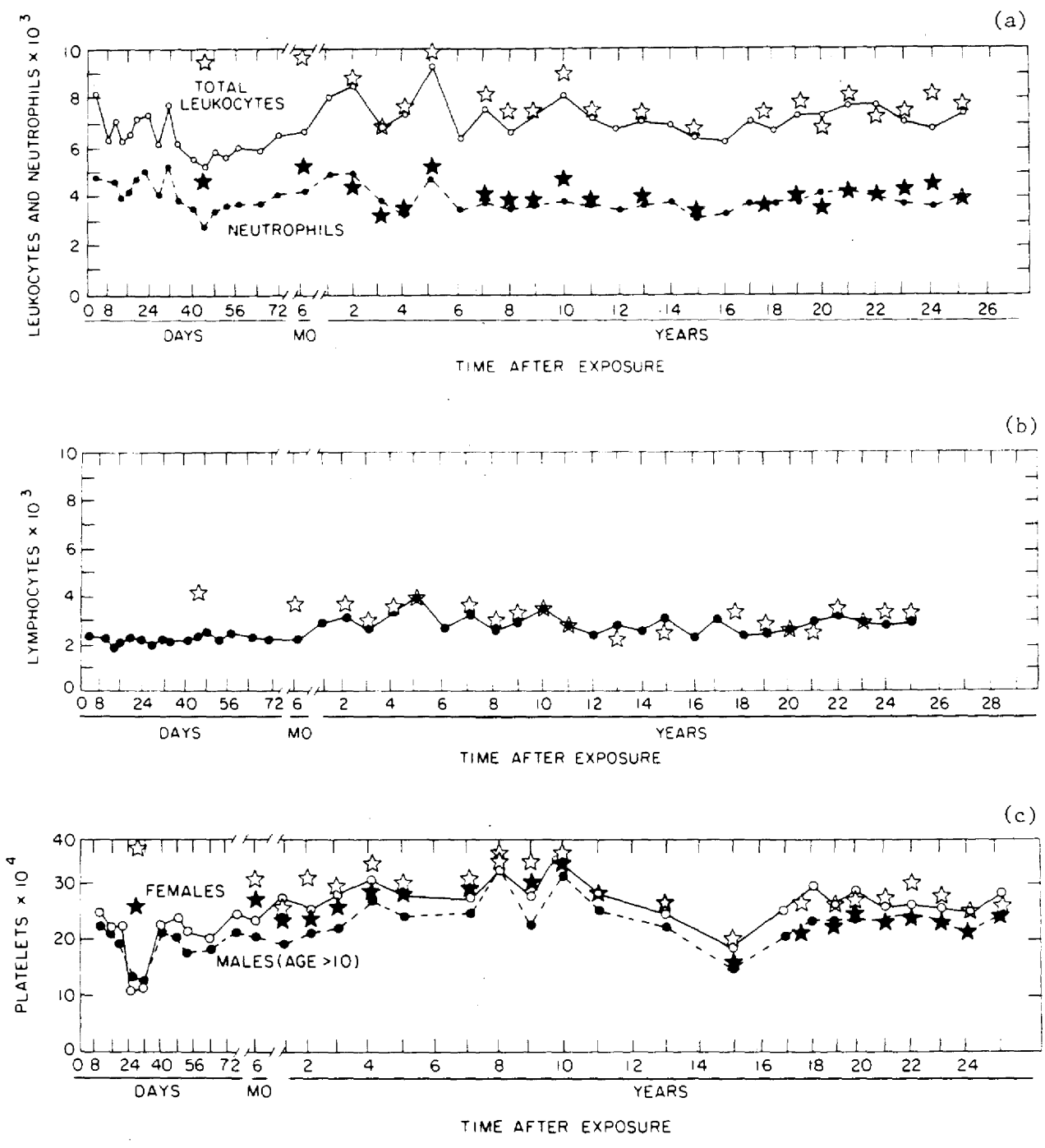


Figure 1. Chronology of mean hematologic values of individuals exposed on Rongelap and Ailingnae (black symbols) relative to comparison populations (white symbols). (a) Total leukocyte and neutrophil counts. (b) Lymphocyte count. (c) Platelet counts.

heel or ear. Subsequently, venipuncture specimens anticoagulated with heparin were used. Since 1973, Na₂EDTA has been used as the anticoagulant. Duplicate pipettes were filled for leukocyte and platelet counts and diluted with 3% acetic acid or 1% ammonium oxalate, respectively, and each was then dispensed into a single hemocytometer chamber after 10-minute rotations and counted by phase microscopy after settling 10 minutes. Hematocrits were measured in heparinized capillary tubes. One-hundred-cell differential counts were performed on Wright's stained blood smear and used to calculate absolute concentrations of leukocyte subsets. Hemoglobin concentration after conversion to cyanmethemoglobin was measured with a Lumitron colorimeter.

Hemocytometrics were used for leukocyte counts until the introduction of a Coulter counter during the third annual survey (1957). Erythrocyte counts were also performed with the Coulter instrument, and modifications in orifice diameter allowed electronic counts to replace phase microscopy for platelets after the fourteenth annual survey. The Coulter counters were superseded in 1973 by instruments from General Science for both leukocyte (MK-3) and platelet (MK-4) enumeration. In 1978, a J.T. Baker Instruments (Milford, CT) MK-4/HC platelet counting system was adopted, along with a Baker MK-40 four-parameter cell counter to measure leukocytes, erythrocytes, hemoglobin, and hematocrit.

Initially, hematologic measurements in exposed individuals were repeated in duplicate or triplicate at weekly intervals. By 1962, a repeat determination was made only if an abnormal value was observed.

C. Results and Discussion

Specific mean hematologic values over the last five-year survey period are presented in Figures 2 to 4, segregated on the basis of exposure group and sex. It should be emphasized that the values for the Ailingnae group represent means of only 4 to 8 determinations (Table 1), and this clearly contributes to their variability. No statistically significant differences were demonstrable among the three groups exposed to radiation and their appropriate comparison populations for any of the mean hematologic values recorded during this period. Certain measurements showed tendencies to segregate on the basis of sex, however, regardless of exposure group. These included increased platelet counts in females (Figure 4) and the expected increases in various red cell parameters in males (Figure 3). Variation between sexes in platelet concentrations has been observed consistently throughout the 26-year study period and appears to represent a true anthropometric distinction in the Marshallese, as it does in Caucasians. The sporadic very low values for individual platelet counts shown in Figure 7 most likely represent technical artifacts.

Despite the lack of significant variance among group means, a number of individuals exhibited sufficient deviations in certain hematologic measurements to require followup assessments. Figures 5 to 7 record individual values segregated by exposure group, sex, and time of study between 1975 and 1979 for persons whose hemograms contained values outside the ranges 4,280 to 10,640/ μ l leukocytes, 10.2 to 17.2 g/dl hemoglobin, and 120,000 to 372,000/ μ l platelets. These ranges represent values more than one standard deviation

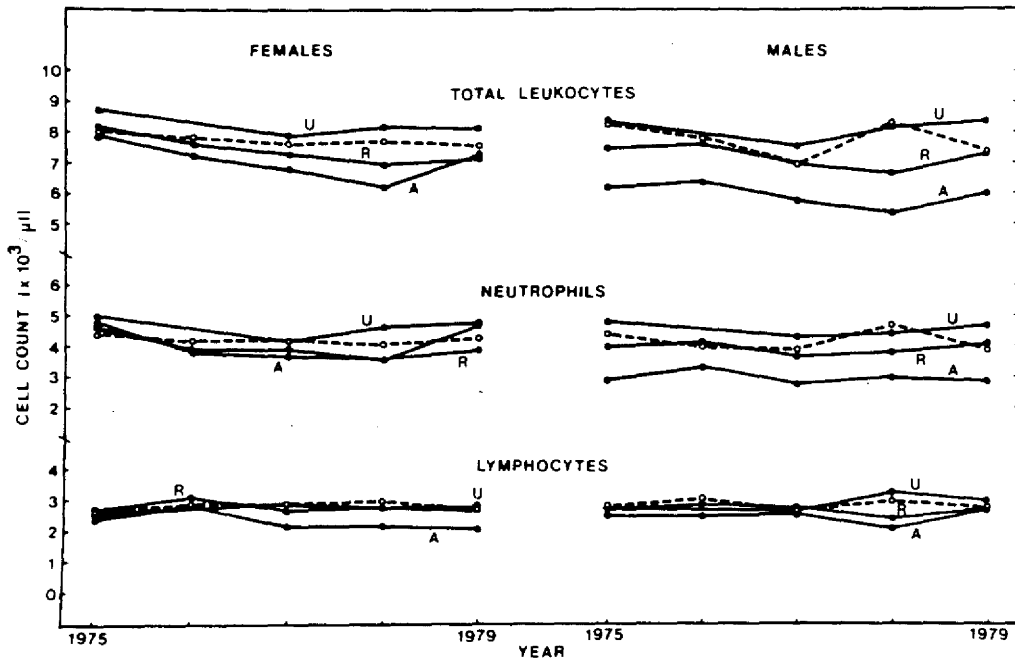


Figure 2. Mean leukocyte counts in various groups over last 5-year period. R, A, and U indicate exposed populations from Rongelap, Ailingnae, and Utirik, respectively. Values for comparison populations of unexposed individuals from Rongelap are indicated by open symbols and broken lines.

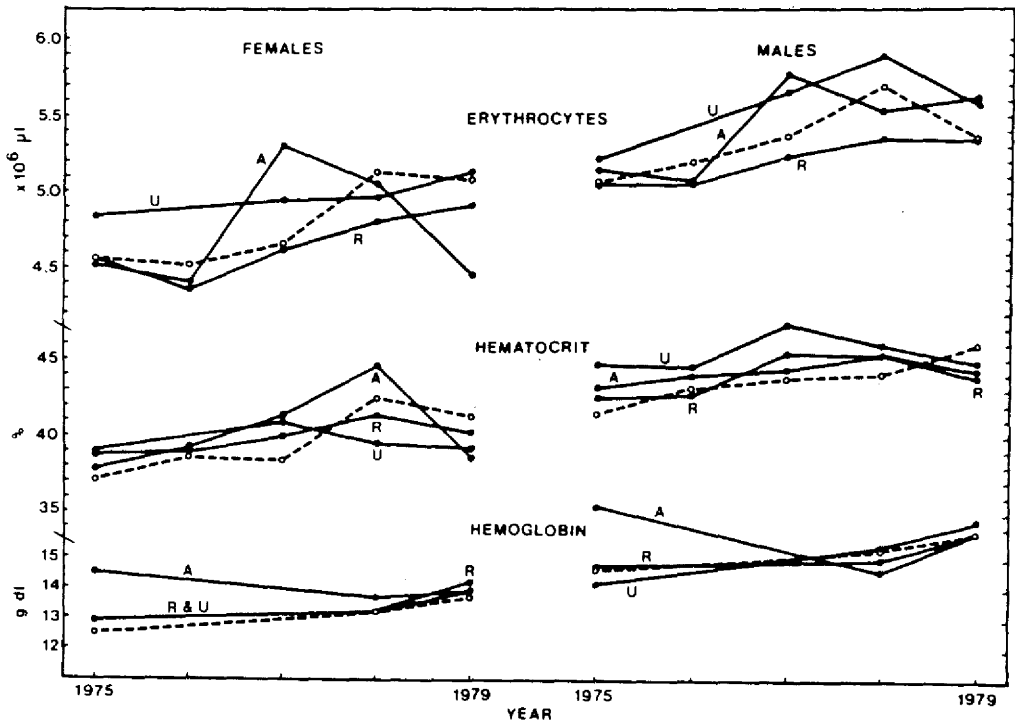


Figure 3. Mean erythrocyte values for exposed and comparison populations. Abbreviations as for Figure 2.

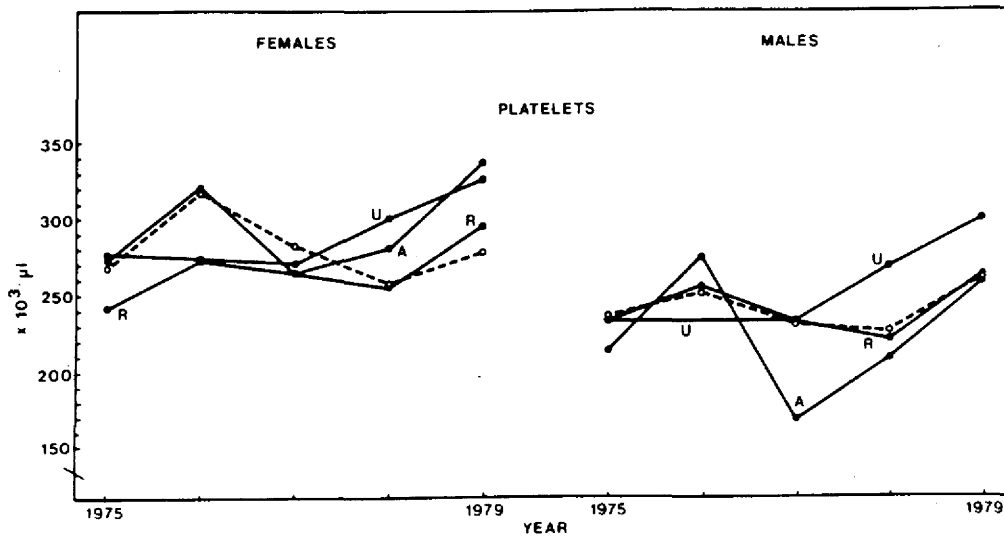


Figure 4. Mean platelet counts for exposed and comparison populations. Abbreviations as for Figure 2.

Table 1. Mean numbers of individuals in groups providing hematologic values in Figures 2 to 7.

	Sex	Rongelap	Ailingnae	Utirik	Control
Leukocytes	F	25(24-27)*	8(7-8)	57(54-62)	64(54-73)
	M	25(23-25)	5(4-5)	39(34-43)	54(36-57)
Erythrocytes and platelets	F	25(24-27)	8(7-8)	57(55-67)	64(54-71)
	M	23(22-24)	4(4-5)	40(34-46)	46(36-54)

*Range over five-year period.

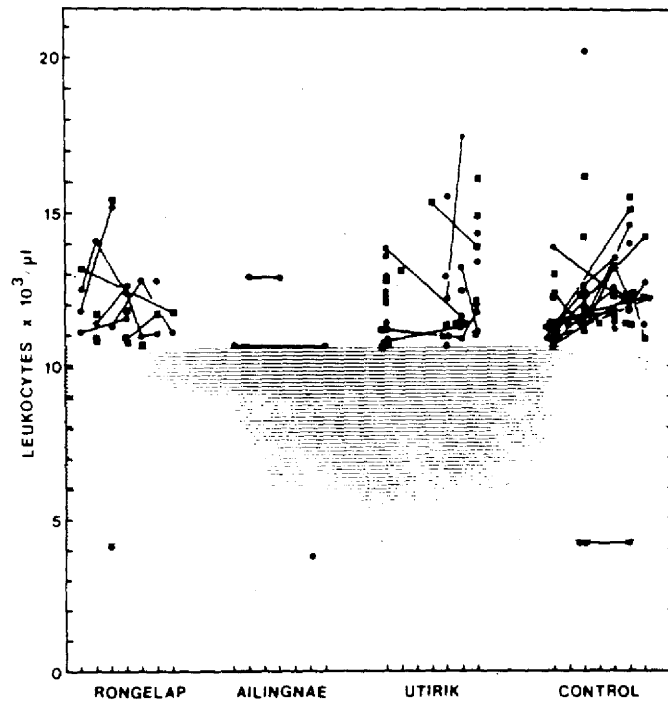


Figure 5. Occurrence of leukocyte counts beyond the range 4,280 to 10,640/ μ l. Females and males are represented by round and square symbols, respectively. Lines connect multiple values on the same individual at different times. The abscissa marks represent seven successive field surveys, during the 5-year study period: Spring 1975, Fall 1975, Spring 1976, Fall 1976, and Spring 1977, 1978, and 1979.

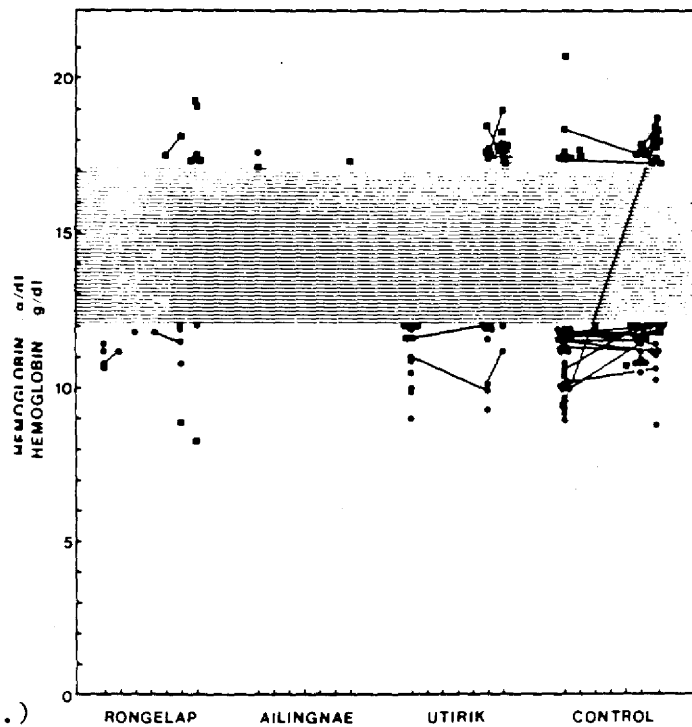


Figure 6. Individual hemoglobin values beyond the range 12.0 to 17.2 g/dl. (See legend for Fig. 5.)

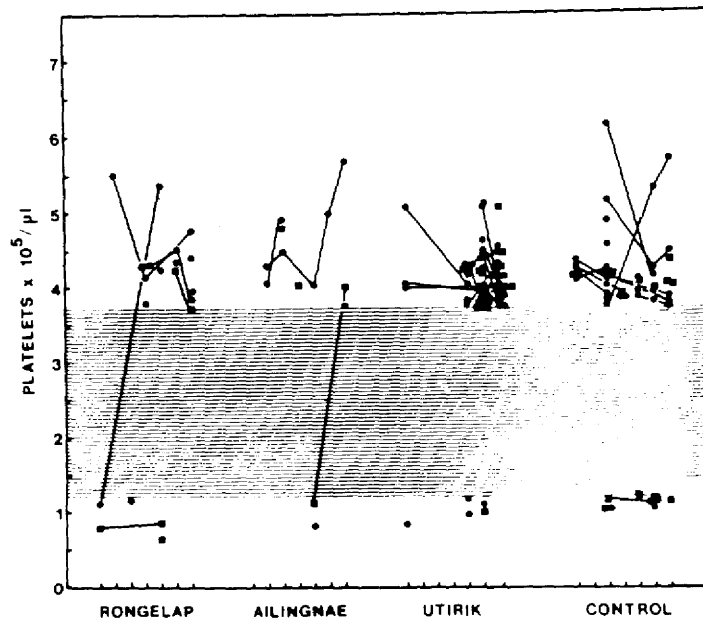


Figure 7. Individual platelet counts beyond the range 120,000 to 372,000/ μ l. (See legend for Figure 5.)

from the mean for leukocytes and platelets and less than two standard deviations below the mean for hemoglobin.

As shown in Table 2, the occurrence of values exceeding these limits was not significantly more frequent in radiation-exposed groups than in the comparison population, but again there were tendencies toward variation on the basis of sex. The increased platelet concentration in females, regardless of group, has already been mentioned. Low platelet or leukocyte concentrations were infrequently observed in both sexes and were rarely persistent, and probably resulted from technical errors (Figures 5, 7). Relative leukocytosis occurred in one-quarter to one-third of all groups studied (Figure 5).

Hemoglobin concentration above 17.2 g/dl occurred only once in a single female out of an average of more than 150 studied on seven occasions during the five-year period, whereas approximately one-third of the men, both control and radiation-exposed, exhibited a relative erythrocytosis (Table 2, Figure 6). Anemia, on the other hand, if defined as hemoglobin concentration below 12.0 g/dl, was several times more frequent in the female populations than in their male counterparts (Table 2, Figure 6), especially in younger women. It is notable that lowered hemoglobin occurred twice as frequently (73%) in the control population as in the exposed female groups (36% of those on Rongelap, 28% of those on Utirik). A tendency toward microcytosis has been noted previously in these women, but serum iron concentrations and reticulocyte counts have been normal, and vitamin B₁₂ levels have been considerably elevated (7). Despite the frequency of mild anemia by hemogram criteria, symptoms or signs of clinically significant anemia were rare. Previous studies have also indicated that total blood volume and red cell mass may be generally lower in

Table 2. Frequency of abnormal hematologic values over 5-year study period, 1975-1979.

	Sex	Rongelap	Ailingnae	Utirik	Control
Leukocytes ($>10,640/\mu\text{l}$)	F	6/28* (24%)	2/8 (25%)	22/57 (39%)	18/64 (28%)
	M	9/25 (36%)	0/5 (0%)	12/39 (31%)	18/50 (36%)
Hemoglobin ($>17.2 \text{ g/dl}$)	F	0/25 (0%)	1/8 (13%)	0/57 (0%)	0/64 (0%)
	M	7/25 (28%)	2/5 (40%)	15/39 (38%)	17/50 (34%)
Hemoglobin ($<12.0 \text{ g/dl}$)	F	9/25 (36%)	0/8 (0%)	16/57 (28%)	47/64 (73%)
	M	2/25 (8%)	0/5 (0%)	3/39 (8%)	6/50 (12%)
Platelets ($>372,000/\mu\text{l}$)	F	7/25 (31%)	4/8 (50%)	29/57 (51%)	20/64 (31%)
	M	2/25 (8%)	1/5 (20%)	12/39 (31%)	8/50 (16%)

*Denominators are average numbers of individuals seen in each category on annual or semiannual field trips.

the Marshallese than in Americans (11). Peripheral blood eosinophilia in the region of 5% was noted consistently in previous studies and has persisted during the past five-year interval with no clear differences among the various groups.

The children of individuals in the exposed and comparison populations have also been followed hematologically with the results recorded in Table 3. Differences between sexes for mean values of platelets, erythrocytes, hemoglobin, and leukocytes were not as prominently nor as consistently seen as in their parents. No significant differences in any measurement could be related to exposure status, but the numbers of individuals in each subset were relatively small.

The established association between radiation exposure and development of leukemia has focused attention on this potential in the Marshallese. In 1972, a 19-year-old, who was the youngest male exposed on Rongelap in 1954, developed and rapidly succumbed to acute myelogenous leukemia. He presented with asymptomatic leukopenia ($2000/\mu\text{l}$) and thrombocytopenia ($120,000/\mu\text{l}$) detected on the routine annual survey, and the diagnosis was quickly established by bone marrow examination. His history and clinical course have been reported in detail previously (1,33), and he represents the only instance of leukemia in this series. Statistical calculations, based on the best available data for leukemia incidences in the U.S. and Micronesia, indicate a 5- to 15-fold greater probability that this Marshallese case was radiation-induced

rather than spontaneous.* The latent period for development of leukemia after radiation varies from 6 months to more than 30 years (46). Accordingly, lifetime studies of the exposed Marshallese are required.

*A number of hematological examinations for leukemia have been carried out over the years including studies of blood smears for immature forms, basophil counts, and alkaline phosphatase staining, yielding negative results. We are grateful to Dr. W. Maloney and Ms. Tullin at Harvard Medical School for assisting with these studies.

Table 3. Summary of hematological data from offspring of Rongelap and Utirik subjects (1977-1979).

Group	Year	Age (yr)	No. in group		Platelets ($\times 10^3/\mu\text{l}$)		Erythrocytes ($\times 10^6/\mu\text{l}$)		Hematocrit (%)		Hemoglobin (g/dl)		Total leukocytes ($\times 10^3/\mu\text{l}$)		Neutrophils ($\times 10^3/\mu\text{l}$)		Lymphocytes ($\times 10^3/\mu\text{l}$)	
			M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Rongelap exposed	1977	15-23	3	4	-	-	4.84	4.96	38.0	40.0	-	-	7.1	7.5	4.4	4.8	2.1	2.1
	1978	15-24	6	10	240	235	5.45	5.68	46.2	47.5	14.8	13.5	7.1	7.6	3.9	4.5	2.9	2.8
	1979	15-25	10	10	290	282	5.16	4.68	43.3	37.4	16.1	13.3	7.7	9.0	4.1	5.0	3.2	3.4
	1979	5-15	24	16	-	-	4.93	5.11	38.0	39.4	12.8	13.1	9.3	9.2	4.6	4.6	3.7	3.7
Utirik exposed	1977	15-23	7	4	207	339	6.59	5.01	53.0	42.0	-	-	9.6	7.5	5.3	3.5	3.5	3.4
	1978	15-24	3	11	269	334	7.57	5.08	51.0	41.0	17.0	13.5	10.5	9.3	6.9	5.6	2.9	3.2
	1979	15-25	8	14	344	370	5.87	4.91	44.1	39.3	16.1	13.3	7.7	10.2	4.2	6.0	3.0	3.4
	1979	5-15	34	20	-	-	5.11	5.00	39.0	37.1	12.9	12.9	9.5	10.0	4.7	4.8	3.6	3.7
Rongelap unexposed	1977	15-23	9	2	-	-	6.50	5.56	49.0	42.0	-	-	7.2	7.8	3.5	4.3	3.0	2.9
	1978	15-24	6	6	218	208	5.89	5.23	49.0	47.0	14.4	11.9	7.1	7.4	3.7	4.5	3.0	2.6
	1979	15-25	16	3	293	372	5.11	5.16	42.1	38.7	15.2	13.4	8.5	8.9	4.8	4.9	3.2	3.5
	1979	5-15	29	25	-	-	4.80	4.82	37.2	37.7	12.4	12.5	9.7	8.5	5.1	4.3	3.8	3.4

IV. GROWTH AND DEVELOPMENT*

A. Background

The various anthropomorphic data on the Rongelap children have been tabulated periodically in previous annual reports (1,9-13), and ongoing analyses have also been published in the open literature (21,24,27,28). Interval skeletal age analyses were recorded in the 1963 and 1974 reports (10,1).

Beginning several years after exposure it was noted that, for boys, the statural growth curve for the exposed group lagged behind the curve for the unexposed group. This lag appeared to be due primarily to the slowed growth in the group of boys exposed at <5 years of age. It was first thought that the growth retardation might be a direct radiation effect (21), but subsequent findings established radiogenic hypofunction of the thyroid gland as its cause (20-year report) (1).

Assessment of the pattern of growth and development of the individuals who were children (<18 years old) on March 1, 1954, has been a consistent component of the pediatric examinations of the Rongelap people. Data interpretation has been complicated by radiation injury to the thyroid gland, partial or total thyroidectomies in the children who developed thyroid abnormalities, and administration of TSH suppressive doses of thyroid hormone to the exposed Rongelap population since September 1965 (when the youngest exposed child was 11 years old).

Analyses presented in this report are limited to the population of Rongelap Atoll.

B. Methods

In 1957 the population repatriated to Rongelap included (in addition to the exposed returnees) a sizable number of children who had not been exposed to fallout radiation. Some were Rongelap natives who had been away at the time of fallout, and others were relatives of residents. Since these children were of the same stock (blood relations) and would live post-return under the same environmental conditions as the exposed population, they were selected as unexposed controls. During 1957, 1958, and 1959, the control population was carefully characterized. Its members are identified in Appendix 11 of ref. 11. The same examinations were conducted on these children as on the exposed population.

From the very first examination, growth data have been recorded. During the first 3 years the measurements consisted of weight, standing height, sitting height, length of upper extremity, arm span, biacromial width, intercristal width, head circumference, abdominal circumference, and left calf circumference. In 1958 the battery of body measurements was standardized to include weight, stature, sitting height, head circumference, head width, head length, chest circumference, chest width, chest depth, buttock circumference,

*Dr. W.W. Sutow (M.D. Anderson Hospital, Houston, TX) and Dr. R.A. Conard and Mr. K. Thompson (BNL).

left calf circumference, biacromial diameter, and bicristal diameter. Standardized techniques (47-49) were used. The status of secondary sex characteristics was evaluated by inspection with the methodology described by Greulich et al. (50,51), Reynolds and Wines (52,53), and Shuttleworth (54). History of menarche in girls, hair distribution, breast development, and penile and testicular development in boys were recorded during these examinations.

In 1958 apparent discrepancies regarding birth dates were noted in the charts of many children. The absence of recorded birth information in the Marshall Islands seriously complicated the verification of ages. Detailed genealogical and biological histories were compiled for the Rongelap population in 1958-1960. The reconstruction of birth chronologies was based on intensive evaluation of frequently contradictory information derived from the following sources:

- Dates of birth reported by parents.
- Dates of birth recorded occasionally in ledgers kept by the village magistrate.
- Limited number of birth certificates (not always accurate) on file at the courthouse in Majuro.
- Birth order of children within each family unit.
- Ranking of childhood population in terms of age by parents.
- Ranking of childhood population in terms of age by the children (particularly age peers), by relatives, and by friends living in the village.

A table of most probable birth dates was derived for the Rongelap childhood population. Biologic compatibility of the birth dates within each family was carefully checked, and the compatibility of physiologic status with age was also determined for each child. The presumptive dates of birth, shown for each individual in Appendices 11, 12, and 13 of ref. 11, have been used in the calculations of chronological ages for analyses of growth and development.

Roentgenographic documentation of osseous maturation (x raying of the left hand and wrist) was initiated in the exposed children in 1957. A major effort was made in 1958 to examine the skeletal maturation of both exposed and unexposed children. Unfortunately these valuable baseline films were lost at sea during transport. This created a gap of almost 3 years when no radiographs were available on a number of children in the spurt phase of growth. Thereafter roentgenographic studies of the left hand and wrist were included at irregular intervals. These were particularly difficult under field conditions and presented many technical problems, but the minimal number of roentgenograms eventually obtained permitted a reasonable assessment of the longitudinal skeletal development of each child through the chronological age of 16 or 17 years in the girls and 18 in the boys.

Skeletal age determinations were made by inspection with the techniques and standards published by Greulich and Pyle (51). Early analyses of the skeletal age data were included in the reports of previous surveys (11-13). Comparisons between the exposed and unexposed children were made primarily in the group who were <10 years old on March 1, 1954. This group was further subdivided into two categories: those <5 years old on March 1, 1954, and those aged 5 to 10.

The data on children >10 years old on March 1, 1954, could not be analyzed in detail. The number of children (particularly in the exposed group) in each age category was extremely small. Also, by the time satisfactory

roentgenograms were obtained for most of them (1961 to 1963), even the youngest members of this group were already approaching skeletal maturity.

C. Results

Statural growth data are given in Tables 1 and 2 of Appendix III and in Figure 1. Three age groupings were used: 0 to 5, 5 to 10, and 10 to 18 years old as of March 1, 1954. The two younger age groups were combined (age 0 to 10) for some of the analyses. The numbers of exposed subjects in the 10 to 18 year age groups were extremely small.

Figure 1 demonstrates a consistent retardation of stature among the boys exposed at age <10. The differences are statistically significant only between ages 9 and 16, apparently because thyroid medication was administered to the exposed people on Rongelap after 1963. Figure 1 also indicates that statural retardation occurred in both subgroups (age 0 to 5 and 5 to 10 at exposure) but was more marked in the younger one. Statural growth in the few boys exposed at age >10 showed no differences from that in unexposed boys.

Among the girls the statural growth curve (Fig. 1) for those exposed to fallout at age 0 to 10 was significantly retarded at chronological ages of 6 to 7 years compared with that for the unexposed girls. Figure 1 also shows that the statural retardation occurred in girls exposed at age <5 but not in those exposed at age 5 to 10, and disappeared by about age 9. The curves for girls exposed at age 10 to 18 are quite similar to those for unexposed girls.

These findings suggest that retardation in stature among the exposed girls occurred earlier and was less prominent and of shorter duration than among the exposed boys.

Osseous maturation among exposed boys was significantly retarded compared with that in unexposed age peers (see Fig. 2). This retardation was particularly prominent when the boys were 14, 15, and 16 years old, and Figure 2 indicates that it occurred in both age groups (those aged <5 and aged 5 to 10 in 1954).

Figure 2 also shows a similar comparison among girls. For the entire group exposed at age <10, skeletal maturation lagged significantly behind that in the unexposed girls until about age 10, and thereafter the gap progressively narrowed. Figure 2 suggests that this retardation in osseous maturation among exposed girls occurred primarily among those exposed at age <5 and to a very limited degree in those exposed at age 5 to 10.

D. Discussion

Growth studies on young people exposed to radiation from the atomic bombs in Hiroshima and Nagasaki showed that their adult heights were significantly lower than those of the controls (55). Similar analyses were carried out on statural data from inhabitants of Rongelap and Ailingnae Atolls who were exposed as children to fallout radiation. The presumptive adult (final) stature for each exposed child is tabulated in Appendix III. This stature is either the plateau value when several measurements remained the same, or the latest measurement (made after the subject was >20 years old) if the latest prior measurement had continued to show increase.

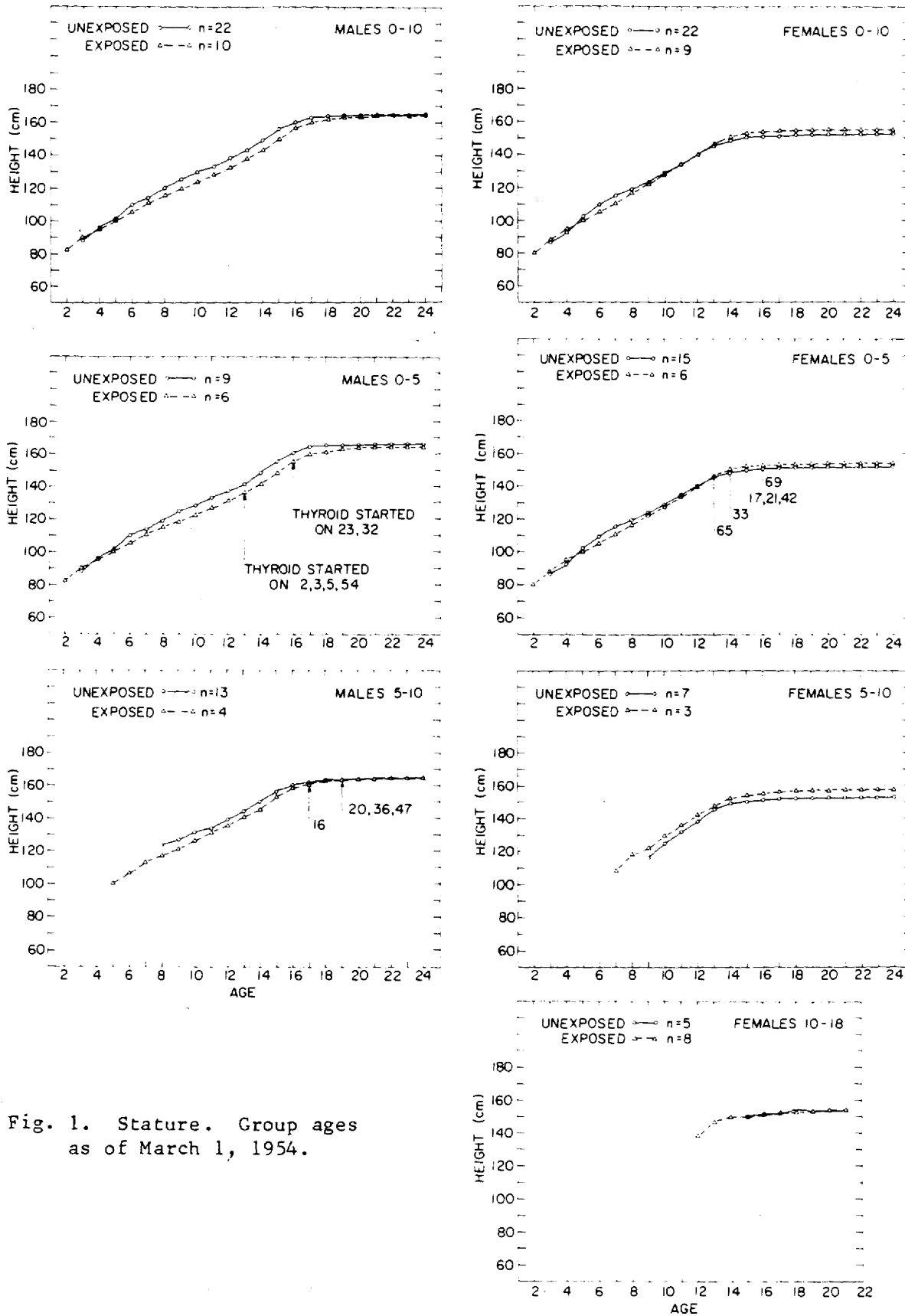


Fig. 1. Stature. Group ages as of March 1, 1954.

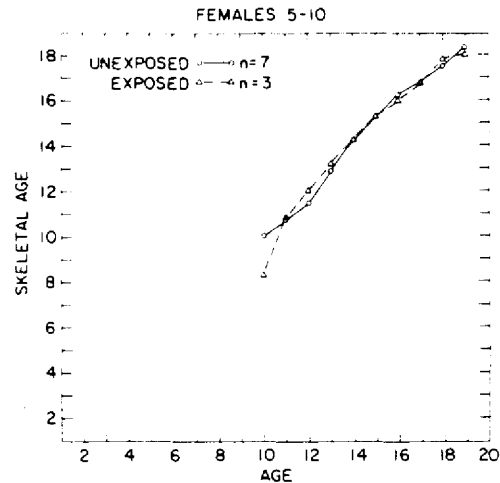
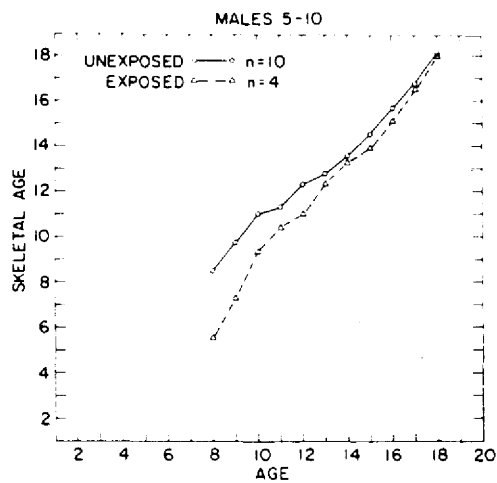
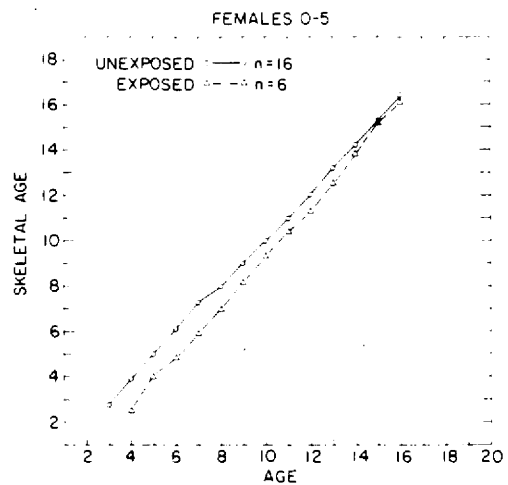
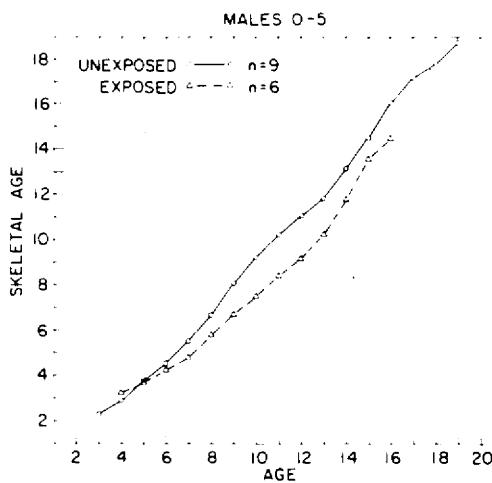
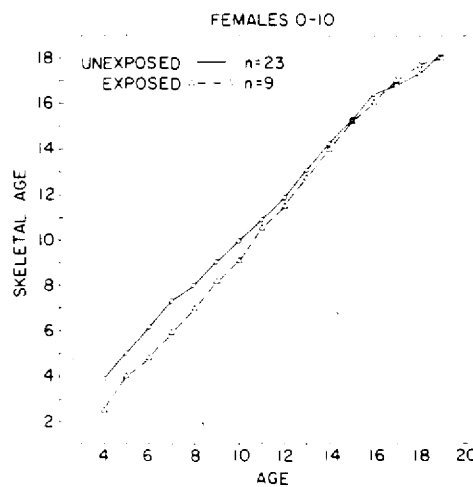
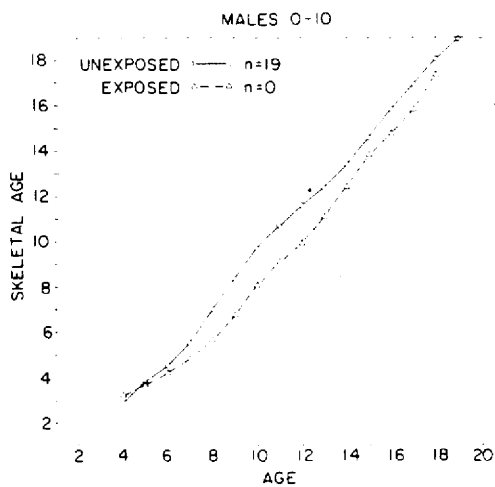


Fig. 2. Skeletal age. Group ages as of March 1, 1954.

It is generally assumed that adult height is attained when the skeletal age is 17 to 18 years in girls and 18 to 19 in boys (50,52,248), but actual measurements on the Marshallese population showed that many subjects continued to increase in stature with advancing chronological age, even after age 30, although the late increments were almost always very small. After the Marshallese reached age 16, absences from the island at the time of survey became more frequent; therefore, the time when adult stature was actually attained is uncertain for many individuals.

Statistical analyses (Appendix III) of the data on adult (final) stature of the Rongelap inhabitants who were in the pediatric age group on March 1, 1954, gave the following results:

- In the unexposed group, for both boys and girls, there was no significant difference in mean adult stature between those born after 1944 (≤ 10 years old on March 1, 1954) and those born before 1945 (> 10 years old on March 1, 1954).

- In the exposed group, for both boys and girls, there was no significant difference in mean adult stature between those born after 1944 and those born before 1945.

- For both boys and girls, there was no significant difference in mean adult stature between those who were exposed on Rongelap and Ailingnae to fallout radiation and those who were not.

Since osseous maturation is dependent on normal thyroid function, it is reasonable to assume that its retardation in exposed children was due to radiation damage to the thyroid glands. The marked retardation of skeletal maturation followed by dramatic improvement after the administration of thyroid hormone has been documented in the children who were clinically hypothyroid (13). The catch-up phenomenon in respect to osseous maturation can reasonably be attributed to the administration of thyroid hormone to the exposed populations, many of whom were subclinically hypothyroid (see Section IX.C.2).

V. AGING, IMMUNOLOGICAL, CHROMOSOME, AND GENETIC STUDIES

A. Aging Studies

Numerous empirical studies concerned with possible radiation-induced aging effects have been carried out on exposed Rongelap people (8,11-15), similar to those carried out on the Japanese survivors (56-63,207). On several occasions Rongelap people were given a battery of nonspecific tests for aging (9,12,13). Some of these tests were based on subjective assessment, on a 0 to 4+ scale, of items such as greyness of hair, arcus senilis, senile changes in the skin, balding, etc., but most involved direct measurements of items such as skin looseness, skin elasticity, visual accommodation, visual acuity, hearing (audiometric), blood pressure, neuromuscular function (light extinction test), hand strength (dynamometer), vibratory sense (vibrometer), and lean body mass (whole-body potassium by gamma spectrographic analysis). Comparison of these values in the exposed and unexposed Marshallese showed no significant differences. The biological age scores (average percent score) for the two groups are about the same. Aging studies also resulted in negative findings in the Japanese survivors, and they have not been pursued in the Marshallese during the past 5 years.

Beebe et al. (63), from mortality studies of the Japanese exposed to the atomic bombs, report that they do not find support for the belief that diseases other than cancer are involved in the late mortality effect and that "to the extent that the hypothesis of accelerated aging requires that radiation increase mortality from disease generally, these findings cast doubt upon that hypothesis."

B. Immunological Studies

A number of empirical studies for possible radiation effects on immunological status have been carried out on the Rongelap people in past years (6,8,11-15,30-32), similar to those conducted on the Japanese survivors. These studies were reviewed in the 20-year report (1) and may be briefly summarized as follows:

- Neither the acute depression of blood elements nor delayed recovery of these elements was reflected in any apparent increased susceptibility to disease.
- At 3 years post-exposure, tests of antibody response to tetanus toxoid showed no significant difference between the exposed and unexposed people (6).
- Assays for immunoproteins showed increased levels of gamma globulins (particularly the IgG moiety) with increasing age but no differences between exposed and unexposed people (30).
- Lymphocyte function as measured by response to phytohemagglutinin (PHA) stimulation, and acetylation of histones in lymphocyte nuclei, both showed decreases with aging but no radiation effects (30,64).
- Chromosome counts in PHA-stimulated lymphocytes showed hyper- and hypo-diploid changes in certain age groups that may have been related to radiation exposure (32).

Thus several indications have been seen of impairment or borderline deficiency of the immunological status in the exposed Rongelap people in earlier years, but no evidence that such deficiency was related to disease incidence, with the possible exception that the increased development of thyroid malignancy in the exposed Rongelap people may be an indication of reduced immunological surveillance. Recent rises of leukocyte and gamma globulin levels to control values indicate some degree of recovery, but better tests for immunological status are needed.

C. Chromosome and Genetic Studies

1. Chromosome Studies

In 1964 chromosome preparations were obtained from lymphocytes cultured from the peripheral blood of 43 exposed (21 age <20; 22, age >20) and 8 unexposed Rongelap people (65). Chromosome aberrations were noted in 23 of the exposed and in 5 of the unexposed Marshallese, but the exposed group had a number of two-break aberrations (represented by dicentric chromosomes, translocations, and a ring form) that are thought to be associated with radiation exposure. No two-hit aberrations were found in the unexposed group, but both groups had an unusual number of acentric fragments, the cause of which is not known. Paradoxically, the lower-exposure Ailingnae group had more aberrations than the Rongelap group who had a higher exposure. These studies indicate that a small but significant number of chromosome aberrations persisted in blood lymphocytes in some Marshallese as late as 10 years after exposure. The results are consistent with those of similar studies on the exposed Japanese fishermen (66), on victims of other radiation accidents (67), and on Japanese bomb survivors (68).

2. Isoleucine Misincorporation in Hemoglobin A of Marshallese*

Adult human hemoglobin A has no coded isoleucine; thus, the presence of isoleucine in hemoglobin A must result from errors in transcription or translation or from somatic mutations (1,35,37). Between 1974 and 1978, analyses were made of the isoleucine content (35) in hemoglobin A of 52 exposed Marshallese, 4 of whom were exposed in utero; 25 sex- and age-matched controls; and 5 children born after 1954, one or both of whose parents had been exposed. The frequency of isoleucine substitution for other amino acids in hemoglobin A was calculated by dividing the nanomoles of isoleucine by the total nanomoles of all other amino acids in each sample. The average frequencies are shown in Table 1. Values $>5 \times 10^{-5}$ are considered to be above the normal range. Among 25 controls, 4 showed values $>5 \times 10^{-5}$, but repeat analyses on two of these, the following year, gave values $<5 \times 10^{-5}$. Among 48 persons exposed when 1 to 30 years of age, 13 showed isoleucine substitution frequencies $>5 \times 10^{-5}$. Values for 11 of them were between 5.85 and 19.79×10^{-5} . As a group, only the persons exposed to 175 R had values significantly different from

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controls, although two hemoglobin samples, 6A and 8A, from the group of 9 individuals exposed to 69 R had high contents of isoleucine.

Table 1. Frequency of substitution of isoleucine for other amino acids in human hemoglobin from Marshallese.

Exposure (R)	No. of samples	Substitution frequency \pm SEM ($\times 10^5$)	p value*
0 controls	25	3.09 \pm 0.33	
175	39	4.77 \pm 0.67	0.05 > p > 0.025
69	9	4.45 \pm 1.16	NS
175 <u>in utero</u>	3	3.26 \pm 0.64	NS
69 <u>in utero</u>	1	6.84	NS
0 offspring	5	5.24 \pm 0.85	NS

*Probability of significant difference from controls.

Blood samples were obtained from 9 exposed persons in successive years to determine whether fluctuations in isoleucine content occurred. The data are shown in Table 2. Fluctuations noted for samples 3R, 24R, 35R, and 71R could be due to variant clones of erythrocytes arising from individual stem cells, which appear and disappear from the peripheral circulation. Such fluctuations have not been observed in specimens from normal laboratory personnel.

Table 2. Frequency of substitution of isoleucine in samples analyzed in consecutive years.

Exposure (R)	Sample number	Substitution frequency ($\times 10^5$)		
		1974	1975	1976
175	3R	19.79	1.76	6.69
175	24R	13.45	7.00	
175	33R	4.74	2.16	
175	35R	5.19	2.17	
175	71R	8.29	1.45	2.85
69	6A	6.98	6.29	
69	41A		2.56	3.10
69	44A	4.04	2.17	
69	45A	3.65	3.23	

Studies are now being done at Oak Ridge National Laboratory on the misincorporation of isoleucine into hemoglobins of experimental mammals in attempts to understand the basis for the elevated isoleucine content in the hemoglobin of some Marshallese. The natural frequency of misincorporation of isoleucine in hemoglobins of marmoset, sheep, and cow and in the alpha and beta chains of pig and rabbit, respectively, is between 2.2 and 5.0×10^{-5} (69). In irradiated animals the misincorporation appears to be due primarily to translational errors rather than to somatic mutations; in humans it probably represents a combination of translational errors and somatic mutations.

3. Detection of Mutant Proteins*

As the least biased approach currently available to an estimation of the potential genetic effects of the exposures sustained by the Marshallese, a series of proteins of the blood serum and erythrocytes have been examined by electrophoresis (34) for genetic variants, in samples derived from children born to persons exposed on Rongelap, Ailingnae, and Utirik and from children born to parents sustaining no unusual radiation exposure. The proteins are as follows: adenosine deaminase, adenylate kinase, aldolase, carbonic anhydrase, 2,3-diphosphoglyceromutase, galactose-1-phosphate uridylyltransferase, indophenol "oxidase," isocitrate dehydrogenase, lactate dehydrogenase, malate dehydrogenase, nucleoside phosphorylase, peptidase A, peptidase B, phosphoglucomutase-1, phosphoglucomutase-2, 6-phosphogluconate dehydrogenase, phosphoglycerate kinase, phosphohexose isomerase, triosephosphate isomerase, albumin, ceruloplasmin, haptoglobin, hemoglobin A, hemoglobin A₂, and transferrin.

The theory is that some portion of the total mutational spectrum will manifest itself in these children as variant proteins present in the child but not in either parent. Further, one would expect a higher frequency of mutational events in the children of exposed than of non-exposed parents. On the other hand, it was realized from the first that the number of children available for study was very small indeed, and it was almost inconceivable that a genetic effect of the irradiation experience could be detected. The control children are of two types: those born to unexposed parents, and those born to exposed parents before the irradiation. In the control population we have tested 1897 gene products for the occurrence of mutation, with no positive findings. In the children born to exposed subjects, we have tested 1835 gene products, again with no mutations. Present knowledge about the frequency of both spontaneous and radiation-induced mutations detectable by electrophoresis in humans indicates that no single population, even the survivors in Hiroshima and Nagasaki, is of sufficient size to answer some of the questions concerning radiation effects. It will probably be necessary to pool the results of studies on a number of different types of populations in order to advance the question materially; the observations on the Marshallese are thus part of a larger body of data which is slowly accumulating.

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VI. PARASITOLOGIC SURVEYS AND SUPPRESSIVE ANTI-HELMINTH TREATMENT ON RONGELAP AND UTIRIK ATOLLS, MARSHALL ISLANDS, 1977-1979*

A. Background

The first formal parasitologic survey within the area exposed to fallout was conducted on Rongelap Atoll in 1958 (14), one year after the return of its inhabitants. At that time, stools from 181 persons were examined by standardized direct saline mounts and by formalin-ether concentration, and revealed an overall 65% rate of infection with parasites considered at least potentially pathogenic. Included were Trichuris trichiura (34.3%), hookworm (5.5%), pathogenic (large race) Entamoeba histolytica (18.2%), and Giardia lamblia (6.9%). No human Ascaris was detected on Rongelap at that time; however, several species of non-pathogenic intestinal protozoa were identified. Not unexpectedly, trichuriasis was especially prevalent in the 6 to 20-year age group, which had an infection rate of 70.0%. Eosinophilia (>5%) was found in 67.8% of 109 individuals tested.

Although anti-parasitic treatment of various kinds was given sporadically on an individual basis during subsequent years, no systematic attempt at island-wide treatment was made on Rongelap until 1977-8, when a broad-spectrum helminth eradication/suppression effort was undertaken. By that time it had become clear that roundworm (Ascaris) infection had been introduced and was a significant problem to the atoll inhabitants. A similar effort was made on Utirik in 1978-9, but it was limited to the use of an agent known to be primarily ascaricidal. These efforts were made possible by generous donations of mebendazole (Vermox^R) by Ortho Pharmaceuticals and of pyrantel pamoate (Antiminth^R) by Roerig Division of Pfizer Pharmaceuticals. The sampling and treatment methods employed and the results obtained are described here. Although treatment was aimed only at intestinal helminths, some information regarding the prevalence of intestinal protozoa was also gathered. The latter data are presented insofar as they are available (since sampling methods best suited for diagnosis of helminthic infection may be inadequate for identifying intestinal protozoa), and the results for the two atolls are compared.

B. Methods

Because donations of anthelmintics were obtained at different times, the sampling/treatment schedules on the two atolls were not concurrent. Treatment with mebendazole on Rongelap began after an initial stool sampling in June 1977. Treatment with pyrantel pamoate on Utirik began after a first

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sampling in March 1978. Both immediate follow-up periods extended through September 1979, but a "final" long-term sampling follow-up is planned for November 1980, possibly as a prelude to institution of long-term parasite-suppressive efforts.

The treatment plan for the two atolls, though not theoretically ideal, was based on logistical realities as to what would be attainable in the context of health surveys and physician visits. Following initial stool surveys, treatment with each agent was to be given at quarterly intervals to all inhabitants of the respective atolls except pregnant women and children aged <2 years. Follow-up surveys were to be conducted just before the third quarterly treatment and 9 months thereafter. On Rongelap the schedule was maintained, but ship damage caused schedule alterations during the eradication/suppression attempt on Utirik which resulted in some variation from the treatment/sampling plan. The actual schedules attained are shown in Table 1.

Table 1. Sampling (S) and treatment (T) schedules on Rongelap and Utirik Atolls, 1977-1979.

		Rongelap		Utirik	
1977:	June	S	T	-	-
	September	-	T	-	-
1978:	January	S	T	-	-
	March	-	-	S	T
	June	-	-	-	-
	September	S	-	S	T
1979:	January	-	-	-	T
	March	-	-	-	-
	June	-	-	-	-
	September	S	-	S	-

Sampling. To the extent that they were in any way reachable, all inhabitants of Rongelap Atoll were prevailed upon to submit stool specimens at each sampling period. In spite of strong fecal taboos, samples were obtained from at least 90% of the population by diligent follow-up of dispensed stool containers.

The larger population of Utirik (~300) precluded the possibility of total sampling during the limited survey period. Instead, a cohort of 20+% of the population was followed to the extent possible, and was used as an index of the population as a whole. If cohort members were not present on the island during a survey (away at school, on a visit, etc.), replacements were picked at random to fill out the three categories: adult males, adult females, and children. Again, diligent follow-up of dispensed containers provided the requisite population samples.

Processing of Specimens. An aliquot of 0.5 to 1 g of each specimen returned each day was put into an individually identified 1-dram vial

containing 1.5 ml of newly mixed merthiolate-iodine-formalin (MIF) (70) and thoroughly comminuted to ensure adequate fixation. The preserved samples were transported to the Tropical Infectious Disease Research Program Laboratory, U.S. Public Health Service Hospital, New Orleans, LA, where they were examined both by a standardized direct smear method (2 mg) and by an ether concentration technique using the entire sample.

Treatment. Treatment on Rongelap consisted of mebendazole, 100 mg (one chewable tablet) twice daily for 3 days, monitored either personally by the survey physician or under his supervision by the island Health Aide. At least 90% of the inhabitants present during the quarterly visits and eligible for treatment (pregnant women and children aged <2 years were excluded) were so treated at the scheduled quarterly intervals.

Treatment on Utirik with pyrantel pamoate suspension, 10 mg per pound body weight, single dose, was given to at least 90% of the eligible inhabitants present during the quarterly visits indicated in Table 1. Body weight was determined with a portable scale. Coverage of the population was attained by using survey lists and by many miles of footwork on this relatively small island.

C. Results and Discussion

Intestinal Protozoa - Rongelap and Utirik Atolls. Intestinal protozoa observed during the last survey on Rongelap Atoll (September 1979) included amebae (not differentiated into pathogenic and non-pathogenic species) in 26.5% of specimens, and Giardia lamblia in 17.6%; no Balantidium coli were seen despite the large number of free-roaming pigs on the island.

Intestinal protozoa found in Utirik Atoll inhabitants in September 1979, concurrently with a minor epidemic of mild diarrheal disease, included amebae in 7.6%, Giardia lamblia in 5.1%, and Balantidium coli in 7.6%, the Giardia and Balantidium being present in surprisingly large numbers in some specimens. Amebae identified included Entamoeba histolytica (cysts and trophozoites), Entamoeba coli, and Iodamoeba butschlii. It must be stressed that, since the survey was concerned almost exclusively with intestinal helminths, whereas MIF is not the field fixative of choice for direct observation of protozoa, these results cannot be considered definitive. Nevertheless, the presence of the primary protozoal pathogens, Giardia lamblia, Entamoeba histolytica, and Balantidium coli, on Utirik Atoll was verified under circumstances not inconsistent with their being involved in the etiology of the diarrhea observed. During the November 1980 survey, appropriate materials for surveying protozoa will be included.

Intestinal Helminths - Rongelap Atoll. Intestinal helminths found in Rongelap Atoll inhabitants before and during the period of suppressive treatment with mebendazole are listed in Table 2 (A and B) (71).

As in 1958, Trichuris trichiura was the most prevalent parasite detected. At the start of the current survey in June 1977, 73.0% of the population tested (163) was infected, including 80.2% of children (96) and 62.4% of adults (67); this represents a greater than twofold increase since the 1958 survey.

Table 2. Percent of stools tested found positive for various helminth eggs.

	Positive			Negative	No. tested	Percent of total group tested
	Trichuris	Ascaris	Hookworm			
A. Rongelap Atoll, 1977-1979, Group aged 2-14 years (estimated total persons = 106)						
Jun 77	80.2	38.5	1.0	15.6	96	90
Rx (Jun)						
Rx (Sep)						
Jan 78	22.7	3.4	0.0	76.1	88	83
Rx (Jan)						
Sep 78	20.0	4.6	0.0	76.9	65	61
Sep 79	68.2	22.7	0.0	18.2	22	21
B. Rongelap Atoll, 1977-1979, Group aged ≥ 15 years (estimated total persons = 74)						
Jun 77	62.4	4.4	2.9	34.3	67	90
Rx (Jun)						
Rx (Sep)						
Jan 78	8.6	0.0	0.0	91.3	58	78
Rx (Jan)						
Sep 78	2.3	2.3	0.0	92.8	42	57
Sep 79	12.5	6.2	0.0	75.0	16	22
C. Utirik Atoll, 1978-1979, Group aged 2-14 years (estimated total persons = 136)						
Mar 78	100	44.9	0	0	29	21
Rx (Mar)						
Sep 78	97.0	23.4	0	1.6	64	46
Rx (Sep)						
Rx (Jan)						
Sep 79	96.4	18.8	3.7	3.7	53	39
D. Utirik Atoll, 1978-1979, Group aged ≥ 15 years (estimated total persons = 128)						
Mar 78	83.9	10.8	5.4	16.2	37	29
Rx (Mar)						
Sep 78	88.5	11.5	3.8	7.7	26	20
Rx (Sep)						
Rx (Jan)						
Sep 79	92.4	15.4	0	7.7	26	20

Ascaris lumbricoides, not found at all in the 1958 study, was detected in 24.5% of those tested, in 1977, including 38.5% of children and 4.4% of adults. Infestation by worms was related to the post-fallout period by the Rongelapese, who appear to give less credence to the concept of introduction being the result of increased inter-atoll contact made possible by the greater availability of Trust Territory shipping.

The prevalence of hookworm, detected in only 3 individuals (1.8%), was virtually unchanged since 1958, if the increased potential for absence of study subjects from the island is taken into consideration.

Only 23.4% of the population tested appeared to be helminth-free at the beginning of the current study, including 15.6% of children and 34.3% of adults.

Effects of Treatment - Rongelap Atoll. Population-wide treatment with mebendazole on Rongelap resulted in a dramatic reduction in population worm burden, clearly evident at the interim stool sampling conducted in January 1978, 3 months after the second quarterly treatment (Table 2, A and B). Percent reductions of 79% and 92% of initial worm burdens of Trichuris trichiura and Ascaris lumbricoides, respectively, had been effected, and hookworm was not detected. Of even greater significance is that 9 months after the last (January 1978) treatment course, these reductions were still very much in evidence (September 1978). Nevertheless, one year later (September 1979) a not-unexpected resurgence of infection had taken place, although the gains effected by the treatment had not been entirely eliminated.

Intestinal Helminths - Utirik Atoll. Intestinal helminths found in the Utirik Atoll inhabitants tested (>20% of the population) are listed in Table 2 (C and D) (4). As on Rongelap, Trichuris trichiura was the most prevalent parasite, but the level of infection on Utirik was even higher: 91% of the sample tested (24% of the population). Ascaris lumbricoides was present in 25.8% of the initial Utirik samples, a level virtually identical with that on Rongelap before suppressive treatment. The hookworm level on Utirik, only 2.2% positive specimens, was also quite comparable with that found initially on Rongelap. None of the children tested, and only 16.2% of the adults were helminth-free.

Effects of Treatment - Utirik Atoll. Population-wide helminth-suppressive measures on Utirik were only against Ascaris lumbricoides and hookworm, and consisted of three treatments (see Table 1) with pyrantel pamoate, an anthelmintic not considered to have any effect against Trichuris. (The trichuricide oxantel pamoate was to have been used in conjunction with the ascaricide pyrantel pamoate, but it was not available because of FDA restrictions on its use in populations under U.S. jurisdiction.) Their effectiveness even against pyrantel pamoate's main target, Ascaris lumbricoides, was disappointing: the reduction was only 21% at 6 months after the first treatment, and only 31% at 9 months after the third treatment (compared with 96% at 9 months after the third treatment with mebendazole on Rongelap). As expected, the trichuriasis level was not reduced, the mean being 93.0% throughout the study. The hookworm level was 2.5% at the conclusion of the suppressive effort.

Eosinophilia - Rongelap and Utirik Atolls. Because intestinal nematodes are a common cause of blood eosinophilia, particularly (but not exclusively) during the tissue-migration phase of the parasitic life cycle, peripheral eosinophil counts were correlated with temporal events of the suppressive

population treatments, as shown in Figure 1 (72). Of interest are: the drop in mean absolute eosinophil counts on Rongelap Atoll during broad-spectrum anthelmintic treatment with mebendazole, followed by resurgence during the post-treatment period; and the relatively stable eosinophilia on Utirik, despite ascaricidal treatment, which appears to correlate with temporal observations on helminth prevalence on that atoll.

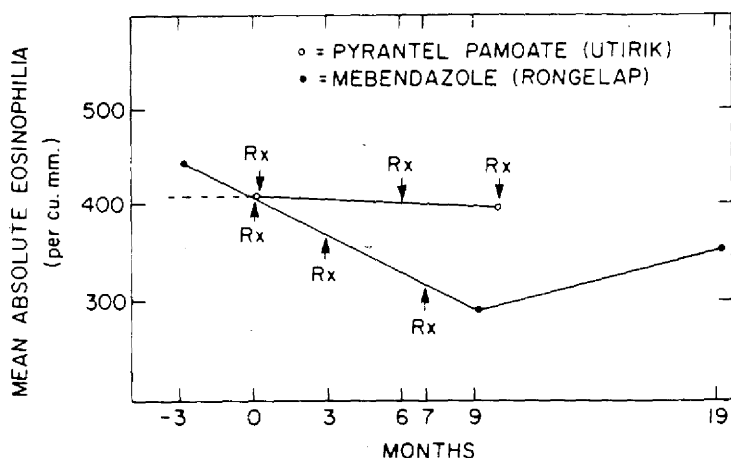


Fig. 1. Peripheral eosinophilia in populations treated for intestinal parasites.

D. Conclusions

The results of the parasitic surveys undertaken during suppressive efforts on Rongelap Atoll from 1977 to 1979 and on Utirik Atoll from 1978 to 1979 have indicated the presence of those intestinal helminths expected in non-urban populations living in the tropical climate of the mid-Pacific, and, though with less complete documentation, also of the expected intestinal protozoa.

The introduction of Ascaris lumbricoides onto Rongelap Atoll following the 1958 survey is well documented in this study. However, the extent of its success in becoming established, as well as its presence to the same extent on Utirik Atoll, suggest that its absence during the 1958 survey may have been partly anomalous, and may have resulted from the Rongelapese population's preceding three-year absence from their island. Certainly, the people are now very aware of the presence of roundworm. The extent to which diarrheal disease may be attributed to endemic intestinal parasites is unclear, although a partial cause-and-effect relationship is quite probable with regard to the protozoal pathogens detected. On the other hand, the results of a recent report on shigellosis in the Marshall Islands (73) would suggest that bacterial species may also be involved in diarrhea on the outer atolls; considerable contact now occurs (albeit at infrequent intervals) between Rongelap, Utirik, Ebeye, and Majuro, on the latter two of which an outbreak of Shigella flexneri diarrheal illness was well documented.

Attempts at suppression of endemic intestinal helminths on Rongelap and Utirik, with a different regimen on each, underlined the effectiveness of mebendazole (the more costly) and raised serious questions as to the effectiveness of the recommended dosage of pyrantel pamoate under the logistic constraints of the timing of BNL visits to the outer atolls. Of considerable significance in the context of suppressive treatment is the prolonged suppression of parasitosis obtained with mebendazole, as well as its attainable effectiveness against all three endemic helminth parasites. Even 9 months after the last of three quarterly treatments, Ascaris and Trichuris prevalence was reduced by 84.7% and 72.3%, respectively. This suggests that, notwithstanding the arrival of parasitized persons on the quarterly Marshall Islands "field trip" ship - as was also occurring during the survey period - treatment of the entire population every six months (after an initial three-quarterly suppression) should keep these atolls at a very low level of helminthic infection (this would be especially true if preventive treatment were given to all persons coming from infected areas at the time of their disembarking from the Marshall Islands vessels). Such a program could be instituted as early as November 1980, beginning with a complete parasitic survey, provided that mebendazole were available and that a conscientious health aide could be recruited to ensure both complete population treatment and treatment of all persons disembarking from Marshall Islands ships. With such conscientious suppression, virtually complete freedom from intestinal helminths could be anticipated in a very few years. Suitable measures against pathogenic intestinal protozoa could also be anticipated in due course.

VII. DIABETES SURVEY*

Diabetes mellitus is perceived to be an important public health problem among the people of the Pacific islands. Health surveys among several different populations in Micronesia and Polynesia have indicated very high prevalences of diabetes compared with that in more affluent societies (74-76,208). These surveys suggest that the diabetes in the Micronesian populations is predominantly of the maturity-onset, Type II form, being relatively asymptomatic despite marked hyperglycemia. One of the most detailed of the Micronesian surveys, that dealing with the population of Nauru (77), found a diabetes prevalence among the highest ever reported in any population. In the population aged 15 and older, 10.4% of individuals were known to have diabetes before the survey, and 34.4% of the total population were found to have diabetes according to the criterion of a 2-hr post-prandial blood glucose >160 mg% (186). An additional 11.3% of the population showed borderline glucose tolerance, with post-prandial blood sugars between 140 and 159 mg%. Among the 52 known diabetics, complications associated with diabetes were very common: 45% of them had demonstrable retinopathy, and 33% of them had some form of renal dysfunction (76). In addition, 12 of the known diabetics included in the original studies had died from diabetes-related causes.

To determine the severity of the health problem presented by diabetes in the Marshall Island populations of Micronesia, a survey to determine carbohydrate tolerance and diabetes-related health problems was initiated in 1974. Over the next several years historical data taking, physical examinations, and laboratory evaluations were carried out on 437 individuals aged >15, of whom 410 were examined at least during the first survey of 1974. This initial report is based primarily on laboratory results of fasting and 2-hr post-prandial blood sugar determinations made during the 1974 studies. Subsequently, post-prandial blood glucose values were obtained as well as additional laboratory determinations of lipid and uric acid levels. Of the 410 people examined in 1974, 45.6% were male and 54.4% female. Most of the individuals studied came from the two principal islands, 170 listing their home as Utirik and 120 as Rongelap.

Of the individuals included in the study, 57 (14% of those examined during 1974) reported that they had been previously diagnosed as diabetic. Of those previously diagnosed, 59% had been found diabetic within the preceding 5 yr, 26% at 6 to 10 yr before the survey, and 15% more than 10 yr before. At the time of the survey, 39 of the 57 were being treated with oral hypoglycemic agents and none with insulin. Three individuals had reported onset prior to age 20 (ages 2, 10, and 17). The age distribution for the diagnosed diabetics in the survey showed 6% aged <24 yr, 8% aged 25 to 34 yr, 8% aged 35 to 44 yr, 31% aged 45 to 54 yr, 31% aged 55 to 64, and 33% aged >65. Of the 263 individuals who were able to provide information, 43.3% reported a positive family history of diabetes. In this population, there was not a significant

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relationship between positive family history and the presence of diagnosed diabetes prior to the survey.

During the 1974 survey, fasting blood glucose values were obtained for 139 individuals. Of these, 19.5% had FBS values >130 mg%, and 13.7% had values >160 mg%. These 139 people included 32 individuals with previously diagnosed diabetes, some of whom exhibited normal fasting and 2-hr post-prandial blood sugars in this survey. With these 32 excluded, 7.5% of the remaining individuals showed FBS >130 mg%, and 5.6% showed >160 mg%. In the 1974 survey, 2-hr post-prandial blood sugar was measured on 277 individuals, including only 19 previously diagnosed diabetics. The data on all 277 individuals showed 19.2% with post-prandial blood sugar values >130 mg% and 8.7% with values >160 mg%. With the known diabetics excluded, these percentages were 15.5 and 5.4 respectively. Of the previously diagnosed diabetics, 67.7% were female, but on the basis of post-prandial blood sugar >130 mg%, no significant difference was found between the sexes with regard to carbohydrate intolerance: 24 of 129 males and 27 of 144 females had values >130 mg%, and 10 males and 13 females had values >160 mg%. This is in contrast to the findings in other similar surveys in the Pacific, which show diabetes considerably more common in females (77). Relative weight had a significant although rather weak effect on carbohydrate tolerance. Measurements using a ponderal index (wt/ht^2) showed the correlation between relative weight and fasting blood sugar to be $r = 0.33$ ($p = 0.001$) and that with post-prandial blood sugar to be $r = 0.31$ ($p = 0.001$). Also examined was the relationship within the female population between number of pregnancies and previous diagnosis of diabetes or carbohydrate intolerance indicated by either the fasting or the post-prandial blood sugar value. First analysis of these data indicated no relationship between these variables in the Marshall Islands population, but further study is under way.

The data from previous diagnoses and from the two measures of glucose tolerance can be used to define a group of individuals with altered carbohydrate tolerance. This group includes all previously diagnosed diabetics and all individuals with either a fasting blood glucose level >130 mg% or a 2-hr post-prandial blood glucose level >160 mg%. This group of affected persons comprises 17.3% of the population, and is composed of 65% females and 35% males. The age distribution of affected individuals in the Marshall Island population, by sex, is given in Table 1. The age group-specific prevalence of carbohydrate abnormalities increases by age groups in this population, with females showing greater percentages in all groups. Affected persons comprise 13.3% of all males examined and 20.7% of all females.

Table 1. Age distribution of carbohydrate abnormalities (defined in text) in the Marshall Island population (numbers in parentheses are sample sizes).

Age group:	0-24	25-34	35-44	45-54	55-64	>65	Total
	% Affected						
Male	0 (57)	6.1 (33)	10.0 (20)	29.2 (24)	27.3 (33)	28.6 (14)	13.3 (181)
Female	7.5 (53)	7.7 (52)	17.2 (29)	37.5 (40)	45.8 (24)	33.3 (15)	20.7 (213)

This categorization of individuals into an "affected" and an "unaffected" group has been used to investigate the distribution of the morbid complications which often accompany diabetes. As expected, compared with unaffected individuals, affected ones showed greater frequencies of polyuria (75.0 vs 37.8%) and polydipsia (72.3 vs 45.1%). Recent weight loss was reported by 48.8% of the affected group and 22.1% of the unaffected group. Itching was reported by 60.5% of the affected group and 30.5% of the unaffected. In females, pruritis vulvae was reported by 20.8% of the affected persons and by none of the unaffected ones.

Previous studies on other populations in the Pacific suggested that the more important complications of diabetes were very similar to those observed in Caucasian populations (74,77). The analysis of the affected population in the Marshall Islands does not completely support such a contention. Fundoscopic examination revealed diabetic retinopathy in only one of the 54 affected individuals examined. An additional four had exudates in the fundi, but so did three of the 263 unaffected individuals examined. Exudates did not appear to be related to the degree of hypertension in this population. Cataracts were found in 24.1% of the affected individuals and 13.6% of the unaffected, but this difference might reflect age since the affected group was older. Abnormalities of the extremities were very unusual in this population, and no difference was found between affected and unaffected groups except for amputations of the leg in three previously diagnosed individuals. (Other amputations were reported, but were not seen during the 1974 survey.) Peripheral pulses were absent in only 5% of the affected group (2% of the unaffected). Absence of dorsalis pedis pulse occurred in only one affected and five unaffected persons (not significantly different in frequency). Absence of posterior tibial pulses was somewhat more common, occurring in 12.7% of affected persons but only 3.1% of unaffected ones. The presence or absence of reflexes was also used to investigate the prevalence of peripheral neuropathies. Ankle jerks were not elicited in 68.3% of the affected population tested, compared with 20.9% of the unaffected. Knee jerks were absent in 50.7% of the affected individuals but in only 17.5% of the unaffected ones. Brachioradialis reflex was absent in 28.6% of the affected group and 8.2% of the unaffected group.

Kidney function could be evaluated crudely by measuring proteinuria. Some indication of proteinuria was seen in 61.7% of affected individuals and 15.9% of unaffected ones, as tabulated below.

<u>Group</u>	<u>Proteinuria:</u>				<u>Total</u>
	1+	2+	3+	4+	
Affected	17.0	12.8	6.4	25.5	61.7%
Unaffected	3.1	1.3	-	11.5	15.9%

However, proteinuria did not appear to be correlated with the level of glucose intolerance as measured by fasting or post-prandial blood glucose values when corrected for age, sex, and level of obesity. Glycosuria was found in 80.6% of the affected population (at 4+ levels in 20.9%), compared with 14.4% of the unaffected population. Glycosuria was significantly correlated with fasting blood sugar and post-prandial blood sugar even with corrections for sex, age, and obesity. Symptoms of sexual dysfunction were reported in ~13% of the entire population, and in 21.3% of affected individuals. Paresthesias, at least

some of the time, were reported by 77.8% of the affected population and by 47.9% of the unaffected population.

Data have also been obtained on levels of plasma cholesterol, triglycerides, and uric acid. Zimmet et al. (77) reported a high prevalence of elevated uric acid levels and gout in the Micronesian inhabitants of Nauru, and such a pattern has also been reported for Polynesians (79). In the Nauru population 64% of men and 60% of women aged >20 had elevated serum uric acid levels (>7 mg% in men and 6 mg% in women). In the 1974 survey of the Marshall Islands, of 347 individuals tested, 23.1% had uric acid levels >7 mg%. Elevated triglycerides, >200 mg%, were found in 4.8% of all subjects examined, but none of the people tested had cholesterol values >300 mg%.

Relationships among the various measurements (fasting blood sugar, 2-hr post-prandial blood sugar, serum cholesterol, serum triglycerides, uric acid values, and diastolic and systolic blood pressures) were studied, with corrections for the confounding effects of sex, age, and obesity (as measured by the ponderal index wt/ht^2). As expected, significant partial correlations were observed between systolic and diastolic blood pressures, between cholesterol and triglyceride levels, and between the two measures of blood glucose. Additionally, triglyceride level was significantly correlated with both measures of blood glucose, with uric acid level, and with diastolic blood pressure. Uric acid levels showed additional significant partial correlations with both cholesterol level and the two measures of blood pressure. All other comparisons were not significant when the effects of age, sex, and obesity were accounted for.

Thus, preliminary evaluation of the data collected during the diabetes survey of 1974 suggests a very high incidence of diabetes mellitus in the population of the Marshall Islands, which, although perhaps not as high as that observed in some Micronesian populations (77), is consistent with the general pattern seen in several Pacific populations (75-80). The diabetes of the Marshall Islands is primarily of the adult-onset type, probably associated with obesity, and may be less severe than similar Type II diabetes seen in Caucasians despite quite significant hyperglycemia. It does not appear to require insulin treatment to prevent ketosis. Two features of this form of diabetes deserve further study. (a) Despite the apparent excess of females over males among previously diagnosed diabetics in this population, no apparent sex difference was found in the distribution of either of the measures of blood glucose levels in the 1974 survey. (b) The involvement of complications, especially diabetic retinopathy and severe peripheral vascular disorders, seems to be less marked in this population. Cardiovascular disease attributed to diabetes was not seen during the 1974 survey, but further studies would be necessary to determine the prevalence of diabetes-related macrovascular disease.

The population of the Marshall Islands appears to have a high prevalence not only of abnormalities of glucose metabolism but also of elevated serum uric acid levels. Whether this is accompanied by gout, as in some other Pacific populations, also remains to be studied (78,186).

Additional data collected during the 1974 survey and further investigations of the relationships among the variables reported above are currently being evaluated so that a more complete report can be prepared on the impact of diabetes on this population. It is hoped that this information will provide a better characterization of the problem of diabetes in the Marshall Islands and will serve as a basis for its treatment and management.

VIII. NEOPLASIA, NON-THYROID

A. Malignancies

Table 1 lists the malignancies in the exposed Rongelap and Utirik and unexposed Marshallese groups. (As indicated in Section II.C, the causes of many of the deaths over the years have been uncertain.)

The most extensive data on the late effects of radiation on human beings appear in the reports on the Japanese victims of the atomic bombs at Hiroshima and Nagasaki. Beebe et al. (62) report that "although there have been 14,405 deaths from natural causes other than cancer, analysis of the whole material and its major components provided no support for the belief that diseases other than cancer are involved in the late mortality effect." The following cancers are listed by Beebe et al. (61,63) and other authors as being related to radiation exposure in the Japanese: leukemia (81-83,204), thyroid (84-87), lung (88), breast (89), gastrointestinal (stomach) (90,205), salivary gland (62), urinary tract (91), lymphoma (92), multiple myeloma (206), and possibly involvement of the large bowel, liver, and perhaps other organs (56,62,93-95). In Appendix V, from Shapiro (96), cancers in irradiated populations are tabulated. Despite differences in ethnicity and in types of exposure, the radiation-related cancers in the Marshallese would be expected to be generally similar to those reported in the Japanese. The only malignancies noted thus far that appeared to be related to radiation exposure (Table 1) are those of the thyroid in the Rongelap and Utirik populations and one case each of leukemia and cancer of the stomach in the Rongelap group. Thyroid neoplasia is discussed separately in Section IX.C.1.

The leukemia case has been discussed in detail in the 20-year report (1) and elsewhere (33). Acute myelogenous leukemia developed in a 19-year-old Marshallese male who had been exposed to 175 rads of gamma radiation at one year of age. At age 13 he had a subtotal thyroidectomy for removal of adenomatous nodules and was put on suppressive thyroxin treatment. He was treated for leukemia at the National Cancer Institute in Bethesda, MD, but responded poorly and died six weeks later. A preleukemic finding from 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 the development of leukemia.

The death from cancer of the stomach occurred in a 64-year-old Rongelap male who had been exposed to 175 rads of gamma radiation. The cancers of the female genital tract listed in Table 1 are not likely to be related to radiation exposure, on the basis of the Japanese data, particularly since they developed only a few years after exposure, and in older women.

Table 2 shows the expected number of malignancies that might be due to radiation exposure, calculated by using the risk estimates (cases/ 10^6 people/rad/yr) for the Japanese (97,99). Statistics on the spontaneous incidence of cancers of the various organs in the general Marshallese populations (with the possible exception of our data on the thyroid) are not sufficient to allow estimation of spontaneous incidence in the Marshallese study groups. However, statistics on other world populations (98) indicate that the number of spontaneous cancers would be small. Table 2 shows that, except for the thyroid tumors, the small numbers of radiation-related cancers that might be expected

in the Marshallese populations would be difficult, if not impossible, to distinguish from spontaneous tumors.

Table 1. Malignancies.

Age*	Sex	Year of death	Type
<u>Rongelap exposed</u>			
60	F	1959	Ovary
60	F	1962	Cervix**
71	F	1966	Uterus**
19	M	1972	Acute myelogenous leukemia
64	M	1974	Stomach
31	F		Thyroid
36	F		"
45	F		"
55	F		"
<u>Utirik exposed</u>			
64	M	1959	Rectum(?)**
43	F		Thyroid
29	F		"
62	F		"
<u>Unexposed</u>			
68	F	1960	Cervix**
29	M		Thyroid
33	M		"
68	M		"
51	F		"
55	F		"

*Age at development of malignancy.

**Not confirmed by biopsy or autopsy.

B. Benign Tumors

Thyroid nodules will be discussed in Section X.C.1, below. A number of other benign tumors, such as sebaceous cysts and lipomas, have been detected in both exposed and unexposed populations, and many have been removed. The number of such tumors appeared to be in the normal range of expectancy. Other benign tumors included a giant cell type removed from the finger of an exposed Rongelap female and a neurofibroma removed from the neck (near the thyroid) of an exposed Rongelap female.

Table 2. Expected malignancies in Marshallese* in 25 years based on risk estimates (cases/10⁶/rad/yr) (99) for exposed Japanese.**

Type	Expected		Observed	
	M	F	M	F
Leukemia (20-yr risk period)	0.5	0.3	1	0
Thyroid	1.4	3.7	0	7
Breast	0	1.1	0	0
Lung	0.7	0.7	0	0
Stomach	0.3	0.3	1	0
All cancers	2.4	4.5	2	7

*The combined exposed populations of Rongelap and Utirik (244 people), with an average whole-body dose of 62 rads and thyroid dose of 202 rads per person.

**Risks are estimated to have the following male/female ratio: leukemia 3/2; thyroid 2.2/5.8; breast 0/5.8; lung 3-6/3.9; stomach 1.5/1.7; all cancers 12.8/23.1. These risks are age-weighted averages with certain stipulations noted in Table V-14 of ref. 99.

Skin. Because of the extensive radiation exposure of the skin of the Rongelap people and the development of acute lesions and epilation, careful examinations of the skin for possible late changes have been continued. Residual scarring and pigment changes as well as histopathological changes have been described previously (2). A notable finding was the development of a number of benign nevi in former areas of beta burns of the neck in several women, also described previously (11); there has been no further development of such lesions in recent years. The absence of chronic radiation dermatitis and of developing skin cancers is notable in view of the extensive radiation lesions of the skin that had occurred in the majority of the exposed Rongelap people. As has been pointed out, the low mean energy of the beta radiation may not have caused sufficient injury to the germinal layer of the skin to result in late effects, or skin cancer may have a longer latent period and may yet appear.

C. Pituitary Tumor*

A Rongelap woman who had been exposed to fallout radiation at age 20 underwent a thyroidectomy in 1969 (at age 36) with a finding of an invasive

*Drs. J. Robbins (NIH, Bethesda, MD) and R.A. Conard (BNL).

papillary carcinoma and lymph node metastases. She was reoperated in 1972 because two radioactive sites were seen in the neck on ^{131}I scanning, but no recurrent disease was found at surgery. During examination at Tripler Army Medical Center in April 1976, a routine skull x-ray showed erosion of the anterior floor of the sella turcica and a mass extending into the sphenoid sinus. There were no related symptoms and no visual field loss, and menses were normal. Thyroid hormone treatment had been discontinued for radioiodine testing, and the serum thyroid stimulating hormone (TSH) was elevated (Table 3A). Serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were high and growth hormone (GH) was normal.

Table 3. Endocrine function tests on pituitary tumor case: hormone levels (normal values in parentheses).

A. April 1976			
Serum	TSH	9.8	$\mu\text{U/ml}$ (<5)
	FSH	116	mIU/ml (20-30)
	LH	59	mIU/ml (<20)
	GH	4	ng/ml (0.2-5)
	T ₄	0.3	$\mu\text{g/dl}$ (5-10)
	T ₃	16	ng/dl (60-160)
B. May 1976			
Serum	FSH	31.2	mIU/ml (follicular 9-27, midcycle 7-41)
		27.8	mIU/ml (luteal 5-15, postmenopausal 35-217)
	LH	18.2	mIU/ml (follicular 6-27, midcycle 45-154)
		17.6	mIU/ml (luteal 5-17, postmenopausal 39-96)
	PRL	9.1	ng/ml (16.2 \pm <2)
		8.0	ng/ml
	estradiol	44	pg/ml (follicular 10-100, midcycle 170-770)
		58	pg/ml (luteal 190-340, postmenopausal <10-140)
	AM cortisol	10	$\mu\text{g/dl}$ (6-26)
		11	$\mu\text{g/dl}$
	T ₄	9.4	$\mu\text{g/dl}$ (4.6-10.7)
	FT ₄	2.7	ng/dl (1.0-2.3)
	T ₃	149	ng/dl (110-230)
Urine	17-OH corticoids	1.6, 2.2, 1.2, 1.5	mg/24 hr (2.0-6.0)
	17-ketosteroids	4.0, 5.0, 2.0, 4.0	mg/24 hr (9.0-22.0)

She was admitted to the Clinical Center of the National Institutes of Health on 18 May 1976 for further study. Laboratory tests showed normal electrolytes, and the results of endocrine function tests (Table 3B) were within normal limits except for a slight decrease in the 24-hr urinary 17-hydroxycorticoids and 17-ketosteroids. Skull x rays and sella tomograms revealed an asymmetric erosion in the anterior floor of the sella with extension of a soft tissue mass into the sphenoid sinus. Computerized tomography showed no supracellular extension. Visual fields were normal.

It was concluded that the patient had a non-functioning pituitary adenoma with essentially normal endocrine function (except for surgical athyreosis), and that surgery was not required and would increase the risk of hypopituitarism. Because of the large size and extension of the tumor, however, therapeutic x ray was administered to the pituitary (4000 R over a 3-week period). This was well tolerated.

Subsequent endocrinological studies have resulted in normal findings. The patient's visual fields have been tested regularly and have been normal. In 1977 her serum cortisol level was 9.9 and later 16 $\mu\text{g}/100\text{ ml}$, and in 1978 it was 19 $\mu\text{g}/100\text{ ml}$ (normal range 5-20), indicating normal pituitary function.

In the past the patient has had regular pregnancies, having 14 children, the last one in 1968 at age 35. Though she still menstruates regularly, she has suffered from menorrhagia in the past few years, and an endometrial biopsy revealed proliferative endometrium and basalia. This may have influenced the lack of further pregnancies in recent years.

Since there have been a number of reports of development of pituitary hypertrophy and tumor formation associated with hypothyroidism in animals (100-102) and human beings (103-106), this etiology must be considered. The only evidence of a hypothyroid state in this patient has been on those occasions when she was taken off thyroxin treatment in preparation for testing (Table 4). Since her thyroxin levels at those times were low or in the low-normal range, it appears that her pituitary was responding to thyroid deficiency and that the tumor was not autonomously responsible for the TSH elevations. The possibility that thyroid hypofunction led to the development of pituitary tumor in this case seems unlikely because long-standing hypothyroidism is usually required to produce such tumors, and this was not apparent in her case.

Table 4. Thyroid Hormone Levels in Pituitary Tumor Case.

Year	T ₄ ($\mu\text{g}/\text{dl}$)	TSH ($\mu\text{U}/\text{dl}$)	Year	T ₄ ($\mu\text{g}/\text{dl}$)	TSH ($\mu\text{U}/\text{dl}$)
1965	8.6	2.2	1975	5.8	5.9
1967		1.0	1976 ^c	0.5	115
1969 ^a		1.7	1977 (Mar)	5.4	3.8
1972 ^b	0.4	110.0	1977 (Sep)	9.0	5.6
1973	17.8		1978	6.7	1.8
1974		1.0			

^aThyroidectomy. Presurgical levels.

^bOff T₄ Rx for testing.

^cPituitary tumor discovered. Off T₄ for testing.

Since the patient had been exposed to 175 R of whole-body gamma radiation, the possible influence of such exposure on the development of the pituitary adenoma must be considered. Intracranial tumors have been reported, possibly associated with radiation exposure (107,108,197), but these were mainly gliomas, meningiomas, neurinomas, etc., and not pituitary adenomas. In a study of the Japanese exposed to the A-bomb, Seyama et al. (109) reported an increase in certain types of intracranial tumors in a group exposed to 100 R or more, but no increase in pituitary adenomas. Therefore, the association of radiation exposure with the development of the pituitary tumor in this patient does not seem likely.

IX. THYROID ABNORMALITIES*

It has been clearly demonstrated that the most serious late effects of accidental exposure to fallout in the Marshallese residing on Rongelap and Utirik Atolls on March 1, 1954, has been related to radiation injury to the thyroid, as evidenced by development of nodularities and hypofunction of the gland. Such injury was due to exposure to penetrating gamma radiation and internal absorption of radionuclides during the two-day period prior to their evacuation. In this section, thyroid effects are summarized. Emphasis is on the findings during the past seven years. In Appendix II, the estimated thyroid doses are discussed. Since the principal effects of thyroid exposure, development of nodules (benign and malignant) and hypofunction, are dose dependent, the establishment of thyroid dose is most important in order to derive dose-effect relationships. Unfortunately, it must be stated at the outset that the thyroid dose estimates are subject to considerable uncertainty and may, at least in some cases, be considerably higher than estimated.

The effect of thyroid injury on growth and development in the children is described in Section IV.

A. Background (Chronology of Developments)

Beginning several years after exposure it was noted that some children exposed at <10 years of age showed growth retardation, particularly boys exposed at <5 years of age (see Section IV), but the cause was not immediately apparent. It was recognized that thyroid hormone deficiency due to thyroid injury could result in such growth retardation, but examinations during this early period did not reveal any thyroid abnormalities, and the PBI levels in these children as well as in all Marshallese were in the normal to high range. The growth retardation gradually became more apparent, and at 8 years post exposure two boys were recognized to be stunted in growth. They had been exposed at one year of age and gradually developed atrophy of the thyroid gland and signs of myxedema with puffy faces, dry skin, sluggish reflexes, and bony dysgenesis of the humerus and femur.

In 1965 a satisfactory method for serum thyroxine analysis by ion exchange column became available. Studies by this method showed that some of the children did indeed have low serum thyroxine levels. Control observations on unexposed Marshallese revealed that many of them had unusually high

*The following persons assisted the senior author in the preparation of this report or were actively involved in some of the special studies: Surgical findings--Dr. B. Dobyms (Cleveland Metropolitan General Hospital, Cleveland, OH); Histopathology--Dr. D.E. Paglia (U. of California, Los Angeles); Hypothyroidism--Dr. B.R. Larsen (Peter Bent Brigham Hospital, Boston, MA); Clinical--Drs. J.B. Rall, J. Robbins, and J. Wolff (NIH, Bethesda, MD); Dr. J.T. Nicoloff (U. of Southern California, Los Angeles); Dr. B. Colcock (Lahey Clinic, Boston, MA, Ret.); Drs. H. Pratt, K. Knudsen, and W. Adams (BNL); Dr. C.S. Hill, Jr. (M.D. Anderson Hospital, Houston, TX); Dr. D.D. Becker (Cornell Medical Center, New York, NY). See p. 55 for list of pathologists.

iodoprotein levels, leading to a false interpretation of protein-bound iodine (PBI) determinations. It became apparent only then that low serum thyroxine (T_4) levels in some of the children had probably been masked by high levels of iodoprotein. Several children with slight growth retardation had lowered T_4 levels. The hypothyroidism appeared to be from primary thyroid damage and not secondary to pituitary damage, since tests for growth hormone in several growth-retarded children were normal, and their serum thyroid-stimulating hormone (TSH) levels were elevated.

In 1963, 9 years after exposure, a 12-year-old exposed Rongelap girl was found to have an asymptomatic nodule of the thyroid gland. Development of thyroid nodules has continued in other exposed Rongelap and Ailingnae people and in the past decade in the Utirik group. Two of three Rongelap children exposed in utero developed thyroid nodules during the past 6 years. At this time (1981) a total of 46 exposed Marshallese (29 in the Rongelap/Ailingnae group and 17 in the Utirik group) have developed nodules, and 42 of these have undergone surgery. In the unexposed comparison population 35 of 600 people in the age-matched control group have been found to have nodules and 14 of these have undergone surgery (see Section IX.C. and Appendix IV, Table 1).

In 1965 the seriousness of the development of thyroid lesions in the Rongelap people became more evident, and preventive treatment with thyroid hormone was instituted in the Rongelap group. Later (1969) the Ailingnae group was also included. The difficulties in carrying out the treatment regimen will be referred to in Section IX.C.4.

With increasing development of thyroid abnormalities it has become apparent that the original control group of unexposed Rongelap people was numerically inadequate for proper evaluation of the thyroid findings in the exposed people. Therefore, during the past decade thyroid surveys have included all available unexposed Rongelap and Utirik people as well as some people at Likiep and Wotje atolls. More than 1200 of these people have been examined. About half of them were in the same age range as the exposed people, and the others were in the younger age group (born after 1954).

During the last seven years, specific radioimmunoassay techniques for measurement of serum T_4 and TSH have been employed to monitor the population for evidence of hypothyroidism (1,36,110). Results have shown that at least one-half of those who had thyroid surgery, and supposedly were taking thyroid replacement medication, had significant elevations in serum TSH on one or more occasions, indicating lack of compliance with the thyroxine replacement schedule and also indicating the inadequacy of residual thyroid tissue in patients with subtotal thyroidectomies to maintain the euthyroid state without compensatory increases in TSH secretion. These observations led to attempts to determine the degree of thyroid function in exposed populations of both Rongelap and Utirik, which necessitated temporary discontinuation of the thyroid hormone in the Rongelap group. (The Utirik group was not routinely receiving such treatment.)

In earlier studies, discussed in detail in the 20-year report (1), a number of individuals with apparently normal thyroid glands were found to have subnormal increments in plasma T_4 24 hours after receiving 10 units of TSH intramuscularly. The mean increment in T_4 in 25 exposed Marshallese was 2.35 $\mu\text{g/dl}$ (SD = 1.2), whereas the increment in a control group of unexposed euthyroid Rongelap and Utirik individuals was 4.2 $\mu\text{g/dl}$ (SD = 1.3). This was significantly greater than in the exposed subjects ($p > 0.001$). A number of

exposed individuals had T_4 increments of $<1.5 \mu\text{g/dl}$. In addition, several exposed individuals with intact thyroid glands have periodically shown modest TSH elevations. These observations stimulated attempts to evaluate residual thyroid function in all exposed individuals (1,36).

B. Methods

1. Thyroid Examinations

Examinations included inspection, palpation, and auscultation of the neck and thyroid gland; notation of any clinical signs of thyroid dysfunction; quantitative assays of serum iodine, thyroid hormones, and iodoproteins; and special studies of thyroid function as described below. Suspected nodules were examined by other team physicians for confirmation and were recorded by description and full-scale drawings. Some nodules were so indistinct on initial examination that they were not evaluated further at the time but received special attention on subsequent surveys, often by the same physicians utilizing the medical records and annotated drawings as a basis for comparison.

Since, in most cases, a diagnosis could not be firmly established without histopathologic evaluation, surgical exploration was usually recommended for patients with clinically suspicious findings. Age and general health status of these patients were important considerations in view of travel requirements. Surgery was sometimes deferred because of poor health and/or old age, favorable response of thyroid nodules to thyroxine therapy, or unavailability of the individual for close followup examinations. Those consenting to surgery were generally admitted to hospitals in the United States after initial evaluation at Brookhaven National Laboratory Medical Research Center. Preoperative thyroid studies included iodine uptake, scans, and determination of thyroid hormone and autoantibody levels. Aside from a few cases at Tripler Army Hospital in Honolulu, surgical procedures during the past decade were performed exclusively at Cleveland Metropolitan General Hospital.

2. Pathologic Evaluation

All excised tissues were examined by the pathologists associated with each hospital where surgery was performed. In the past these have also included U.S. Naval Hospital, Guam; Ishoda Memorial Hospital, Majuro; and New England Deaconess Hospital, Boston. In addition to gross and microscopic pathologic evaluations, selected slides from each specimen were referred for review to a number of pathologists who had special expertise in diseases of the thyroid.* Working diagnoses for individual patients were assigned on the basis of evaluations obtained from all these sources at the time.

*Drs. S. Warren (deceased), W.A. Meissner, and M. Legg (New England Deaconess Hospital, Boston, MA); J.D. Reid and M. Petrelli (Cleveland Metropolitan General Hospital); J. Oertel (Armed Forces Institute of Pathology, Walter Reed Army Medical Center, Washington, DC); L.B. Woolner (Mayo Clinic, Rochester, MN); A.L. Vickery (Massachusetts General Hospital, Boston); L.V. Ackerman (S.U.N.Y. Stony Brook, NY); W. Hawk (Cleveland Clinic, Cleveland, OH); and D. Slatkin (BNL).

More recently, all available pathologic specimens, including microscopic slides and paraffin embedded tissues, and the pertinent records were assembled into a central archive at Brookhaven National Laboratory. This allowed re-evaluation of these materials according to prescribed histopathologic criteria and in context with pre- and postoperative clinical data, findings at surgery, and gross pathologic descriptions and drawings. An ad hoc committee of pathologists,* most of whom had examined some material previously, and the surgeon** who had performed virtually all the thyroid operations since 1969, simultaneously reviewed sixty of these cases. Variable numbers of slides were available for review, depending upon the thyroid protocols used by the various surgical pathology groups. In some cases the small number of slides (as few as one to three) increased the possibility of missing occult carcinomas simply through sampling error. Microscopic slides were unavailable for review in three cases (Nos. 23, 54, 3074).

Patients were identified by name and identification number but not by exposure group. Pathologists did not have access to their previous diagnoses, if any, until after conclusions were reached in each individual case. A slight modification (see Section IX.C.1.d, Histopathology) of the World Health Organization classification of thyroid tumors was adopted by the committee beforehand to ensure standardization of nomenclature. In addition, uniform morphologic criteria for distinguishing among categories were reviewed and approved.

3. Thyroid Function

Evidence of mild hypothyroidism, designated "biochemical thyroid hypofunction," can often be found in patients with thyroid enlargement by sensitive assays for serum TSH levels (111). Such patients may have normal serum T_4 concentrations (albeit in the lower range of normal) and yet have mild elevations in serum TSH and exaggerated TSH responses to thyrotropin releasing hormone (TRH) infusion. Usually they are not hypothyroid clinically, since the thyroid dysfunction may be so mild that elevated TSH can maintain serum thyroid hormone concentrations in the normal or near normal range. Accordingly, the most sensitive test for evaluation of possible thyroid hypofunction is determination of serum TSH concentration. In some cases this may be supplemented by measuring the TSH response to TRH, though there is excellent correlation between basal and stimulated TSH (1,36).

Prophylactic thyroxine supplement was discontinued in the Marshallese being tested at least 2 to 3 months and in some cases 6 months prior to testing for thyroid function, but strict adherence to this regimen could not be verified in all instances, an important consideration when evaluating the results given in Appendix IV, Table 2.

Serum was obtained for measurement of TSH, T_4 , and T_3 charcoal uptake (thyroxine-binding globulin index, TBGI). This last test measures the fraction of tracer T_3 bound to charcoal after a 30-minute incubation, a value which is compared with that for a quality-control pool assayed simultaneously

*Drs. L.V. Ackerman, W.A. Meissner, D.E. Paglia (University of California, Los Angeles), J.D. Reid, A.L. Vickery, and L.B. Woolner.

**Dr. B.M. Dobyns (Cleveland Metropolitan General Hospital).

(112,113). Accordingly, the TBGI parallels the free fraction of the thyroid hormones in serum.

Normal values for serum T_4 range from 5.0 to 10.2 $\mu\text{g}/\text{dl}$ in patients with normal concentrations of thyroxine-binding globulin (TBG), and the normal mean value for TSH is 2 $\mu\text{U}/\text{ml}$ with an upper limit of 4 $\mu\text{U}/\text{ml}$ (110). For reasons to be explained, an upper limit of normal of 6 $\mu\text{U}/\text{ml}$ was employed in some analyses of these data. In some of the exposed individuals, 500 μg of TRH was given intravenously and TSH was measured 20 minutes later. Controls for these studies were nonexposed Marshallese living on either Rongelap or Utirik. Serum T_3 concentrations were measured in many of these subjects but are not presented here because they are not pertinent to the present discussion.

Fortunately some unused surplus samples of plasma, obtained for T_4 measurements on the exposed Rongelap people as early as 1963, had been preserved in a frozen state. A retrospective study was done on these samples using the present assay techniques to measure T_4 and TSH levels in those that had been taken from individuals prior to surgery.

C. Findings

Except for thyroid nodularity, it is noteworthy that other thyroid diseases such as thyroiditis have been absent in this population. Also, evidence of thyroid dysfunction with hyper- or hypofunction was rarely seen except for hypofunction in the exposed Rongelap people, described below.

1. Thyroid Nodules

(a) Clinical Characteristics

Thyroid nodules were almost always asymptomatic, and patients were often totally unaware of their presence. In a few cases, nodules were tender, and in rare instances patients complained of sensations of neck fullness and/or discomfort on swallowing. Associated lymph-adenopathy was rare. None of the individuals with thyroid nodules showed clinical evidence of thyroid dysfunction, though serum hormone assays indicated subclinical hypofunction in some (see Section IX.C.2). As noted earlier, myxedema secondary to thyroid ablation developed in two exposed Rongelap boys eight years after radiation exposure.

(b) Prevalence

Table 1 summarizes the prevalence of thyroid abnormalities in the exposed and age-matched comparison populations. In Appendix IV, Table 1, individual cases with positive findings are listed along with estimated thyroid doses, age at detection of abnormality, diagnosis, and date and place of surgery.

Since 1974, additional thyroid nodules have been detected in 5 exposed Rongelap people, 9 exposed Utirik people, and 14 unexposed people. Not listed in Table 1 of Appendix IV are a number of cases in which palpation of nodules was questionable, i.e., could not be confirmed definitely by a majority of examiners. As pointed out in Section IX.B, surgery was not performed in some cases because of old age, poor health, or other reasons. All of these patients are being carefully followed.

Before any discussion of the data presented in Table 1, the reader should be reminded of certain caveats concerning the unexposed comparison populations used in these studies. These populations consisted of a group of unexposed people of Rongelap (established in 1958) that has varied in number from 150 to 200, who have been examined regularly, and additional groups of unexposed people from the atolls of Rongelap, Utirik, Likiep, and Wotje added during the past ten years. The latter groups contain many children who were not included in the present analysis, but were used in determining an all-age prevalence of thyroid abnormalities (see Appendix I).

As pointed out in Appendix I, it is unlikely that the low doses from residual radiation that some of these people in the comparison groups received would produce any detectable thyroidal effects. Of the unexposed populations, the best comparison group is that established in 1958, when individuals were matched for age and sex. Unfortunately this group has suffered attrition over the years, and adequate matching of new persons to replace those missing has not been possible. The more recent thyroid comparison groups have had fewer examinations (some only one) and encompass only segments of the island populations. In addition, an element of possible bias in this group is that some people may have presented themselves for examination because of a suspected thyroid problem. This would tend artefactually to increase the incidence of thyroid disease in the control groups. An opposite bias may occur because most of the established control groups were examined many times over a long period as compared with the added control groups so that the fractional incidence of thyroid disease in the exposed population shown in Table 1, even after correction, may be too high.

Table 2 compares the prevalence of thyroid nodules in the two control groups and in the combined groups. Individual island listings for prevalence of thyroid nodules can be found in Appendix I. The data in Table 2 indicate no significant difference between findings in the two comparison groups; therefore, the data from the two groups combined were used in the calculations for Table 1. Nevertheless, the caveats referred to above should be kept in mind in interpreting the prevalence and risk calculations.

Table 1 shows a considerably greater prevalence of thyroid abnormalities (total and malignant nodules and hypofunction) in the exposed Rongelap-Ailingnae groups than in the Utirik and age-matched comparison populations, particularly in the youngest Rongelap age group.* The Utirik group shows a slightly greater prevalence of thyroid abnormalities than does the comparison population, but the youngest Utirik age group appears to be comparatively less affected than the corresponding young Rongelap group.

Table 3 shows that the observed versus expected ratios are greater for the Rongelap-Ailingnae group than for the Utirik group on the basis of prevalence in the unexposed Marshallese.

*Prevalence and risks for benign nodules are not presented in Table 1 since 5 of 46 nodule cases in the exposed and 15 of 35 nodules in the unexposed (age-matched) groups did not have surgery. (See Table 1, Appendix IV.) Carcinoma prevalence is presented with the realization that values possibly represent an underestimate of prevalence in view of the unoperated cases.

Table 1. Summary of thyroid abnormalities in the Marshallese, 1981.
(Corrected = matched control value subtracted.)*

Group age 1954	Est. thy.		Total nodules		Carcinoma		Hypofunction**		Total lesions			
	No.	dose, rad	No.	%	Correc- ted %	No.	%	Correc- ted %	No.	%	Correc- ted %	
<u>Rongelap</u>												
<10	22	810-1150†	17	77.3	74.7	1	4.5	3.6	3	13.6	13.6	88.0
10-18	12	335- 810	3	25.0	17.4	1	8.3	8.3				17.4
>18	33	335	3	9.1	1.2	2	6.1	5.4	4	11.8	11.9	13.2
Total	67	556 av.	23	34.3	28.5	4	6.0	5.2	7	10.4	10.1	38.7
<u>Ailingnae</u>												
<10	7	275-450	2	28.6	26.0							26.0
10-18	1	190										
>18	11	135	4	36.4	28.5				1	9.0	8.8	37.3
Total	19	217 av.	6	31.6	35.8				1	5.2	5.0	30.8
<u>Rong. + Ail.</u>												
<10	29	275-1150	19	65.5	62.8	1	3.4	2.5	3	10.3	10.3	73.1
10-18	13	190- 810	3	23.1	15.5	1	7.7	7.7				15.5
>18	44	135- 335	7	15.9	8.0	2	4.5	3.8	5	11.4	11.1	19.1
Total	86	482 av.	29	33.7	27.9	4	4.7	4.0	8	9.3	9.0	36.9
<u>Utirik</u>												
<10	64	60-95	5	4.7	5.2	1	1.6	0.7				5.2
10-18	21	30-60	3	14.2	6.7	1	4.8	4.8				6.7
>18	79	30	9	11.4	3.5	1	1.3	0.6				3.5
Total	164	51 av.	17	9.1	4.6	3	1.8	1.1				4.6
<u>Matched controls, unexposed</u>												
<10	229		6	2.6		2	0.9					2.6††
10-18	79		6	7.6		1	1.3		1	1.3		8.9
>18	292		23	7.9		2	0.7		1	0.3		8.2
Total	600		35	5.8		5	0.8		2	0.3		6.2

*The cancer estimates are possibly underestimated since all unoperated nodules were considered benign for these calculations. Occult carcinomas were not included under carcinoma.

**No nodule cases with hypofunction are included. (See Tables 1 and 2, Appendix IV.)

†The lower dose estimates for the <10 group were used for in utero cases.

††No correction necessary.

Table 2. Percent of unexposed Marshallese (born before 1954) with thyroid nodules.

Age group (1954)	Established (1958) group (Rongelap) total			Added groups* total			Combined groups total		
	%		Carcinoma**	%		Carcinoma**	%		Carcinoma**
	No.	Nods.		No.	Nods.		No.	Nods.	
<10	58	3.4	1.7	171	2.3	0.6	229	2.6	0.9
10-18	29	6.9	0	50	8.0	0	79	7.6	0
>18	98	9.2	1.0	194	7.2	0.5	292	7.9	0.7
All	86	6.9	1.1	415	5.3	0.5	600	5.8	0.7

*Added unexposed people of Rongelap, Utirik, Wotje, and Likiep. See Table 1, Appendix I, for island breakdown.

**The carcinomas may be underestimated since all unoperated nodules were considered benign for these calculations. Occult papillary carcinomas not included under carcinoma.

Table 3. Observed/expected thyroid nodules.*

Group	Exposure Age	No.	Total nodules	Carcinoma**
Rongelap	<18	42	22/1.6	2/0.4
"	>18	44	7/3.5	2/0.3
Utirik	<18	85	8/3.3	2/0.8
"	>18	79	9/5.7	1/0.6

*Based on unexposed Marshallese prevalence: <18, total nodules 3.9%, carcinoma 1.0%; >18, total nodules 7.9%, carcinoma 0.7%.

**Does not include occult papillary carcinomas.

Figures 1 and 2 show the age distribution of thyroid nodules in the various populations. The greater prevalence of nodules in the younger age group of exposed Rongelap-Ailingnae people is in contrast to the greater prevalence in the older age groups in the comparison population. The latter distribution has been noted in other unexposed world populations (see Table 4, Appendix I).

Figure 3 shows the cumulative percentage of thyroid nodules for the different age and exposure groups over the years. The curve of cumulative increase appears to be leveling off for the Rongelap and Ailingnae groups over the past decade, as would be expected, since the numbers of unaffected people are fewer. The Utirik group shows a slight increase.

Sex ratios of thyroid nodules (surgical cases only) were as follows:

<u>Group</u>	<u>Total nodules</u>	<u>Benign</u>	<u>Carcinomas</u>
	M/F	M/F	M/F
Exposed	10/35	10/28	0/7
Unexposed*	6/14	2/13	4/1

As has been noted in other populations of the world, the preponderance of thyroid nodules was in the females in both exposed and unexposed populations. In the Marshallese, though the males accounted for a larger fraction of nodules in the exposed than in the unexposed groups, the reverse was observed for cancer. The number of cases is too small for this finding to be meaningful. The ratio of benign to malignant lesions for the exposed groups was 38/7 and for the unexposed 15/5. As pointed out in previous reports, the radiation exposure may have reduced the cancer ratio in the exposed group ("overkill" effect) compared with that in the unexposed group.

(c) Gross Findings at Surgery

Because of the care taken in clinical examinations, thyroid nodules were often detected and surgically explored while still quite small. Though many of these were thought to be single nodules by palpation, most were found at surgery to be multiple. Thyroid glands were seldom diffusely enlarged. Aside from the nodules that were present, the remainder of the glandular parenchyma consistently appeared normal on gross examination.

When pathologically malignant lesions were discovered, they were often not the nodules that had drawn primary attention preoperatively. In addition to distinct nodules, any areas with gross irregularities were also resected, no matter how minute.

It is noteworthy that some thyroids, particularly in earlier cases among the exposed Rongelap group, showed increased numbers of fine tortuous capillaries over the gland surfaces. These resembled thyroids seen in certain cases of Grave's disease that had been inadequately treated with ¹³¹I and were subsequently treated by thyroidectomy. This feature has not been noted in the irradiated people from Utirik.

*The Likiep and Wotje groups were not included since they were seen only once.

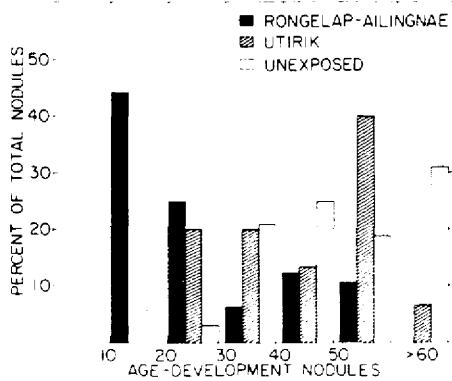


Fig. 1. Percent of total nodules appearing at various ages, 1979.

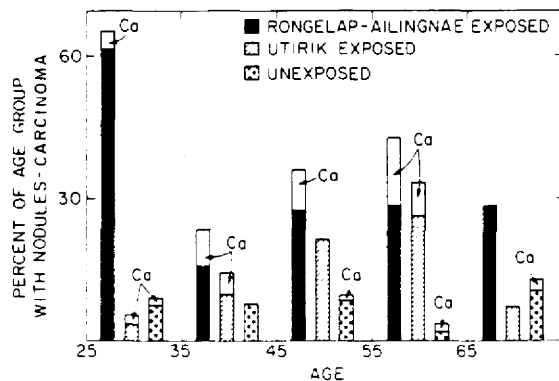


Fig. 2. Percent of persons with nodules in various age groups, 1979.

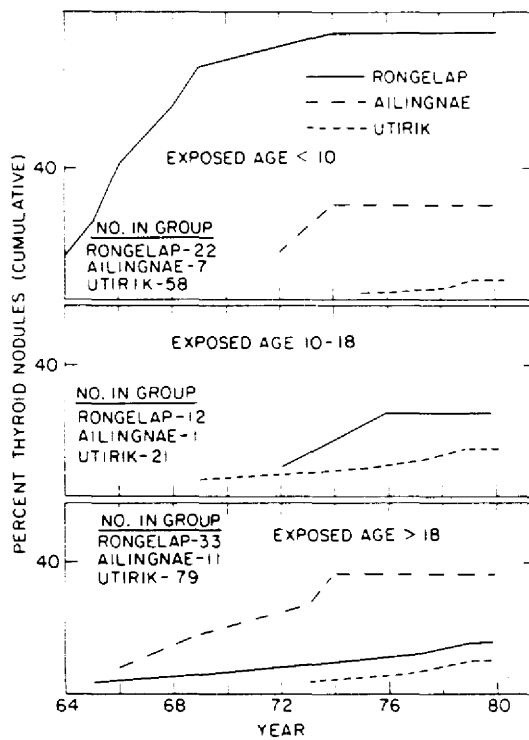


Fig. 3. Cumulative percent of persons with nodules, by year.

(d) Histopathology

Table 4 presents individual histopathologic diagnoses obtained on thyroid tissues resected from 63 Marshallese within the various study groups. Two patients required second operations: an exposed Rongelap woman (No. 15), who had recurrence of adenomatous nodules in residual thyroid tissue 10 years after initial resection, and a man exposed on Utirik (No. 2279) whose thyroid nodule was considered benign on frozen section but was found to contain papillary carcinoma on permanent sections. Four patients (No. 37, 40, 1556, 2261) had no distinct diagnostic lesion on pathologic examination. Their palpable thyroid irregularities appeared to have been secondary to normal anatomic variation and/or nonspecific focal fibrosis.

The diagnostic categories in Table 4 are essentially those recommended by the World Health Organization (114) with minor modifications; the term, adenomatous nodule, was used to designate focal proliferative lesions that did not fulfill the usual criteria of true neoplasms. These were characterized by histologic changes typical of adenomatous (nodular) goiter (114,115) or nodular hyperplasia (116), but they usually presented as localized rather than diffuse alterations, possibly in part because of early detection. As noted in Table 4, most of these had histologic evidence of hyperplasia, such as hyperplastic papillae or solid areas of hypercellularity, accompanied by variable amounts of fibrosis or other evidence of regressive changes.

The term, atypical adenoma or atypical adenomatous nodule, was applied to respective lesions that had more pronounced hypercellularity or variations in architectural patterns or cytologic characteristics but were devoid of clear histologic evidence of carcinoma, such as transcapsular infiltration or vascular invasion.

Infiltrative tumors designated papillary carcinoma often contained significant follicular components and therefore might justifiably be termed mixed papillary-follicular carcinomas. There was a conspicuous lack of psammoma body formation. In several, there were relatively few papillations, but cytologic features of the neoplastic epithelium (e.g., overlapping, vesicular nuclei) were deemed sufficiently distinctive to merit the designation, papillary. Such mixed tumors, even with marked predominance of follicular elements, were classed as papillary carcinomas in this study since most authorities (41,43,44,116,118,121-123,125,128), but not all (148,153), consider them to behave in a clinically benign fashion of pure papillary carcinomas. Pure follicular carcinomas, which tend toward more aggressive clinical behavior than papillary tumors (41,44,115,116,118,121,125,153) have not been observed in the Marshallese, although some of the follicular lesions (e.g., Nos. 2221, 3006, 5059) exhibited focal, partial capsular infiltration. The potential clinical expression of such lesions, had they not been excised at early stages, obviously remains speculative.

The term, occult papillary carcinoma, was used for those minute papillary tumors found coincidentally with nonneoplastic nodular disease. These were equivalent to the W.H.O. classification of "non-encapsulated (occult) sclerosing carcinoma" (114) and corresponded to the "non-encapsulated sclerosing tumor" described by Hazard et al. (124,126) and "occult sclerosing carcinoma" of Klinck and Winship (127). These were never found as isolated, palpable lesions, but in each instance occurred with variable degrees of fibrosis in association with hyperplastic adenomatous nodules. Their totally benign clinical behavior, even in the presence of regional lymph node

Table 4. Histopathologic diagnoses of thyroid nodules among Marshallese study populations.

Patient No. & sex	Age at surgery	Years post exposure	Pathologic diagnosis	Remarks
<u>Rongelap exposed</u>				
21 F	13	10 1/2	Adenomatous nodules	Hyperplasia
17 F	12	10 1/2	Adenomatous nodule	Hyperplasia
69 F	15	10 1/2	Adenomatous nodule	Hyperplasia
2 M	12	11	Adenomatous nodule	Hyperplasia
20 M	18	11	Adenomatous nodule	Hyperplasia
64 F	41	11	Papillary carcinoma	Lymph node metastases
33 F	13	12	Adenomatous nodules	Hyperplasia, fibrosis
42 F	13	12	Adenomatous nodules	Papillary hyperplasia
61 F	20	12	Adenomatous nodules	
65 F	13	12	Adenomatous nodule	Fibrosis
19 M	14	14 1/2	Adenomatous nodule	Hyperplasia
23 M	19	14 1/2	Adenomatous nodule	
54 M	14	14 1/2	Adenomatous nodule	
18 F	34	15 1/2	Papillary carcinoma	
36 M	21	15 1/2	Adenomatous nodules	Hyperplasia
72 F	20	15 1/2	Papillary carcinoma	Lymph node metastases
15 F	22, 32	15 1/2, 25	Adenomatous nodules	
75 F	24	18 1/2	Adenomatous nodules with follicular adenoma	
40 M	46	19	No diagnostic lesion	Fibrosis
83 M	24	20	Adenomatous nodule	Focal hypercellularity
74 F	34	22	Papillary carcinoma	
37 M	45	23 1/2	No diagnostic lesion	
66 F	54	25 1/2	Adenomatous nodule	Papillary hyperplasia, fibrosis
85 M	25	25 1/2	Adenomatous nodules	
<u>Ailingnae exposed</u>				
59 F	53	12	Adenomatous nodule	Hyperplasia
8 F	18	18	Adenomatous nodule	Hyperplasia, focal atypia
45 F	45	19	Adenomatous nodule	
51 F	45	20	Adenomatous nodule	Fibrosis
53 F	33	27	Adenomatous nodules with occult papillary carcinoma	

Table 4 (cont'd)

Patient No. & sex	Age at surgery	Years post exposure	Pathologic diagnosis	Remarks
<u>Utirik exposed</u>				
2229 F	32	15 1/2	Follicular carcinoma	Divided opinion: atypical adenoma
2208 F	53	19	Adenomatous nodules	
2212 F	53	19	Adenomatous nodules with Hürthle cell adenoma	Hyperplasia
2221 F	73	19	Adenomatous nodules with follicular adenoma	Hyperplasia, focal atypia
2160 F	25	21 1/2	Papillary carcinoma	Hyperplasia
2150 M	34	22	Follicular adenoma	
2194 F	59	22	Papillary carcinoma	Lymph node metastases
2261x M	50	23 1/2	No diagnostic lesion	
2236 M	35	24	Follicular adenoma	Focal hyperplasia
2193 F	56	25 1/2	Adenomatous nodules	Papillary hyperplasia
2195 F	49	25 1/2	Adenomatous nodule	
2215 F	58	25 1/2	Adenomatous nodules with occult papillary carcinoma	
2147 F	30	25 1/2	Adenomatous nodules	Diffuse
2196 F	63	26 1/2	Adenomatous nodules	
2239 F	29	27	Adenomatous nodules	
2132 F	28	27	Adenomatous nodule	Fibrosis
<u>Rongelap unexposed controls</u>				
938 F	33		Adenomatous nodule	
829 F	41		Adenomatous nodule	Papillary hyperplasia
841 F	41		Adenomatous nodules with occult papillary carcinoma	
1007 M	66		Papillary carcinoma	Fibrosis, hyperplasia
1573 M	28		Papillary carcinoma	
867 F	50		Adenomatous nodule	Fibrosis
4023 F	44		Adenomatous nodule	Papillary hyperplasia
1556 F	34		No diagnostic lesion	

Table 4 (cont'd)

Patient No. & sex	Age at surgery	Years post exposure	Pathologic diagnosis	Remarks
<u>Utirik unexposed controls</u>				
*2279 M	21,23		Papillary carcinoma	Lymph node metastases
3074 F	22		Adenoma	
3058 F	56		Adenomatous nodule	
3042 F	50		Papillary carcinoma	Lymph node metastases
3006 M	78		Adenomatous nodules with follicular adenoma	Focal atypia
3096 F	56		Atypical adenomatous nodules	Focal hypercellularity
3023 F	39		Adenomatous nodule	Marked papillary hyperplasia
<u>Wotje unexposed controls</u>				
5027 M	32		Papillary carcinoma	
5030 M	36		Adenomatous nodule	Focal hyperplasia
5059 F	49		Atypical adenomatous nodule with adenoma	Focal hyperplasia, borderline atypia

*In the younger (non-age-matched) group.

metastases, is well documented (41,87,117,120,125,126,129,130,254-256,260). In only one case (No. 72) was there evidence of cervical lymph node metastases from a clinically occult papillary carcinoma (see Figure 4).

Lymph node metastases note in Table 4 were all limited to regional cervical nodes. There has been no evidence of distant metastasis in any of the Marshallese, nor has there been local recurrence of any resected carcinoma. Other forms of thyroid malignancies, such as medullary, squamous, anaplastic, or sarcomatous, have not been observed.

Table 5 summarizes the distribution of these tumors among exposure groups. The prevalence of these lesions within the study population subsets has been discussed in Section III.1.b. No specific type of histologic lesion appeared directly attributable to radiation, since they occurred in similar relative proportions in both exposed and unexposed groups, but histologic and cytologic changes consistent with radiation injury were observed in some of the exposed individuals. These included the postirradiation interstitial fibrosis, lymphocytic thyroiditis, and oxyphilic changes noted by other investigators (257,258).

In a number of instances, more than one diagnosis applied to a single patient. Most of the specific lesions, such as papillary carcinomas, occurred in a local milieu of adenomatous nodularity, but the latter was recorded as a separate diagnosis only when it was judged to be a significant contributor to the palpable nodularity. When carcinoma was found, it was not always the clinically suspicious nodule that originally prompted surgery, a circumstance experienced by a number of other investigators (148,153,257).

Favus et al. (153) reported the frequent coexistence of adenomatous hyperplasia and radiogenic papillary or mixed carcinomas. As noted in Table 4, the present study included numerous cases in which prominently hyperplastic foci, often with papillary configurations, occurred within adenomatous nodules. In two of these cases (Nos. 8 and 2221), focal atypia was also noted. Otherwise, there was no histologic evidence to suggest that such hyperplastic areas might eventually progress to carcinoma, especially since they were also commonly observed among the nonirradiated control populations. The reasons for such highly localized, exuberant responses to TSH stimulation remain unclear, however, and radiogenic injury cannot be ruled out as one potential cause. Studies of children with thyroid exposures of <1000 rads led Spitalnik and Straus to suggest that focal hyperplasia in such cases might represent a premalignant alteration (258).

Many of the references cited indicate that radiation-induced papillary or mixed carcinomas of the thyroid usually represent low-grade malignancies with relatively little or no clinical significance in terms of patient morbidity or mortality. Factors that appear to influence prognosis adversely include nonpapillary histology, size of the primary, local extent, local recurrence rate, and distant metastases, but not regional lymph node metastases. The single most important adverse prognostic indicator may be onset at more than 40 to 45 years of age (41-44,45,118,119,121-123,125). Of the fourteen Marshallese with either occult or overt papillary carcinomas, five were in the older age group, three of whom were radiation exposed. Of the five with cervical node metastases, one (No. 3042) was in the unexposed comparison population from Utirik.

Since the preponderance of cases among the Marshallese was in the younger age group, and all were papillary carcinomas devoid of local recurrence or



Figure 4. Cut surfaces of left thyroid lobe (Patient No. 72) demonstrating adenomatous nodules and minute primary papillary carcinoma (arrow) responsible for cervical lymph node metastases. (From B.M. Dobyns.)

Table 5. Summary of histopathologic diagnoses according to exposure group.

Group	No. in population	No. with surgery	Diagnoses*					No Diagnostic Lesion
			Adenomatous nodule(s)	Adenoma	Atypical adenoma or adenomatous nodule	Papillary carcinoma	Occult papillary carcinoma	
<u>EXPOSED</u>								
Rongelap	67	24	18	1		4		2
Ailingnae	19	5	5		1		1	
Utirik	164	16	10	4	1	3	1	1
Total:	250	45	33	5	2	7	2	3
<u>UNEXPOSED</u>								
Rongelap	668	8	5			2	1	1
Utirik	473	7	3	2	1	2		
Wotje	162	3	1	1	1	1		
Total:	1303	18	9	3	2	5	1	1

*Includes more than one diagnosis in some cases (see text). One other case, No. 980, an unexposed Rongelap female, who had surgery recently (diagnosis, adenoma) is not included in the table.

distant metastases, the clinical prognoses for these individuals remains highly favorable. Although fourteen of these tumors were classified morphologically as malignant neoplasms (carcinomas), either occult or overt, it should be emphasized that the lay term "cancer," with its ominous implications, should not be applied to such clinically benign lesions, a point well noted by others (255,259).

2. Thyroidal Hypofunction

Criteria used in defining biochemical thyroid function were developed from findings in the control and exposed Utirik populations presented in Table 6.* In the initial series, an upper limit of 3 μ U TSH/ml serum was selected, since baseline studies in 25 unexposed Marshallese who were clinically and biochemically euthyroid yielded a mean value of 2.0 μ U/ml (SD = 0.73) with a range of 0.5 to 3.0 μ U/ml. Serum TSH concentrations in this group after injection with 500 μ g of TRH averaged 11.5 μ U/ml (SD = 4.5) with a range of 4.7 to 20.0 μ U/ml. These results are similar to those obtained in other normal populations with respect to both basal TSH and TRH-induced TSH release (111,130,131).

Table 6. Number of subjects with elevated serum TSH concentrations in control and exposed Marshallese populations (1975-1979).

Subjects	Initial Series		Second Series	
	Tested once	Single TSH ≥ 3 μ U/ml	Tested two or more times	Two TSH values ≥ 6 μ U/ml
Control (unexposed Marshallese)	115	11 (10%)	67	2 (3.0%)
Utirik exposed (thyroid dose <95 rads)	99	12 (12%)	101	0
Rongelap-Ailingnae exposed (No prior surgery)	43	11 (26%)	36	7 (19%)

As shown in Table 6, only 10% of a control population of 115 had serum TSH concentrations >3 μ U/ml. In the the Utirik population exposed to relatively low doses of radioiodine, 12% had single TSH values >3 μ U/ml. These results suggested that there was no difference between these two populations with respect to the prevalence of elevated serum TSH. In the exposed (but

*Data from the exposed Utirik group were combined with the data from the unexposed group because that group showed no evidence of thyroid hypofunction associated with the low doses to their thyroids.

unoperated) Rongelap populations, the prevalence of serum TSH >3 $\mu\text{U}/\text{ml}$ was 26%, more than twice that in the two other populations, suggesting the presence of some degree of thyroid dysfunction in this group.

The occurrence of 10% of control values >3 $\mu\text{U}/\text{ml}$ for serum TSH concentration and the occurrence of only one value >5 $\mu\text{U}/\text{ml}$ in either the control or the exposed Utirik populations justified the selection of 6 $\mu\text{U}/\text{ml}$ as a tentative upper limit of normal. A minimum of two separate determinations of serum TSH in each individual was established as an additional requirement. Recent studies of normal individuals (in the U.S.) using this TSH immunoassay indicated that a persistent serum TSH of 6 $\mu\text{U}/\text{ml}$ for 6 hours achieved by constant TRH infusion results in significant increases in serum T_3 and T_4 over this time period (132). Therefore a serum TSH concentration >6 $\mu\text{U}/\text{ml}$ as measured by this TSH assay represents a biologically significant elevation. Of 67 control and 101 Utirik exposed individuals assayed at least twice, only one had a serum TSH concentration >6 $\mu\text{U}/\text{ml}$ (Table 6). This 55-year-old woman (subject No. 982) had serum TSH values of 6.3 and 6.5 $\mu\text{U}/\text{ml}$ and in 1978 had a serum T_4 of 6.4 $\mu\text{g}/\text{dl}$ with a TBGI of 0.76 (normal range = 0.85 to 1.10). Tests for antimicrosomal and antithyroglobulin antibodies were negative.

These criteria for thyroid dysfunction were clearly biochemical since none of the patients had clinical hypothyroidism. The results were, however, specific enough to permit classification and eliminate errors that might be due to variations in the assay and/or physiological variations. When these more specific criteria were applied to the exposed Rongelap populations (Table 6, second series), there were still eight individuals with TSH values ≥ 6 $\mu\text{U}/\text{ml}$ on two occasions. Other pertinent observations on these individuals are presented in Table 7.

The first two individuals listed in Table 7 (Nos. 3 and 5) were exposed at age 1 year (thyroid doses 1150 rads or more). Representative serum TSH values may not be maximal, especially in the case of subject No. 3, since he generally adhered to the recommendations regarding thyroid replacement medication, which was never intentionally stopped in these two. Subject No. 5, however, often had substantial elevations in TSH and markedly reduced serum T_4 , indicating that he did not take thyroxine regularly.

In the remaining five individuals in Table 7, serum TSH values between 6 and 10 $\mu\text{U}/\text{ml}$ were obtained on various occasions. In most, the serum T_4 or estimated free thyroxine index (obtained by multiplying the serum T_4 by the TBGI, normal range 4.7 to 10.6) was in the low or low-normal range, as noted in other individuals with mild thyroid hypofunction (111). Thus, while subjects No. 34 and 78 had serum T_4 concentrations within the normal range, they both had a subnormal TBGI, indicating that the concentrations of unoccupied TBG binding sites were elevated in these sera. Since the normal range for serum T_4 is dependent on the quantity of circulating TBG, such subjects should have a higher serum T_4 . All of the individuals with mild biochemical hypothyroidism listed in this table were exposed between the ages of 25 and 45 years and are now aged 50 to 70.

To determine whether increased age could be associated with an increase in serum TSH, as observed in other surveys (133), serum TSH values in control and exposed Utirik patients in this age group were examined. Only one individual (No. 982) was found to be abnormal out of a total of 53 tested. About two-thirds of these subjects had at least two serum TSH determinations, and none of the remaining had a TSH concentration >4 $\mu\text{U}/\text{ml}$. Therefore the

Table 7. Results of serum analyses in exposed Marshallese subjects with at least two TSH assays ≥ 6 μ U/ml (1980).

Subject No. & sex	Date of sample	Serum TSH (μ U/ml)	Serum T ₄ (μ g/dl)	TBGI (units)	Age at exposure	Estimated thyroid dose (rads)
3M	1977	69	2.5	0.95	1	1150
5M	1963	500	0.5	0.71	1	1150
4M	1972	6.0	7.3	--	38	335
	1974	7.0	5.4	0.82		
16M	1969	6.3	4.4	0.89	39	135
	1979	6.5	4.9	0.91		
34F	1974	6.3	7.1	--	45	335
	1979	8.3	8.0	0.74		
71F	1974	10	4.2	--	27	335
	1977	7	5.2	0.98		
78F	1977	6.6	6.1	0.82	37	335
	1979	8.8	7.6	0.68		
32M	1980	7.3	5.1	0.89	3	1050

Normal control range: 0-6.0 5.0-10.2 0.85-1.10

observation of elevated TSH in the individuals listed in Table 7 cannot be attributed to age alone. No. 4 and No. 78 were among those in whom TSH stimulation tests had been performed earlier. Both had T₄ increments of <1 μ g/dl 24 hours following 10 units TSH administration, a clearly subnormal response showing that these thyroids had no capacity to respond to increased demand.

To evaluate the pituitary/thyroid axis more completely, TRH studies were done in some individuals. Results on subjects No. 4, 71, and 78 are given in Figure 5. Data from subject No. 74, discussed below, are also shown. This patient had surgery subsequent to the test and is therefore categorized separately (Table 8). Subjects No. 4, 71, and 78 all were hyperresponsive to TRH stimulation, with serum TSH values at 20 min >22 μ U/ml, which is the 97.5% confidence interval for mean normal responses in the Marshallese.

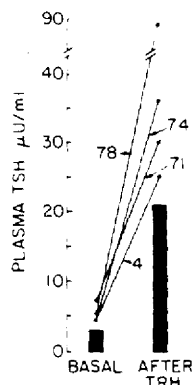


Figure 5. Basal plasma TSH and TRH-stimulated TSH in euthyroid Marshallese and in four exposed subjects with biochemical evidence of impaired thyroid function. Plasma was obtained 20 min after infusion of 500 μ g TRH. The upper limits of the normal range are indicated by the shaded bars.

Table 8. Results of retrospective analyses suggesting the presence of thyroid dysfunction prior to surgery in certain exposed Marshallese (1980).

Subject No. & sex	Date of serum sample	Serum TSH (μ U/ml)	Serum T ₄ (μ g/dl)	TBGI (units)	Age at exposure (years)	Estimated thyroid dose (rads)
2M	1963	22	6.5	0.84	2	1100
19M	1963	6.9	5.7	1.01	5	1000
	1965	8.2	9.5	0.80		
33F	1966	22	8.3	0.82	1	1150
69F	1963	470	1.4	0.64	4	1000
74F	1972	16.3	--	--	15	425
83M*	1974	6.7	3.3	0.98	<u>in utero</u>	>175
Normal control range:		0-6.0	5-10.2	0.85-1.10		

*This infant's mother (No. 74) had an estimated thyroid dose of 425 rads.

It was of interest to measure TSH in frozen plasma samples obtained years earlier to determine whether individuals might have had evidence of thyroid dysfunction prior to surgery. In many cases only one sample obtained prior to surgery was available. The criterion used in these instances was that serum TSH be ≥ 6 μ U/ml on at least one occasion. It was assumed, but not proved, that TSH is relatively stable in plasma samples stored at -20° F for prolonged periods. This conclusion was supported by results on subject No. 5, who had a serum TSH of 500 μ U/ml in a sample obtained in 1963, but obviously it is uncertain what that value would have been had this specimen been measured fresh. Since all subjects were on T₄ therapy after 1963, it should be assumed that these results might underestimate the prevalence of presurgical hypothyroidism. In any case, six individuals exhibited biochemical evidence of mild to severe degree of hypothyroidism prior to surgery (Table 8).

The most marked abnormality was observed in subject No. 69, in whom a serum TSH of 470 μ U/ml was found in a sample obtained in 1963. This subject had surgery performed in 1964. Three individuals had modest elevations in serum TSH, between 16 and 22 μ U/ml, and the remaining two had mild abnormalities. Most but not all of these elevated serum TSH values were associated with decreased serum free-thyroxine indices, and all were in subjects exposed at a young age, four receiving an estimated thyroid dose ≥ 1000 rads. Receiving lower thyroid doses were No. 74, who was 15 at the time of exposure, and No. 83, who was in utero (gestational age ≈ 6 mo). These results appear to be consistent with observations in subjects No. 3 and 5.

In addition to the results on the above 13 subjects in Tables 7 and 8, which indicated primary thyroid dysfunction as a consequence of radiation

exposure, the results on four other exposed, unoperated individuals had a single TSH determination $>6 \mu\text{U/ml}$. All of these individuals had TRH-induced TSH responses between 30 and 35 $\mu\text{U/ml}$. Therefore it is possible that in the next few years additional individuals will be identified who meet the criteria for biochemical thyroid dysfunction. None of the subjects with elevated serum TSH had detectable antithyroglobulin or thyroid antimicrosomal antibodies.

3. Thyroid Abnormalities in Cases Exposed In Utero

In the Rongelap group, exposed to 175 rads of whole-body radiation, there were three people exposed in utero. Benign tumors of the thyroid have been removed from two of these: adenomatoid nodules removed at age 24 from a male (No. 83) exposed at the end of the second trimester, and a hyperplastic nodule removed at age 26 from a male (No. 85) exposed at the end of the first trimester. A female (No. 86) exposed in the first trimester has developed no detectable thyroid abnormalities. In the Ailingnae group (69-rad whole body exposure) there was one exposure at the end of the first trimester, and in the Utirik group (14-rad whole body exposure) there were six in utero exposures. No thyroid abnormalities have appeared in any of these cases.

The total thyroid doses in these cases cannot be accurately estimated. The function of the fetal thyroid at the time of exposure is an important factor in such estimations. A few reports are available concerning function of the fetal thyroid gland at various stages of gestation (134-137). The gland is thought not to accumulate iodine before the 12th week of gestation, but thereafter becomes increasingly active, and at birth is more active than in the adult or child. In case No. 83, at the time of exposure -- 22 weeks gestation -- the thyroid was probably functioning sufficiently to have absorbed a significant amount of radioiodines from the mother's blood. In case No. 85, it is unlikely that the thyroid was sufficiently functional at 12 weeks gestation to have absorbed a significant amount of radioiodines from the mother, and the development of the thyroid nodule may have been associated with the gamma exposure. Data on the time of gestation and degree of exposure in the six Utirik cases are uncertain, but their thyroid doses both from whole-body and from possible radioiodine exposure would have been far less than those of the Rongelap group, and this is consistent with the lack of findings in that group.

Neither of the in utero exposed children who developed thyroid nodules showed any impairment in growth and development (see Section IV). No. 83 had an elevated TSH level prior to surgery, but without evidence of clinical hypothyroidism. The thyroid status of the mothers of the two in utero cases who developed thyroid nodularity is of interest. The mother of No. 83 was exposed at age 15 to an estimated thyroid dose of 175 rads gamma radiation plus 250 rads from radioiodines and developed a thyroid cancer at age 32. She showed evidence of biochemical hypothyroidism prior to surgery (Section IX.C.2.). The mother of No. 85 was exposed at age 17 to an estimated thyroid dose of 175 rads gamma radiation plus 160 rads from radioiodines. She has not developed nodularity of the thyroid gland, but hypertrophy of the pyramidal lobe at age 43 was noted.

A number of cases of myxedema have been reported following in utero exposure during treatment of the mother with large doses of radioiodines for hyperthyroidism (mCi amounts, compared with probable μCi amounts in the

Marshallese) (138-141). These two individuals exposed in utero described here appear to be the first known cases developing thyroid nodules after radioiodine exposure.

4. Problems Associated With the Thyroid Hormone Treatment Program

In 1965 a BNL thyroid advisory panel recommended that the exposed Rongelap people be placed on thyroid hormone treatment for life as a prophylactic measure to reduce the risk of further thyroid nodule development (by suppression of TSH levels) and possibly enhance growth and development in some of the children in whom this was retarded.* Since that time, the exposed Rongelap people have been receiving daily (or weekly) treatment with synthetic L-thyroxine (Synthroid, Flint Drug Co.). The Ailingnae people were also placed on the hormone treatment regimen in 1969 because of the development of thyroid nodules in that group. In the exposed Utirik population and in the unexposed groups, hormone treatment has been used only in those who have had thyroid surgery and, in some cases, to test the response of thyroid nodules to a trial treatment with the hormone. The Synthroid doses used usually have been 0.3 mg/day for people <50 years of age and 0.2 mg/day for those >50. However, the dosage has been adjusted downward in some elderly people and in a few people who showed symptoms on the dose given.

As pointed out in past reports, there have been problems of maintaining a strict hormone treatment regimen in all of the people. Most of the people take the medication faithfully, but a number of them have been careless in maintaining the regularity of treatment in spite of continued efforts by the medical team and the resident physician and his aides to impress upon them the importance of the treatment program. Omission of medication has been particularly serious in patients who had undergone thyroid surgery. A number of these have from time to time shown elevated serum TSH levels and a few questionable signs of hypothyroidism. Fortunately, except in one case (described below), treatment was resumed before serious consequences developed. In spite of all efforts, some post-operative patients still become lax at times about regularity of medication, as indicated by elevated serum TSH levels.

As discussed previously (see Section IX.A.), two Rongelap boys exposed at one year of age received larger doses to the thyroid (perhaps >2000 or more rads) and developed hypothyroidism with stunted growth associated with atrophy of the thyroid gland. One of these responded satisfactorily to treatment with hormone, showing enhanced growth and development and no clinical evidence of hypothyroidism in spite of occasional elevations of serum TSH levels. The other case, however, though he had responded to the treatment with improved growth status, has become a serious problem with regard to maintaining thyroid treatment. On a number of occasions, he has exhibited periods of apathy, development of behavioral problems along with some degree of mental retardation, and refusal of food at times. This was associated with high levels of TSH. He has been hospitalized on several occasions with severe hypothyroidism. The above findings indicate the importance of maintaining a strict treatment

*The rationale for such treatment has been supported by the finding that development of thyroid tumors in experimental animals is completely prevented by hypophysectomy (142).

regimen in this population, and increased efforts in this direction seem to indicate an improved trend.

The favorable effect of the hormone treatment in improving growth and development in some of the growth-retarded children is discussed in past reports (1,27) and in Section IV. It remains uncertain whether the treatment has had an effect in preventing formation of thyroid nodules. Some exposed individuals have developed nodules while taking medication conscientiously.

5. Iodoprotein Studies

In the course of serum hormone measurements to monitor possible radiation effects on thyroid function, it was fortuitously discovered that the native people in the Marshall Islands normally have a serum iodoprotein level higher than that found in Western people, even while residing in the Marshall Islands -- see Table 32 of the 20-yr report (1). The finding of serum iodoprotein in athyrotic Marshallese suggested that this substance arose outside the thyroid gland. It was postulated that it might be iodoalbumin or other serum protein iodinated by blood leukocytes in the context of chronic inflammatory disease such as parasitic infestation. There is still no proof for this hypothesis. In 1973, serum thyroglobulin was measured in a number of individuals from various groups; the findings are summarized in the 20-year report (Figs. 41 and 42) (1). Thyroglobulin levels were the same as in the U.S. normal population and thus could not explain the elevated serum iodoprotein. In addition, it was found that Rongelap and Utirik people who had had thyroid surgery tended to have lower than normal serum thyroglobulin levels. This may have been the result of thyroid gland removal or more likely of suppression by thyroxine therapy. The major significance of the elevated iodoprotein is that it was responsible in the early phase of the Marshall Island surveys for failure to recognize hypothyroidism. The serum protein bound iodine was the routine screening test at that time. Since the development of radioimmunoassays for T_4 , T_3 , and TSH and their application in the surveys, this problem is no longer important.

D. Discussion of Thyroid Findings

The most definite and widespread late effects of exposure to fallout in the Marshallese have been related to the latent development of thyroid nodularity, benign and malignant; the development of nodules in two children exposed in utero; growth retardation in some of the children; and, more recently, the finding of hypofunction in some exposed people with and without evidence of other thyroid abnormalities. The role of radiation exposure in the etiology of thyroid abnormalities in the Marshallese seems clear. There are no known goitrogens that might play a role, and the iodine intake of these people is adequate as indicated by adequate levels of iodine in food sources and in the urine.

During the past five years thyroid examinations of unexposed populations of Marshallese have been expanded for comparison with those exposed to fallout. The results have been important in the evaluation of findings in the exposed people. As discussed in Appendix I, the incidence of thyroid abnormalities in these unexposed Marshallese does not appear to be very

different from the incidences in other world populations, which suggests that there is nothing unusual in the environment of the Marshall Islands that might predispose to thyroid abnormalities.

The numbers of thyroid abnormalities detected in the various exposed Marshallese groups were roughly related to the calculated thyroid doses in the groups, i.e., greatest in the Rongelap, less in the Ailingnae, and least in the Utirik group, as indicated in Table 1 and Figure 3. However, because of the small numbers of people involved and uncertainties of the doses received, the data do not lend themselves to dose-response analysis.

Numerous animal studies have shown the association between radiation exposure and the later development of thyroid neoplasia (143-145,198,199). There are increasing reports of the development of thyroid abnormalities in children many years after therapeutic irradiation of the head and neck (with thyroid exposure) (146-171,200-203). The incidence of thyroid tumors was increased in the survivors of the atomic bombings of Japan (84-86,172). Reports of tumorigenic effects of radioiodines are more limited in man (173-180), and ^{131}I has considerably less effect than x-radiation and other penetrating radiations in this regard. The few studies of late thyroid effects following diagnostic use of ^{131}I have indicated generally negative findings (175,176).*

Besides the Marshallese exposed in 1954, the only other people that may possibly have had a similar type of exposure were those residing in the Nevada-Utah area during the Nevada testing program. Children living in this area were later examined for thyroid abnormalities. The thyroid dose in these children has been estimated at about 18 rem (maximum 120 rem) (181). The amount of short-lived iodine isotopes involved is not known. No increase in the incidence of thyroid abnormalities was detected in these children compared with unexposed children in Arizona, also examined in that study.

Several points should be made regarding the thyroid dose estimates in the Marshallese children. Table 9 (see also Appendix IV, Table 4) shows that radiation risk estimates for the development of thyroid nodularities or carcinoma in the Marshallese approximate those for populations exposed to x-radiation and for Japanese atomic bomb survivors. The internal absorption of radioiodines before evacuation of the Marshallese from their home islands was a most important source of radiation exposure to the thyroid gland. On the basis of known facts regarding risk, the estimated doses of gamma radiation alone would not have been sufficient to induce the observed findings. It is known that ^{131}I is considerably less effective in producing thyroid abnormalities than x-radiation (183-185,187), and, since it has been demonstrated that the shorter-lived isotopes of iodine are more destructive to the thyroid than ^{131}I (188-192) because of greater penetration of their beta rays and faster dose rate, it seems likely that their presence played an important role in thyroid injury and may partly account for the unexpectedly higher risk estimates than would be expected from ^{131}I alone. However, several points should be repeated. The dose estimates in the Marshallese are only approximate, and

*Doses from diagnostic use of ^{131}I vary from about 10 to 200 rads (194).

Table 9. Risks of thyroid nodularity from radiation in children.*

Group (years follow-up)	Type rad	Dose (rads)	Risk	
			Benign	Carcinoma
Rongelap (27)	I β , γ	710-1150	26.7	1.6
Ailingnae (27)	"	280-450	29.4	0
Utirik (27)	"	60-95	16.7	3.8
All of above	"	312 (av)	24.4	1.9
Rochester (25)	x-ray (162)	119 (av)		3.0
Ann Arbor (17)	x-ray (162)	20 (av)	24.0	2.2
Beach & Dolphin (20)	x-ray (182)			1.7
UNSCEAR (17)	x-ray (97)			0.5-1.5
ABCC (20)	γ ,n (172)	20-1000		1.3 (all ages)
ABCC (20)	γ ,n (172)	<20		0.2 (all ages)
Modan et al.	x-ray (163)	6-6.5	12.3	4.2
Albert et al.				
Maxon (21.5)	x-ray (164)	270 (av)		1.5

*Risk is calculated from the equation $\frac{\text{No. of cases} \times 10^{-6}}{\text{dose} \times \text{years at risk}}$. (See Table 4, Appendix IV.) Unoperated cases in the Marshallese groups were not included in the estimates. The incidence in the matched comparison Marshallese population has been subtracted from that in the exposed groups in determining the risk. If the actual number of years at risk were used, i.e., subtraction of latent period, the risk values would be higher in the Marshallese.

studies under way indicate that they may be too low.* Considerable variation in individual thyroid doses probably resulted from differences in food and water consumption at the time of the fallout. The greatest uncertainty was in doses to the children. Undoubtedly, the two boys exposed at one year of age who developed thyroid atrophy and myxedema received doses well above those calculated, as explained in Appendix II.

From the Marshallese experience it appears that there is a greater propensity to develop thyroid nodularities after radioiodine exposure in the children than in the adults. This 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 about 18 at maturity) and increased

*Even if the Marshallese thyroid doses were twice as high, the risk estimates would still be higher than would be accounted for on the basis of ^{131}I exposure alone.

metabolic function of the thyroids of young children (237). It was observed, however, that the risk for carcinoma was greater in the older exposed groups than in the children. (See Table 4, Appendix IV.) This may be related to the higher doses in the children ("overkill effect"). (See Appendix II.)

The finding of thyroid nodules in two children who were exposed in utero on Rongelap indicates the importance of fetal irradiation of the thyroid gland by radioiodines absorbed by the mother. Since there were only three children exposed in utero on Rongelap, this finding seems significant.

Though thyroidal hypofunction had been noted earlier in some exposed Rongelap children, this finding has been more recently noted in adults of this population who had received lower thyroid doses and who had not exhibited thyroid nodularity. The appearance of hypothyroidism following accidental exposure to radioactive iodines contained in fallout has not been previously reported except in this Marshallese population. Studies of Rallison et al. did not show an increased number of cases of overt hypothyroidism in children exposed to low levels of fallout in Utah (181). Most previous studies of the effects of radioiodine on human thyroid function have consisted of evaluations of the risk of hypothyroidism developing after various quantities of ^{131}I administered for the treatment of hyperthyroidism (173,209). Such treatment generally results in thyroidal doses >5000 rads.

The most severe thyroidal hypofunction was noted in 6 of 22 Rongelap children exposed at age <10 years (Table 8). As pointed out, this group had received thyroid doses about three times as great as that of the adults because of the smaller size of their thyroid glands. While the thyroidal hypofunction in the prospectively studied, older-age group (Table 7), was generally less pronounced, the plasma TSH concentrations were considerably greater than those found in the control Marshallese population and the FT_4I results were reduced. It is pertinent to note that, using the same TSH assay as employed in these studies, a plasma TSH of 6 $\mu\text{U}/\text{ml}$ maintained for 6 hr by TRH infusion results in significant stimulation of the thyroid glands in normal individuals (132). Further evidence of decreased thyroid reserve in this prospective study was a decreased response to TSH and enhanced TRH responsiveness. Thyroidal hypofunction was noted in only one individual exposed on Ailingnae, none in the groups exposed on Utirik Atoll, and only one in the unexposed group. The abnormal plasma TSH concentrations were not found in a comparably aged, euthyroid, unexposed population, which indicated that this finding was not a manifestation of age alone. No individuals were found to have elevated titres of antimicrosomal or antithyroglobulin antibodies.

On the basis of studies of ^{131}I treatment of primary hypothyroidism, it has been estimated that 4 to 5 cases of hypothyroidism/ 10^6 persons/year/rad would appear from thyroidal exposures to ^{131}I in excess of 2500 rem (163, 173,174). This risk factor was used to estimate the number of hypothyroid cases that might be expected in the more heavily exposed Rongelap population at 25 years after exposure. In the 22 Rongelap individuals who were <10 years of age at the time of exposure (using a mean estimated dose of 1200 rads), only 3 hypothyroid cases would be expected, whereas 7 of these children were hypothyroid within 14 years of exposure. Among 45 Rongelap individuals who were >10 years of age at the time of exposure (average thyroidal dose of about 387 rads), two cases of hypothyroidism would be expected whereas four were noted in this group. These numbers are considerably higher than expected on the basis of ^{131}I risk data.

As has been pointed out, more than half of the thyroidal exposure in the Marshallese was due to the more energetic and destructive short-lived isotopes of iodine. Hence the use of risk data for ^{131}I exposure will give considerably lower estimates for hypothyroidism than would be expected for the Marshallese subjects.

Several other explanations may contribute to the discrepancy between the observed and predicted number of hypothyroid patients. The estimates of thyroidal exposure, particularly that due to the short-lived isotopes of iodine, is only approximate for the reasons already discussed and could have been underestimated. Second, the hypothyroidism from which the risk estimates were derived was based largely on clinical evidence of hypothyroidism, whereas the present study has employed sensitive biochemical techniques not generally used in previous studies. A third consideration is that the early and severe thyroid dysfunction occurred in individuals exposed as very young children whereas the risk estimates are based almost exclusively on data obtained in adults with hyperthyroidism. The radiosensitivity of the young thyroid, at least for neoplastic changes, is greater than that in older patients (193). It is apparent that the true prevalence of hypothyroidism is not definable in this population because of thyroid surgery in many of the patients at highest risk.

From the results in Table 8 one must consider the possibility that an elevation in TSH could have contributed to the development of the early thyroid nodularity. Such a possibility justifies the prophylactic administration of T_4 in the exposed Rongelap and Ailingnae population even in the absence of clinical symptoms or signs of thyroid dysfunction. This conclusion is also supported by the well-recognized relationship between irradiation, elevated TSH, and thyroid carcinoma found in animal studies (142,144) though no such relationship has been reported in man.

The latent period between exposure and development of thyroid nodules appears to be longer in the groups receiving lower thyroid doses (see Figure 3). In view of the small number of cases, however, this possible association is only suggestive. The later development of thyroid hypofunction in those Rongelap people receiving lower doses would seem to be a reasonable expectation because, with less cell damage and with failure of cellular replacement less critical, it would take longer for accumulative cell deficit (loss at mitosis) to result in recognizable hypofunction.

The data of Table 9 are contrary to expectations in several respects. The risk of thyroid cancer is lower in both Rongelap and Utirik in the younger age groups (<10 years at irradiation) than in the older populations. This is quite surprising as most evidence suggests that not only thyroid carcinoma but also leukemia and carcinogenesis generally are more likely induced in children than adults (99). De Lawter and Winship (150), for example, in a long-term follow-up of adults with Graves' disease who were treated with x rays, found no thyroid cancers, whereas at a rate of 3 per 10^6 person-years per rad, some 33 cases would have been expected. The other peculiarity is the high rate of carcinoma in the older groups (risk of 5.5 thyroid cancers/ 10^6 person-years/rad in the Rongelap group). Finally, the induction of myxedema with a thyroid dose of 1150 rads in two children is surely unexpected, as is the overall rate of hypothyroidism of 9% in the total Rongelap group. Since all of the numbers involved are small, the absolute risk figures have a high probable error. Nonetheless, it is possible to explain these data if we assume the estimates

of radiation dose to the thyroid are too low, at least in some of the people, by a factor of 3 or 4. This would account for the high incidence of hypothyroidism. It would also account for a relatively low risk for thyroid cancer in the children, since such a level of radiation would be expected to damage the thyroid so severely that cell death would, in many instances, inhibit cell division that might result in malignant changes (195). Since the dose calculations, derived from counting of a single pooled specimen of urine, require many assumptions, an underestimate is not unlikely.

It is quite likely that the final tally of thyroid abnormalities in the Marshallese is incomplete at this time since new lesions are still becoming clinically evident. The mean latent period for radiation-induced thyroid tumors may be as long as 30 years (196). Recent observations suggesting that as many as 25 years may pass between exposure to radioiodine and the appearance of even minimal biochemical thyroid abnormalities make it clear that long-term follow-up of the Marshallese must continue.

X. RADIOLOGICAL MONITORING OF PERSONNEL AND ENVIRONMENT

Radiological monitoring of personnel and environment of the islands affected by the 1954 fallout accident is reviewed in detail in Appendix II (Dose Assessment) and in the 20-year report (1). The findings will only be briefly summarized here.

A. Background

The medical team assumed responsibility for the personnel monitoring of the Rongelap and Utirik people in 1954 and for that of the Bikini people returning to live on their home island in 1969. In 1978, both environmental and personnel monitoring responsibilities were transferred from the Medical Department to the Safety and Environmental Protection Division of this Laboratory. Numerous radiological surveys for environmental contamination have been carried out on Rongelap, Utirik, Bikini, and Enewetak (210-225). These studies have provided important information on the movements of radionuclides through marine and terrestrial life to man and have aided in the evaluation of the body burdens of radionuclides in the inhabitants of these islands.

B. Methods

Methodology for personnel monitoring has been discussed in detail in previous reports (8,18,22). Personnel monitoring has consisted of regular radiochemical analyses of urine specimens from inhabitants along with whole-body gamma spectrographic analyses for gamma emitters with special shielding arrangements (first a 21-ton steel room and later a "shadow-shield" bed and chair arrangement of lead bricks).

C. Results and Comments

1. Rongelap and Utirik

The radionuclides absorbed at the time of the fallout from consumption of contaminated food and water and inhalation are tabulated for the Rongelap people in Table 2 of Appendix II. Only radioiodines were absorbed to above acceptable levels. The full impact of the thyroid injury resulting from absorption of radionuclides of iodine was not appreciated until much later when development of thyroid nodules and stunting of growth in some of the children occurred. As discussed in Appendix II, the dose calculations for the thyroid have been subject to many uncertainties and can only be considered approximate. The absorption of radionuclides other than iodine has not resulted in any detectable injury, and the doses to the target tissues from these radionuclides are thought to have been quite low though no precise doses have been calculated.

By six months, radiochemical urine analyses revealed barely detectable levels of radionuclides in the Rongelap people. When they returned to their

island in 1957, they accumulated low levels of radionuclides (principally ^{65}Zn , ^{137}Cs , ^{90}Sr , and ^{55}Fe) from marine and plant foods -- primarily pandanus, coconuts, breadfruit, coconut crabs, and fish. (The crabs are a food delicacy, which, because of unexpectedly high levels of absorbed radiocesium and strontium, had to be banned from the diet until recently when the levels became acceptable.) The people were also exposed to low levels of residual gamma radiation over and above the natural background radiation. Figures 1 and 2 of Appendix II show the changes in estimated body burdens of ^{137}Cs , ^{65}Zn , and ^{90}Sr in the Rongelap people. ^{90}Sr reached its highest levels of about 12 nCi in adults and 22 nCi in children between 1962 and 1965 and thereafter showed a downward trend. ^{137}Cs body burdens in adults reached a peak in about 1965 of roughly 0.7 μCi (23% of the permissible level for general populations). The ^{65}Zn level reached a peak of 0.5 μCi during the first year or so after the return, generally below the ^{137}Cs level, and became non-detectable thereafter. From the data in Table 4, Appendix II, the total-body dose for inhabitants living full-time on Rongelap from 1957 to 1979 was estimated to be nearly 4 rads. It should be noted that the actual dose was probably lower because the people spent about half their time away visiting other atolls.

Since 1957, the people who had returned to live on Utirik Island have been included in the personnel monitoring program. The estimates of initial exposure for the Utirik people, particularly for the thyroid gland, were subject to greater uncertainties than those for the Rongelap people. Not the least of these uncertainties was the degree of exposure to short-lived isotopes of iodine in the Utirik population. Available data, however, indicate that exposure of the Utirik people was considerably below that of the Rongelap people, perhaps 1/10 as much. (Radioanalyses of animal, plant, and other samples from Utirik shortly after the accident showed levels about 1/10 of those for samples from Rongelap.) Following their return, the levels of accumulated long-lived radionuclides in the Utirik people, measured at the same time as in the Rongelap people, were only about 1/3 as high. However, since these people returned to live on Utirik in July 1954 (three years before the return of the Rongelap people in 1957), during the first few years they were exposed to somewhat higher levels of radionuclides, particularly ^{65}Zn , than were the Rongelap people on their return. This accounts for the higher body burdens estimated in Appendix II for the Utirik inhabitants during the first few years after their return. The total-body dose for inhabitants living on Utirik full-time from 1954 to 1979 was estimated to be about 17 rads, due mostly to the early contribution of ^{65}Zn . Again, the actual exposure was probably lower because the people were away about half the time visiting other atolls.

Reexamination of dosimetry analyses for the Rongelap and Utirik people, for both initial and residual exposures, is being carried out at this Laboratory. Personnel and environmental monitoring are being continued on a regular basis.

2. Bikini

In 1946, before Operation Crossroads, the residents of Bikini were evacuated. After stays at Rongelap and Kwajalein which proved unsatisfactory, they were relocated on Kili Island in the southern Marshalls, which also

proved unsatisfactory. The Enewetak people were relocated at Ujelang Atoll to the south after their evacuation.

After the 1958 moratorium on atmospheric nuclear testing, numerous radiological surveys were done on Bikini and later on Enewetak Atoll. In 1967, the principal radionuclides contributing to the gamma radiation field on Bikini and its neighboring island of Enue were ^{137}Cs , ^{60}Co , ^{125}Sb , and ^{155}Eu ; slight amounts of plutonium were also found. Considerable variation was seen in the degree of contamination of individual islands comprising the atolls of Bikini and Enewetak.

In 1968, an Ad hoc Committee reviewed the survey results for Bikini and decided that Enue and Bikini Islands were safe for habitation, with certain measures recommended to reduce exposure. In 1969, about 30 people started work on Bikini Atoll (living on Enue), and in 1971 several Bikini families moved back to Bikini Island. The number of people increased to about 145 by 1978 before their relocation. Annual radiological monitoring of personnel was carried out beginning in 1969 as well as numerous radiological surveys of the island (13,218-221,225). Personnel monitoring consisted of annual radiochemical urine bioassays and whole-body gamma spectrographic analyses in 1974 and 1977 by the medical group. Since that time whole-body counting and other personnel monitoring as well as environmental studies have been carried out by the BNL Safety and Environmental Protection Division.

The estimated doses to the Bikini people from the environmental contamination were so low that medical examinations were not indicated. However, on visits to the island, the doctors have held "sick call," and in 1978 the people were given complete physicals by the visiting medical team. Since the relocation of the people in 1979, medical examinations have been done on these Bikini people living on Majuro Atoll. No thyroid or other radiation-related problems were noted. Personnel monitoring has also continued on this population.

When the people returned to Bikini, they received a continuing complete food subsidy from the Trust Territory Government. Before locally grown fruits (coconuts, pandanus, breadfruit, etc.) became available, radioassays showed body burdens well within acceptable ranges. When these fruits became available, radioassays showed radionuclide levels (particularly ^{137}Cs and ^{90}Sr) that were higher than expected, and the people were admonished not to eat the locally grown foods. In spite of this warning, radiochemical urine analyses and whole-body counting of personnel showed a continuing increase in body burdens of these radionuclides to levels that were considered unacceptable. Also, low levels of plutonium were thought to be detected, but this finding has not been verified, and contamination of the samples is thought to have been a factor. Because of these unexpected and unfavorable developments, the people were again removed from Bikini in August 1978.

The results of personnel monitoring of the Bikini inhabitants are presented in Appendix II. From the residence period between 1969 and 1978, exposure data indicate that a maximally exposed person on Bikini received a dose equivalent commitment of 3 rem, and the population average dose equivalent commitment was 1.2 rem (223).

The Bikini inhabitants are now living on atolls in the southern Marshalls and are being monitored at intervals. The results show a continuing reduction in their body burdens.

XI. SUMMARY AND COMMENTS

Until 1954, the Japanese at Hiroshima and Nagasaki were the only human populations exposed to significant radiation from nuclear detonations. As a result of the Bravo accident in 1954, following the detonation of a megaton nuclear device in the Pacific, 250 Marshallese, 28 American servicemen, and 23 Japanese fishermen were exposed to a relatively unknown hazard, radioactive fallout. The medical observations of the exposed Marshallese over the past 27 years have resulted in significant findings reported in numerous publications. Health care and treatment of the exposed people during the course of the surveys and examinations also represent an important contribution. The medical findings provide the only knowledge about the effects of radioactive fallout on human beings from detonation of nuclear devices.

The exposure of the Marshallese to fallout radiation differs in several important respects from the exposure of the Japanese at Hiroshima and Nagasaki. In Japan, there were many casualties from blast and heat effects, and psychological trauma was extreme. The Marshallese, being far removed from the site of detonation, had no effects from blast or burns, and the psychological effects of their experience appeared to be minimal. Radiation effects in the Japanese were due to whole-body exposure to gamma and neutron radiation from the detonating bomb with insignificant fallout. Their exposure resulted in acute effects with high early mortality, and in late effects involving principally the development of malignancies, with leukemia appearing first and solid tumors later. Radiation effects in the Marshallese were related only to fallout exposure: whole-body gamma irradiation (no neutron exposure); skin irradiation from deposition of fallout on the body; and internal exposure due to absorption of radionuclides (principally radioiodines) from ingestion of radioactively contaminated food and water and inhalation of fallout particles.

As emphasized in this report, many uncertainties were involved in calculating the early radiation dose received by the Marshallese prior to their evacuation. This was particularly true for the internal dose calculations (thyroid dosimetry). Estimates of early exposures for whole-body gamma radiation were 175 rads on Rongelap, 69 rads on Ailingnae, and 14 rads on Utirik. Clinical findings (principally hematologic) generally supported these estimates. For Rongelap, thyroid dose estimates varied from 335 rads in adults to 700-1400 to perhaps >2000 rads in young children. For Ailingnae and Utirik Atolls, thyroid dose estimates were roughly parallel to gamma dose estimates.

People living on Rongelap, Utirik, and Bikini since the 1954 accident have been exposed to low doses of radiation, delivered at a slow dose rate, from residual contamination (see Appendix II). No detectable effects of this low exposure have been noted, and it is unlikely that any will be. Periodic personnel and environmental radiological monitoring is carried out on these atolls and on inhabitants who have moved to other atolls.

It now appears that the early thyroid dose calculations may have resulted in underestimation, and all the dosimetry calculations are being reevaluated at this Laboratory on the basis of more recent data that have become available.

The findings in the exposed Marshallese populations are briefly summarized as follows.

A. Early Observations

Whole-body gamma exposure in the Rongelap and to a lesser extent in the Ailingnae people resulted in transient anorexia, nausea, and vomiting. Depression of blood leukocytes and platelets to about half normal levels by 4 to 6 weeks was not accompanied by any detectable increase in infections or bleeding tendency, and there was no associated mortality. The exposed Utirik population had no early gastrointestinal symptoms, and only a slight depression of blood platelets was detectable on a statistical basis. Recovery of blood elements to near normal levels was evident by one year, though a slight continuing lag in complete recovery was noted in the Rongelap people during the first decade.

Fallout deposition on the skin resulted in transient superficial radiation ("beta") burns and spotty epilation of the head in about 90% of the Rongelap people. Skin findings were less prevalent in the Ailingnae people and absent in the Utirik group.

Of the spectrum of radionuclides absorbed internally, only the isotopes of iodine exceeded the maximum permissible concentration and resulted in detectable effects later. No early symptoms due to the internally absorbed nuclides were noted. Radiochemical urine analyses at 6 months showed the presence of barely detectable radioactivity.

B. Late Observations

The general health of the exposed Marshallese people (except for abnormalities associated with thyroid injury) has remained good and about the same as that observed in the unexposed populations examined. Vital statistics suggest that mortality and fertility rates have been about the same in the exposed as in the unexposed people. During the first four years there appeared to be an increase in incidence of 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 did not reveal any detectable abnormalities in the children of exposed parents that might have been related to radiation exposure. Probably related to radiation exposure was the finding of a slight increase in chromosomal aberrations in the lymphocytes of some Rongelap people at 10 years after exposure. No increase in degenerative diseases (cardiovascular, arthritis, neuromuscular) or diabetes has been detected in the exposed people. Ophthalmological examinations (including slit-lamp studies) have not shown any remarkable differences in eye abnormalities between exposed and unexposed groups. No radiogenic cataracts have been noted.

In 1972 a Rongelap male, exposed at one year of age, died of acute myelogenous leukemia, and another Rongelap male died from carcinoma of the stomach. These diseases may have been related to radiation exposure. No other malignancies (except for thyroid carcinoma) have been noted which were likely to be related to radiation exposure. No skin malignancies have been detected.

The most widespread late effect of fallout exposure in the Marshallese has been the development of thyroid abnormalities - benign and malignant neoplasms and hypofunction of the gland. These, as well as growth retardation

associated with thyroid injury in some of the children, have been discussed in detail in this report. The greatest incidence of these abnormalities has been in the higher-dose Rongelap group, particularly in children exposed at <10 years of age, with less incidence in the Ailingnae group and least incidence in the lower-dose Utirik group. The recent development of thyroid nodules in two Rongelap males exposed in utero indicates that radioiodines may be passed from mother to fetus.

Almost all patients, including those in the unexposed group with thyroid nodules, have had thyroid surgery in U.S. hospitals. A wide spectrum of lesions has been found.

Thyroid hypofunction, not related to thyroidectomy, was first noted in two Rongelap boys who developed frank hypothyroidism with growth retardation. Biochemical (subclinical) hypothyroidism has been noted in some prior to thyroid surgery for nodule removal. More recently, about 6 adults (5 Rongelap, 1 Ailingnae), who received lower doses than the children and showed no detectable thyroid nodularity, have developed biochemical hypothyroidism. No hypofunction of the thyroid has been detected in the exposed Utirik population.

C. Comments

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 (249). To ascertain the degree of radioiodine absorption, it would be helpful to have direct instrument readings over the thyroid, with leg or arm readings as a control; also, urine levels of radioiodine would be helpful.

With regard to late effects in persons receiving significant radiation doses to the whole body or thyroid, regular follow-up examinations should be done over the ensuing years with particular attention to hematological status, development of cancer, and thyroid abnormalities. 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. During follow-up thyroid examinations, determination of serum TSH levels would be desirable, since the Marshallese experience has shown this test to be a most sensitive indication of reduced thyroid function. In addition, thyroid uptake studies of radioiodine and scans of the gland should be considered. Any distinct thyroid nodules should be surgically removed. If thyroxin treatment is not already a part of the treatment regimen, it should be instituted in surgical cases as well as any cases showing deficiency of thyroid function. Patients who have had malignant lesions removed should of course have regular follow-up examinations.

Although the later development of thyroid malignancy is a serious problem, the consequences are not as likely to be fatal as those of other types of malignancies. With the medical and surgical treatment of thyroid disease now available, death associated with malignant tumors of the thyroid is unlikely except in the case of the most malignant types, which appear to be rare in irradiated groups.

As has been pointed out, the uncertainty of dose estimates in the Marshallese has hampered evaluation of dose-response relationships,

particularly with regard to the thyroid. More information would be desirable concerning certain aspects of thyroid exposure. More data are needed on the contribution of short-lived iodine radioisotopes, including relative abundance and distribution as a function of time, dose fractionation, etc. Also, the dose-response relationship of these isotopes in the thyroid compared with ^{131}I and gamma radiation needs further investigation; such studies should be done in large animals, perhaps sheep or swine, having thyroid glands comparable in size to human glands.

Since radioelements other than iodine may have been involved in the thyroid exposure of the Marshallese, further information is needed on such elements that might be present in fallout. Certain elements are known to show relatively greater affinity for deposition in the thyroid than in other organs. Radium and thorium (226,227), barium (226), americium (228,229), plutonium (228-230), and calcium (226,231,232) have been found in animal thyroid glands. Robison et al. (231) have shown that calcium is concentrated in the lining of thyroid follicles with small localized areas of calcification in human thyroid glands. Haeberli et al. (232) have reported rapid incorporation of ^{45}Ca in the rat thyroid. In view of the abundance of calcium in the atoll environment, perhaps consideration should be given to the possibility of a neutron-induced calcium isotope that might have been involved in the thyroid exposure of the Marshallese. Autoradiographic and other studies of animal thyroids removed at surgery or autopsy might be helpful in this regard. It should be noted that the elements referred to above are absorbed by the thyroid to a much smaller degree than iodine, and it seems unlikely that they would contribute significantly to the thyroid dose.

Very little is known about the effects of low doses of radioiodine radiation on the thyroid. One source of information comprises thyroid studies on people given diagnostic doses of ^{131}I in the early days, when doses were higher than now used. It is hoped that further information from such studies will be forthcoming so that a better evaluation can be made of low-dose effects and of the relative importance of ^{131}I exposure on the thyroid.

The development of thyroid nodules in two of three Rongelap children exposed in utero emphasizes the probable importance of radioiodine absorption by the fetus from the mother. More precise information regarding fetal iodine uptake at various stages of gestation is needed. ^{129}I , a long-lived isotope with low radioactivity and a high cross section for neutron activation, might be administered to pregnant women in cases where abortion is indicated. Neutron activation of ^{129}I in the thyroid gland removed from the fetus would provide precise information on uptake of iodine by the gland at the given stage of gestation.

In view of the greater relative sensitivity of the child's thyroid, further information on thyroid weights and thyroid function in children of various ages would be helpful.

In conclusion, in view of the possible further development of thyroid abnormalities and other late effects of radiation in the exposed Marshallese people, it is necessary that regular examinations and provision for adequate health care be continued throughout their lifetime.

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Appendix I

INCIDENCE OF THYROID DISEASE IN THE COMPARISON POPULATIONS

In Section IX.A the importance of obtaining an "unexposed" comparison population for evaluation of thyroid findings in the exposed Rongelap and Utirik people was discussed. The purpose of this appendix is to examine the usefulness of the comparison populations used in these studies with regard to possible thyroid effects from residual radiation exposure during their habitation on Rongelap and Utirik Atolls. The expected occurrence of radiation-induced thyroid nodularities and cancer in this population will be calculated by using available risk data on thyroid findings in the exposed Rongelap people and in persons receiving thyroid irradiation from x-ray treatment. The observed thyroid findings in the comparison population will be compared with findings from U.S. statistics.

A. Thyroid Findings in Comparison Populations

Table 1 lists the percents of positive thyroid findings in exposed and comparison populations, and Table 2 the individual cases within the comparison populations with length of stay on the home island. These latter data are incomplete and uncertain in many cases, but tend to show that an average estimated stay of one-half time (10 to 12 yrs) on their island is not unreasonable. Some people with thyroid nodules have never lived on their home island since 1954.

B. Expected Cases of Thyroid Nodules in Comparison Populations Based on Estimated Radiation Exposure Levels

In Appendix II data are presented indicating that if people lived continuously to 1979 on Rongelap since their return in 1957, and on Utirik since July 1954, they might have received an average thyroid dose of about 4.5 rem on Rongelap and 16 rem on Utirik.* However, a more realistic dose is thought to be roughly half of these values (2.25 rem for Rongelap and 8 rem for Utirik), mainly because of absences from the home island on visits to other atolls. On the average the children probably received about half the adult thyroid exposure because their lower ages result in shorter residence time. In the case of the Utirik people, food subsidization during the first few years, when ^{65}Zn was by far the greatest contributor to the internal dose, reduced the dependence on fish, which was the major source of that radionuclide. Also, many of the unexposed Utirik people probably did not return until later, when the ^{65}Zn contribution was less. Since risk data for radiation effects to be used below are necessarily derived from acute exposures, the contributions

*Since radioiodines had virtually decayed by the time the people moved back to Rongelap and Utirik, this exposure was due almost entirely to other radionuclides.

Table 1. Percent of persons in Marshallese populations having thyroid nodules (1979).

Group	Age <18 in 1954*			Age >18 in 1954		
	No.	% with nodules	% with carcinoma	No.	% with nodules	% with carcinoma
<u>Exposed in 1954</u>						
Rongelap**	42	52.4	4.8	44	15.9	4.5
Utirik	85	9.4	2.4	79	11.4	1.3
<u>Comparison populations</u>						
Rongelap	553	0.7	0.2	115	11.3	0.9
Utirik	435	1.4	0.2	38	7.9	2.6 (1 case)
Wotje	103	3.9	1.0	59	6.8	0.0
Likiep	102	1.0	0.0	90	4.4	0.0
ALL	1193	1.2	0.25	292	8.2	0.7

*The comparison populations include children not yet born in 1954. Unexposed prevalence not subtracted from exposed estimates.

**Includes 19 people exposed on Ailingnae.

from natural radiation might have been subtracted from the above estimates. Exposure to natural radiation during the years the people were away from their home island was not added to the above doses since comparisons are to be made with unexposed population statistics, in which such exposure is inherent.

Table 3 shows the expected percentage of persons with thyroid nodules and cancer due to exposure to residual radiation on Rongelap and Utirik. Estimates are calculated for the highest exposure doses assuming continuous habitation on the islands (half-time habitation for children). The table shows that the percentage of people with thyroid nodules and cancer would not be detectable in a population this size and would be far below the spontaneous incidence. The data presented are probably overestimates in view of the factors discussed above.

Table 2. Length of stay on home island of unexposed Marshallese developing thyroid nodules at age >12 (S=surgery).

Group (No. in group)			
Pt. No.	Sex	Age (1979)	Length of stay on island (yr)
<u>Rongelap (668)</u>			
1573	M	29	0
829	F	40	3
938	F	40	3
841	F	46	11
858	F	80(?)	11 (died 1973)
867	F	51	3
858	F	(?)	13 (?)
4023	F	45	2
910	M	49	6
1007	M	68	12
1575	F	73	0
4014	F	62	0
1554	F	60	?
980	F	28	5
1524	M	38	4
4009	M	35	13
882	M	48	24 (?)
<u>Utirik (473)</u>			
3074	F	26	5
3015	F	41	2 (?)
3006	M	78	1 (?)
3042	F	51	14
3058	F	52	13
2279	M	23	15 (?)
3565	F	24	?
3555	F	23	?
<u>Wotje (162)</u>			
5061	F	26	MT [†]
	F	26	MT
5027	M	33	MT
5030	M	36	MT
5059	F	53	MT
5074	F	68	MT
3096	F	55	MT
5053	F	68	MT
<u>Likiep (173 in 1970)</u>			
	M	61	MT
	M	85(?)	MT
	F	73	MT
	M	91(?)	MT
	F	65	1954-1970
3023	F	23	?

[†]MT = Probably most of the time.

*A small focus of "occult" cancer reported by a minority of pathologists. Such occult lesions are not infrequently found at autopsy and are generally considered to be of little clinical significance.

Table 3. Expected percent of persons with thyroid nodules in comparison populations based on estimated doses.

Group	Est. dose (rem)	% Nodules (cases/no.)		% Carcinoma (cases/no.)	
		Rong. risk (total) ¹	X-ray risk (benign) ²	Rong. risk (total) ¹	X-ray risk (benign) ²
<u>Children³</u>					
Rongelap	2.25	0.1% (0.2/553)	0.07% (0.4/557)	<0.01% (0.04/557)	0.02 (0.1/557)
Utirik	8.0	0.6% (2.7/435)	0.2% (1.1/435)	0.03 (0.15/435)	0.01 (0.4/435)
<u>Adults³</u>					
Rongelap	4.5	0.2% (0.01/115)		0.06 (0.07/115)	
Utirik	16.0	0.5% (0.2/38)		0.2% (0.08/38)	

¹Using risk data for exposed Rongelap and Ailingnae people (25 years), cases per million per rad per year: children (exposed at age <10), total 31, cancer 1.7; adults (exposed at age >10), total 14.6, cancer 5.6.

²Using Maxon's (163) estimates of absolute risk (cases per million per rad per year), 12.3 for benign nodules and 4.2 for cancer, based on combined data of Coleman et al. (233), Hemplemann (162), Modan (166), and Albert (200) on children treated with x-irradiation. Recently Maxon, on the basis of later data, has revised his risk estimate for thyroid cancer downward to 1.5 cases/10⁶ persons/rad/yr (164). Use of this value would lower the expected risk in the populations listed in this table. Also, preliminary results of reassessment of thyroid doses indicate a possible increase in estimated dose which could lower the Rongelap risk factors.

³Children: age <10 in 1954; adults: age >10 in 1954. Children were considered to have lived 11 yr on Rongelap or 13 yr on Utirik and to have received half the total dose. Adults were considered to have lived 22 yr on Rongelap and 25 yr on Utirik, and their total estimated doses are listed.

C. Comparison of Thyroid Findings in Marshallese Comparison Populations With Those in Other Unexposed Populations

A number of statistical reports have been published on thyroid neoplasia in populations not exposed to radiation (see Fig. 1). These statistics show considerable variation, and some populations appear to be more prone to development of thyroid cancer.

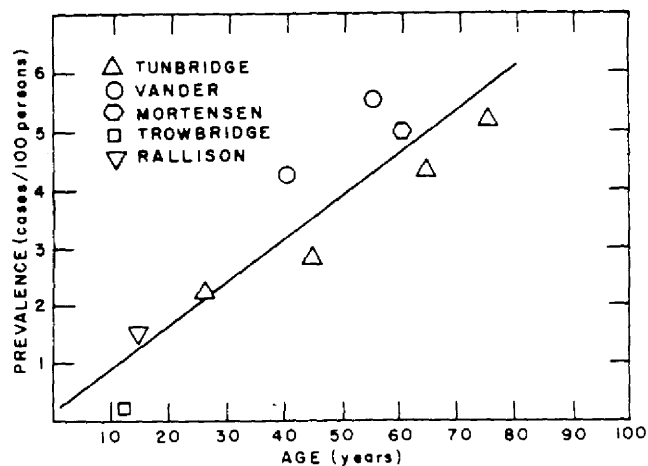


Fig. 1. Prevalence of spontaneous thyroid nodules. From Maxon et al. (164).

The data in Table 4, taken from a Nuclear Regulatory Commission Report (234), summarize the estimated occurrence of thyroid neoplasms in the general U.S. population compared with data on the Marshallese comparison population. In the Marshallese comparison population, as in other unexposed populations, the preponderance of thyroid nodules is in the older age group, whereas in the exposed Rongelap people the reverse is true. This appears to be the case in other exposed populations also.* About 1300 children living in Utah were exposed to fallout from the Nevada tests in the 1950s (181), receiving doses estimated to be considerably higher than those to the Marshallese control populations, and they had no detectable increase in thyroid abnormalities compared with the unexposed populations in Arizona.

Table 4. Prevalence of thyroid nodules and cancer in unexposed Marshallese and U.S. populations.

Age group	Prevalence of nodularity (%)		Prevalence of cancer (%)	
	U.S.	Marshallese	U.S.	Marshallese
0-19	0.8	2.6	0.08	0.9
20-39	2.6	7.9	0.31	0.7
40-59	4.3		0.52	
60-80	6.1		0.73	

*The slightly higher prevalence of nodules and carcinoma may be related to the more rigorous examinations given that group compared with reported surveys of other world populations.

Appendix II

DOSE ASSESSMENT*

A. Early Radiation**

1. Source

The ionizing radiation exposure of the Marshallese was due entirely to fallout, since the detonation site was too far away for thermal, blast, or direct irradiation effects. (In contrast, direct effects were responsible for all the injuries from the atomic bombs in Hiroshima and Nagasaki, with little or no fallout.) The fireball from the 1954 Bravo device, detonated from a tower, touched the surface of the earth at Bikini, and large amounts of material were drawn up and mixed with fission products in the bomb cloud. Because of an unpredicted shift in the winds in the upper atmosphere, fallout was deposited in a cigar-shaped area 20 to 40 miles wide extending \sim 200 miles to the east of Bikini (see Figure 1 in the text). The radioactivity was due to fission products and some neutron-induced radionuclides; little fissile material was noted. The radiation was therefore almost entirely from gamma and beta rays of varying energy from numerous neutron-rich radionuclides. The time after detonation when fallout began was estimated as 4 to 6 hr at Rongelap, \sim 7 hr at Rongerik, and 22 hr at Utirik, and the fallout duration as 12 hr, with most of the dose delivered early in that period. Table 1 shows fallout exposure data on the atolls.

Table 1. Estimated gamma exposure (measurements in air).

Atoll	No.* people	Approx. time fallout began	Time of evacuation	Instrument readings (mR/hr)	Est. γ exposure (R)
Rongelap	64	H+4 to 6 hr	H+50 hr (16 people) H+51 hr (48 people)	375, H+7 days	175
Ailingnae	18	H+4 to 6 hr	H+58 hr	100, H+9 days	69
Rongerik	28	H+6.8 hr	H+28.5 hr (8 men) H+34 hr (20 men)	280, H+9 days	78
Utirik	157	H+22 hr	Started at H+55 hr	40, H+8 days	14

*Does not include people exposed in utero.

*Dr. S.H. Cohn (Medical Department, BNL) and Messrs. E.T. Lessard, N.A. Greenhouse, and R.P. Miltenberger and Dr. J. Naidu (Safety and Environmental Protection Division, BNL) assisted with this Appendix.

**A reevaluation of the early whole-body and internal organ doses is in progress at Brookhaven National Laboratory. Incomplete results give some indication that the previously estimated thyroid doses may be too low. Since the results are preliminary, they are not included in this report.

In conclusion, on the basis of the similarity of findings in the Marshallese comparison populations and in other world populations, there is no apparent reason to suspect that there is anything unusual, including excessive radiation, in the environments of these atolls--compared with other environments--which might promote carcinogenesis; hence this population appears suitable for comparative purposes for detection of radiation effects in the exposed Rongelap and Utirik subjects.

If further studies suggest that there is an increase in benign and malignant neoplasms on some of the other atolls which may have received low exposures, then causes other than radiation should be sought, not only in that population but in Marshallese populations in general.

2. Gamma (Whole-Body) Dose

The fallout (where seen) resembled snow or mist and was deposited relatively homogeneously so that the individuals on each island were considered to have received about the same estimated dose of gamma radiation. The children may have had a somewhat higher dose than that calculated for the adults because, being smaller, their bodies offered less self-shielding. This possibility is supported by the higher incidence of early nausea and vomiting and the greater depression of blood elements in the young children. The flimsy houses afforded little attenuation of the radiation. The whole-body doses were calculated from measurements with radiation field survey instruments held 3 ft above the ground, made about a week after the detonation, by extrapolation to the time of exposure with the energy spectrum and decay taken into consideration. Table 1 shows the calculated gamma doses for the different populations exposed. In view of the 2π geometry of exposure, the midline doses to individuals were higher than those obtained with the usual bilateral exposure of x-radiation. More detailed treatment of the acute exposure estimates may be found in ref. 2.

3. Skin Dose

The dose to the skin surface was much greater than the whole-body gamma dose because of the large amount of particulate radiation absorbed by the skin. The actual skin doses, although impossible to calculate, probably amounted to more than 1000 rads, and their range of values, due to different amounts of fallout sticking to different areas, accounted for the spotty nature and varying intensity of lesions. The extensiveness of the beta burns in each island group correlated roughly with the amount of fallout visible on their island. Most of the skin dose was due to fallout deposited directly on the skin, but some was due to beta radiation from fallout on the ground (estimated at Rongelap to be 2000 rads at the level of the dorsum of the feet, on the basis of continuous exposure and no shielding). It was fortunate that the beta radiation had an average energy insufficient to penetrate deeply into the skin and therefore resulted for the most part in superficial damage burns. The average beta particle probably did not penetrate much beyond the basal layer of the skin ($\sqrt{100}$ μm). However, since epilation occurred in many people, the region of the hair follicles must have received an absorbed dose at least equal to the minimal epilating dose of 400 rads of 200-kVp x rays.

4. Internal Doses

Internal absorption of radionuclides was due to inhalation as the radioactive cloud passed over and to ingestion of food and water contaminated with fallout, water probably being a major source. Drinking water is obtained by collecting rainfall from the roofs into catchments, and a slight rain was reported on Rongelap the night of the fallout. Since the cisterns were almost empty, the dilution effect was minimal. Water was being rationed at that time, and it was drunk in spite of warnings from the health aide. On Rongerik food and water were better protected from fallout deposition.

Internal levels of radionuclides absorbed from the fallout were assessed by numerous radiochemical analyses of urine samples, beginning 15 days post

exposure, for ^{89}Sr , ^{140}Ba , ^{131}I , the rare earth group, and fissile material. As expected, the Rongelap people had the highest body burdens. By 6 months, beta activity in the urine samples was barely detectable. Table 2 shows the main isotopes found at day 1 (extrapolated values) and at day 82. The agreement between the findings at the two laboratories is close considering the techniques available at that time. Levels in the Ailingnae group were about one-half and in the Americans about one-quarter the levels in the Rongelap group. Only isotopes of iodine, strontium, barium, and a few rare earth elements were detected in any significant degree. In the Rongelap group, at day 1, ^{89}Sr and ^{131}I were near the maximum permissible levels, and the estimated total amount of radioactive material in the gastrointestinal tract was about 3 mCi; whether this had any relation to the early gastrointestinal symptoms is not known.

Table 2. Estimated body burden (μCi) of Rongelap people.

	Activity* at day 1	Activity** at day 82	Max. perm. total body burden
^{89}Sr	1.6 - 2.2	0.19	40
^{140}Ba	0.34- 2.7	0.021	9
Rare earth group	0 - 1.2	0.03	
^{131}I (in thyroid gland)	6.4 -11.2		0.7
^{103}Ru	0 - 0.013	-	50
^{45}Ca	0 - 0.019	0.0	200
Fissile material	0 - 0.016 (μg)	0.0	0.4

*From U.S. Naval Radiological Defense Laboratory.

**From Los Alamos Scientific Laboratory.

The total whole-body or bone-marrow dose from the absorbed nuclides was not calculated because of the variety and varied energies of these radiations. However, the dose is thought to have been quite small compared with the whole-body gamma dose.

5. Thyroid Doses*

The fallout produced several possible sources of radiation exposure to the thyroid gland. The gamma radiation resulted in thyroid doses of 175 rads in the Rongelap people, 69 rads in the Ailingnae people, and 14 rads in the Utirik group. Iodine isotopes are produced in relatively high yields by the

*See second footnote at beginning of this Appendix.

fission process. Some are too short-lived to be of consequence, but ^{131}I , ^{132}I , ^{133}I , and ^{135}I are sufficiently long-lived to cause a considerable dose to the thyroid following internal absorption and concentration in that gland, and these were absorbed both via inhalation and via ingestion in food and water (see App. 2 of ref. 12). Other internally absorbed isotopes (see Table 2) were not thought to be significantly absorbed by the thyroid and probably contributed little to the dose to that gland. Conversely, the radioiodines contributed only slightly to the whole-body radiation dose.

During the early period after the fallout, radioiodine was recognized as possibly the most hazardous constituent, but the estimated dose to the gland of 100 to 150 rads was not considered sufficient to cause later development of thyroid abnormalities. No acute effects were noted in any of the people that could be related to the internal absorption of radioiodines or other radionuclides. Contamination of the skin resulting in extensive beta burns in the neck region in 70% of the people probably did not contribute to the thyroid dose because of the low energy of the beta radiation. Possibly slight absorption of radioiodines through the skin occurred.

When the people returned to Rongelap and Utirik to live, no radioactive isotopes of iodine remained (except possibly very slight amounts of ^{129}I), and the principal remaining nuclides (^{137}Cs , ^{90}Sr , ^{65}Zn , ^{60}Co , ^{55}Fe), which were absorbed to low levels in the people, probably contributed only low doses to the thyroid. (See Section B, below.)

When thyroid lesions began developing in the Rongelap children in 1963, the dose to the thyroid of the Rongelap people was reevaluated by James (19). His estimates of the gamma dose agreed approximately with the previous estimate of 175 rads. Calculation of the dosage from radioiodines unfortunately had to be based on a single, pooled urine sample from Rongelap people collected 15 days post exposure. Harris at Los Alamos had reported a low level of ^{131}I in this sample and had calculated a one-day thyroid content of 11.2 μCi based on the assumption of 0.1% urinary excretion of the maximum thyroid burden on the 15th day (235).

James (19) calculated doses for absorption from both inhalation and ingestion. He noted that 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 isotopes in producing thyroid effects in the Marshallese is referred to in Section IX of the text. The dose to the thyroid of a Rongelap adult (including gamma) was calculated as about 335 rads (220 to 450 rads) and to that of a 3-yr-old Rongelap child as 700 to 1400 rads. (The spread is due to uncertainties in estimating dose from absorption of radioiodines by inhalation versus ingestion.) It should be noted that the thyroid glands of 1-yr-old children are only about two-thirds the size of those of 3-yr-olds and therefore might have received 2000 rads or more.

With the assumption that the ratio of whole-body gamma doses to thyroid doses was about the same for people exposed on Ailingnae and Utirik as for the Rongelap people, James' calculations were used to estimate thyroid doses in the Ailingnae and Utirik groups; the results were 135 rads for the Ailingnae adults and 31 rads for the Utirik adults. The children's thyroid doses were based on the weight of the gland at various ages (247). By using a linear relationship between the thyroid size and the dose calculated by James, the doses to individual children were taken from regression lines drawn for the three exposed populations; these are given in Table 3. In retrospect, the

Table 3. Estimated whole-body (gamma) and thyroid doses (rad).

Population	No.	Whole-body dose	Thyroid dose (incl. gamma), at exposure age:		
			<10	10-18	>18
Rongelap	65	175	810-1800	335-810	335
Ailingnae	18	69	275-450	190	135
Utirik	158	14	60-95	30-60	30

estimated average dose of 1000 rads to the thyroids of young children appears to be low; certainly for two boys who developed thyroid atrophy and myxedema. The calculated doses are obviously rough estimates. The incompatibility of these observed effects with the calculated doses based on ^{131}I must be related partly to the short-lived iodine isotopes (see refs. 188-192). However, the option must be kept open that the actual doses were higher than those estimated and that possibly other radionuclides may have been absorbed by the bones and contributed to the dose.

B. Residual Radiation (Accumulated Exposure From Habitation on Rongelap or Utirik Atoll)

1. Early Calculations

The subject will be only briefly reviewed here. More detailed treatment for earlier estimates can be found in the refs. 1, 13, 18, and 22.

When the Rongelap and Utirik people returned to live on their home islands, these atolls, although considered radiologically safe for habitation, still had low levels of residual radiation. Before the Utirik people returned in July 1954 and the Rongelap people in July 1957, they had largely excreted the radionuclides initially absorbed at the time of the fallout. By six months, radiochemical analyses of urines of the Rongelap population revealed barely detectable radioactivity (see Table 2).

A number of radiological surveys on Rongelap and Utirik following the accident showed low levels of residual gamma radiation and small amounts of radionuclides in the soil, water, and plant, animal and marine life. The principal isotopes were ^{137}Cs , ^{90}Sr , ^{65}Zn , and ^{55}Fe , though very low levels of several other isotopes were found. When the people returned, personnel monitoring procedures showed low body burdens of these isotopes absorbed from the environment. (The short-lived isotopes of iodine had long since died out.) The major contributing food plants were pandanus and coconut. The coconut crab, a food delicacy, had to be banned from the diet for >15 years because of unacceptable levels of radioactivity. Measurable levels of ^{55}Fe were found in the blood of Rongelap people (1,236), but since they were <1/100 of the maximum permissible body burden, this was not considered a significant hazard.

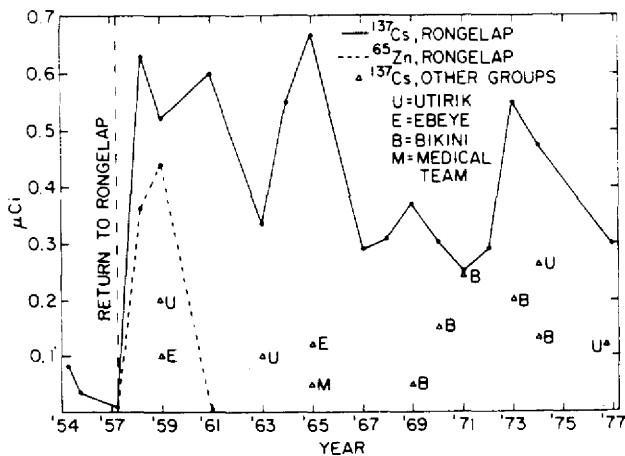


Fig. 1. Body burdens of gamma emitters.

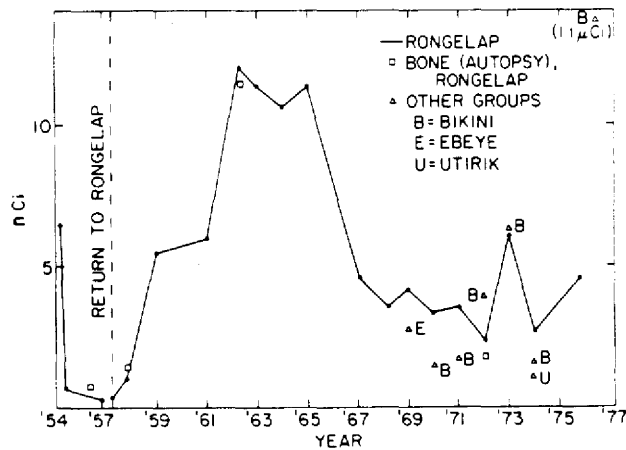


Fig. 2. Body burdens of ^{90}Sr .

The body burdens of radionuclides tended to reach equilibrium with the environment in several years and then gradually to become lower. Figures 1 and 2 show estimated body burdens of gamma emitters and ^{90}Sr over the years.

^{90}Sr body burdens reached their highest level during 1962 to 1965 at about 12 nCi in adults and 22 nCi in children, about 6 and 11% respectively of the maximum permissible lifetime body burden levels for the population at large; i.e., 1/10 the ICRP value. Analyses of bone samples from several autopsies during the past 20 years gave estimated ^{90}Sr body burdens similar to those obtained from urinalysis (see Figure 2). ^{137}Cs body burdens also reached their peak in about 1965, at nearly 0.7 μCi (23% of the permissible level for the general population). The body burdens of the Utirik people were considerably below those of the Rongelapese.

2. Reevaluation

This section, by E. Lessard and N. Greenhouse, summarizes their reevaluation of the doses accumulated to 1979 from residual radiation exposure by populations living on Rongelap and Utirik Islands since 1954.

A dosimetric summary for the Rongelap and Utirik adult populations is given in Table 4. This information was obtained by methods outlined in BNL 51257, A Reconstruction of Chronic Dose Equivalents for Rongelap and Utirik Residents - 1954 to 1980. Briefly, a multicompartiment model for declining continuous uptake was developed, based on the results of historic and contemporary urine bioassay and whole-body counting data. Daily activity ingestion rates were extracted from the model and input quantities and used in conjunction with current metabolic models for internal dosimetry.

Tables 5 and 6 illustrate adult mean values for the body burdens on Rongelap and Utirik, respectively. These body burden histories are the result of direct body burden measurements or indirect body burden estimates based on urine bioassay measurements. Derived body burdens were calculated for Utirik during appropriate years when measured data were lacking. A mean ratio of 2.55 to 1.0 was observed in the Rongelap to Utirik body burdens for ^{65}Zn ,

Table 4. Cumulative (1979) dose equivalent summary (rem) for adults (classified as persons ≥ 16 years of age upon return to Utirik in June 1954 or to Rongelap in June 1957 and having a mean body mass ≥ 60 kg).

Nuclide	Utirik	Rongelap	Utirik	Rongelap
	<u>Total-body</u>		<u>Thyroid</u>	
^{90}Sr	0.0118	0.0267	0.000749	0.00169
^{55}Fe	0.0329	0.0230	0.0594	0.0415
^{137}Cs	1.13	1.71	1.55	2.35
^{60}Co	0.507	0.0143	0.359	0.0101
^{65}Zn	12.5	0.0757	11.1	0.0672
Total internal	14.2	1.85	13.1	2.47
Net external*	3.19	2.02	3.19	2.02
Total	17.4	3.87	16.3	4.49
	<u>Red marrow</u>		<u>Testes-ovaries</u>	
^{90}Sr	0.0537	0.123	0.000749-0.000749	0.00169-0.0016
^{55}Fe	0.0603	0.0422	0.0583-0.0620	0.0736-0.0433
^{137}Cs	1.70	2.57	1.54-1.74	2.33-2.63
^{60}Co	0.629	0.0177	0.442-1.78	0.0125-0.0520
^{65}Zn	17.2	0.103	11.3-16.3	0.0685-0.0988
Total internal	19.6	2.86	13.3-19.9	2.49-2.82
Net external*	3.19	2.02	3.19	2.02
Total	22.8	4.88	16.5-23.1	4.51-4.84
	<u>Lower large intestine wall</u>		<u>Liver</u>	
^{90}Sr	0.225	0.567	0.000671	0.00152
^{55}Fe	0.0666	0.0465	0.115	0.0804
^{137}Cs	0.591	0.895	1.81	2.74
^{60}Co	4.66	0.132	0.792	0.0223
^{65}Zn	15.0	0.0910	16.5	0.136
Total internal	20.5	1.73	19.2	2.98
Net external*	3.19	2.02	3.19	2.02
Total	23.7	3.75	22.4	5.00

*A value of 0.73 rads in tissue of interest per roentgen measured in air at one meter above the surface was used to convert exposure in air to dose equivalent. The source was assumed to be exponential distribution of ^{137}Cs activity with depth in soil, typical of aged fallout (B.G. Bennett, Health Physics 19:757-67, 1970). Because of the multidirectional nature of the source, variation of dose with depth of organ is minimal. External doses are adjusted for lifestyle variations (e.g., standing, sitting, fishing, etc.).

Table 5. Rongelap adult body burdens, 1979 (NA = not analyzed).

	Males		Females		All adults		Days post return
	Body burden (μCi)	Number of persons	Body burden (μCi)	Number of persons	Body burden (μCi)	Number of persons	
^{60}Co	2.9×10^{-5}	NA	1.7×10^{-5}	NA	2.3×10^{-5}	NA	1
	1.0×10^{-2}	37	7.8×10^{-3}	37	9.0×10^{-3}	74	1370
	2.5×10^{-3}	45	2.0×10^{-3}	45	2.2×10^{-3}	90	2831
^{65}Zn	4.3×10^{-2}	NA	3.8×10^{-2}	NA	4.1×10^{-2}	NA	1
	4.3×10^{-1}	30	3.8×10^{-1}	12	4.1×10^{-1}	42	304
	6.2×10^{-1}	32	5.0×10^{-1}	27	5.6×10^{-1}	59	638
	9.5×10^{-2}	38	8.5×10^{-2}	23	9.0×10^{-2}	61	1370
^{55}Fe	4.3×10^{-1}	28	4.0×10^{-1}	32	4.1×10^{-1}	60	4626
^{90}Sr	1.9×10^{-4}	NA	1.4×10^{-4}	NA	1.7×10^{-4}	NA	1
	3.7×10^{-3}	11	2.8×10^{-3}	4	3.4×10^{-3}	15	304
	5.7×10^{-3}	24	3.5×10^{-3}	16	4.8×10^{-3}	40	639
	3.7×10^{-3}	9	1.6×10^{-3}	4	3.0×10^{-3}	13	1370
	8.8×10^{-3}	12	7.9×10^{-3}	13	8.4×10^{-3}	25	2100
	7.9×10^{-3}	11	7.4×10^{-3}	7	7.7×10^{-3}	18	2466
	2.8×10^{-3}	12	4.6×10^{-3}	12	3.7×10^{-3}	24	3561
	3.9×10^{-3}	11	3.1×10^{-3}	11	3.5×10^{-3}	22	3927
	4.1×10^{-3}	11	3.3×10^{-3}	13	3.6×10^{-3}	24	4292
	1.3×10^{-3}	8	3.3×10^{-3}	11	2.5×10^{-3}	19	4657
	3.1×10^{-3}	8	2.8×10^{-3}	7	3.0×10^{-3}	15	5022
	2.0×10^{-3}	5	1.4×10^{-3}	7	1.6×10^{-3}	12	5388
	6.6×10^{-3}	4	4.2×10^{-3}	7	4.3×10^{-3}	13	5753
	3.3×10^{-3}	10	1.7×10^{-3}	4	2.8×10^{-3}	14	6118
	4.4×10^{-3}	23	NA	0	NA	NA	7579
	6.3×10^{-4}	24	4.6×10^{-4}	19	5.5×10^{-4}	43	8097
^{137}Cs	1.4×10^{-2}	NA	8.4×10^{-3}	NA	1.1×10^{-2}	NA	1
	8.7×10^{-1}	NA	5.2×10^{-1}	NA	6.8×10^{-1}	NA	304
	7.9×10^{-1}	47	4.1×10^{-1}	49	5.7×10^{-1}	96	639
	9.5×10^{-1}	37	4.7×10^{-1}	37	6.7×10^{-1}	74	1370
	9.4×10^{-1}	44	4.9×10^{-1}	45	6.8×10^{-1}	89	2831
	4.8×10^{-1}	22	3.0×10^{-1}	24	3.9×10^{-1}	46	6118
	3.0×10^{-1}	30	1.9×10^{-1}	21	2.5×10^{-1}	51	7213
	1.8×10^{-1}	19	1.7×10^{-1}	18	1.7×10^{-1}	37	8097

Table 6. Utirik adult body burdens, 1979 (D = ratio-derived; NA = not analyzed).

	Males		Females		All adults			
	Body burden (μCi)	Number of persons	Body burden (μCi)	Number of persons	Body burden (μCi)	Number of persons	Days post return	
^{60}Co	D	4.0×10^{-3}			3.5×10^{-3}		2464	
	D	9.7×10^{-4}			8.7×10^{-4}		3924	
^{65}Zn		3.5×10^{-1} *		-				
		2.7×10^{-1}	2					
	D	3.7×10^{-2}	14	1.6×10^{-1}	15	2.1×10^{-1}	29	1734
							2464	
^{55}Fe	D	1.7×10^{-1}		1.6×10^{-1}		1.6×10^{-1}	6114	
^{90}Sr		1.4×10^{-3}	5	2.4×10^{-3}	2	1.7×10^{-3}	7	1734
		1.2×10^{-3}	5	1.3×10^{-3}	6	1.3×10^{-3}	11	7213
		NA	12	NA	12	NA	24	8669
		1.5×10^{-4}	14	1.5×10^{-4}	17	1.5×10^{-4}	31	9225
^{137}Cs		4.1×10^{-1}	NA	2.7×10^{-1}	NA	3.3×10^{-1}	NA	1004
		2.9×10^{-1}	15	2.0×10^{-1}	15	2.5×10^{-1}	30	1734
		2.6×10^{-1}	9	1.3×10^{-1}	13	1.8×10^{-1}	22	7213
		1.2×10^{-1}	27	7.8×10^{-2}	21	1.0×10^{-1}	48	8309
		6.2×10^{-2}	19	4.3×10^{-2}	17	5.3×10^{-2}	36	9225

*Measured at Argonne, not used in dosimetry.

^{90}Sr , and ^{137}Cs . The standard deviation on this ratio is 15%. These ratios were determined only when the body burden for the nuclide of interest had reached a maximum. Thus a significant time passed on Rongelap, 2 to 3 years post return, before a body burden comparison was valid.

It was observed, in all cases, that the population mean body burdens were lower by a factor of 3 than the highest for any individual in the population. The population mean dose equivalent and maximum dose equivalent likewise differed by a factor of 3. The population average daily activity ingestion rate and maximum value differed by a factor of 4. For the nuclides ^{137}Cs and ^{65}Zn , a substantial sub-group in the population, children and infants, received a dose equivalent higher than the population mean value.

From the above data of Lessard and Greenhouse the highest estimated average accumulated dose equivalents to the thyroid glands, including that from background, due to residual radiation exposure (from both external and internal sources) for individuals living full time on Utirik since 1954 and on Rongelap since 1957 were, respectively, 16.3 rem and 4.49 rem. The dose equivalents from ^{65}Zn calculated for the Utirik people (acquired largely in the first year or two) were probably considerably higher than those actually received because these people subsisted to a great extent on food subsidies during the first few years after the accident. Also, the unexposed people returning to live on Utirik probably received lower doses than calculated because they generally arrived on the island at a later date than did the exposed people. It should be pointed out that the Marshallese visit other atolls for varying periods of time, and this would tend to reduce their exposure. Questioning of the inhabitants brought out that they may spend as much as half their time away from their home atoll.

Even though personnel monitoring at Rongelap and Utirik included some people who may have returned recently and would therefore have had somewhat lower body burdens of radionuclides at that time, this factor is not considered to reduce the average dose equivalent estimates of the resident population greatly because the majority of the people tested had been living on the island for several years or more. However, in view of the estimate of half-time habitation on the home islands, it does not seem unreasonable to assume that the total average dose to the population from residual radiation might be about half of what it would have been with full-time residence. It was not considered necessary to add the exposure from natural radiation acquired while away on other atolls since the Marshallese populations are to be compared with unexposed populations in whom such exposure is inherent.*

Since most of the data on radiation effects in human beings are based on acute exposures, with uncertainty regarding the degree of reduced effectiveness of low-dose chronic radiation exposure, no attempt has been made at this time to add the early and residual dose equivalents in the exposed Marshallese.

C. Bikini Dose Estimates

Greenhouse et al. (223) have calculated the total dose equivalent to the Bikini inhabitants from both external and internal sources, and these data are summarized in Table 7. They state that "...for residence periods between the years 1969 and 1978 these figures evince a maximally exposed person receiving a whole-body dose equivalent and commitment of 3 rem, and a population average dose and commitment of 1.2 rem from man-made radioactivity on Bikini Island." The levels were so low that quantification was difficult. The levels did not appear to be much higher than noted in other world populations.

*For purposes of comparison, the estimated whole-body doses are not very different from those received by the average U.S. citizen (5 rem in 25 yr) or by an inhabitant of Denver (some 7 rem in 25 yr). People living on the monozite ponds of South America or India probably receive even greater doses than the Marshallese.

Table 7. Total-body dosimetric average for external plus internal sources for former Bikini residents.

Population description	Number of persons	Mean residence interval (yr)	Dose equivalent during residence interval (mrem)	Dose equivalent commitment (mrem)
Adult males	17	4.9	1100	110
Adult females	16	4.3	830	85
Children (age 5-14)	12	4.4	1200	140

D. Other Atolls

The possible dose equivalents to people on some other atolls in the northern Marshalls such as Likiep and Wotje would no doubt be considerably below those to people living on Rongelap and Utirik, and the relative exposure to the potent short-lived iodine isotopes would probably be considerably less. The lower contamination of the islands in the southern rim of each test atoll (Bikini and Enewetak) compared with that in the northern areas of the atoll indicates that the southern thrust of the fallout was much less than the easterly and northeasterly thrust.

E. Reliability of Early Exposure Estimates

The absorbed dose estimates to the exposed Marshallese are approximate, and the uncertainties in many of the parameters involved in obtaining them make it impossible to state their statistical reliability.

1. Whole-Body Doses (Gamma Radiation)

Since the radiometric readings on each inhabited island were relatively uniform, the gamma doses received by the individuals on a particular island are not thought to have varied greatly. However, the children, being smaller, may have received somewhat higher doses than the adults. Judging by the clinical findings in the exposed people, the dose estimates did not appear to be far out of line with what one might expect on the basis of human and animal exposure data. The early gastrointestinal symptoms implied significant exposure in the Rongelap people. The reduced symptoms in the populations on Ailingnae and Rongerik and their absence in the Utirik group were in conformity with the lower doses received by these populations. The degree of hematological depression (and the lack of clinical evidence of such depression, without lethality) is commensurate with the dose estimates in the Rongelap population. The lesser hematological depression in the Ailingnae and Rongerik groups and its absence (except for the slight decrease in platelets detectable only on a

population basis) in the Utirik group were in accord with the estimated lower doses of radiation in these groups.

2. Skin Doses

The skin exposure may have been several hundred to a few thousand rads. Symptoms of itching and burning of the skin were widespread in the Rongelap group. The lesser skin symptoms in the Ailingnae and Rongerik groups and their absence in the Utirik group were in conformity with the reduced fallout exposure of these atolls. Also, the reduced number of "beta" burns and epilation in the Ailingnae and Rongerik groups than in the Rongelap group and their absence in the Utirik group was in line with the lesser fallout exposure on these atolls. Though beta burns were numerous, particularly in the Rongelap group, the superficial nature of the lesions with rapid healing and regrowth of hair was in conformity with the low penetrability of the beta radiation. The lack of any evidence of chronic radiation dermatitis or development of skin cancer in later years is also indicative of this.

3. Internal Doses to Individual Organs or Tissues

The widespread differences in energy spectra of the internally absorbed radionuclides made calculations of absorbed doses to the whole body and bone marrow extremely difficult. However, except for the thyroid, these absorbed doses are believed to have been small compared with the whole-body external exposure.

Many uncertainties made the thyroid dose estimates difficult: only the first pooled samples, at 15 days post exposure, in the Rongelap and Rongerik personnel showed ^{131}I , and the levels were low; the degree of urinary excretion of iodine at 15 days is uncertain; the amounts of potent short-lived iodine isotopes present at the time of the fallout, particularly on the more distant atolls are unknown; the relative importance of absorption of radionuclides via ingestion of contaminated food and water versus inhalation is uncertain; and the thyroid dose is different in adults and children because of the size of the thyroid gland, etc.* In spite of these difficulties it does not seem likely that the radiation doses to the thyroids would be too far removed from those calculated by James (19) since there should be a rough proportionality between the gamma dose estimates and the amount of radioiodines in the fallout, taking into account the time of arrival of the fallout; and, as pointed out above, there does not appear to be a great discrepancy between the gamma dose estimates and the clinical findings. However, there could have been considerable variation among thyroid doses in different individuals depending on the amount of food and water consumed at the time of the fallout. As pointed out earlier, the two Rongelap boys who developed atrophy of the thyroid with myxedema and other children probably received doses considerably higher than James' estimates for the 3-year-old children because of the smaller size of their glands. Other factors which might have contributed to the higher doses in the small children were (a) that playing in close contact with the contaminated ground increased their ingestion, etc., which is borne

*See second footnote at beginning of this Appendix.

out by higher urine radioactivity; and (b) that iodine uptake is thought to be greater in infants because higher activity and metabolism of the gland are indicated by the finding of higher protein-bound iodine in infants (237). It seems possible that the thyroid doses received by the two boys who developed myxedema may well have been in the range known to produce such an effect. On a risk/rad basis thyroid tumors produced from the calculated doses of the Rongelap people appeared to be about equal to those reported to have resulted from x-ray exposure. Since a large component of the thyroid dose in the Marshallese is due to radioactive iodine, it is surmised that the presence of more energetic shorter-lived isotopes of iodine with faster dose rates may have at least partly accounted for this finding. (See Section IX.D.) The very slight additional accumulative exposure to the thyroid glands due to residual radiation on the home islands is not thought to have added significantly to their thyroid dose.

Appendix III

GROWTH AND DEVELOPMENT DATA

Table 1. Comparison of adult (final) statures.

1. Exposed males n = 15 $\bar{m} = 164.43 \pm 1.42$	vs	unexposed males n = 22 $\bar{m} = 163.86 \pm 1.06$
2. Exposed females n = 22 $\bar{m} = 154.94 \pm 0.76$	vs	unexposed females n = 26 $\bar{m} = 153.10 \pm 0.84$
3. Exposed males (born after 3/1/45) n = 12 $\bar{m} = 163.86 \pm 1.58$	vs	unexposed males (born after 3/1/45) n = 14 $\bar{m} = 165.07 \pm 1.26$
4. Exposed females (born after 3/1/45) n = 13 $\bar{m} = 155.53 \pm 1.18$	vs	unexposed females (born after 3/1/45) n = 20 $\bar{m} = 152.69 \pm 0.95$
5. Unexposed males (born before 1945) n = 8 $\bar{m} = 161.74 \pm 1.76$	vs	unexposed males (born after 3/1/45) n = 14 $\bar{m} = 165.07 \pm 1.26$
6. Unexposed females (born before 1945) n = 6 $\bar{m} = 152.69 \pm 0.95$	vs	unexposed females (born after 3/1/45) n = 20 $\bar{m} = 154.48 \pm 1.91$
7. Exposed males (born before 1945) n = 3 $\bar{m} = 166.73 \pm 3.52$	vs	unexposed males (born after 3/1/45) n = 12 $\bar{m} = 163.86 \pm 1.58$
8. Exposed females (born before 1945) n = 9 $\bar{m} = 154.07 \pm 0.75$	vs	unexposed females (born after 3/1/45) n = 13 $\bar{m} = 155.54 \pm 1.18$

Table 2. Final statures (cm), exposed groups (Age = chronological age when final stature was attained; * data too uncertain for extrapolation).

Age (yr)	Subject No. (M)	Final stature	Age	Subject No. (F)	Final stature	Age
<u>Rongelap</u>						
0-5	2	169.0	*	17	159.0	22
	3	160.0	*	21	150.8	20
	5	152.0	*	33	160.5	15
	23	170.0	19	42	149.5	*
	32	166.5	*	65	147.0	20
5-10	54	167.9	*	69	160.0	*
	19	159.0	*	15	159.2	*
	20	161.5	18	61	154.9	19
10-18	36	167.5	22	72	159.0	*
	47	170.1	21			
	26	175.4	17	22	156.8	22
	35	160.5	*	24	151.5	*
	73	172.0	*	39	155.5	*
				49	154.3	*
				67	156.2	17
			70	151.5	20	
			74	159.8	16	
<u>Ailingnae</u>						
0-5	813	164.0	17	805	160.0	19
	814	161.0	20	811	148.0	19
	815	168.0	*	812	157.5	*
	817	172.0	*	816	155.0	*
	818	177.0	*	909	144.4	*
	863	165.1	*	911	148.0	*
	912	163.0	*	925	149.4	19
	913	163.0	*	926	160.5	*
	921	*		955	154.5	24
				960	152.0	*
				962	152.0	*
				978	154.0	*
				980	153.0	19
				996	147.7	16
5-10	819	*	*	21	150.1	*
	820	166.0	*	891	153.2	19
	822	162.0	*	950	155.4	20
	824	*	*	959	153.2	19
	869	*	*	965	148.5	18
	874	*	*	993	155.0	16
	887	*	*	998	155.9	17
	892	161.3	18			
	919	160.0	*			
	939	166.0	*			
	940	*				
	976	*				
977	*					
10-18	823	167.5	*	825	153.0	18
	827	160.6	*	826	153.6	*
	828	151.4	18	829	154.0	*
	830	163.0	21	832	147.3	*
	831	160.0	21	876	161.0	20
	885	166.3	*			
	967	160.0	19			
971	164.8	19				

Appendix IV

THYROID TABLES

Table 1. Individual listing of thyroid abnormalities in Marshallese, 1980.
This does not include cases with indiscrete thyroid masses.*

Under "Hypofunction," two TSH levels ≥ 6 $\mu\text{U/dl}$ were considered positive, except that in presurgical cases one such level was considered positive because only one or a few samples were available for testing; two levels ≥ 3 were considered suggestive. Ca = carcinoma.

Pt. No. & sex	Age 1979	Est. thyroid dose (rads)	Thyroid Nodularities			Hypofunction
			Age at detection	Surgery	Diagnosis	TSH ($\mu\text{U/dl}$)
(a) <u>Rongelap exposed at age <10</u> (includes 2 <u>in utero</u> : No. 83 and 85)						
3 M	26	1150				>400(myxedema)
5 M	26	1150				" "
33 F	26	1150	13	Bost. '66	Adenomatous nod.	22
54 M	26	1150	13	Bost. '68	" "	
65 F	26	1150	13	Bost. '66	" "	
2 M	27	1100	12	Bost. '65	" "	22
17 F	28	1050	12	Guam '64	" "	
19 M	30	1000	14	Bost. '68	" "	6.2, 8.2
21 F	28	1050	13	Guam '64	" "	
42 F	28	1050	13	Bost. '66	" "	
23 M	29	1000	19	Bost. '68	" "	
69 F	29	1000	15	Guam '64	" "	470
72 F	31	900	14	Cleve. '69	Papillary Ca	4.9
15 F	32	855	17	Cleve. '69'79	Adenomatous nod.	4.7
20 M	32	855	18	Bost. '65	" "	
36 M	32	855	21	Cleve. '69	" "	
61 F	33	810	20	Bost. '66	" "	5.2, 6.7
32 M	28	1050	28			6.7, 7.3
83 M	25	?	24	Cleve. '74	" "	
85 M	25	?	25	Cleve. '79	Hyperpl. nodule	
(b) <u>Rongelap exposed at age 10-18</u>						
75 F	40	655	24	Cleve. '72	Adenoma	
67 F	38	520	24		Nodules '74	
74 F	40	425	32	Cleve. '76	Papillary Ca	

*Three cases (2 exposed and 1 control) are not included in the table since nodules palpated clinically did not reveal demonstrable pathology at surgery. (See Table 3).

Table 1 (cont'd)

Pt. No. & sex	Age 1979	Est. thyroid dose (rads)	Age at detection	Thyroid Nodularities		Hypofunction
				Surgery	Diagnosis	TSH (μ U/dl)
(c) <u>Rongelap exposed at age >18</u>						
18 F	45	335	34	Cleve. '69	Papillary Ca	
64 F	55	335	41	Bost. '65	Papillary Ca	
4 M	63	335				6.0, 7.0
78 F	62	335				6.6, 8.8
71 F	52	335				6.5, 7.0
34 F	70	335				6.3, 8.3
66 F	55	335	55	Cleve. '79	Adenomatous nod.	
(d) <u>Ailingnae exposed at age <10</u>						
8 F	26	450	18	Cleve. '72	Adenomatous nod.	
53 F	33	320	28	Cleve. '81	Occult Pap. Ca and adenomatous nod.	
(e) <u>Ailingnae exposed at age 10-18: NONE</u>						
(f) <u>Ailingnae exposed at age >18</u>						
51 F	50	135	45	Cleve. '74	Adenoma	
45 F	57	135	51	Cleve. '73	Adenomatous nod.	
41 M	69	135			Nodule	
59 F	--	135	53	Bost. '66	Adenomatous nod. (died '68, age 54)	
16 M	64	135				6.4, 6.5
(g) <u>Utirik exposed at age <10</u>						
2160 F	29	80	25	Cleve. '75	Papillary Ca	
2154 F	31	75	28		Nodule reduced '79	
2147 F	26	90	25	Cleve. '79	Adenomatous nod.	
2239 F	28	80	28	Cleve. '81	" "	
2132 F	27	80	27	Cleve. '81	" "	
(h) <u>Utirik exposed at age 10-18</u>						
2150 M	37	54	33	Cleve. '76	Adenoma	
2229 F	43	31	32	Cleve. '69	Papillary Ca vs. atypical adenoma	
2236 M	36	55	34	Hono. '78	Adenoma	

Table 1 (cont'd)

Pt. No. & sex	Age 1979	Est. thyroid dose (rads)	Age at detection	Thyroid Nodularities		Hypofunction
				Surgery	Diagnosis	TSH (μ U/dl)
(i) <u>Utirik exposed at age >18</u>						
2194 F	62	31	58	Cleve. '76	Papillary Ca	
2208 F	60	31	53	Cleve. '73	Adenomatous nod.	
2212 F	60	31	53	Cleve. '73	" "	
2221 F	79	31	73	Cleve. '73	" "	
2258 M	--	31	60		Adenomatous nod. (died '70, age 63)	
2193 F	54	31	53	Cleve. '79	" "	4.6(presurg.)
2195 F	49	31	48	Cleve. '79	" "	
2215 F	58	31	58	Cleve. '79	Occult Pap. Ca	
2196 F	61	31	61	Cleve. '80	Adenomatous nod.	

Pt. No. & sex	Age 1979	Atoll	Thyroid Nodularities		Hypofunction
			Surgery	Diagnosis	TSH (μ U/dl)
(j) <u>Unexposed Marshallese age <10 in 1954 (940, includes unborn: age <25 in 1979)</u>					
1573 M	29	Rongelap	Hono. '78	Papillary Ca	
3074 F	26	Utirik	Majuro '75	Adenoma	
2279 M**	23	Utirik	Hono. '74, Cleve. '79	Follicular Ca	
2365 F**	24	Utirik		Nodular Lt. lobe	
3555 F**	22	Utirik	Majuro '71(?)	Adenomatous nod.	
5061 F	26	Wotje		Nodule	
F	26	Wotje		"	
5027 M	33	Wotje	Hono. '78	Papillary Ca	
980 F	27	Rongelap	Cleve. '81	Adenomatous nod.	

**Not in matched age group.

Table 1 (cont'd)

Pt. No. & sex	Age 1979	Atoll	Thyroid Nodularities		Hypofunction
			Surgery	Diagnosis	TSH (μ U/dl)
<u>(k) Unexposed Marshallese age 10-18 in 1954</u>					
829 F	40	Rongelap	Cleve. '73	Adenomatous nod.	
938 F	40	Rongelap	Majuro '71	" "	
3015 F	41	Utirik		Nodule Lt. lobe	
3028 F	39	Utirik	Cleve. '79	Adenomatous nod.	
5030 M	36	Wotje	Cleve. '79	" "	
3023 F	39	Likiep	Cleve. '79	" "	
1536 M	36	Rongelap			7.7, 6.3
<u>(l) Unexposed Marshallese age >18 in 1954</u>					
882 M	47	Rongelap		Nodule	
841 F	46	Rongelap	Cleve. '74	Occult Pap. Ca	
858 F	80?	Rongelap		Large goiter	
867 F	51	Rongelap	Hono. '78	Adenomatous nod.	
898 F	~70	Rongelap		Nodules	
4009 M	34	Rongelap		Nodule, Rt. lobe	
4023 F	45	Rongelap	Hono. '78	Adenomatous nod.	
910 M	49	Rongelap		Nodule	
1524 M	37	Rongelap		Small nodules	
1575 F	73	Rongelap		Nodules (no surg.; poor health)	
4014 F	62	Rongelap		Nodules (" " " ")	
982 F	59	Rongelap			6.3, 6.5
1007 M	68	Rongelap	Cleve. '77	Papillary Ca	
3042 F	51	Utirik	Hono. '78	Pap.-Follic. Ca	
3058 F	52	Utirik	Hono. '78	Adenomatous nod.	
3006 M	78	Utirik	Cleve. '79	Adenoma	
5059 F	49	Wotje	Cleve. '79	Adenomatous nod.	
5074 F	53	Wotje		Nodule	
5053 F	68	Wotje		Nodule	
3096 F	55	Wotje	Cleve. '79	Adenomatous nod.	
M	69	Likiep		Nodule Rt. lobe	
M	?(old)	Likiep		Nodule Rt. lobe	
F	73	Likiep		Nodule Rt. lobe	
M	73?	Likiep		Nodular Lt. lobe	

Table 2. Thyroid hypofunction as indicated by TSH level in $\mu\text{U}/\text{dl}$.
 (Two TSH levels $\geq 6 \mu\text{U}/\text{dl}$ were considered positive evidence of hypofunction, or one such level in presurgical cases, which was often all that was available before surgery; two TSH levels $\geq 3 \mu\text{U}/\text{dl}$ were considered suggestive.)

Pt. No. & sex	Age 1979	1963 1966	1966 1971	1972	1973	1974	1975	1976	1977	1978	1979	1980
<u>Rongelap exposed, including Ailingnae</u>												
<u>Positive</u>												
3 M	26	22.0					>60			>500	>40	2.8
4 M	63	2.7	3.2	6.0		7.0	3.5	5.4			1.8, 4.8	2.7
5 M	26	500.0	475.0			32.0					>40	35.0
16 M	64	4.6	1.2	5.0	6.0	5.3			4.1	6.4	6.5	
34 F	69			1.9		6.3	4.8		4.2	3.6	8.3, 1.5	<2.5
71 F	52		4.4	11.6	7.0	10.0	6.5	3.2	7.0	4.1	4.8	
78 F	61		1.4, 2.3			5.2	<1.2	5.4	6.6	3.0	8.8	
2 M	26	22.0										
19 M	30	6.9, 8.2										
33 F	26	22.0										
69 F	29	470.0										
83 M	25	5.2, 6.7										
74 F	40	5.3, 16.3										
32 M	28		4.7, 1.3		<1.0				3.2		6.7, 6.7	7.3
<u>Suggestive</u>												
47 M	32	2.4		2.5		7.0	<1.2	2.0	3.2, 2.3	2.8	5.0	<2.5
76 M	35	2.6, 3.3	1.6	3.9, 7.0	3.3	4.7	<1.2	1.5	3.2, 1.6	2.8	1.0	<2.5
7 M	60	2.8	1.2	1.9		2.1	<1.2		5.3, 2.3	1.0	2.2	4.1
63 F	60	2.9	<1.0, 1.6	<2.5		6.3	<1.2	3.3	2.6	2.2	5.5	<2.5
15 F	31		3.5, 4.7									
72 F	31											
45 F	56	3.0, 2.0			4.9							

Table 2 (cont'd)

Pt. No. & sex	Age	1963 1966	1966 1971	1972	1973	1974	1975	1976	1977	1978	1979	1980
<u>Utirik exposed</u>												
<u>Positive:</u> NONE												
<u>Suggestive</u>												
2237 M	32						1.5				3.5	4.0
2218 F	25			3.6			3.2	3.5	4.3	5.4	6.5,	<2.5
											2.4	
2104 F	48			4.9	<5.0		2.6		5.3	3.6	4.6,	2.8
											3.2	
2140 F	70						<1.2		2.9	5.6,	4.3	
										7.0		
2232 M	26								3.7	4.4	7.3	5.4
2254 F	30			4.8	4.8		3.5		2.4	3.6	4.6	
2197 F	28						1.1		2.4		3.5	4.6
<u>Presurgical</u>												
2215 F	58										8.2	
											Pos	
2193 F	56										4.6	
											Sug	
<u>Unexposed, Rongelap and Utirik</u>												
<u>Positive</u>												
982 F	59			5.6	4.2		1.8		6.2	6.3	6.5	
1519 M	36									7.7	2.3	6.3
<u>Suggestive</u>												
3006 M	78								4.0	4.6		4.5
1556 F	34						5.0		2.4		3.4	

Table 3. Thyroid surgery, chronological listing
(Ca = carcinoma; pap. = papillary; foll. = follicular).

Pt. No. & sex	Isl. ¹ exp.	Age at surgery	Yr. of surgery	Place of surgery	Diagnosis
17 F	R-E	14	1964	Guam ²	Adenomatous nodule
69 F	"	17	"	"	" "
21 F	"	13	"	"	" "
2 M	"	13	1965	Boston ³	" "
20 M	"	18	"	"	" "
64 F	"	41	"	"	Ca (pap.)
33 F	"	13	1966	"	Adenomatous nodule
65 F	"	13	"	"	" "
42 F	"	15	"	"	" "
61 F	"	20	"	"	" "
59 F	A-E	46	"	"	" "
54 ⁴ M	R-E	13	1968	"	" "
23 M	"	18	"	"	" "
19 M	"	17	"	"	" "
72 F	"	22	1969	Clev. ⁵	Ca (pap.)
15 F	"	22	"	"	Adenomatous nodule
18 F	"	36	"	"	Ca (pap.)
36 M	"	22	"	"	Adenomatous nodule
2229 F	U-E	33	"	"	Ca (pap.)
938 F	R-C	32	1971	Majuro ⁶	Adenomatous nodule
75 F	R-E	30	1972	Clev.	" "
8 F	A-E	19	"	"	" "
2208 F	U-E	54	1973	"	" "
2212 F	"	54	"	"	" "
2221 F	"	73	"	"	" "
40 M	R-E	48	"	"	No diagnosis
45 F	A-E	51	"	"	Adenomatous nodule
829 F	R-C	34	"	"	" "
83 ⁷ M	R-E	20	1974	"	" "
51 F	A-E	45	"	"	Adenoma
841 F	R-C	41	"	"	Occult Ca
2160 F	U-E	25	1975	"	Ca (pap.)
3074 F	U-C	25	"	Majuro	Adenoma
2150 M	U-E	34	1976	Cleve.	"
2194 F	"	59	"	"	Ca (pap.)
74 F	R-E	34	"	"	Ca (pap.)
37 M	"	43	1977	"	No diagnosis
2261 M	U-E	50	"	"	" "
1007 M	R-C	66	"	"	Ca (pap.)
2236 M	U-E	35	1978	Hono. ⁸	Adenoma

Table 3 (cont'd)

Pt. No. & sex	Isl. ¹ exp.	Age at surgery	Yr. of surgery	Place of surgery	Diagnosis
3042 F	U-C	50	"	"	Ca (pap.-foll.)
3058 F	"	56	"	"	Adenomatous nodule
1573 M	R-C	28	"	"	Ca (pap.)
867 F	"	50	"	"	Adenomatous nodule
4023 F	"	44	"	"	" "
5027 M	W-C	32	"	"	Ca (pap.)
66 F	R-E	54	1979	Cleve.	Adenomatous nodule
85 ⁷ M	"	25	"	"	" "
2193 F	U-E	56	"	"	" "
2195 F	"	49	"	"	" "
2215 F	"	58	"	"	Occult pap. Ca
3023 F	U-C	39	"	"	Adenomatous nodule
5030 M	W-C	36	"	"	" "
5059 F	"	49	"	"	" "
2147 F	U-E	30	"	"	" "
1556 F	R-C	34	"	"	Normal
3006 M	U-C	78	"	"	Adenoma
3096 F	W-C	56	"	"	Adenomatous nodule
15	R-E	32	"	"	" "
2279 M	U-C	18	1974	Hono.	Ca (foll.)
" M	"	23	1979	Clev.	Recurrent Ca
3555 F	"	13	1970	Majuro	Adenomatous nodule
53 F	R-E	35	1981	Cleve.	Occ. pap. Ca
2239 F	U-E	30	1981	"	Adenomatous nodule
2132 F	U-E	28	1981	"	" "
2196 F	U-E	63	1980	"	" "
980 F	R-C	29	1981	"	Adenoma

¹R-E = Rongelap exposed; R-C = Rongelap unexposed; A-E = Ailingnae exposed;
U-E = Utirik exposed; U-C = Utirik unexposed; W-C = Wotje unexposed.

²Surgery at U.S. Naval Hospital, Guam, M.I., by Dr. Broadus.

³Surgery at New England Deaconess Hospital, Boston, MA, by Dr. B. Colcock.

⁴Died of acute myelogenous leukemia 1972.

⁵Surgery at Cleveland Metropolitan General Hospital, Cleveland, OH, by
Dr. B. Dobyms.

⁶Surgery at the Ishoda Memorial Hospital, Majuro, M.I.

⁷Exposed in utero.

⁸Surgery at Tripler Army Hospital, Honolulu, Hawaii, by Dr. B. Dobyms.

Table 4. Estimated thyroid risk due to radiation for exposed Marshallese 27 years after exposure. (Corrected for incidence in age-matched unexposed populations.)*

Age group	No.	Av. dose	Nodules				Hypothyroid		All	
			Total**	Risk	Ca	Risk	No.	Risk	No.	Risk
<u>Rongelap</u>										
<10***	19	1000	14.6	28.5	0.8	1.6	3	5.8	17.6	34.3
>10	45	387	2.5	5.3	2.6	5.5	3.8	8.1	6.3	13.4
Total	64	569	17.1	17.4	3.4	3.5	6.8	6.9	23.9	24.3
<u>Ailingnae</u>										
<10***	6	379	1.8	29.3					1.8	29.3
>10	12	140	3.1	68.3			1.0	22.0	4.1	90.4
Total	18	233	4.9	43.3			1.0	8.8	5.9	52.1
<u>Utirik</u>										
<10***	58	84	3.5	26.6	0.5	3.8			3.5	26.6
>10	100	35	4.2	44.4	1.2	12.7			4.2	44.4
Total	158	53	7.7	34.1	1.7	7.5			7.7	34.1
<u>All</u>										
<10	83	314	19.9	28.3	1.3	1.8	3.0	4.3	22.9	32.5
>10	157	144	9.8	16.1	3.8	6.2	4.8	7.9	14.6	23.9
Total	240	203	29.7	22.6	5.1	3.9	7.8	5.9	37.5	28.6

*Since it is possible that the thyroid doses used may be too low, on the basis of reevaluation analyses now in progress, the above risk estimates may be too high. If the actual years at risk were used, i.e., years until development of abnormality or death, the total number of years would be reduced and the risk factors would be higher. The cancer risk is probably underestimated since a number of people with nodules were not operated upon. The risk for benign nodules was not included since a large number of unoperated cases were likely to have been benign.

**Includes also unoperated cases.

***Does not include the groups exposed in utero because of dose uncertainty.

Appendix V

Findings of Epidemiological Studies of Cancer in Irradiated Populations
 (From J. Shapiro, *Radiation Protection*, pp. 260-4, Harvard U. Press, Cambridge, MA, 1972)

Subject of study	Follow-up time (yr)	Dose (R or rads)	No. of persons ^d	Form of cancer	No. of cases	
					Observed in exposed group ^b	Expected if not exposed ^c
1. Hiroshima and Nagasaki A-bomb survivors (bomb exploded 1945). Brill et al., 1962 (81)	5-13	0-20	85,070	Leukemia	21	19.1
		21-80	13,184	Leukemia	6	3.0
		81-320	8,695	Leukemia	24	2.0
2. Hiroshima and Nagasaki A-bomb survivors (women) Wanebo et al., 1968 (238)	13-21	0-9	3,082	Breast cancer	3	7.3
		10-39	1,262	Breast cancer	5	3
		40-89	857	Breast cancer	2	2
		90-199	802	Breast cancer	5	2
		>200	841	Breast cancer	6	2.3
		Unknown	840	Breast cancer	2	2.3
3. Hiroshima and Nagasaki A-bomb survivors exposed prenatally Jablon and Kato, 1970 (93)	10	Unexposed control	1,292	All cancers	1	0.75
		>64,500 person-rads ^d				
4. Japanese A-bomb survivors exposed within 1400 m of detonation (died 1950-1962). Angevine and Jablon, 1964 (95)	17		1,215	All cancers, autopsies except leukemia	61	56.8
5. Children exposed prenatally due to abdominal x-ray to mother (exposed 1945-1956 and died before end of 1958). Court Brown et al., 1960 (239)	2-12		39,166	Leukemia	9	10.5
6. Children exposed prenatally (born in 1947-1954 and died before end of 1960). MacMahon, 1962 (240)	4-13	1-2	77,000 ^e	All cancers	85	60
7. Infants who received irradiation of chest before age 6 mo. in treatment for enlarged thymus (treated 1926-1957, follow-up in 1963). Hempelmann et al., 1967 (160)	13-38	61-600	Lower dose group 2,207 (32,226 person-yr at risk) ^f	Thyroid	4	0.07
				Thyroid (benign)	6	80
			Higher dose group 498 (11,485 person-yr at risk)	Leukemia	3	1.45
				Thyroid	14	0.6
				Thyroid (benign)	15	60
				Leukemia	3	57
8. Infants irradiated routinely with x-rays to anterior mediastinum through small (4 X 4 cm) port, 7 days after birth, as "apparently harmless and perhaps beneficial procedure" (x-ray 1938-46, follow-up 1956-58). Conti et al., 1960 (146)	10-20	75-450	1,401	Thyroid carcinoma	0	0.03
		mostly 150	including 244 with enlarged thymus	Leukemia	0	0.95
9. Children treated with x-rays to head, neck, or chest for various benign conditions, mainly "enlarged" thymus and adenitis, treated before age 16 and followed till age 23. Saenger et al., 1960 (202)	>11	<50 (4%)	1,644	Thyroid	11	0
		(83%) 50-200 (36%) 200-600 (33%)		Thyroid (benign)	7	0
10. Children treated before age 16 with x-rays for enlarged thymus, pertussis, and head and neck diseases, and died before age 23 (treated 1930-1956, follow-up 1940-1956). Murray et al., 1959 (241)	Up to 23	Not given	3,872	Leukemia	7	1.4

Subject of study	Follow-up time (yr)	Dose (R or rads)	No. of persons ^d	Form of cancer	No. of cases	
					Observed in exposed group ^b	Expected if not exposed ^c
11. Patients (most between ages 10-40) treated with x-rays for benign lesions in neck, mainly for tuberculous adenitis (treated between 1920-50) Hantford et al., 1962 (158)	10-40	100-2000	295	Thyroid	8	0.1
12. Patients, ages 20-70, treated with x-rays to thyroid for benign disorders. DeLawter and Winship, 1963 (150)	10-35	1500-2000	222	Thyroid	0	
13. Hyperthyroid patients treated with ¹³¹ I (treated 1946-64, followup through June 1967). Saenger et al., 1968 (250)	3-21	7-15 rads to bone marrow (9 mCi ¹³¹ I av.)	18,370 (119,000 person yr at risk)	Leukemia	17	11.9
Comparison group treated by surgery and not given ¹³¹ I. Saenger et al., 1968 (250)	-	-	10,731 (114,000 person yr at risk)	Leukemia	16	11.4
14. Hyperthyroid patients, ages 20-60, treated with x-rays (treated 1946-53, follow-up 1959-61) Shelne et al., 1962 (178)	5-15	Not given	182	Thyroid (probable) Multiple benign thyroid nodules	1 7	
15. Patients treated with x-rays to spine for ankylosing spondylitis (treated 1935-54, follow-up to Jan. 1963). Court Brown and Doll, 1965 (242)	5-28	250-2500 to spinal marrow, approx. 7% of spinal dose to other sensitive areas.	34,302 (165,631 man yr at risk)	Leukemia Aplastic anemia Cancer of heavily irradiated sites (after 6 yr)	60 16 200	6.8 6.1 107
16. Patients treated with x-rays for cancer of the cervix. Hutchison, 1968 (243)	4-8	300-1500 av. (31%) to bone marrow	27,793 (57,121 person yr)	Leukemia Lymphatic malignancy	4 6	5.1 6.3
17. American radiologists (died 1948-1964). Lewis, 1970 (244)	Through 1964		530 deaths	Leukemia Multiple myeloma Aplastic anemia	13 5 5	3.91 1.01 2.3
18. American radiologists. Warren and Lombard, 1966 (245)	Through 1960		5,982	Leukemia		
				1940-44	4	0.5
				1945-49	7	.86
				1950-54	6	1.26
				1955-60	7	2.05
19. American radiologists. Seltser and Sartwell, 1965 (246)	1935-58		3,521 (48,895 person yr)	Ages 35-49 Leukemia Other cancer Total deaths Ages 50-64 Leukemia Other cancer Total deaths Ages 65-79 Leukemia Other cancer Total deaths	2 9 79 8 54 339	1.9 7.3 61.5 1.1 32 271.5
20. Radium dial painters and others who ingested radium and thorium. Evans, 1967 (251)	More than 40		420	Bone	No significant clinical signs of malignancies for body burdens <0.5 μCi ²²⁶ Ra	
21. Uranium miners exposed to radon gas and decay products, follow-up 1950-63. Wagoner et al., 1965 (234)			3,415	Lung	22	5.7

^aThis refers to the number of individuals at risk unless otherwise specified.

^bThe information needed to determine the number of cases is obtained by either following a designated study population or by working back from a review of all death certificates in a defined geographical area.

^cThe numbers in this column are based on available statistical data for unexposed populations.

^dThe term person-rads pertains to the dose imparted to a population and is equal to the sum of the doses incurred by the individuals in the population.

^eThis figure is based on a systematic sampling of the population rather than a review of all the records.

^fThe term person years at risk is the sum of the number of years in which the disease could develop in each member of the group.

Appendix VI

A SUMMARY OF THE FINDINGS OVER THE 25-YEAR PERIOD ON THE JAPANESE FISHERMEN EXPOSED TO FALLOUT IN 1954

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On March 1, 1954, 23 Japanese fishermen aged from 18 to 39 were exposed to radioactive fallout produced by a thermonuclear test explosion performed by U.S. authorities at Bikini Atoll. They were the crew of a tuna fishing boat, The 5th Lucky Dragon.

The location of the boat was 166°58' E and 11°53' N. At about 3:50 a.m. (Japanese standard time) while fishing for tuna, they saw a huge red light in the west, and they heard detonationlike sounds 7 to 8 minutes later. At about 7 a.m. white ashes began to fall on the boat and continued to fall for about 4.5 hours. After 14 days' navigation, the fishermen returned to their harbor, Yaizu, on March 14, 1954. After landing, all were found to have been injured by the radioactive materials. Seven of them were hospitalized in the Tokyo University Hospital and the other 16 were sent to the First National Hospital of Tokyo by March 28. They were discharged from both hospitals in May 1955, except for one fatal case who died on September 23, 1954. After being discharged, most of them have been examined so far as possible on an annual basis.

A. Mode of Irradiation and Estimated Radiation Dose

During the most intensive fallout the fishermen could not keep their mouths and eyes open. Fallout deposited on the deck was thick enough to show footprints. Irradiation was received in the following three ways:

- From the radioactive materials adhering to the skin.
- Externally from the radioactive materials in the cabins, on the deck, etc.
- Internally from the radioactive materials entering various organs.

Estimation of radiation dose to skin as well as the dose by internal exposure was difficult. On the other hand, the estimated external radiation dose was 170 to 600 rad for 14 days, about half or more being received on the first day. The dose to each person differed depending on his behavior on the boat and the position of his cabin.

The integrated dose to thyroid glands from ^{131}I was calculated to be about 20 to 120 rad by external counting. Besides ^{131}I , other iodine isotopes, mainly ^{133}I and ^{135}I , contributed to the irradiation of thyroid glands. Assuming that the fishermen inhaled radioiodine isotopes for 5 hours after the detonation, the total thyroid dose from incorporated iodine isotopes was estimated to have been about 80 to 450 rad.

Urine samples collected at 4 weeks after the explosion revealed significant amounts of radioactivity. However, the radioactivity decreased rapidly; at about 6 months post detonation it was barely detectable. In the analysis after 8.5 years and 10 years the levels of ^{137}Cs and ^{90}Sr in urine were the

same as those of normal Japanese. At the same time, the results of whole-body counting showed no significant difference between fishermen and controls. The radioactivity in several organs of the fatal case was higher than in controls, but still low.

B. Clinical and Laboratory Findings

1. General Symptoms and Signs

Soon after the initial exposure most of the fishermen experienced anorexia, fatigue, and lachrymation, and some experienced nausea and vomiting.

2. Skin Lesions

Skin lesions were caused by beta irradiation. Shortly after the exposure, erythema appeared, which was followed by edema, vesicle formation, erosion, ulceration, or necrosis. Epilation was observed in 20 cases, becoming complete in the two cases who did not wear hats during the ash fall. The skin lesions were similar to ordinary radiodermatitis histologically. The skin injuries recovered gradually. At present, 25 years after the exposure, a few cases show depigmentation, pigmentation, and capillary dilatation. Atrophy of epidermis with narrowed stratum granulosum was noted in histological sections of these areas examined 10 years after the exposure.

3. Hematology

a. Leukocytes: The total number of leukocytes decreased gradually, showing minimum counts at 4 to 8 weeks. Five cases revealed a count of $<2000/\text{mm}^3$; 13 cases, <3000 , and 5 cases, <4000 . In one case, the leukocyte level was depressed to 800. A correlation was found between these minimum counts and the external gamma dose of each individual. At first lymphopenia was noted, and then neutropenia became marked. After 8 weeks recovery was noted. In many cases remarkable eosinophilia was observed at that time. In some cases immature neutrophils appeared in peripheral blood to a slight degree.

b. Erythrocytes: In severe cases slight anemia was observed, accompanied by the depression of reticulocytes. Color indices were >1.0 . The Price-Jones curves of erythrocyte diameter were displaced to the right of normal at first, but returned to almost normal after one year.

c. Platelets: Platelet counts showed increasing depression, reaching a minimum at 4 to 7 weeks ($15,000$ to $100,000/\text{mm}^3$). Slight coagulation disturbances were observed in a few cases.

d. Bone marrow: In severe cases bone marrow was highly hypoplastic at the critical stage, followed by a general increase in cellularity. Recovery was not complete even after a year. At the recovery stage coexistence of hypoplastic and hyperplastic areas was observed in histological sections.

e. Morphological abnormalities: Several morphological abnormalities, e.g., abnormal granules in lymphocytes or neutrophils, vacuoles in various leukocytes and megakaryocytes, giant nuclei and hypersegmentation of neutrophils, binuclear lymphocytes, abnormal mitosis of erythroblasts, etc.,

were observed for about one year, especially at the critical and recovery stages. A slight increase of "mitotically connected abnormalities" was found in bone marrow smears of a few cases after 10 years.

f. Recovery: The cumulative distribution curves of numbers of leukocytes, erythrocytes, and platelets were notably displaced to the left of normal at the critical stage. Though the curves of erythrocytes and platelets were the same as in normal Japanese people after 2 years, the curve of leukocytes was still displaced slightly to the left of normal even after 6 years.

4. Cytogenetics

Follow-up of chromosome observations in blood cells has been performed since 1964. Even 25 years after exposure, cells with chromosome abnormalities (both dicentric and ring and Cs cells) are found in the peripheral lymphocytes with much higher frequencies than in normal Japanese people 40 to 50 years of age. The frequency of dicentric and ring forms seems to be decreasing, but Cs cells remained fairly constant at a frequency of 2 to 3%. The frequencies of the chromosome abnormalities in the 1969 examination were found to correspond to the severity of injuries indicated by minimum leukocyte counts at the critical stage. In the bone marrow, cells with chromosome abnormalities (Cs cells) occurred rather consistently with frequencies of >2% at all four times of sampling carried out 13 to 17 years after exposure.

5. Spermatopoiesis

The number of spermatozoa decreased about 2 months after exposure, and azoospermia was found. Both reduced motility and morphological abnormalities of spermatozoa were also observed. Indications of recovery were noted about 2 years after exposure. Since then most of the patients have had healthy children. The testicle of the fatal case, who died 206 days after exposure, showed extremely reduced spermatopoiesis.

6. Other Findings

Disturbances of the liver function were found to a slight degree in a few cases at the time of hospitalization. Later these became more obvious. One of the fishermen who showed remarkable hematological disturbances died from liver damage. During follow-up studies, elevated values of GOT and GPT were observed in several cases. In 1974 ascites developed in two cases, and in one it was accompanied by diabetes mellitus and sepsis. Although both cases recovered, they died of liver cirrhosis in 1974 and 1979 respectively.

Ophthalmological examinations showed slight lenticular opacities in several cases. However, these had no characteristics of radiation-induced cataracts as observed in A-bomb survivors.

Other studies, including thyroid studies, are continuing in order to detect late effects of radiation.