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DR. JACOB ROBBINS: During the nuclear explosion testing in the Pacific Islands in 1954, a combination of circumstances led to the accidental exposure of a group of Marshall Islanders, as well as some U. S. Navy personnel and the crew of a Japanese fishing vessel, the Lucky Dragon, to a rather unusual sort of fallout. In addition to body surface irradiation that led to skin burns and general body irradiation from the surroundings that led to acute radiation sickness, contamination of food and drink with radioactive isotopes of iodine produced pathological alterations of the thyroid gland. Largely through the perseverance of Dr. Robert A. Conard of the Brookhaven National Laboratory, the Marshall Islanders, both exposed and unexposed, have been the subjects of thorough, repetitive examinations by teams of observers sent by the Atomic Energy Commission.

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Dr. Conard will describe the findings as they have developed over the ensuing 12 years. He was a member of the original expedition dispatched by the Atomic Energy Commission and the U. S. Navy and thus can give us a firsthand report of the initial radiation effects. The major emphasis of this Conference, however, will be on the late effects that have become evident only in the last several years. These observations highlight a subject that is currently of considerable theoretical and practical importance—the effects of radiation on the thyroid gland.

The Conference will be opened by Dr. Joseph E. Rall, Director of Intramural Research, National Institute of Arthritis and Metabolic Diseases, who has participated in several of the previous expeditions to the Marshall Islands and who just returned with Dr. Conard a few weeks ago from the latest visit. Dr. Rall will discuss the general problem of radioactive iodine in fallout from nuclear explosions.

RADIOACTIVE IODINE IN FALLOUT FROM NUCLEAR EXPLOSIONS

DR. JOSEPH E. RALL: The heat generated by a moderate-sized fission explosion generally results in a temperature of the order of 10 million K. The complexity of the problems associated with fallout generated

by such an explosion and its widespread distribution has caused a series of high-energy discussions, and sometimes I think the temperature achieved by these discussions has approximated that of the cloud itself.

I will make a few general remarks about four different aspects of fallout from nuclear explosions. The first concerns explosive nuclear devices; the second, radioactive products from these devices; the third, local factors influencing the distribution of these products; and finally, the biological modulation of the fallout products.

Nuclear explosive devices are of two types, the first being the fission reaction that generally involves ^{235}U, ^{233}U, or plutonium. The fission produces an enormous variety of radioisotopes. There are also fusion explosions, and the Bikini explosion that we are presently discussing was a fusion explosion. However, all the fusion explosions have to be triggered by a fission-type explosion in order to achieve the necessary temperature required for fusion, which is of the order of 10 to 100 million K. The fusion explosions are of two types: They are either the deuterium-tritium fusion that produces helium plus neutrons and energy, or the deuterium-deuterium explosion that produces either helium or tritium, and neutrons or, in the case of tritium, a proton, plus energy. The points to remember are [1] fusion explosions are impossible without fission so that there are always fission products, and [2] fusion added to fission gives an enormous increase in the number of neutrons present, and this has an effect on the distribution of the radioactive decay products.

As far as the products themselves are concerned, there is an interesting distribution curve (Figure 1). There are peaks at about 136 mass units and at about 94 mass units for the fission of ^{233}U. There is a slightly different curve for fission of ^{239}Pu and ^{235}U. If the fission occurs in the presence of very high-energy neutrons the peaks

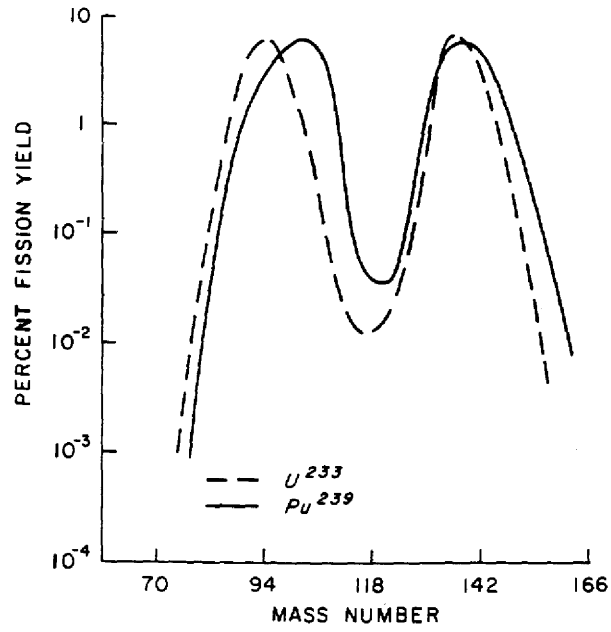

FIGURE 1. Yield of various isotopes from nuclear reactions involving ^{233}U and ^{239}Pu.

may decrease, and finally there may be a relatively smooth curve. In general, however, fission produces an abundance of isotopes with mass around 136 and mass around 94. Just why fission occurs asymmetrically is a matter of some interest I will not discuss. It might be noted that most of the radioactive isotopes of iodine have a mass between 131 and 135 and hence are major fission products.

There is an additional point of interest, namely, neutron excess. ^{235}U (a good fissionable material), for example, has 92 protons in the nucleus and 143 neutrons. If this were to undergo fission directly and symmetrically, it would produce palladium. There is an extensive series of palladium isotopes, and the most abundant of the stable isotopes is ^{106}Pd, which has exactly half the number of protons of uranium but since it has a mass of 106 it has 60 neutrons. Therefore, if there were symmetrical fission of ^{235}U, one would obtain 2 atoms of palladium and an excess of 23 neutrons. This implies that in a fission explosion there is an enormous neutron flux in the explosive device that irradiates the fission products, the container, and anything

around it, producing a variety of isotopes. Most of these isotopes are radioactive and they decay, frequently in a very complicated way. The average number of isotopes in a chain before any given fission fragment reaches a stable isotope is through six different daughter generations.

There are a number of isotopes of major biological importance. First, there are two induced isotopes that should be considered. ^{14}C is a trivial fission product, but because of the intense neutron source there is a nitrogen-neutron reaction giving ^{14}C. It was estimated several years ago that at that time the amount of ^{14}C in the atmosphere was roughly 70% greater than before the first atomic explosion.

^{24}Na is another isotope that is largely an induced isotope, and it is of particular importance in underwater blasts or blasts that are at all close to seawater because of the sodium in the ocean. Under these conditions, a substantial amount of ^{24}Na, which has a 14-hr half-life, can be formed, and in short-term fallout this can be of some importance.

There are three or four other isotopes that are of importance for several reasons. ^{90}Sr, for example, has a 5.3% fission yield; that is, of 100 atoms of uranium, 5.3 atoms (if normalized for mass) end up as ^{90}Sr, so this is a significant fission product. It also has a 28-yr half-life so that it will persist for a long time. Finally, it localizes in bone so that it can be of importance biologically.

The iodine isotopes are clearly of importance. Let me give a few numbers to illustrate variations in fission yield with the type of device and the magnitude of release of radioactive iodine. For ^{238}U and high-energy neutrons as the explosive device, there is a 4.7% yield of ^{131}I. With ^{235}U fission the yield is 3%, and for ^{235}U with thermal neutrons it is 2.9%, so that depending on the device there can be a fairly substantial difference in the amount of production of any given isotope; but in each case ^{131}I is an important product. ^{131}I is clearly significant only in relatively short-term fallout because of its 8-day half-life, and for many years it was not considered to be a serious hazard. ^{132}I has about 4.5% yield; it has a 2.5-hr half-life, so it is only important in very short-term fallout. ^{133}I has a substantial yield, 6%, and a 21-hr half-life, so it is of some importance over the course of perhaps a week. ^{135}I is another radioisotope of iodine; this has a 6.7-hr half-life and is important only for a few days.

There are some other isotopes from fission explosions that must be considered. One is ^{137}Cs, which still can be detected in most exposed individuals in the Marshall Islands. It is also a potential problem because of relatively long-term storage in muscle. Cesium is further worrisome in meat eaters such as Eskimos who eat caribou. There is cerium, which has almost a $\frac{3}{4}$-yr half-life and a substantial fission yield, and finally barium.

The amounts of these isotopes formed are perfectly enormous. Just one example: Explosion of a megaton bomb of the fission type produces enough radioactivity so that if it is evenly distributed over 1,000 square miles it will give in 1 hr a dose rate of the order of 1,000 rads/hr. Hence, a 30-min exposure to this amount of radiation would, in general, be lethal. This is for a 1-megaton bomb, but you may recall that the Russians exploded a 100-megaton bomb a few years ago. The explosion to which the Marshallese were exposed was of the order of 15 megatons.

The lifetime of these fission products is very complicated because there are literally hundreds of isotopes formed, all of different half-lives. There is, however, an empirical "rule of 7" that states that at any given time for the first 8 or 10 days the amount of radioactivity remaining after a fission explosion decreases by a factor of 10 after 7 hr, by a factor of 10^2 at 7^2 hr, and by a factor of 10^3 at 7^3 hr. Therefore, if at 1 hr there are 100 units of radioactivity, at 7 hr

there are 10 units, and at 7 times 7 (49 hr), 1 unit.

A word has to be said about local factors involved, because these have played a major role in the Marshallese explosion. In general, one can differentiate underwater explosions, underground explosions, surface explosions, low-altitude, and high-altitude explosions. One critical factor is whether the fireball created by the explosion touches the earth or the ocean. If it does, it can volatilize as much as 100,000 tons of earth, water, and debris; and this large mass of material produces two effects on fallout. First, the volatilized material is subjected to neutron radiation so that large amounts of induced isotopes are produced, and secondly, as the mass of volatilized material expands and cools, it condenses and produces particles large enough to settle to the ground. In the Marshall Islands after the explosion, there was so much of this material that large white particles drifting down from the sky gave the appearance of a snowfall. This is close-in fallout, and it occurs from 10 to 100 miles from the point of detonation. It results from an injection of large amounts of material into the troposphere (the atmosphere from ground level to 10 miles). Stratospheric injection, which is into the earth's atmosphere more than 10 miles from the ground, results in a much more general fallout because of the much slower settling of debris that has a half-time of some years. In general, this type of injection occurs with high-level explosions, and the fallout is worldwide in distribution.

The biological consequences of radioactive fallout are complicated by several factors. If radioiodine falls out on pasture, cows grazing there can consume relatively large amounts of anything deposited on the grasses. In addition, the iodine is concentrated in the milk 10 to 40 times the level in blood; hence, the radioiodine in milk has been concentrated considerably over that deposited on the ground. Finally, the humans who consume milk concentrate about one third of the radioiodine that they ingest in their own thyroids. Iodine in the human thyroid remains in the gland a long time; in a normal individual iodine in the thyroid has a half-life of 60 days. One additional factor is the problem of the child versus the adult. A 1-year-old child, for example, has a 1-g thyroid; an adult has a 20-g thyroid. The proportional uptake in both is the same, so that the child has roughly 20 times as much radioiodine deposited per gram of thyroid tissue as an adult.

We can rather briefly conclude and point out that fallout depends on a variety of circumstances. It depends on the nuclear device exploded. It depends on where it is exploded so that it can give close-in fallout, medium trophospheric fallout, or long-range stratospheric fallout. The problems associated with fallout depend on the kind of isotopes involved. In the case of iodine it is complicated by biological concentration through cattle and through humans, and there is every reason to expect that it could be a serious consequence of fallout.

DR. ROBBINS: Ordinarily we leave discussion until the end, but we are going to shift emphasis somewhat here, so if anyone in the audience has any questions on the technical matters that Dr. Rall has brought up, we could have some questions now.

DR. JAN WOLFF: Is there a chemical selection at the moment of fission favoring one element of a given mass over another of the same mass?

DR. RALL: In general, there is no chemical fractionation or preference in the production of fission products. The final result, however, depends on whether isotopes of a given mass are stable and how long- or short-lived they may be if they are radioactive.

DR. PHILIPPE V. CARDON: You said that there was a yield of 2.5% for ^{131}I in a thermonuclear explosion. If there is a ground burst does that go up substantially?

DR. RALL: For iodine I do not think it makes much difference because there is not much tellurium or iodine occurring naturally. The main factor would be just an enormous amount of material on which it can condense and be deposited rapidly. For elements like sodium with great natural abundance and that can be produced by neutrons of varying energies, it does make a big difference.

DR. ROBBINS: If there are no further questions we will go on with the second part of our discussion and hear something about the events as they occurred in the Marshall Islands. I am happy to introduce to you Dr. Robert A. Conard, Senior Scientist at the Brookhaven National Laboratory, Upton, N. Y. Dr. Conard was a member of the Naval Medical Research Institute in Bethesda in 1954 and was one of the key members of the team that was formed hurriedly to cope with the unfortunate occurrence in the Pacific Islands. In the years since then Dr. Conard has organized annual expeditions to the Islands and thus was on the scene when the late effects of the radiation became manifest.

RADIOIODINE FALLOUT AND ITS EFFECTS IN THE MARSHALL ISLANDS

DR. ROBERT A. CONARD: Before I go into a discussion of the late effects of radiation resulting from this accident, I would like to review very briefly the accident itself and some of the acute early effects that occurred in the Marshallese people. A large thermonuclear device was detonated on the Bikini Island on March 1, 1954. As Dr. Rall pointed out, this bomb exploded close to the surface of the earth so that the fireball touched the earth and the ocean drawing up tremendous amounts of particulate material into the cloud and this material became mixed with the radioactive fission products. This radioactive material, because it was heavier, fell from the cloud in a downwind direction, contaminating several inhabited atolls to the east. Figure 2 shows a rough map of the Marshall Islands and the area involved in the fallout. On Rongelap Island, 100 miles from Bikini, the fallout resembled a light snow and actually coated the ground and the trees and became deposited on the skin and on the hair of the people. The fallout was less dense the fur-

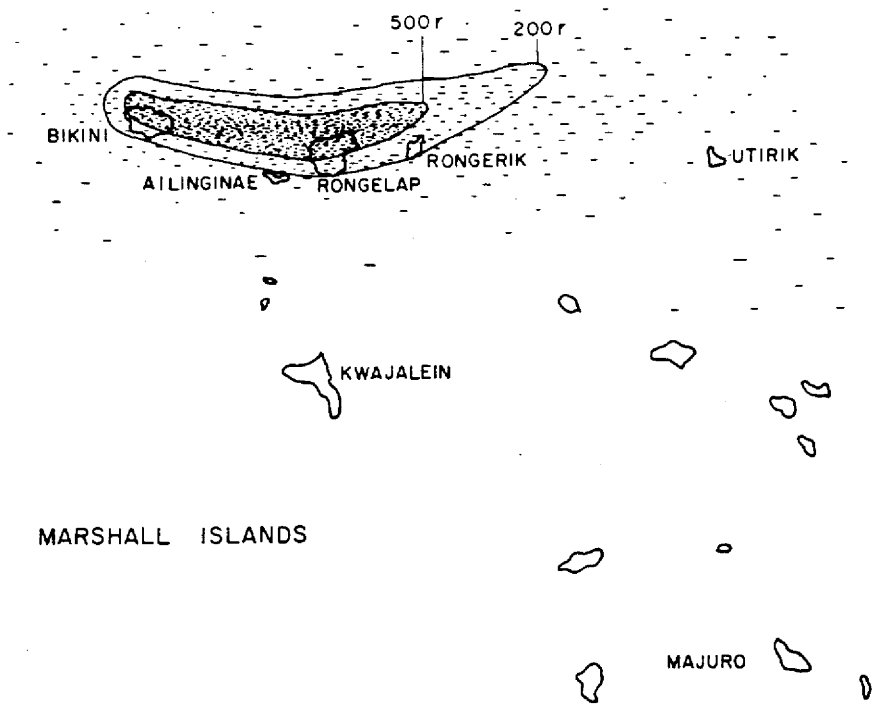

FIGURE 2. Map of fallout area, Marshall Islands, March 1954.

TABLE 1. Summary of Fallout Effects

Group*	Composition	Fallout Observed	Estimated Gamma Dose	Extent of Skin Lesions
			rads	
Rongelap	64 Marshallese	Heavy (snow-like)	175	Extensive
Ailinginae	18 Marshallese	Moderate (mist-like)	69	Less extensive
Rongerik	28 Americans	Moderate (mist-like)	78	Slight
Utirik	157 Marshallese	None	14	No skin lesions or epilation

* Also exposed were 23 Japanese fishermen who received a sublethal dose.

ther east it occurred. There were 64 men, women, and children on Rongelap who received an estimated dose of 175 rads of whole-body gamma radiation. They also suffered extensive skin irradiation from fallout deposit on their bodies and some internal absorption of radioactive materials. There were 18 other Rongelap people on a fishing expedition at an adjacent atoll (Ailinginae), 20 miles to the south, and they received less fallout, with an estimated whole-body dose of 69 rads, less extensive irradiation of the skin, and less internal absorption of radioactive materials. There were 28 American servicemen on Rongerik Island, still further to the east, who received a moderate amount of fallout with very slight skin burns. These men were aware of the fallout dangers and took proper precautions such as staying indoors and taking showers to remove radioactive material from their bodies. The last group, the people of Utirik Island, 157 men, women, and children, saw no fallout at all, and there was a very minimal amount of radiation received, an estimated 14 rads of whole-body radiation. Table 1 lists the populations exposed with estimated doses.

During the first 2-day period, before the Rongelap people were evacuated, many of them became anorexic and had nausea and a few vomited. The majority also complained of itching and burning sensations of the skin, usually on the exposed surfaces of skin that were not covered by clothing.

They were evacuated by ship and planes 2 days after the accident to the Island of Kwajalein, which at that time was a large naval base to the south. We, as members of a special naval medical team, arrived on the scene about 8 days later and carried out extensive examinations on these people for the following 3 months. At the end of that time the Utirik people, who showed no serious effects from their exposure, were returned to their home island, which was considered safe for habitation. But since the island of Rongelap was too radioactive the people of this island, who had sustained more serious exposure effects, had to be moved to a temporary village some 150 miles to the south where they lived for 3 years. The Rongerik servicemen were returned to their duty stations after these examinations.

FIGURE 3. Rongelap Village today. The old village was completely rebuilt.

FIGURE 4. Numerous superficial "beta burns" in a young boy who had little clothing on at time of exposure.

We carry out annual medical surveys on these people. The surveys are sponsored by the Atomic Energy Commission and Brookhaven National Laboratory and are carried out in conjunction with the Medical Department of the Trust Territory of the Pacific Islands. Numerous publications have described the results of these annual surveys (1–10).

In 1957 the Island of Rongelap was monitored and was pronounced safe for habitation, and the people were moved back. Figure 3 shows Rongelap Island today with new construction that is far superior to what they had previously. Over 200 Rongelap people who were not on the island at the time of the accident moved back to Rongelap with the exposed people. This group makes up our comparison population and is a rather good one since [1] most of the people are blood relatives of the exposed people; [2] they match reasonably well for age and sex; and [3] they live under the same environmental conditions.

Now, briefly, what acute effects were noted? In about 2 weeks the deposit of fallout material on the skin resulted in the development of radiation burns that first appeared as pigmented areas. About 90% of the people developed these so-called "beta burns." These pigmented areas usually desquamated in a few days leaving raw depigmented areas, sometimes ulcerations. Figure 4 shows extensive lesions in a young boy. Fortunately, most of these burns were fairly superficial and healed and repigmented within several weeks without any special treatment. Epilation was noted in about 90% of the children and 40% of the adults. This was spotty in nature. In Figure 5 we see epilation in the temple area of a young girl. The hair regrew in all of these people, starting at about 3 months, and by the end of 6 months it had com-

FIGURE 5. Epilation in the temporal area of the scalp of a young girl.

FIGURE 6. Recently developed benign nevi in an area previously affected with "beta burns."

pletely regrown and was of normal color and texture. As a residual effect of these "beta burns" we see scarring in some 20 cases at this time with pigment aberrations persisting in some. Recently we have noted the development of benign nevi in areas that had been involved with "beta burns." Figure 6 shows such lesions. However, there have not been any degenerative changes noted in the skin or any evidence of malignancy.

The whole-body exposure from gamma radiation resulted in potentially the most serious effects. This was reflected largely in depression of the blood cells (Figure 7). The lymphocyte count dropped to about half that of the comparison population by 3 to 4 days, and in the children the lymphocyte count dropped even lower. The neutrophils fell to about half the comparison population levels by about 6 weeks, but fortunately no infections developed that we could blame on the depression of neutrophils. The platelets became depressed to about one third to one eighth of the level of the comparison populations, reaching a nadir at about 28 to 30 days. No bleeding was noted, however, except perhaps for some increased menses in a few women. By 1 year the blood counts recovered, but not quite to the exact level of the comparison populations.

There was a slight weight loss noted in the majority of the people during the first 2 months, but we were not sure whether this was related to radiation exposure or was due to change in environment. However, no illnesses occurred that we could relate to radiation effect. We did not have to use any special form of treatment in these people as a result of exposure to the penetrating gamma radiation. Antibiotics were used for ordinary infections that occurred, but these showed no obvious relation to radiation exposure.

In addition to the whole-body and skin exposure, a third type of radiation exposure was from the internal absorption of radioactive materials by inhalation and ingestion. The island was quite contaminated from the fallout, and the people absorbed significant amounts of radioactive materials in the food and water. We were able to detect this by radiochemical urinalyses beginning a few weeks after the accident. Table 2 shows the radioisotopes that were calculated to be present in these people, extrapolating back to the first day as compared with the activity calculated to be

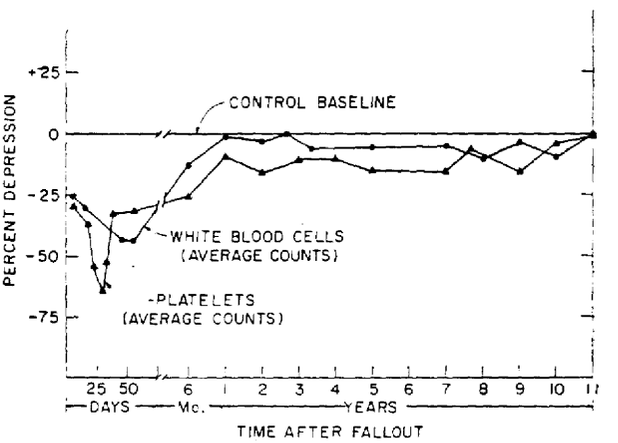

FIGURE 7. Depression of blood elements in Rongelap people (percent depression compared with average counts of unexposed people).

TABLE 2. Estimated Body Burden of Rongelap People

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

present at 82 days after exposure. The most abundant isotopes were those of strontium and iodine. However, the people excreted this material quite rapidly. When they moved back to their home island we were able to detect an increase in body burdens in both exposed and comparison population due to the slight residual activity persisting on the island. This activity was largely due to ^{137}Cs, ^{65}Zn, and ^{90}Sr. The body burdens of these elements have been ascertained from whole-body counting techniques and radiochemical urinalyses. During the first few years after the people of Rongelap moved back the levels showed slight increases in these elements but have since leveled off, and it is believed the people are in equilibrium now with these elements in their environment. The levels are far below the accepted permissible levels.

Until the recent development of thyroid nodules in the Marshallese people there were only a few late effects of radiation that we could relate to radiation with any degree of certainty. A persisting lag in recovery of the white blood cells and platelets until about 11 years' postexposure was believed perhaps to be a lingering effect of radiation exposure on the bone marrow. Figure 7 shows the percent difference in the blood counts of the exposed Rongelap people as compared with those of the unexposed population.

The general health of the people remained about as good in the exposed people as in the unexposed comparison population. Mortality has been slightly greater in the exposed people, and we are not certain if this is related to radiation or not; but there are a larger number of older people in the exposed group, which may partly account for this. Based on birthrates, fertility appears to have been about the same in the exposed and the unexposed people. An increase was noted in miscarriages and stillbirths during the first 4 years after exposure of the women. During this period 13 of 30 pregnancies in the exposed group (41%) ended in stillbirths or miscarriages, compared with only 8 of 49 (16%) in the unexposed women.

We have carried out studies to see if radiation produced any enhancement of aging by attempting to quantify such things as measurement of skin elasticity, hair graying, baldness, visual acuity, accommodation and arcus senilis of the eyes, audiometric measurements, blood pressure, strength, neuromuscular function, and body potassium levels. Most of these criteria showed good correlation with aging. By combining values for these parameters we were able to arrive at a biological age score for each individual. We have not, however, detected any significant difference in aging in the exposed as compared with the unexposed population. Indeed, the subtle effects of aging would probably be most difficult to assess, and perhaps the tests we are using are not sensitive enough to detect the effects of radiation at this dose level.

Degenerative diseases have been studied and compared in the two groups, and we have not seen any difference in prevalence. There have been three cases of cancer: two of the female genital tract in the exposed women and one case of cancer of the thyroid, which I will discuss later. Since the number of cases is so small, we do not know whether this represents any radiation-induced increase in malignancy or not. We have noted only one case of cancer in the unexposed group. There were no radiation-

induced opacities of the lens noted in these people as have been seen in cyclotron workers and the Japanese people exposed to the bombs in Hiroshima and Nagasaki. However, the Marshallese people were not exposed to any neutron irradiation, the relative biological effectiveness of neutron radiation being much higher for cataract formation.

One of the most important findings resulted from growth and development studies of the children. These studies have been carried out under the direction of Dr. W. W. Sutow of the M. D. Anderson Hospital. Extensive anthropometric measurements and skeletal maturation studies, using X rays of the hand and wrist for bone age, have been carried out over the years since exposure (11). It appears that there has been retardation of growth in some children, particularly boys exposed at less than 5 years of age. The growth retardation was most marked in two boys exposed 15 to 18 months of age. Figure 8 shows these two retarded boys. Figure 9 shows the lag in skeletal age in boys exposed at less than 5 years of age compared with the unexposed boys. In the females the lag was less marked. I will have more to say about growth retardation shortly.

FIGURE 8. Two 12-year-old boys showing greatest growth retardation. No obvious mental retardation was noted.

We obtained successful peripheral blood cultures for chromosome studies on the Rongelap people at 10 year postexposure. Dr. Herman Lisco and his group in Boston (who are carrying out the chromosome analysis for us) tell me that a low prevalence of chromosomal aberrations still persists.

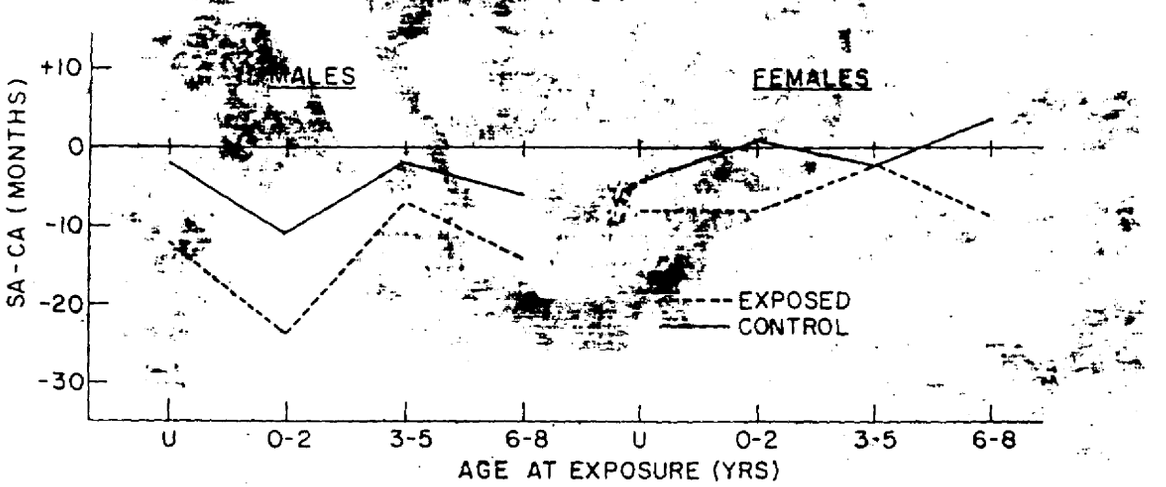

FIGURE 9. Comparison of skeletal age (*SA*) and chronological age (*CA*), 1961 and 1962 (pooled data).

Before we go into the development of thyroid abnormalities in the Rongelap people, I would like to say a few words about the calculations of the radioiodine dose to the thyroid gland that they sustained during the first 2 days on the island. There was no doubt considerable absorption of radioactive iodines from both inhalation as the radioactive cloud passed over them and also from contaminated food and drinking water. Their drinking water was caught in cisterns drained from the roof, and contamination of the water was no doubt increased by a slight rainfall on the night of the fallout. There were few direct data available on which to make an evaluation of the dosimetry, so we had to rely on indirect methods—that is, on radiochemical urinalyses. The first of these were obtained at 15 days after exposure. It was estimated that 0.1% of the isotope would be present at 15 days, and extrapolating back, it was calculated that the thyroid gland contained roughly 11.2 μc of ^{131}I. Dr. Rall pointed out that there are several iodine isotopes present in fallout. In addition to ^{131}I, the isotopes ^{132}I, ^{133}I, and ^{135}I contributed substantially to the dose. In making the calculations, energy dependence per disintegration and the time of absorption of the different isotopes were considered. It was estimated that the adult thyroid gland received approximately 160 rads from radioiodines and of course an additional 175 rads from the gamma radiation. In approximating the dose to 3- to 4-year-old children, the above factors were considered, and, in addition, we considered the difference in pulmonary function and smaller size of the thyroid gland in the child. We know that water rationing was in effect at the time of the fallout, so it is assumed that the children drank as much contaminated water as the adults did, thus absorbing the same amount of radioiodine.

It is estimated that the child's thyroid received roughly between 700 to 1,400 rads from the radioiodines in addition to 175 rads of gamma radiation. That most of these people had beta burns in the neck region over the thyroid was not believed to contribute significantly to the dose to the thyroid gland because of the low energy of the beta radiation in the fallout material.

Over the years we have carried out careful thyroid examinations during the annual surveys. Until 3 years ago the people were considered to have normal thyroid function with no obvious evidence of any thyroid abnormality. Numerous serum protein-bound iodine (PBI) determinations were done, and all appeared in the normal range for these people. The PBI levels in the Marshallese are considerably higher than American levels, which was found to be because there is a large amount of iodoprotein present (12), as we shall discuss later. This may have misled us during these early years. The diet of these people apparently had sufficient iodine but with no overabundance apparent. Urinary excretion studies showed that they averaged about 105 μg in 24 hr in 28 people, which is in the normal range. Cholesterol studies have not shown any significant differences in the exposed and the unexposed people. Thus, there was no reason to suspect that there was any thyroid trouble.

Three years ago we detected the first thyroid nodule in a 12-year-old girl. Since that time the prevalence has been increasing, and we now have 18 cases of thyroid abnormalities, 16 with nodules and 2 with hypothyroidism, the latter showing no nodules. All of these except 1 case occurred in the more heavily exposed Rongelap group that received 175 rads of whole-body radiation. Table 3 lists the thyroid abnormalities with age at exposure, sex, and time of detection. It is noteworthy that the 2 cases of hypothyroidism occurred in the 2 dwarfed boys.

Table 4 shows the distribution of thyroid pathology in the different populations examined. The interesting fact emerges that the highest incidence, 78.9%, of these ab-

TABLE 3. Thyroid Abnormalities in Exposed Rongelap People, 1966

Case	Present Age	Age at Exposure	Sex	Date Abnormality Noted	Findings
		yr			
17	15	3	F	3/63	Benign nodules, complete thyroidectomy 1964. No recurrence.
21	15	3	F	3/64	Benign nodules, complete thyroidectomy, parathyroidectomy 1964. No recurrence.
69	16	4	F	3/64	Benign nodules, partial thyroidectomy 1964. No recurrence.
20	19	7	F	3/65	Benign nodule, partial thyroidectomy 1965. No recurrence.
2	13	1	M	3/65	Benign nodule, partial thyroidectomy 1965. No recurrence.
64	42	30	F	3/65	Malignant nodule, thyroidectomy—surgical and with radioiodine 1965. No recurrence noted on physical examination.*
5	13	1	M	3/65	Hypothyroid, protein-bound iodine (PBI) less than 2 μg/100 ml March 1965, marked retardation of growth; March 1966 growth spurt and improved appearance on hormone.
3	13	1	M	3/65	Hypothyroid, PBI less than 2 μg/100 ml March 1965, marked retardation of growth; March 1966 growth spurt and improved appearance on hormone.
72	18	6	F	9/65	3-mm nodule left lobe. No exam March 1966.
42	15	3	F	9/65	2-mm nodule right lower lobe; March 1966—nodular enlargement entire gland; firm 5-mm nodule right lobe.
61	20	8	F	9/65	6- to 8-mm smooth nodule left lower pole; March 1966 1-cm nodule left lobe.
40	41	29	M	9/65	2-mm nodule right lower pole; March 1966 no nodules detected.
59†	46	36	F	9/65	5-mm nodule midline; March 1966 same.
54	13	1	M	3/66	Nodular enlargement left lobe and isthmus with 2-mm firm nodule.
19	17	5	M	3/66	Multinodular soft goiter—gland 1½ × normal size; 1-cm nodule right lower pole.
36	19	7	M	3/66	About 1-cm nodule—not clearly demarked—right lower pole. Many tiny nodules on surface of gland.
33	13	1	F	3/66	In September 1965 questionable irregular gland. Now definite 5-mm nodule left lobe. ? pretracheal lymph node.
35	13	1	F	3/66	In September 1965 questionable small nodule; now 5-mm nodule right lobe.

* Unable to carry out follow-up thyroid uptake and X-ray studies due to pregnancy.
† Exposed to only 69 rads whole-body radiation and presumably proportionately less thyroid dose.

normalities has occurred in children exposed at less than 10 years of age and in the more heavily exposed Rongelap group. There were 19 children in this group exposed to 175 rads of whole-body irradiation. The 2 severely hypothyroid cases are also in this group. Note that in the Ailinginae group, who received considerably less exposure, there have been no nodules found in the 6 children in that age range. On Utirik Island there were 40 children in the same age range, who received an estimated 55 to 110 rads to their thyroid glands, and there were no cases of thyroid abnormalities seen. In the 61 unexposed children in the comparison population on Rongelap of the

TABLE 4. Thyroid Abnormalities (Nodules and Hypothyroidism)—Marshallese Populations Examined 1964 Through 1966

Island Group	Age (1954) <10 years			Age (1954) 10–19 years			Age (1954) 20–40 years			Age (1954) >40 years†			All Ages	
	No. in Group	Estimated Thyroid Dose*	Abnormalities	No. in Group	Estimated Thyroid Dose*	Abnormalities	No. in Group	Estimated Thyroid Dose*	Abnormalities	No. in Group	Abnormalities		No.	Abnormalities
		rads	%		*rads*	%		*rads*	%		%			%
Rongelap	19	I 700–1,400 γ 175	78.9	12	I 350–600 γ 175	0.0	14	I 160 γ 175	14.3	10	0.0		55	30.9
Ailinginae‡	6	I 275–550 γ 69	0.0	1	I 175–300 γ 69	0.0	4	I 54 γ 69	25.0	3	0.0		14	7.1
Utirik‡	40	I 55–110 γ 14	0.0	16	I 25–55 γ 14	0.0	22	I 16 γ 14	4.5	21	4.8		99	2.0
Unexposed (Rongelap, Utirik)	61	—	0.0	36	—	0.0	48	—	0.0	49	6.1		194	1.5

* I = dose from beta and gamma radionuclides; γ = dose from external gamma radiation.
† Dosage in this group was the same as in the 20- to 40-year group.
‡ In estimating the thyroid doses to the Ailinginae and Utirik exposed groups it was assumed that such doses were proportional to the thyroid doses of the Rongelap exposed group, based on relative whole-body gamma dose received.

same age range, again no thyroid abnormalities have been noted. On Rongelap, among those exposed at an age greater than 10 years, there have been 3 adults with thyroid nodules (5.5%). In the smaller Ailinginae group there was 1 case that represents 12.5%. It should be noted that several nodules have been detected in older people of the Utirik and Rongelap comparison populations. These latter cases were in people over 50 years of age, whereas in the Rongelap exposed adults, the nodules occurred before the age of 50 years.

In view of the seriousness of this development, the highest exposure group on Rongelap was started on thyroid hormone therapy in order to protect the glands against further thyroid-stimulating hormone (TSH) stimulation and hopefully to reduce the possibility of further development of nodules as well as to cause regression of existing nodules. Accordingly, in September of 1965 daily treatment was begun with synthetic thyroxine, 0.3 mg to those under 50 years of age and 0.2 mg to those over 50 years.

Surgery has been performed on 11 subjects. Three were taken to Guam in 1964, where thyroidectomy was carried out at the Naval Hospital. Eight other cases were taken back to the United States to Brookhaven National Laboratory where we carried out a number of thyroid studies before surgery was done in Boston. These studies included iodine uptake, serum TSH level, thyroid scan, basal metabolic rate, PBI, and serum thyroxine level. Thyroglobulin antibody tests were made, but no increase was seen. Dr. Robbins will speak further about these studies. Subtotal thyroidectomy was carried out in Boston by Dr. Bentley Colcock. Total thyroidectomy was carried out on the patient who showed a mixed papillary and follicular carcinoma of the thyroid.

Clinically these nodules have appeared in some cases to be single nodules, but at surgery they were nearly all found to be multinodular. They were usually soft to firm in

consistency, movable, and nontender. We did not detect general glandular enlargement in most cases. Figure 10 shows one of these glands at surgery, indicating the nature of the nodules. Although some clinicians have doubted that we could palpate 2- to 3-mm nodules, our clinical estimate of these tiny nodules was substantiated at surgery. All subjects except adults (one with cancer) were found to have adenomatous goiter. Figure 11 shows a typical microscopic picture of a nodule with the bizarre characteristics of various size follicles, some of which were cystic and filled with colloid, others hemorrhagic, others microfollicular, others macrofollicular, and some with hyperplasia with infolding of the epithelium. This hyperplasia is demonstrated in Figure 12. Sections of these nodules have been studied by a number of pathologists, and a resemblance to the pattern of iodine deficiency goiter has been remarked upon. Most claim that they cannot see actual radiation effects histologically. Figure 13 shows the mixed follicular and papillary carcinoma of the thyroid with blood vessel invasion found in a 41-year-old exposed

FIGURE 10. Surgical exposure of thyroid showing nodules (*Case 17*).

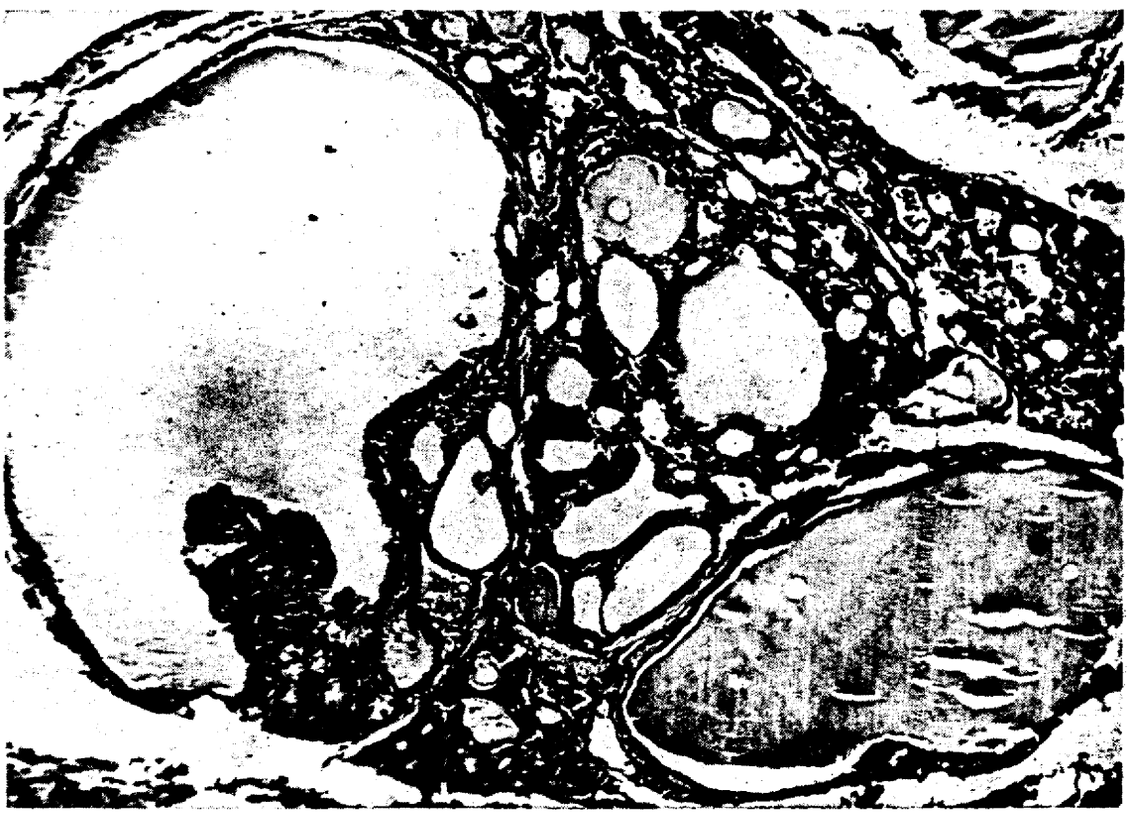

FIGURE 11. Microscopic section of benign adenomatous nodule showing bizarre nature of follicles, some cystic, some microfollicular, some macrofollicular, and some hyperplastic. (Hematoxylin-eosin, × 16.)

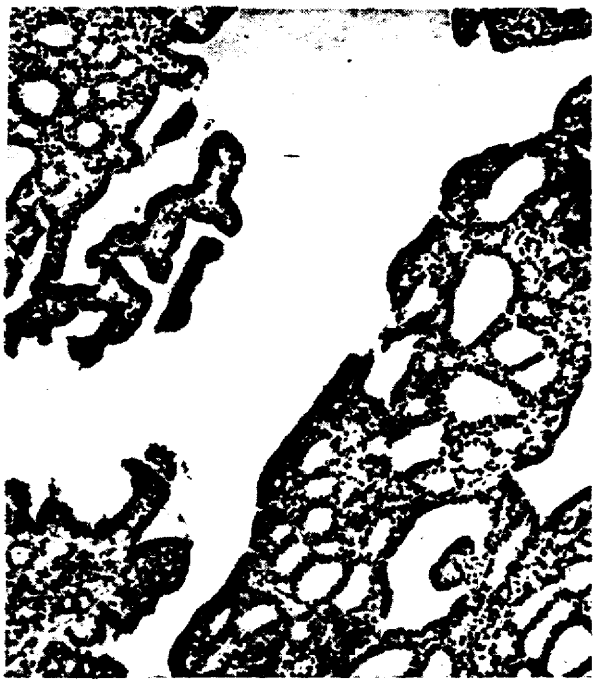

FIGURE 12. Microscopic section of nodule in Figure 7 showing infolding of epithelium in hyperplastic follicle. (Hematoxylin-eosin, × 150.)

woman. There was also localized metastasis into a lymph node. Subsequent studies after complete ablation of her thyroid gland have revealed no indication of metastases. The earlier cases of thyroid abnormalities have been previously described (10, 13).

I would like now to say a few words about thyroid abnormalities as related to growth retardation in the children. As I indicated earlier, we had long been puzzled as to why these children had shown a slight degree of retardation in growth. We knew that the Japanese children had been reported to have some slight retardation, particularly the male Japanese children at Hiroshima, but that picture was confused by such factors as physical and psychic trauma and nutritional deficiencies. We felt that the bone dose in the case of the Marshallese children was too small to account for any direct effect on epiphyseal growth.

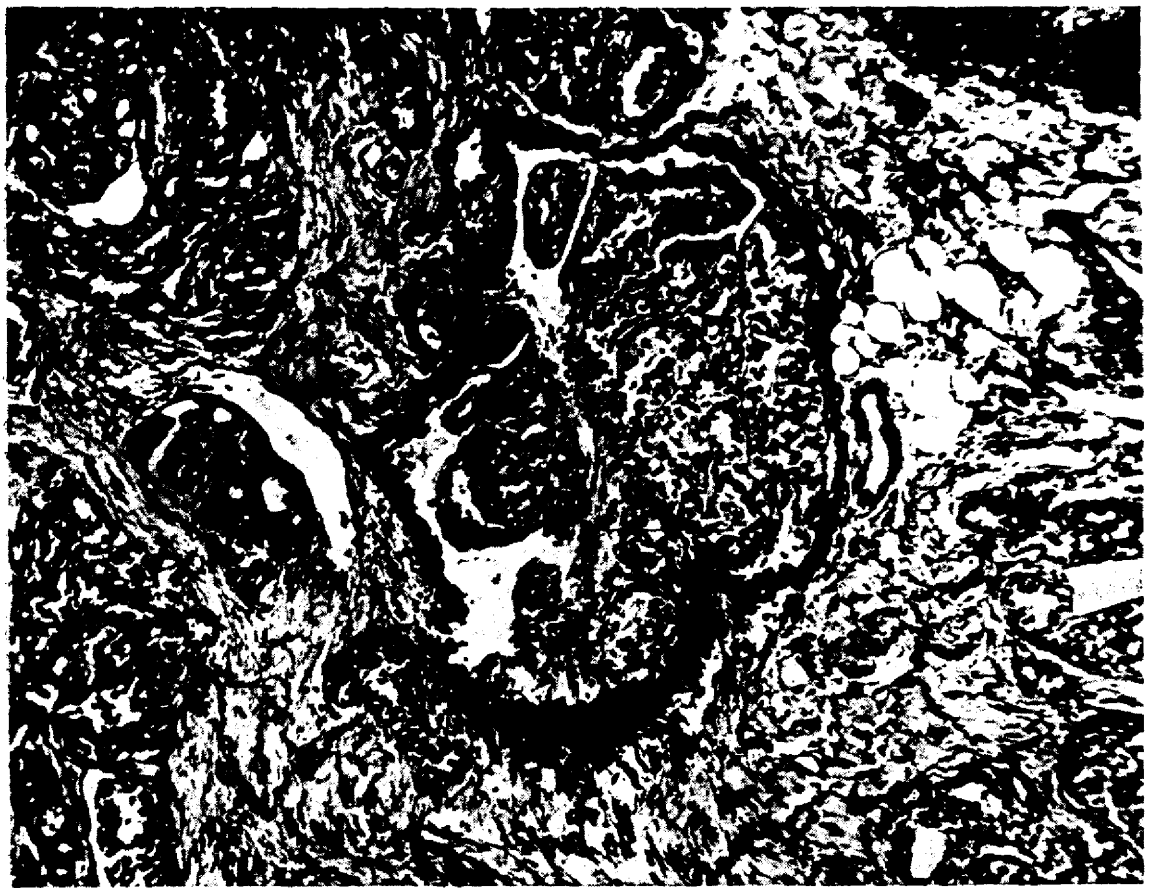

FIGURE 13. Section showing invasion by metastatic papillary and follicular carcinoma of the thyroid into blood vessel (*Case 64*). (Elastic, × 100.)

We know that it takes several thousand rads of local radiation to bone to produce retardation of bone growth. Our estimates of the dose to the bones from the absorption of internal isotopes in the children amounted to only 3 to 4 rads, and it was believed this dose was far too low to be of any signifiance. In searching for an answer, we carried out studies on weanling rats, giving them sublethal doses of radiation and shielding one leg (14). We found that the tibial growth was retarded in both legs, including the shielded leg, the latter representing an indirect effect of radiation. We carried out further pair feeding studies and measured the growth rate of the tibia in unexposed rats who were fed the same reduced amount of food as ingested by the irradiated animals. We found that there was a radiation-induced reduction in food consumption that apparently resulted in nutritionally induced retarded bone growth. However, in regard to the Marshallese, although some weight loss was noted in the children, it is not believed that a nutritional effect was of great significance in contributing to bone growth retardation.

With the recent development of thyroid abnormalities in the Rongelap children, we have fairly strong evidence for the correlation of such abnormalities with growth retardation. The most striking correlation occurred in the case of the two boys with growth retardation who had bone ages of 3 and 5 years at the chronological age of 12. Their PBIs dropped to less than 2 μg/100 ml, they showed coarse facies, dry skin, sluggish achilles reflex returns, and appearance of bony dysgenesis in one case. As will be shown later, their TSH values rose to very high levels, which indicated a primary type of hypothyroidism. Figure 8 shows these stunted boys. The earlier lack of correlation of growth retardation and thyroid deficiency may have been due to the falsely high PBIs. The crucial test of all this is the response of these children to thyroid hormone treatment. At this point I think the results are encouraging. We still have to evaluate the data on many children, but it does look as though there is an effect. The two most retarded boys have shown definite spurts in bone age and stature. Dr. Rall and I have just returned from the Marshall Islands, and we feel that the hormone therapy is also causing some regression in the four cases that still have nodules. One nodule in a 40-year-old man has disappeared. These cases will be reevaluated for surgery on the next survey in March 1967. We have hopes that the hormone treatment will prevent further development of nodules. Whether it will have any effect on the carcinogenic action of radiation remains to be seen.

Thyroid Function in Marshall Islanders

Dr. Robbins: I shall carry on the discussion myself now and bring up first some of the studies that were done on thyroid function in the Marshallese individuals. A complete report of the measurements up until 1966 has been published by Drs. Rall and Conard (12). As Dr. Conard said, in the earlier days of the studies attention was given to the problem of thyroid dysfunction. Although this was looked for quite actively, none was found. Table 5 shows one of the reasons for this, and that is the finding to which he alluded, that the Marshallese people have a higher average PBI and a higher range of PBI than do people living in our part of the world. Table 5 presents the results of studies carried out at various times over the years. When the first values for serum PBI came out high, the question of contamination was brought up. In 1964 the members of the medical team had their blood drawn under exactly the same conditions, and their PBI levels fell in the range that we have come to expect for the PBI in North America. The Marshallese, however, continued to show an elevated PBI with a high mean

TABLE 5. Serum Iodide Measurements in the Marshall Islands

Date	Group	No. Samples	Average	Range	Percent Over 8 μg/100 ml
Protein-bound iodine, *μg/100 ml*					
1959	Marshallese	12	6.2	4.1–9.2	16
1962	Marshallese	14	8.6	4.6–12.0	64
1964	Medical team	10	4.9	2.5–6.9	0
1965	Marshallese—exposed	31	7.6	4.1–11.9	42
1965	Marshallese—unexposed	19	7.0	3.9–10.7	28
Butanol extractable iodine, *μg/100 ml*					
1959	Marshallese	12	4.9	2.7–8.7	

level and individual values going up well into the hyperthyroid range.

In 1965 a comparison was carried out between exposed and nonexposed individuals; there was no difference between them. One evaluation of the butanol extractable serum iodine (BEI) done as far back as 1959 indicated that the BEI—which would be the hormonal iodine—was in the normal range for North America, suggesting that the elevated PBI was not thyroxine-like. Figure 14 shows the distribution of the PBI in the population. The valley at one point was thought to be an artifact due to the small number of individuals sampled, and it was concluded that the PBI levels formed a normal distribution. There was no bimodal distribution or any familial prevalence that would indicate a genetic abnormality or any evidence of two genetic populations in the Islands with respect to PBI levels in blood.

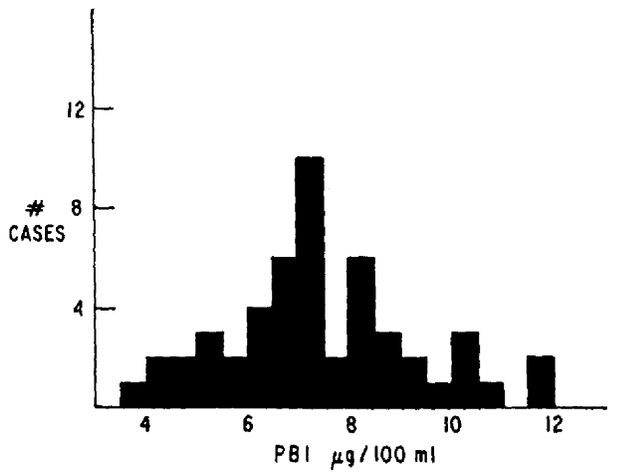

FIGURE 14. Distribution of serum protein-bound iodine in Marshallese individuals. Reproduced with permission from Rall and Conard: *Amer. J. Med.* 40: 882, 1966 (12).

Table 6 shows some later studies in which chromatography on Dowex-1 columns was performed in order to identify the non-hormonal iodine in serum. This procedure (15) separates iodoprotein from iodoamino acids not in peptide linkage. In North Americans (these were normal controls drawn at the NIH) the iodoprotein averaged 0.8 μg/100 ml, whereas in the Marshallese the value was considerably higher with a mean of 2.2 μg/100 ml. The thyroxine iodine average was slightly higher in the Marshallese but probably not significantly.

Recently, with the development of thyroid abnormalities in the exposed Marshallese, it was possible to examine serum iodoprotein levels in patients with thyroid hypofunction. The results, presented in Table 7, suggest that the iodoprotein was largely from an extrathyroidal source since the level was still elevated in patients with atrophic thyroid glands due to radiation (Cases 3 and 5); in thyroidectomized patients, one of whom (Case 69) had little, if any, uptake of ^{132}I into the thyroid (as we will discuss later); and in subjects who had been on suppressive therapy with levothyroxine.

Dr. Conard mentioned that the iodine analyses of urine, which were carried out

in 1965, were in the range that we find in the northeastern United States. In 28 samples, the 24-hr urine excretion was 19 to 279 μg with a mean of 105 μg. This indicated that there was no excessive intake of iodine in the Marshall Islands that might be related to the iodoprotein in the blood and, secondly, that there was no deficiency of iodine that could be related to the later development of goiters. The thyroxine-binding capacity of the thyroxine-binding alpha globulin (TBG) was also measured in sera with elevated PBI levels, and no elevation was found. An increase in TBG could explain an elevated PBI but not a high serum iodoprotein level.

To conclude with this part of the study, the detection of a high blood iodine in Marshallese was an unexpected finding, one that is still not explained. People living in the Marshall Islands, for reasons that are not known, have an unusual elevation of serum iodoprotein.

When Dr. Rall went on one of the expeditions to the Marshall Islands in March 1965, the situation with the abnormal PBIs was known, and he decided to look a little further into the iodine metabolism in these people. He was more interested in the abnormality in Marshallese in general than he was in abnormalities that might exist in the people who were beginning to form nodules just about this time, and all of these studies were done on individuals without nodules. There were 21 Marshallese (all adults) who were studied. Twelve of them were in the exposed group; 9 of them were never exposed to radiation. The results presented in Table 8 showed no difference between these groups of individuals, and they are compared with average normal values that we would find in the United States.

These studies were done with ^{132}I; this isotope was used because of the very low

TABLE 6. Column Chromatographic Analysis of Serum Iodine*

Group	No. Samples	Total Iodine	Iodo-protein	$T_4 + T_3$†
		←μg/100 ml→		
Marshallese	19	7.0	2.2	4.5
North Americans	25	5.1	0.8	3.8

* Average values.
† T_4 = thyroxine, T_3 = triiodothyronine.

TABLE 7. Serum Iodoprotein Levels in Relation to Thyroid Function

Case No.	Total Iodine	PBI*	T_4I†	Iodoprotein‡
	←μg/100 ml→			
Hypothyroid§				
3		3.2	1.0	(2.2)
5		3.1	1.8	(1.3)
65		3.1	1.9	(1.9)
Thyroidectomized§				
17		1.8	<0.5	(>1.3)
21		1.3	<0.5	(>0.8)
64		5.0	2.0	2.9
69		5.7	1.7	(4.0)
Levothyroxine treated‖				
34	10.8 [9.1]		6.5 [4.6]	3.2 [3.3]
59	8.2		5.3	2.8
68	11.8		5.8	6.0

* PBI = protein-bound iodine.
† T_4I = thyroxine iodine.
‡ Iodoprotein levels in parentheses are the difference between PBI and T_4I levels. The others were measured directly by the column method.
§ Levothyroxine stopped approximately 3 weeks before sampling.
‖ Treated with levothyroxine, 0.3 mg/day, for 6 months. Values in brackets are determinations made before starting thyroxine.

TABLE 8. Kinetic Analysis of ^{132}I Studies (March 1965) in Subjects Without Thyroid Abnormality

Group	No. Subjects	Urine*	Thyroid†	Thyroid Fraction‡
Marshallese—exposed	12	1.10 (0.34–2.57)	0.67 (0.33–1.27)	0.40 (0.25–0.65)
Marshallese—unexposed	9	0.81 (0.17–1.99)	0.79 (0.23–1.47)	0.52 (0.26–0.77)
North Americans		2.0	1.0	0.33

Mean and ranges are given.
* Fraction of extrathyroidal iodide excreted in urine per day (λ_{61}).
† Fraction of extrathyroidal iodide transferred to the thyroid per day (λ_{61}).
‡ Theoretical thyroid uptake $\left(\frac{\lambda_{21}}{\lambda_{21} + \lambda_{61}}\right)$.

amount of radiation that it would deliver to the thyroid gland. A ^{132}Te generator was used, capable of producing a supply of ^{132}I for a period of several weeks. Radioiodine accumulation in the neck was measured ½ hr after the oral dose and at hourly intervals for approximately 4 hr. (Details are given in reference 12.) Urine was collected at the end of this time and measured for ^{132}I. The data were analyzed by Dr. Mones Berman, Mathematical Research Branch, National Institute of Arthritis and Metabolic Diseases, using the computer program that he has in operation for kinetic studies and particularly for thyroid studies (16). The calculation used the gross neck uptake, uncorrected for extrathyroidal iodine, and the analysis indicated that the counter "saw" more than 99% of the thyroidal radioactivity and that 8% of the neck radioactivity was extrathyroidal. In Table 8 we have listed the fraction of the body iodide that is taken up in the thyroid per day and the fraction going into the urine per day. Interestingly enough, both of these values compared with United States values are low, again an abnormality for which there is no explanation. The balance between these two depressions was such that when the theoretical maximal thyroid uptake is calculated it actually comes out higher than is normal in the United States. Although the low urinary excretion rate might well be due to incomplete urine collection, which was very difficult under field conditions, this does not significantly alter the calculated thyroid accumulation rate.

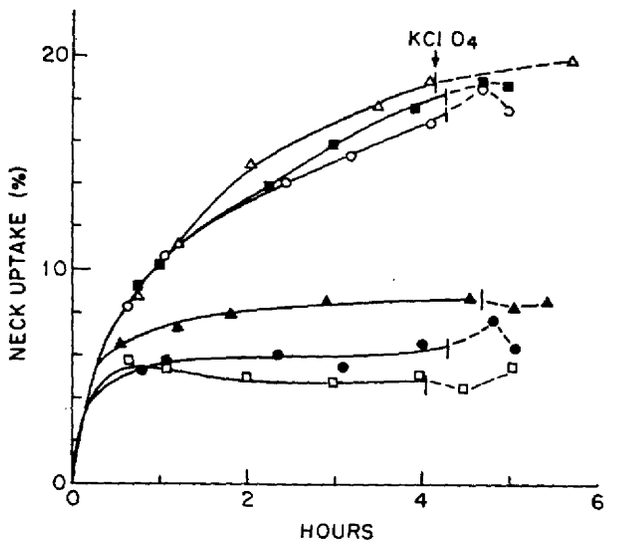

FIGURE 15. Neck accumulation of ^{132}I in subjects with thyroid abnormality. Values are gross neck counts, as percent of dose, uncorrected for blood background after oral administration of ^{132}I. Computer analysis of these data indicates that 7% of the extrathyroidal iodide pool is "seen" by the neck counter. At the vertical lines, 500 mg potassium perchlorate ($KClO_4$) was given by mouth. △ = *Case 54;* ■ = *Case 2* (partial thyroidectomy); ○ = *Case 65;* ▲ = *Case 5;* □ = *Case 3;* ● = *Case 69* (partial thyroidectomy).

I joined the survey for the first time in March 1966. At this time we were interested in doing some further studies on the individuals who had developed thyroid nodules, and we were able to carry out a few such studies. The patients stopped their thyroxine therapy 3 weeks before testing. In

Figure 15 are shown results of the ^{132}I uptake into the neck as a function of time. The uptake patterns fall into two groups. One group had an abrupt rise in neck radioactivity, but this was mostly blood iodide. From there on there was very little change, indicating that these individuals had very little accumulation of iodine in their thyroids. Two of these three subjects were the severely retarded boys to whom Dr. Conard referred, and the results indicate a severe deficiency of thyroid function. The third was a girl who had had a subtotal thyroidectomy approximately a year earlier. The ^{132}I study showed that she had little or no remaining thyroid function, perhaps due to radiation damage to the thyroid remnant. The other three individuals had what appeared to be normal uptake of ^{132}I. One of them had had a subtotal thyroidectomy 1 year before. One subject, who was later operated upon, was a girl with moderate retardation in growth who was found to have a depressed thyroxine level in the blood and so was mildly hypothyroid despite the normal uptake of ^{132}I.

As part of this study we looked to see whether the iodine that was accumulating in the thyroid was being organically bound. There had been some studies earlier (17, 18) on patients treated with radioiodine for hyperthyroidism indicating that radiation damage to the function of irradiated glands may affect different chemical systems differently. The finding was that iodide trapping proceeds normally whereas organification does not, and the iodide that accumulates in the gland could be discharged by giving a competing ion such as potassium perchlorate. The Marshallese patients were, therefore, given 500 mg potassium perchlorate by mouth at about the 4-hr point, and neck measurements were continued. There was no discharge, and therefore we could conclude that there was no defect in organification in the subjects with normal ^{132}I uptake.

In Table 9 we have attempted to summarize some of the pertinent findings in the Marshallese who developed clinical thyroid abnormality. The subjects with thyroid nodules are listed in the order in which the abnormality was detected. The results of kinetic analysis of ^{132}I studies are presented in Table 10. The data in these two tables are presented here in detail since, for the most part, they have not appeared in the earlier publications. The ^{132}I studies performed at the Brookhaven National Laboratory were done on the patients who had come to the United States for surgery. These studies were done preoperatively. The methods were similar except that the neck counts were taken with and without lead interposed between the crystal and the neck in order to correct for the extrathyroidal radioiodine "seen" by the counter, and the measurements were continued for 6 hr in some cases. Computer analysis of the data obtained at the Brookhaven National Laboratory in June 1966 was evaluated in several ways: with or without the corrected neck counts using a lead shield, with or without inclusion of urine data. None of these made an important difference in the value for thyroid accumulation rate, but the uncorrected data gave somewhat greater reliability. The very low urine excretion rates in some cases are probably due to incomplete urine collection and result in comparable errors, in the opposite sense, in the computed thyroid fraction. In Table 10, uncorrected neck counts are used except for the data at Brookhaven National Laboratory, June 1965. In the group studied in the Marshall Islands in March 1966, blood ^{132}I was measured at 2 and 4 hr in order to calculate the iodide space. All subjects had been off levothyroxine therapy for at least 3 weeks unless otherwise indicated. The TSH level in serum was kindly performed by Dr. William Odell of the National Cancer Institute by a radioimmunoassay method.

Several points of interest are revealed by these data. The two subjects with severe growth retardation (Cases 3 and 5) had very low thyroxine iodine levels, little or no accumulation of $^{132}I^-$ by the thyroid, and very high levels of TSH in blood. The latter finding indicates that the growth retardation was due to primary thyroid failure and not to pituitary failure, which was suspected before the appearance of clear-cut thyroid findings. Several of the patients who had had partial thyroidectomy (Cases

TABLE 9. Thyroid Studies in Subjects with Thyroid Abnormality*

Case	Sex	Thyroid Abnormality	Age	Year Tested	Neck ^{132}I Each 4 Hr†		Serum Iodine		Serum TSH‡
					Pre-TSH	Post-TSH	PBI	T_4I	
			yr		*% of dose*		*μg/100 ml*		*mμg/ml*
3	M	Atrophy	13	1965			1.4	0.8	>120
				1966	5		3.2	1.0	159
5	M	Atrophy	13	1965			1.9	0.8	119
				1966	8		3.1	1.8	248
17	F	Nodular goiter	15	1964			6.8		
				1966§			1.8	<0.5	372
21	F	Nodular goiter	15	1964			8.1		
				1966§			1.3	<0.5	440
69	F	Nodular goiter	16	1965§			7.1		
				1966§	6.5		5.7	1.7	125
2	M	Nodular goiter	13	1965	(29)	(23)	7.9	4.2	9.6
				1966§	18		5.2	2.6	26.6
20	M	Nodular goiter	19	1965	(31)	(31)	6.5	4.2	
72	F	Nodular goiter	18	1965			5.3		
42	F	Nodular goiter	15	1966	(15)	(24)	5.7	4.6	<17
61	F	Nodular goiter	20	1966	12† (10)	(24)	7.9	4.9	
54	M	Nodular goiter	13	1965			8.3		<3
				1966	19		5.0	4.3	<17
19	M	Nodular goiter	17	1966§			3.9	3.3	<17
36	M	Nodular goiter	19	1965			4.1		
				1966			4.2	4.3	<17
33	F	Nodular goiter	13	1965			7.0		7.3
				1966	(16)	(24)	5.9	3.8	197
65	F	Nodular goiter	13	1965			4.9	2.1	6.6
				1966	17 (9)	(14)	3.1	1.9	23.5
59	F	Solitary nodule	35	1965			8.2	5.3	
				1966	7‖ (20)	(38)	8.6	4.8	
40	M	Solitary nodule	40	1965			10.3		
64	F	Carcinoma	31	1965	(19)	(28)	8.6	3.4	
				1966§			4.9	2.0	

* TSH = thyroid-stimulating hormone, PBI = protein-bound iodine, T_4I = thyroxine iodine.

† Values in parentheses are "corrected" counts obtained at Brookhaven National Laboratory (see text). The others are not corrected for extrathyroid counts.

‡ Assays in 1965 could not detect levels below 3 mμg/ml. Seven unexposed children in the same age group had <3 mμg/ml. Assays in 1966 could not detect levels below 17 mμg/ml. Three exposed children without thyroid disease (Cases 6, 8, 32) had <17 mμg/ml. Two children exposed in utero (Cases 84, 86) and two unexposed children had <17 mμg/ml.

§ After partial thyroidectomy (for Case 64, total thyroidectomy).

‖ While taking thyroxine.

TABLE 10. Kinetic Analysis of ^{132}I Studies in Subjects with Thyroid Abnormality

Location and Year*	Case No.	Urine†	Thyroid‡	Thyroid Fraction§	Iodide Space
BNL—	2 Pre-TSH	1.20	1.71	0.41	
June 1965	Post-TSH	0.80	1.19	0.60	
	20 Pre-TSH	2.12	2.30	0.49	
	Post-TSH	1.10	1.81	0.62	
	64 Pre-TSH	1.88	1.08	0.36	
	Post-TSH	0.81	1.56	0.66	
Marshalls—	3	0.52	0.005	0.01	
March 1966	5	0.86	0.14	0.14	
	69 (Partial thyroidectomy)	1.13	0.15	0.12	33.3
	2 (Partial thyroidectomy)	1.53	0.92	0.37	20.0
	61 (On thyroxine)	1.26	0.58	0.31	29.0
	54	0.50	0.69	0.58	
	65	1.08	0.72	0.40	20.4
	59 (On thyroxine)	1.65	0.10	0.06	16.9
BNL—	42 Pre-TSH	1.87	1.29	0.41	
June 1966	Post-TSH	0.69	1.30	0.65	
	61 Pre-TSH	0.13	0.48	0.78	
	Post-TSH	0.50	1.67	0.77	
	33 Pre-TSH	0.20	0.97	0.82	
	Post-TSH	0.45	1.57	0.78	
	65 Pre-TSH	1.83	0.82	0.31	
	Post-TSH	2.35	1.14	0.33	
	59 Pre-TSH	3.53	1.51	0.30	
	Post-TSH	1.29	3.09	0.71	

* BNL = Brookhaven National Laboratory.
† Fraction of extrathyroidal iodide excreted in the urine per day (λ_{61}).
‡ Fraction of extrathyroidal iodide transferred to the thyroid per day (λ_{21}).
§ Theoretical thyroid uptake $\left(\frac{\lambda_{21}}{\lambda_{21}+\lambda_{61}}\right)$.

2, 17, 21, and 69) had low thyroxine iodine and elevated blood TSH levels. Therefore, the thyroid remnant had not developed quantitatively normal thyroid function. Three of these subjects (Cases 17, 21, and 69) had their thyroidectomies in 1964 and had not received replacement thyroxine therapy for the first 15 months or longer. Five subjects studied preoperatively (Cases 2, 20, 42, 33, and 65) showed evidence of hypofunctioning thyroid glands or glands that were poorly responsive to excess endogenous or exogenous TSH. In at least two (Cases 2 and 20) there was no response to TSH, so that the glands appeared to be maximally stimulated by endogenous TSH. Analyses of growth data in the Marshallese children are in progress to determine if there is any growth retardation that can be correlated with these findings of thyroid damage. Other subjects, on the other hand, and in particular the adults (Cases 59 and 64), had normal response to TSH or no elevation of blood TSH or both.

To summarize the studies on thyroid function, several things of interest have come to light. First of all, people living in the Marshall Islands, whether or not exposed to radiation, were found to have certain peculiar and unexplained findings. They have an unusual amount of iodoprotein circulating in the blood, which seems to persist even after suppression of thyroid gland function. They also have a somewhat lower rate of radioiodine accumulation in the thyroid gland, compared to North Americans, and perhaps a lower urinary excretion rate of iodide as well. Radiation damage to the thyroid gland resulted in total destruction of thyroid function in two

subjects. In others, there appeared to be partial destruction with the result that TSH secretion was increased; and the glands, although maintaining normal or almost normal hormone production, were operating at their maximal ability. They could not respond to further TSH stimulation. The possible relationship between this state of affairs and the formation of thyroid nodules will be considered in the next discussion.

Radiation Effects on the Thyroid Gland

The foregoing presentation has clearly shown radiation of the thyroid gland by isotopes of radioiodine to be a major feature of the late results of exposure to radioactive fallout. I shall now discuss the subject of thyroid radiation. This subject takes on practical importance in the etiology of certain thyroid tumors and in the clinical use of iodine isotopes for diagnosis and therapy of thyroid diseases. Roughly during the period over which the Marshall Island observations have extended and to some extent before that time, a considerable number of experimental and clinical observations on this problem have been published and have been the subject of several reviews, notably by Doniach (19) and by Lindsay and Chaikoff (20). This work has led to at least a general understanding of radiation-induced thyroid abnormality.

As demonstrated by the Marshall Islanders, the abnormalities fall into two categories—one related to interference with thyroid cell function and the other concerned with the development of neoplastic changes. The Marshall Island findings also demonstrate very well the interplay between these two radiation effects.

In clinical practice, one of the major uses of radioiodine is to produce destruction of thyroid tissue—either the normal gland in patients with intractable angina pectoris, the hyperplastic gland in hyperthyroidism, or neoplastic tissue in metastasizing thyroid carcinoma. Since retention of iodine in the thyroid gland is unique among mammalian tissues, complete destruction can be readily attained by administering a suitably large dose of the isotope. This is achieved with a dose delivering about 50,000 to 75,000 rads. The thyroid tissue is then subject to acute radiation injury, with subsequent inflammation, tissue destruction, and fibrotic healing. This is the desired end result in heart disease and in thyroid carcinoma. In hyperthyroidism, however, the usual aim is to leave the patient with sufficient thyroid function to achieve euthyroidism. By properly adjusting the isotope dosage, this aim can be achieved in a high percentage of patients given about 10,000 rads to the gland.

Studies of these patients after partial thyroid destruction have led to some interesting observations. Injury to the various thyroid metabolic processes may not be uniform. Thus, in some of the patients the accumulation of radioiodine by the thyroid gland remains greater than normal although hormone secretion falls to normal or below. This is due to an injury to the iodine organification mechanism exceeding that to the iodide transport system (17, 18). As discussed earlier, the trapped but nonorganified iodine can be demonstrated by discharging it with an ion such as perchlorate, which competes with iodide for membrane transport. Other examples of uneven metabolic injury have not been described but probably exist.

On the other hand, thyroid function with respect to iodine metabolism and hormone production may appear to be normal in every respect, although the cell is gravely injured. This phenomenon has aroused considerable interest in recent years because only long after successful radiotherapy does this injury become manifest by the late onset of hypothyroidism (21, 22). One possible explanation for this phenomenon is that the radiation has led to lethal mutations in the chromosomes of the thyroid epithelial cells without damage to the rela-

tively small number of genes regulating the synthesis of proteins responsible for thyroid cell function. Cell division in the adult thyroid gland occurs very rarely, and mitosis is almost never seen in histological sections of the normal gland. Consequently, the lethal mutation may not be evident for a very long time. After many years, the cell begins to divide and perishes in the process. The cumulative effect of cell death could readily account for the observed accrual of hypothyroid cases at the rather steady rate of about 2%/year of those treated.

Thus, it is not unexpected to find that hypothyroidism developed insidiously in certain of the exposed Marshallese children. The radiation dose was not so large as to cause extensive cell destruction in the acute phase, but only later did the injured cells succumb.

The two clearly hypothyroid Marshallese children, like patients developing hypothyroidism after radioiodine therapy for hyperthyroidism, did not have any goiter formation. Evidently, the cells are sufficiently injured in these instances so that they fail to respond to the influence of the excess TSH secretion that must accompany falling thyroid function. This phenomenon was demonstrated directly by Doniach (23) who showed that rats treated with 30 μc ^{131}I, or 1,100 rads by X rays, failed to develop goiter when treated briefly with propylthiouracil. Maloof, Dobyns, and Vickery (24) also observed this phenomenon and postulated that, since the stimulated glands showed cellular hypertrophy but no increase in weight, there must have been an impairment of the ability of such irradiated cells to divide.

In the spectrum of radiation dosage to thyroid cells, one might expect to find the situation in which the cell's function is partially impaired but its growth potential is not. Alternatively, unequal damage to cells in the same gland may result in some with impaired function and growth potential and others with less severe injury. The net result could be the development of mild hypothyroidism or the maintenance of euthyroidism only as a result of continued overstimulation by TSH. Under such circumstances, those cells capable of responding may grow and multiply. Furthermore, if the radiation has produced a nonlethal mutation, the progeny of the cell may be abnormal.

This chain of events appears responsible for the majority of the cases of thyroid abnormality among the Marshall Islanders and is found in animals treated with appropriate doses of radioiodine especially when further stimulated by low-iodine diet or antithyroid drugs (19, 20). As pointed out in connection with the histological findings, the thyroid glands of the exposed Marshallese children showed results characteristic of excessive and prolonged thyroid stimulation. Such stimulation, with or without preceding irradiation, leads to the formation of thyroid nodules with a wide variety of histological cell types. Nodular goiter formation of this sort, however, is not limited to children. The explanation for the high prevalence of goiter in the children and the much lower prevalence in the exposed adults is most likely attributable to the fact that the small thyroid glands of the children received a larger, and hence more destructive, dose of radiation.

Sheline, Lindsay, McCormack, and Galante (25) also found in their follow-up of patients treated with thyroid radiation for thyroid disease that of the 8 patients developing thyroid nodules out of a total of 256, 6 had been irradiated before the age of 20 years and 4 before the age of 10 years. Indeed, the latter 4 represented two thirds of all those treated at an age younger than 10 years. Most of them had multiple nodules, much as were found in the Marshall Islanders. It may be that these younger subjects actually received larger radiation doses than the older ones. On the other hand, this seems unlikely to be the

case in these children, who had enlarged thyroid glands when treated, and it may be that the nodule formation was induced in the children by whatever stimulus there is that causes the thyroid to grow to its adult size. Radiation injury in general may be expressed as the product of the degree of cell damage times the mitosis rate of the cells (26), and the child's thyroid grows from about 2 g at age 1 year to 17 g in the adult (27).

The role of thyroid stimulation by TSH in the nodule formation after irradiation is clearly indicated by the findings of Maloof (28). In rats treated with ^{131}I, hypophysectomy or treatment with thyroxine prevented the cellular hypertrophy that was otherwise observed. It was of considerable interest that this treatment also greatly reduced the development of abnormalities in the thyroid cell nuclei (characterized by increase in size, irregularity, and hyperchromatism), thus indicating that these changes were due to cell stimulation rather than to irradiation per se. When thyroxine therapy was stopped, the lesions reappeared. This underscores the fact that thyroid radiation not producing obvious atrophy, inflammation, and fibrosis does not appear to cause any specific cell abnormality recognizable by ordinary histological examination.

Last, I shall discuss the subject that was uppermost in the minds of those who observed the development of what appeared clinically to be solitary thyroid nodules in these children. That is the problem of radiation-induced thyroid carcinoma. Two sorts of evidence have led to the clear demonstration that irradiation is a contributing cause in the development of thyroid cancer. Although thyroid cancer can be produced in animals simply by prolonged thyroid stimulation resulting from iodine deficiency or chronic administration of antithyroid drugs (29), there is abundant experimental evidence to show that the prevalence is increased by antecedent thyroid irradiation (19, 20) just as it is by concomitant treatment with a carcinogen such as acetaminofluorene (19, 29). As demonstrated by the experiments of Doniach (19), summarized in Table 11, the effect of 30 μc of ^{131}I in the rat is similar to that of 1,100 rads of X-ray radiation. This is in the range of radiation dosage to which the Marshall Island children were exposed. It is of interest, also, that the radiation in Doniach's rats increased the prevalence of multinodularity of the thyroid glands in response to goitrogen.

The failure to find thyroid carcinoma in any of the Marshallese children can be attributed, it seems, to a happy chance. There remains a high likelihood that carcinoma would develop in the thyroid remnants remaining in the operated cases, as well as in those not operated upon, unless this is prevented by the administration of suppressive doses of thyroid hormone. The ability

TABLE 11. Induction of Thyroid Tumors in Rats*

Treatment	Rats	With Adenomas	With Adenomatous Replacement	With Carcinomas
	←	*no.*		→
None	41	0	0	0
Methylthiouracil (MTU)	50	39	0	0
30 μc ^{131}I (1,500 rads to thyroid)	52	21	0	0
30 μc ^{131}I + MTU	48	47	27	11
1,100 rads X rays to thyroid	13	4	1	1
1,100 rads X rays + MTU	22	21	17	7

* From Doniach, I: *Brit. Med. Bull.* 14: 181, 1958 (19).

of such TSH suppression to prevent the development of thyroid carcinoma has been shown experimentally in rats (30).

The one carcinoma in the Marshallese adult is quite different from the type of disease about which we have thus far been concerned, since there was no hyperplasia of the surrounding thyroid gland. This was typical, then, of the usual case of thyroid carcinoma occurring in a nonirradiated population. On the other hand, there is considerable evidence that thyroid carcinoma in young adults, and especially in children, is frequently caused by radiation of the cervical area in childhood. Lindsay and Chaikoff (20) have reviewed the various clinical reports on this subject, and Winship and Rosvoll (31) reported that as many as 80% of children with thyroid carcinoma, in a series of 562 cases, have a history of prior cervical irradiation. The amount of radiation, which is usually given in the form of X-ray therapy for thymic hypertrophy or tonsillitis, can be even smaller than that in the Marshallese population, being in the range of 90 to 1,300 rads. This was the dose range in a prospective study of over 4,500 patients in whom thyroid carcinoma developed, on the average, 11 years later in approximately 0.5% of persons exposed to such radiation (20, 32, 33). Although adults may not be immune to radiation-induced tumors—as suggested by the apparent increased prevalence of thyroid cancer in adults exposed to the atomic bomb in Hiroshima (34) and other types of radiation (35, 36)—the propensity for this sequela in children is almost surely related to the fact that in the cells of the growing thyroid gland there must be numerous mitoses, whereas mitoses in the adult gland are rare. The gene alterations leading to cancer formation presumably require cell division for their expression.

It appears clear that the sizable amounts of irradiation that we have been discussing have the potential to produce thyroid neoplasms in a significant number of exposed individuals. It would also seem likely that lesser amounts of radiation, every direct hit on a gene being effective, might also lead to cancer formation. This, however, becomes a problem in disease statistics and is one that is currently engaging the interest of many, thus far with no clear-cut answers. The experience in the Marshall Islands has, at least, served to illuminate one portion of the spectrum of thyroid radiation effects in man.

I would now like to call for questions.

DR. WOLFF: What fraction of the radiation was from ^{131}I?

DR. CONARD: Probably less than half.

DR. WOLFF: In connection with that, was there any ^{129}I? Have you gotten any counts on the material that was removed surgically?

DR. RALL: ^{129}I has a half-life of approximately 17 million years, so that essentially it is unradioactive. For any such molecules in the lifetime we are talking about, they do not decay but are still there to be measured by neutron activation. The question is, would there be any there? Well, we do not know. Maybe we should have measured it. Maybe there is still tissue left. I am afraid that 10 years of biological turnover in the affected individuals would leave almost none of the original iodine around for measurement.

DR. JESSE ROTH: With hyperthyroid patients who have been treated with radioiodine it is common to see a defect where the early uptake of iodine is high, but then a large portion of this iodine is not organified. I was curious as to why it did not seem to show up in these radiated groups.

DR. ROBBINS: I have no real answer. There is a difference in the radiation delivered: The hyperthyroid patients get about 10,000 rads, and these children got about 1,000 rads. Also, these were children who did not have so much damage that they could not grow nodular goiters. The hyperthyroid patients are probably dam-

aged further, but the Marshallese who had greater damage had no uptake, and so we could not test for an organification defect. It is probably a dose effect.

DR. WELLINGTON MOORE: We investigated chromosome changes in Chinese hamster thyroid cells after the administration of different doses of ^{131}I to animals 7 to 10 days of age. Thirty days and a year after injection the thyroids were removed, trypsinized, and cells grown in tissue culture for 3 days. The cells were arrested in metaphase, fixed, and stained for chomosomal analysis. It was found that thyroid cells were quite sensitive to irradiation. Doses as low as 6 rads produced a tenfold increase in the number of cells containing aberrations at 30 days (3.3% versus 0.31% in the control cells). Twenty-five percent of the thyroid cells contained aberrations at a dose of approximately 1,000 rads at 30 days. After 1 year the aberration rate had decreased by three- to fourfold. This was due in part to the increase in gland size associated with the normal growth of the animals. The persistence of the aberrant thyroid cells (approximately one third of the life span) suggests that some of these damaged cells may persist for the remainder of the animal's life.

DR. ROBBINS: Thank you for the comment. That is another area I did not get into because of time. It is of interest that Drs. A. A. Al-Saadi and W. H. Bierwaltes at the University of Michigan School of Medicine have been studying chromosomal aberrations in animals and find aberrations resulting from iodine deficiency and other forms of thyroid stimulation, so they may not be limited to radiation effects, although certainly that could be a contributing cause.

DR. CONARD: Attempts were made to do chromosome studies on cultured thyroid tissue from the operative specimens on the Marshallese. Unfortunately, they were not successful.

SUMMARY

The presence of radioactive isotopes of iodine in fallout from atomic explosions is well known. In the accidental exposure of the inhabitants of one of the Marshall Island after a fusion-type explosion in 1954, thyroid radiation from radioiodine, particularly in the children, was sizable. This resulted in the late development of thyroid insufficiency or thyroid nodules or both in 80% of those children exposed at less than 10 years of age. At the present time, the thyroid effects constitute the only important overt medical problem in the exposed population. Detection of thyroid damage was hindered by its insidious onset and by the unexpected occurrence of elevated blood levels of iodoprotein in the Marshallese population. The greater prevalence of thyroid abnormality in the children is probably due to two factors: a larger radiation dose due to small thyroid size and a greater likelihood of the growing organ to manifest changes resulting from chromosomal alterations. The spectrum of radiation exposure of the thyroid glands in any population is very wide, ranging from stratospheric fallout from atomic explosions and clinical testing with radioiodine isotopes to high radiation rates intentionally produced in therapy of thyroid diseases. The Marshall Island experience will help to define the range in which significant thyroid damage may occur.

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Summario in Interlingua

Le presentia de isotopos radioactive de iodo in le precipitation atmospheric ab explosiones atomic es ben cognoscite. In le exposition accidental del habitantes de un del Insulas Marshall al effectos de un explosion del typo fusional in 1954, le irradiation radio-iodic del thyroides—particularmente de juveniles—esseva considerabile. Isto resultava in le disveloppamento tardive de insufficientia thyroide e/o de nodulos thyroide in 80 pro cento de ille juveniles. Al tempore presente, le effectos thyroide constitue le sol importante patente problema medical in le exponite population. Le detection de damnification thyroide esseva impedite per le lente modo de su declaration e per le inexpectatemente alte concentrationes sanguinee de iodoproteina in le population marshallese in general. Il es probabile que le elevate incidentia de anormalitates thyroide in le juveniles es le effecto de duo factores: (1) Un major intensitate del irradiation in consequentia del minor dimensiones del thyroide e (2) un plus forte susceptibilitate de un organo in crescentia pro manifestar alterationes causate per interferentias chromosomal. Le spectro de possibilitates de exposition del glandulas thyroide a irradiation es extense in omne population. Illo include precipitation stratospheric ab explosiones atomic, tests clinic con isotopos radioactive de iodo, e alte intensitates de irradiation intentionalmente producite in le therapia de morbo thyroide. Le experientia marshallese va adjutar in definir le region de intensitates irradiatori associate con le occurrentia de significative damnos thyroide.

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