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R. A. Conard, M.D., J. E. Rall, M.D., Ph.D., and W. W. Sutow, M.D.

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NODULES of the thyroid gland have been discovered during the past three years in a number of people of Rongelap Island who had been accidentally exposed to radioactive fallout in 1954. The accident was the result of an unpredicted shift in winds after the experimental detonation of a large thermonuclear device at Bikini in the Marshall Islands, which caused radioactive fallout to be deposited on 4 inhabited Marshall Islands to the east. Inhabitants of Rongelap Atoll, about 100 miles away, received the largest amount of fallout. The somatic effects of this radiation have been well documented in a number of medical reports and are summarized elsewhere.[1,2]

This report concerns the recent development of thyroid abnormalities among the 82 people of Rongelap Atoll who received the largest exposure to fallout radiation. Sixty-four of these people were on their home island when the detonation occurred. Eighteen others were fishing on the nearby atoll of Ailinginae. They saw the blinding flash of the detonation in the early morning, followed by a white, snow-like fallout throughout that day. The people on Rongelap Island received the largest exposure: 175 rads of whole-body gamma radiation, thousands of rads to the skin (largely beta) from deposit of fallout material on the body and significant amounts of radionuclides absorbed by inhalation and consumption of contaminated food and water. The 18 people on Ailinginae received less than half the exposure of the other Rongelap people. Both groups were evacuated two days after the accident and lived in a temporary village on a southern island in the Marshall group until 1957, when the radioactive levels had subsided sufficiently on Rongelap to allow their return. During the years after the accident, over 200 Rongelap people or their relatives who had not been exposed to fallout returned to live with the exposed people, and this group has formed an excellent comparison population.

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SUMMARY OF EARLY FINDINGS

The whole-body dose of radiation received proved to be sublethal. Aside from widespread anorexia, nausea and a few cases of vomiting and diarrhea, along with irritation of the skin occurring during the first two days, the most notable effect of the exposure was depression of the blood-forming tissues. Although the peripheral leukocyte counts were reduced to about one half to one third of the normal levels and the platelets to about one third to one eighth of the normal values during the first five or six weeks, neither infection nor bleeding clearly related to radiation effects (except possibly menorrhagia in a few women) was observed. Recovery of peripheral blood elements was nearly complete by one year but lagged thereafter; the mean levels remained slightly below those of the comparison population through ten years post exposure. However, the survey at eleven years showed levels of peripheral blood elements that appeared to be about the same in the exposed as in the unexposed people.

Radiation lesions ("beta burns") of the skin and spotty epilation of the head were widespread, beginning about two weeks after exposure. The most common sites for the burns were the head, neck, axilla, antecubital fossae and dorsa of the feet. Most of the lesions were superficial and healed without grossly visible sequelae. However, some of the lesions were deeper and resulted in pigment changes and scarring that have persisted. The hair in all cases regrew in six months and was normal in color and texture.

Absorption of radionuclides in the fallout from inhalation and from consumption of contaminated food and water was detected by radiochemical analyses of urine. The highest body burdens occurred during the first two days on the Island before they were evacuated, when they were exposed to an envi-

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ronment highly contaminated with radioactive material. The radioisotopes of strontium, barium and iodine, along with some of the rare earths, were absorbed in greatest amount. Probably, only isotopes of iodine exceeded the accepted permissible levels. No acute effects of exposure from the internally absorbed radionuclides were observed. Since their return to Rongelap in 1957 the people have been exposed to low levels of certain residual radionuclides – namely, Cs^{137}, Zn^{65} (this is an induced radioelement) and Sr^{90}. Body burdens appear to have reached equilibrium with the environmental levels of these elements, and are well below the accepted permissible range.

Later Findings

Evaluation of the general health status, illnesses, mortality, fertility and aging over the eleven years since exposure has revealed no significant differences between the exposed and the unexposed populations that could be attributed directly to radiation. The slight lag in recovery of peripheral blood elements has not affected their resistance to disease and immunologic competence. Although the birth rate has been about the same in the exposed and unexposed groups there was an apparent increase in miscarriages and stillbirths in the exposed women as compared with the unexposed women over the four years after exposure (41 per cent, or 13 of 32 pregnancies in the exposed, as compared with 16 per cent, or 8 of 49 pregnancies in the unexposed women over a comparable period). A few congenital abnormalities have been observed in babies born to exposed women, but no correlation with radiation seems possible at present. Slit-lamp observations have failed to reveal radiation-induced opacities of the lens. Studies of growth and development[3] comparing 42 exposed with 75 unexposed children have revealed a slight retardation of growth in the boys exposed at one to five years of age, most marked in those exposed at twelve and eighteen months of age. The possibility that radiation was a causative factor will be discussed later.

Consideration of the Radiation Dose to the Thyroid Gland

Calculation of the dose to the thyroid gland from radioactive iodine requires knowledge of its uptake by the gland, its half-life in the gland, the size of the gland and the relative proportion of the several radioisotopes of iodine. Unfortunately, in the present situation few data of a direct nature are available. The relative distribution of radioiodines in fallout is well known. In addition to I^{131}, the isotopes of I^{133}, I^{135} and to a lesser extent I^{132} contributed significantly to the thyroid dose. The only data available are radiochemical analyses of pooled urine samples taken fifteen days and longer after the fallout. Three separate estimates of the dose to the thyroid glands of adult Rongelap people from radioiodines have been made: 150 rads (from direct measurements of urinary I^{131})[4]; 100 rads (by indirect measurements using animals – pigs removed from Rongelap – and Marshallese urinary-excretion data)[5]; and 160 rads (based on recent recalculations of early data).[6] The last recalculations[6] were based on analysis of pooled urine samples mainly from adult Rongelap people taken fifteen days after detonation; an estimate of the one-day thyroid content of I^{131} was 11.2 microcuries (5.6 to 22.4 microcuries) assuming that 0.1 per cent (0.05 to 0.2 per cent) of the maximum thyroid burden was excreted in the urine on the fifteenth day. The dose of 160 rads to the adult thyroid gland was calculated from oral intake and inhalation of the various iodine isotopes, considering their fission yield, the average energy deposited in the thyroid gland per disintegration and the time of absorption. The dose to the thyroid glands of children three to four years old was then calculated by means of these factors with consideration of pulmonary function and the thyroid size[7] of a child that age. Water was regarded as the main source of iodine ingestion, and since water was being rationed at the time of the fallout, it was assumed that the children drank the same amount of water as adults and therefore had the same thyroid burden of radioiodines. Because of the small size of the gland the beta dose of radiation to the gland was substantially larger. The total estimated dose from the various iodine isotopes to the child's gland was about 1000 rads, with a minimum of about 700 rads and a maximum of 1400 rads. The glands received an additional 175 rads from external gamma radiation. Details of these calculations have been given by James and Gofman.[6]

Though the skin overlying the thyroid gland was frequently the site of "beta burns" it is not believed that the deposits of radioactive materials in this area added significantly to the thyroid dose since most of the beta irradiations were of insufficient energies to have penetrated to the depth of the gland.

Abnormalities of the Thyroid Gland

Physical examinations have always included careful inspection of the thyroid region in both exposed and unexposed comparison groups. In addition, determinations of the level of protein-bound iodine and cholesterol in serum have been carried out at various intervals since 1959 in some persons. Until 1963 no thyroid abnormality was detected in either the exposed or the comparison population, except for 1 case of asymptomatic diffuse thyroid enlargement seen in an unexposed woman. The average level of serum protein-bound iodine was found to be elevated in both the exposed and comparison populations. It is believed that this is a racial characteristic, and that the increase is partly due to an increased level of the iodoprotein fraction of serum.[8] No significant differences were noted between the mean protein-bound iodine and cholesterol levels in

the exposed as compared with the unexposed population. Determinations of basal metabolic rate were not done owing to difficulties of carrying out the procedures under field conditions. Dietary iodine has apparently been adequate. In 28 cases the mean twenty-four-hour urinary iodine excretion was 105 microgm. (range, 19.5 to 279 microgm.).

In 1963, nine years after the accident, a twelve-year-old girl in the exposed group was found to have a nodule of the thyroid gland. In 1964, 2 additional cases with thyroid nodules were found in exposed girls thirteen and fourteen years old. In March, 1965, 3 additional cases in exposed people were noted in boys thirteen and eighteen years of age and in the first adult, a forty-one-year-old woman. In September, 1965, a further examination was carried out, and 5 additional exposed people with nodules varying in size from 2 to 8 mm. were found. One of these was a forty-five-year-old woman in the group that received only an estimated 69 rads. In addition, there were 5 people in whom the thyroid gland appeared to be roughened or minimal nodularity was considered likely. These cases are not included in Table 1 because of the minimal nature of the physical findings. Table 1 lists the cases with thyroid abnormalities. Table 2 shows the incidence of thyroid disease in the more heavily exposed group of 55 living Rongelap people as a function of age. The 1 case in the less exposed group of 16 is not included. Not including the 5 recent cases with minimal changes, the incidence of thyroid abnormalities (nodules in addition to hypothyroidism) was highest in the children exposed at less than ten years of age (55 per cent of this group). The greater incidence in females (8 of 16) than in males (5 of 13) exposed is in line with the greater incidence of thyroid abnormalities usually noted in the female.

The first 6 patients have been hospitalized and have undergone surgery. These cases are briefly summarized below. Their response to the radiation was similar to that outlined above, and only specific differences are noted here.

Case Reports

Case 1. a 14-year-old Marshallese girl, was 3 years old when exposed to radioactive fallout. Her response to this radiation was typical of the group. Clinically, she has remained euthyroid throughout the period of observation (in 1957 the cholesterol was 135 mg., and in 1964 the protein-bound iodine was 6.8 microgm. per 100 ml.).

In March, 1963, she was found to have a 2-cm. nontender, firm nodule of the left lobe of the thyroid gland. In August, 1964, a total thyroidectomy was performed, with dissection of the anterior compartment of the neck. (It was at first thought from the frozen section that the nodules were malignant.) Grossly, the glands showed multiple nodules with cystic and hemorrhagic areas (Fig. 1). The gland weighed 12 gm. The pathological diagnosis was adenomatoid goiter. The microscopical appearance was reported as follows:

> Among the nodular formations . . . there are adenomatoid nodules, with and without regeneration and hemorrhage, and adenomas, some consisting of very pale, almost clear cells. Numerous papillary formations present are somewhat alarming. However, no evidence of malignant change is found. In some places the intranodular thyroid tissue is arranged in lozenge-shaped masses associated with somewhat atypical cells.

The recovery from the operation was uneventful except for a transitory episode of hypoparathyroid tetany, and the patient is being treated with levothyroxine, 0.3 mg. per day.

Case 2. , a 14-year-old Marshallese girl, was exposed to fallout at 3 years of age and showed a typical course. She was apparently euthyroid during repeated examinations (the protein-bound iodine being 7.4 microgm. in 1958 and 8.1 microgm. per 100 ml. in 1964, and the cholesterol being 128 mg. per 100 ml. in 1959).

In March, 1964, a firm, nontender nodule, 1.5 cm. in diameter, was discovered in the left lobe of the thyroid gland. In August, 1964, a total thyroidectomy was per-

Table 1. *Thyroid Abnormalities in Exposed Marshallese.**

Patient	Present Age	Age at Exposure	Sex	Date Abnormality Noted	Diagnosis	Treatment
	yr.	yr.				
	14	3	F	3/63	Adenomatoid thyroid nodules	Complete thyroidectomy (1964)
	14	3	F	3/64	Adenomatoid thyroid nodules	Complete thyroidectomy & parathyroidectomy (1964)
	15	4	F	3/64	Adenomatoid thyroid nodules	Partial thyroidectomy (1964)
	18	7	M	3/65	Adenomatoid thyroid nodules	Partial thyroidectomy (1965)
	12	1	M	3/65	Adenomatoid thyroid nodules	Partial thyroidectomy (1965)
	41	30	F	3/65	Papillary & follicular thyroid carcinoma	Thyroidectomy—surgical & with radioiodine (1965)
	17	6	F	9/65	3-mm. nodule of left lobe	Levothyroxine, 0.3 mg./day
	14	3	F	9/65	2-mm. nodule of right lower lobe	Levothyroxine, 0.3 mg./day
	19	8	F	9/65	6-8-mm., smooth nodule of left lower pole	Levothyroxine, 0.3 mg./day
	40	29	M	9/65	2-mm. nodule of right lower pole	Levothyroxine, 0.3 mg./day
	45	34	F	9/65	5-mm. nodule at midline	Levothyroxine, 0.3 mg./day
	12	1	M	3/65	Hypothyroidism protein-bound iodine < 2 microgm./100 ml. (Mar. 1965); marked retardation of growth.	Levothyroxine, 0.3 mg./day
	12	1	M	3/65	Hypothyroidism protein-bound iodine < 2 microgm./100 ml. (Mar. 1965); marked retardation of growth.	Levothyroxine, 0.3 mg./day

*Does not include 5 patients believed to have minimal thyroid irregularities (2 were 12-yr. old girls, 1 a 26-yr.-old woman, & 2 men 31 & 37 yr. of age); no thyroid nodules detected in 200 unexposed Rongelap people.
†Exposed to only 69 r of whole-body radiation (see text).

TABLE 2. *Thyroid Abnormalities in the More Heavily Exposed Marshallese Group.**

Exposure rads	No. Exposed	Nodules		Hypothyroidism		Total Abnormalities	
		No. of cases	Percentage	No. of cases	Percentage	No. of cases	Percentage of group
0-5	13	5	38.5	2	15.4	7	53.8
6-10	5	3	60.0	—	—	3	60.0
11-15	5	0	0.0	—	—	0	0.0
16-20	6	0	0.0	—	—	0	0.0
> 20	26	2	7.7	—	—	2	7.7

*5 cases with minimal thyroid abnormalities not included; 1 45-yr.-old woman in less exposed group in whom thyroid nodule developed also not included.

formed. The gland was multinodular, with nodules up to about 1 cm. in diameter, and weighed about 12 gm. The histopathological diagnosis was adenomatoid goiter. The histologic description was as follows:

> The thyroid sections . . . show multiple adenomatoid nodules of widely varying pattern. Most of them contain papillary formations that make it necessary to consider the possibility of carcinoma. Although a few microscopical fields on high-power examination appear bizarre it is believed that the overall picture does not justify a diagnosis of neoplastic disease.

A state of persistent hypoparathyroidism followed the operation, necessitating the use of vitamin D_2 as well as thyroid-replacement therapy.

CASE 3. , a 15-year-old girl, was exposed to fallout at the age of 4 with signs and symptoms typical of the group. In March, 1964, at 14 years of age, she was found to have a small, nontender thyroid nodule (2 or 3 mm. in size) in the isthmus. The right lobe, isthmus and medial half of the left lobe were removed. Many nodules were present, varying in size up to 5 mm. in diameter. The following was reported:

> The normal thyroid architecture is effaced by small nodules showing varying degrees of atrophy and hyperplasia. Some nodules consist of microfollicular tissue, and some show luxuriant papillary growth, whereas others are colloid cysts with flattened epithelium. There are foci of hemorrhage and calcification. Dense fibrous septums separate nodules. The diagnosis was adenomatoid goiter.

Recovery was uneventful, and the patient is being treated with levothyroxine, 0.3 mg. per day.

CASE 4. , a 12-year-old boy, was exposed to fallout at 1 year of age. During the ten-year period after exposure, he was found to show a lag in growth, based on anthropometric studies and radiographic determination of bone age, so that he has continued 1 to 1½ years behind unexposed children of his age. He has had no obvious evidence of thyroid malfunction. During the past several years 2 determinations of protein-bound iodine and 1 of cholesterol have been within the normal range. He has remained in generally good health.

In March, 1965, he was found to have a 2-cm., nontender but firm, freely movable nodule in the right lobe of the thyroid gland. No lymphadenopathy was palpated. He was taken to Brookhaven National Laboratory in June. Thyroid-function tests showed the following results: serum iodine fractionation (by column chromatography[8]) was 7.1 microgm. total, 2.0 microgm. iodoprotein and 4.2 microgm. per 100 ml. thyronine fraction ($T_4 + T_3$); the cholesterol was 167 mg. per 100 ml., with 145 mg. in the esterified form; thyroid autoantibodies (the tanned red-cell technic was used in all these determinations) indicated a titer under 1:16; the basal metabolic rate was −23 per cent; a thyroid scan (Tc^{99M}) showed possible nodularity of the right lobe; studies of I^{132} uptake disclosed a level of 39 per cent at 6 hours. After TSH stimulation with 10 *USP* units daily for 3 days the uptake showed a slight decrease, with no increase in the level of protein-bound iodine. Hematologic examination and x-ray study of the chest were considered to be within normal limits.

The right lobe of the thyroid gland was removed at the New England Baptist Hospital and showed multiple nodules up to 1.2 cm. in diameter. The pathological diagnosis was adenomatous goiter.

Recovery from surgery was uneventful, and in September, 1965, treatment with levothyroxine was instituted.

CASE 5. an 18-year-old Marshallese boy, was exposed to fallout at the age of 7. Since recovery from the acute effects of radiation he has been in generally good health, and thought to be euthyroid (in 1958 the protein-bound iodine was 7.0 microgm. per 100 ml.). Compared with unexposed boys of the same age, however, he had shown a slight degree of retardation in growth based on anthropometric and bone-age studies.

In March, 1965, a firm nodule, 1.5 cm. in diameter, was noted in the lower right pole of the gland. He was taken to Brookhaven National Laboratory for study and later to the New England Baptist Hospital for surgery. Thyroid work-up showed the following data: iodine fractionation of serum indicated a total iodine of 6.5 microgm., iodoprotein of 1.3 microgm. and thyronine ($T_4 + T_3$) of 4.2 microgm. per 100 ml.; thyroid autoantibodies were under 1:16; the cholesterol was 170 mg. per 100 ml., with 144 mg. in the esterified form; the basal metabolic rate was −12 per cent; a thyroid scan (Tc^{99M}) showed a "cold" nodule in the lower right lobe; studies of I^{132} uptake revealed 40 per cent uptake in 6 hours, with 32.5 per cent urinary excretion at that time. After TSH, 10 *USP* units daily for 3 days, the uptake at 6 hours was 33.7 per cent, with a urinary excretion of 18.5 per cent. The protein-bound iodine at that time was about the same as before TSH stimulation. Films of the chest and an electrocardiogram were normal. Hematologic studies were not remarkable.

The right lobe of the thyroid gland containing multiple nodules was removed. The nodules varied in size up to 1 cm. and were pale gray to deep red, firm and pulpy and semicystic. The diagnosis was adenomatous goiter.

CASE 6. , a 41-year-old Marshallese woman, was exposed to fallout at 30 years of age. Since recovery from radiation she has remained in relatively good health, with no serious illnesses or injuries. She has had 9 children, 4 of them born since the fallout exposure. She has apparently remained euthyroid. The protein-bound iodine in March, 1965, was 10.0 microgm. (high normal for the Marshallese), and the serum cholesterol in 1958 was 249 mg. per 100 ml.

In March, 1965, a 1-cm. nodule, hard but not tender, was found in the right lower pole of the thyroid gland. No lymphadenopathy was detectable. She was taken to Brookhaven National Laboratory for study and later to the New England Baptist Hospital for surgery. Thyroid work-up revealed the following values: on serum iodine fractionation the total iodine was 8.5 microgm., the iodoprotein fraction 4.5 microgm., the thyronine fraction ($T_4 + T_3$) 3.4 microgm., and the protein-bound iodine 7.5 microgm. per 100 ml.; the serum cholesterol was 239 mg. per 100 ml. (in the esterified form, 183 mg.); the basal metabolic rate was −27 per cent;

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thyroid autoantibodies were present in a titer under 1:16. A thyroid scan showed a large "cold" nodule replacing the lower pole of the right lobe of the gland. X-ray examination of the chest and bones gave no evidence of metastatic lesions. A study of thyroid uptake with I^{132} showed a 6-hour value of 22.3 per cent, with urinary excretion of 33 per cent. After treatment with TSH, 10 units daily for 3 days, thyroid uptake had increased to 33 per cent, and the protein-bound iodine was 8.0 microgm. per 100 ml. Hematologic studies were not contributory.

A subtotal thyroidectomy, leaving a small portion of the left lobe, was carried out. It was reported that 2 nodules, each approximately 1 cm. in diameter, were present, and the pathological diagnosis was "mixed papillary and follicular carcinoma of right lobe, with blood-vessel invasion and metastasis to 1 lymph node and normal right parathyroid gland; (the left lobe of the thyroid gland shows no significant changes)."

Recovery from the operation was uneventful. The patient was then given 10 units of TSH daily for 3 days, and on the 4th day, 30 mc. of I^{131} to destroy the remaining thyroid tissue. The subsequent course has been uneventful, and treatment with levothyroxine was started in August, 1965.

Gross Appearance of the Thyroid Glands

In all 5 children operated upon (Cases 1-5) the multinodular character of the glands was notable at surgery although on prior clinical examination, the nodules had appeared to be solitary. The nodules varied in size from 1 mm. to several centimeters, in consistence from fluctuant to relatively hard and in color from pale gray to pink to red; cyst formation was present in many, and some had hemorrhagic areas. Figure 1 shows the gross appearance at operation in Case 1. In the patient with carcinoma (Case 6) the gland did not show the same degree of nodularity, except for the presence of 2 firm, yellow nodules about 1 cm. in diameter (Fig. 2).

Microscopical Appearance

The microscopical appearance of all the benign nodular glands was characteristic of adenomatoid goiter and varied mainly in the degree of change. The architecture of the gland was disrupted by the nodules of widely varying sizes, some containing microfollicular elements with and without colloid; others were atrophic, some contained large cysts with colloid, some with hemorrhage, and still others showed extensive proliferation of the epithelial layers with marked infolding, giving an "arboreal" appearance. Figure 1 indicates some of the changes.

The tumor in Case 6 showing papillary and follicular carcinoma, with invasion of blood vessels and a lymph node, is demonstrated in Figure 2.

Thyroid Abnormality in Boys Showing Retarded Growth

Two twelve-year-old boys (. and .), who had been exposed at fifteen and eighteen months of age respectively, have had the greatest retardation of growth and development. . (Fig. 3) has shown no change in bone maturation since 1961 and at present has a bone age of that of a three-year-old child. The bone age of . has showed continuing slow growth and in 1965 was five and a

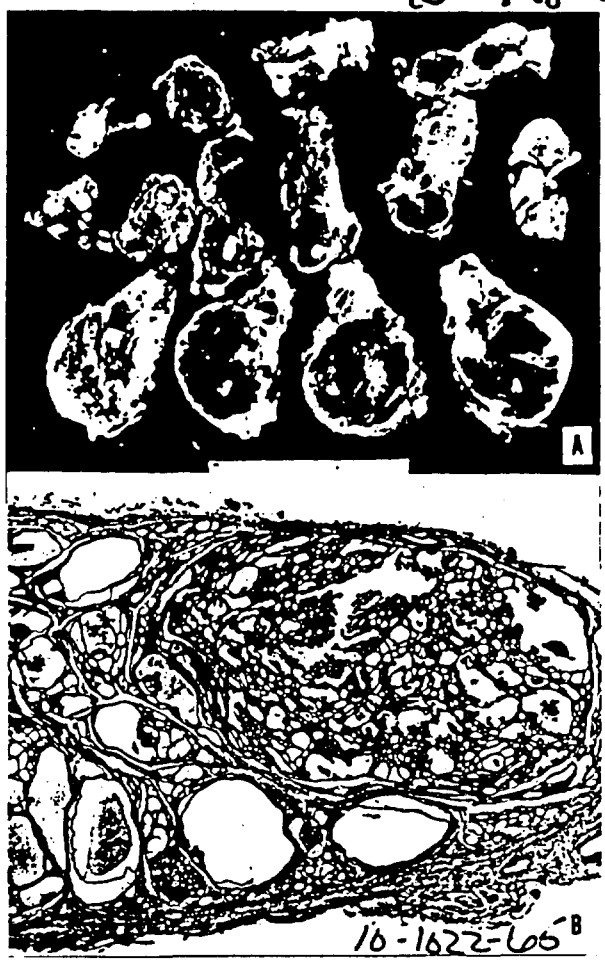

FIGURE 1. *Benign Adenomatoid Thyroid Nodules in a Fourteen-Year-Old Girl ( ).*

The gross specimen of the sectioned gland (A) *indicates the nodular character. The microscopical section* (B) *shows wide variations in follicle sizes (original magnification X14): some are small and atrophic, and others are large and cystic. The nodule at the upper right shows hyperplasia, with papillary infolding of epithelium.*

half years. Both these boys in 1965 have the height of normal seven-year-old Marshallese boys. Their dwarfism has been particularly marked in comparison with younger siblings who now are taller than they are (Fig. 3).[3] During the past year in both cases the levels of protein-bound iodine have dropped below 2 microgm. per 100 ml. Before that time they had levels in the normal range, and they had been considered to be euthyroid. They now have definite signs of hypothyroidism, with nonpalpable thyroid glands, and Achilles reflexes with the typical sluggish return. These boys do not appear to show mental retardation. TSH levels (in March, 1965) were elevated in both boys (more than 120 and 119 millimicrogm. per milliliter), corroborating the impression of primary hypothyroidism.* Other exposed male children in the retarded group (but

*We are indebted to Dr. William Odell, at the National Institutes of Health, for carrying out the TSH determinations.

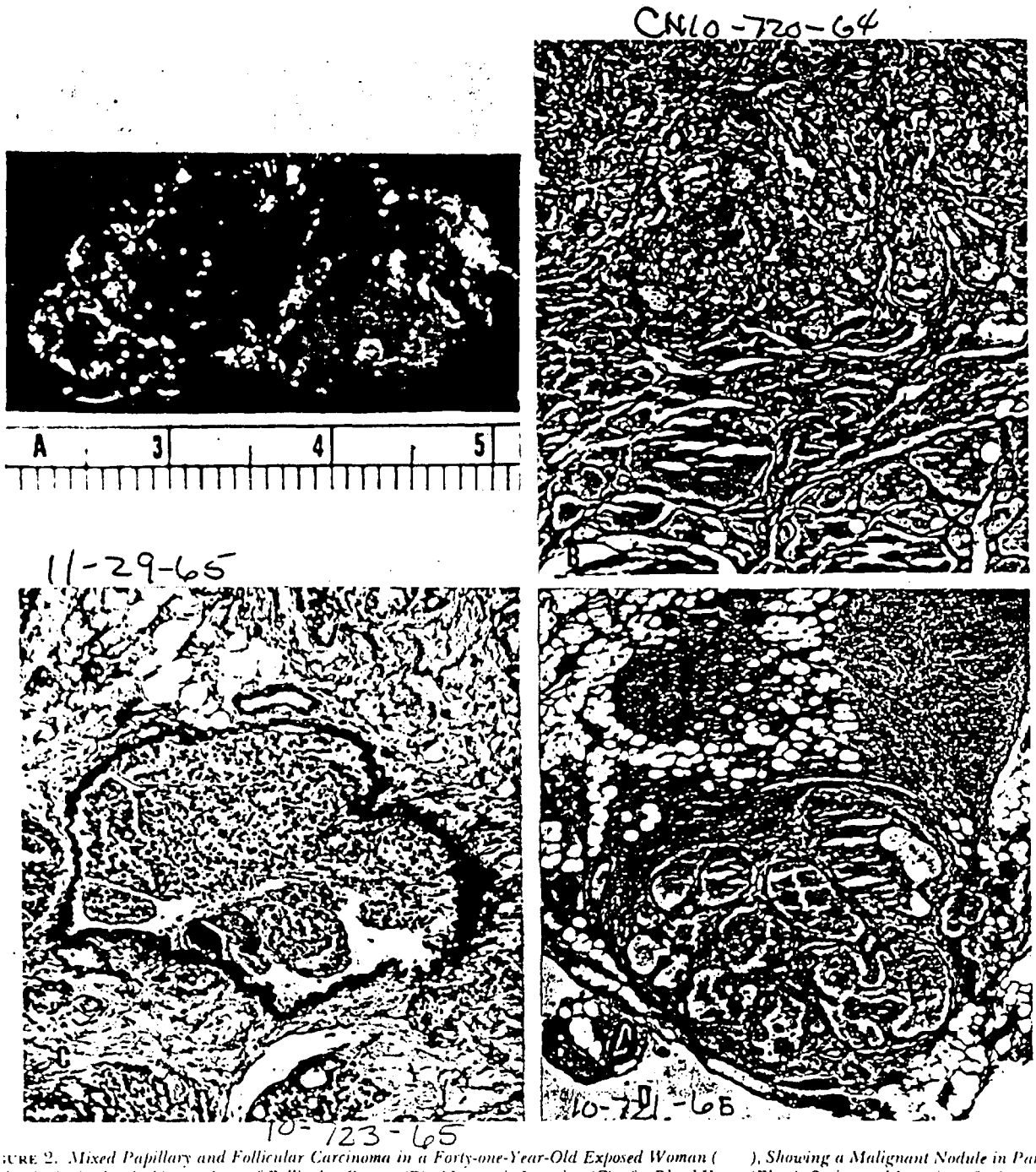

FIGURE 2. *Mixed Papillary and Follicular Carcinoma in a Forty-one-Year-Old Exposed Woman ( ), Showing a Malignant Nodule in Part of the Excised Gland* (A), *an Area of Follicular Cancer* (B), *Metastatic Invasion* (C) *of a Blood Vessel (Elastic Stain) and Invasion of a Lymph Node* (D).

less retarded than these patients) have levels of protein-bound iodine that have remained normal. However, it is significant that recent TSH determinations showed slightly elevated levels in 2 of the less retarded children. Two of the boys (and .) with thyroid nodules were in the group with retardation of growth and development. It is interesting in these latter cases that, though the levels of protein-bound iodine were normal, 1 had a slightly elevated TSH level (9.6 millimicrogm. per milliliter), and both showed almost no response to TSH stimulation. The possible correlation of growth retardation with thyroid irradiation will be discussed later.

After extensive discussion, it was decided to institute treatment with levothyroxine in the more heavily exposed group, which was done in September, 1965.

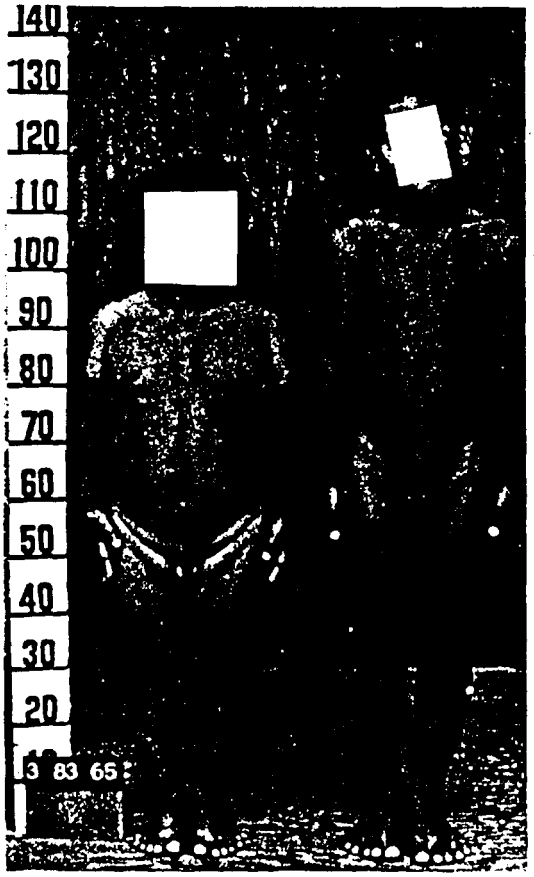

FIGURE 3. *Marked Growth Retardation and Hypothyroidism in a Boy Exposed to Fallout at Eighteen Months of Age.*
The taller boy standing beside him is his brother, who is a year younger.

outside Neg

DISCUSSION

Adenomas and cancers of the thyroid gland can be produced in laboratory animals by a variety of agents or regimens that interfere with the ability of the gland to synthesize thyroid hormone. Iodine deficiency,[9] agents that chemically inhibit thyroxine synthesis such as thiouracil,[10-14] x-irradiation of the gland,[15-17] and irradiation of the gland with I^{131},[18-20] have all been shown to produce both benign and malignant neoplasms. Furthermore, subtotal thyroidectomy in the rat has been reported to cause adenoma formation in the remaining thyroid tissue two years later.[21,22] All these procedures produce hypothyroidism of varying degree, which serves as an effective stimulant to the secretion of TSH by the pituitary gland. Under the influence of TSH the thyroid gland first undergoes diffuse hyperplasia and hypertrophy and finally adenoma formation. In the cases of iodine deficiency and partial thyroidectomy, it is probable that no drug or carcinogenic agent is involved; also, the incidence of carcinomas after these treatments is relatively low. The incidence of thyroid carcinoma after a combination of a carcinogenic agent (such as radiation or acetylaminofluorene) and any factor that causes hypothyroidism is much higher.[23] Radiation by either x-rays or I^{131} is particularly effective since it simultaneously acts as a carcinogen and, by impairing the functional capacity of the gland, also induces TSH secretion and thyroid stimulation.

Several aspects of radiation damage may be considered. Cytoplasmic damage may result in enough functional damage to result in cell death, or repair may occur if the damage is not too extensive. Injury to nuclear material may result in death of the cell if enough deoxynucleic acid (DNA) is altered so that the process of its transformation for synthesis of protein is seriously inhibited. Restoration of DNA may occur after these damaging effects, as has been so well studied after ultraviolet irradiation in bacteria.[24] On the other hand, DNA that is not restored, may not affect cell function if that portion of the DNA is repressed and not undergoing transformation, but cell death may occur after division. It is likely that that the same process of division in cells carrying damaged DNA may be a critical factor in carcinogenesis although the mechanism is obscure. Obviously, any factor that stimulates the thyroid gland to cause cell division will accelerate this process. Hypothyroidism produced by radiation damage to some of the thyroid cells will result in such stimulation.

Increased sensitivity of children's thyroid glands to the development of neoplastic changes from radiation exposure has been amply demonstrated. A series of retrospective and prospective studies have clearly shown the causal relation of irradiation of the thymic region in infants and the later development of thyroid cancer.[25-28] In addition, the development of adenomatous lesions of the gland in children five to eleven years after treatment with I^{131} for thyrotoxicosis has been reported.[29,30] Doniach[31] points out that cell division in the growing thyroid gland of the child may be a factor in this increased sensitivity to irradiation. On the average, 3 to 4 cell divisions are assumed to occur as the infant gland grows from a size of about 1.5 gm. to a mature 17-gm. gland.[7] It thus seems reasonable to consider the enhanced tumorogenic effect of irradiation in children to be due to the necessity for division of cells whose nuclei have previously been injured by radiation. The adult gland, on the other hand, would not be as prone to such radiation effects, since cell division is not believed to occur normally in the mature gland (mitotic figures are usually not discernible).[27,32] Any factor, therefore, that causes increased secretion of TSH and thyroid hyperplasia will favor the development of neoplasia in a previously irradiated thyroid gland. Though the relation between adenomatous and malignant changes is not clear it is apparent that the same situations predispose to the development of both types of change.

The occurrence of adenomatoid nodules and 1 carcinoma of the gland in the Marshallese who re-

ceived thyroid irradiation in 1954 seems to conform in a general way to the concepts outlined above. Radiation appears to have been the cause of the thyroid abnormalities seen, since 200 natives of the same ethnic background and living under identical conditions showed no thyroid disease. Furthermore, there is no evidence that these people have been exposed to other factors that might cause pathologic changes in the gland: urinalyses indicate that the iodine intake is adequate, and no dietary goitrogenic factors have been implicated. In addition, the data in the present study show a much greater incidence of thyroid disease in children than in adults in accord with the findings cited above. This greater sensitivity of infants may also be related to the relative magnitudes of the dose of radiation received, the infant gland probably receiving five to ten times the radiation dose that an average adult's gland received. The dose range of from 700 to 1400 rads delivered to the children's thyroid glands is similar to the doses received during thymic irradiation. The apparently greater incidence of pathologic changes in the glands of the Marshallese is not clear. It may be related to a greater dose of radiation received by the Marshallese since the calculations for thyroid dose in these people is subject, as noted above, to large uncertainties.

There appears to be an increased incidence of thyroid carcinoma in inhabitants of Hiroshima and Nagasaki exposed to radiation from the atomic-bomb explosions. The numbers are small, however, comprising 19 cases in a combined exposed group of almost 15,000 individuals, as compared to 2 cases in slightly less than 5000 unexposed individuals.[33] These people were exposed to varying doses of external radiation to the thyroid gland but not to internal exposure from radioiodine.

The growth retardation previously noted in some of the exposed children has been assumed to be due to the radiation, but the mechanism has not been known.[3] With the recent development of frank hypothyroidism in 2 of the most retarded boys in the exposed group hypothyroidism seems the most likely cause. In 2 other retarded boys (and) thyroid nodules have developed. However, it is interesting that the exposed girls have shown very little retardation of growth and development although the nodules are more prevalent among them. Except for the 2 boys with hypothyroidism, the rest of the children with growth retardation have shown normal protein-bound iodine and cholesterol values. Minimal hypothyroidism may have been missed and may be enough to account for the growth retardation seen. The finding of high TSH levels in the 2 most retarded boys with hypothyroidism and slight elevation in 2 other retarded children strongly indicates primary hypothyroidism. The growth response of these children after thyroid feeding will offer an interesting therapeutic test of the hypothyroid etiology of the growth retardation.

The treatment of the exposed group with levothyroxine deserves some further comment. Bielschowsky[23] and Astwood and Cassidy[34] have reviewed the favorable effects of thyroid treatment of patients with nodules of the thyroid gland. The only experimental evidence found directly applicable to the Marshallese situation is a paper by Nichols et al.[35] and unpublished data by Godwin[36] demonstrating a reduced incidence of I^{131}-induced adenomas in rats treated with thyroid hormone. This form of treatment, therefore, seems reasonable in the Marshallese.

The implications of the present findings are twofold. In the first place, contrary to previous concepts, the quantity of radioisotopes of iodine in fallout of the close-in type associated with atomic-bomb detonations must be regarded as a major long-term hazard. Secondly, the development of hypothyroidism, of thyroid adenomatoid lesions and of a thyroid carcinoma after doses of radioiodine that deliver 300 to 1400 rads to the gland makes caution in the use of radioiodine necessary

Summary and Conclusions

Pathologic changes in the thyroid gland were found in a number of Marshallese people of Rongelap Island who were accidentally exposed to radioactive fallout in 1954. Definite thyroid nodules were noted in 11 people, minimal changes in 5 others, and hypothyroidism in 2. All but 1 case occurred in the more heavily exposed population (55 living of the original 64 persons), who received about 175 rads of whole-body gamma radiation, burns of the skin from fallout products and internal absorption of fission products. One case with a nodule was noted in an adult woman in the smaller Rongelap group (16 of the 18 are still alive) that had received less than half the exposure of the other group. In 200 individuals of a control group not exposed no such thyroid abnormalities were found. In the more heavily exposed group, thyroid abnormalities developed in 55 per cent of children exposed at less than ten years of age. Five children were found at surgery to have benign adenomatous goiters. The 1 adult patient had a mixed papillary and follicular carcinoma, with localized metastasis. Two boys showed marked retardation of growth, apparently owing to primary hypothyroidism.

The radiation etiology in these cases appears to be reasonably certain in view of the following facts: the thyroid glands received a substantial dose of radiation from radioiodines and external gamma radiation (adults about 300 rads, and children about 700 to 1400 rads); and the incidence of thyroid abnormalities was high in the exposed group and absent in an unexposed control population living on the same island.

The present findings suggest that the seriousness of the internal hazard associated with fallout, particularly from radioiodine, must be revised upward.

The high incidence of thyroid abnormality in the Marshallese emphasizes the caution with which radiation must be used clinically, particularly in children.

A resurvey of the Rongelap people was completed in March, 1966, since this paper was written. The data are not analyzed, and only a preliminary statement can be made. There were 5 new cases of thyroid nodules, all in children. The increase was possibly related to inadequate thyroid-hormone treatment in some cases. However, some beneficial effect of the treatment was noted, since a nodule disappeared in 1 case, and there appears to have been increased growth rate in some of the retarded children. It is planned to bring some of these patients to the United States for further study and possibly surgery. The results of these latest studies will be the subject of a further communication.

Surgery on Cases 1 through 3 was performed by Captain C. A. Broaddus (MC), USN (United States Naval Hospital, Guam), and on Cases 4 through 6 by Dr. Bentley P. Colcock (Lahey Clinic). The pathological diagnoses were by Dr. G. H. Klinck (Armed Forces Institute of Pathology) in Cases 1 and 2, by Dr. H. A. Johnson (Medical Department, Brookhaven National Laboratory) in Case 3, and by Dr. W. A. Meissner (New England Deaconess Hospital), in Cases 4 through 6.

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References

1. Cronkite, E. P., et al. Response of human beings accidentally exposed to significant fall-out radiation. *J.A.M.A.* **159**:430-434, 1955.
2. Conard, R. A., and Hicking, A. Medical findings in Marshallese people exposed to fallout radiation: results from ten-year study. *J.A.M.A.* **192**:457-459, 1965.
3. Sutow, W. W., Conard, R. A., and Griffith, K. M. Growth status of children exposed to fallout radiation on Marshall Islands. *Pediatrics* **36**:721-731, 1965.
4. Harris, P. Unpublished data.
5. Cohn, S. H., et al. Internal deposition of radionuclides in human beings and animals. In United States Atomic Energy Commission. *Some Effects of Ionizing Radiation on Human Beings: A report on the Marshallese and Americans accidentally exposed to radiation from fallout and a discussion of radiation injury in the human being.* Edited by E. P. Cronkite, V. P. Bond and C. L. Dunham. 106 pp. Washington, D.C.: Government Printing Office, 1956. Chapter 5. (AEC-TID 5358.)
6. James, R., and Gofman, J. UCRL 12273, December, 1964.
7. Mochizuki, Y., Mowafy, R., and Pasternack, B. Weights of human thyroids in New York City. *Health Physics* **9**:1299-1301, 1963.
8. Rall, J. E., and Conard, R. A. Elevation of serum protein-bound iodine level in inhabitants of Marshall Islands. *Am. J. Med.* (in press).
9. Axelrad, A., and Leblond, C. P. Thyroid tumor induction in rats by low iodine diet with and without 2-acetylaminofluorene. *Proc. Am. A. Cancer Research* **1**:2, 1953.
10. Griesbach, W. E., Kennedy, T. H., and Purves, H. D. Studies on experimental goitre. VI. Thyroid adenomata in rats on Brassica seed diet. *Brit. J. Exper. Path.* **26**:18-24, 1945.
11. Paschkis, K. E., Cantarow, A., and Stasney, J. Influence of thiouracil on carcinoma induced by 2-acetaminofluorene. *Cancer Research* **8**:257-263, 1948.
12. Money, W. L., and Rawson, R. W. Experimental production of thyroid tumors in rat exposed to prolonged treatment with thiouracil. *Cancer* **3**:321-335, 1950.
13. Morris, H. P., and Green, C. D. Role of thiouracil in induction, growth and transplantability of mouse thyroid tumors. *Science* **114**:44-46, 1951.
14. Wollman, S. H. Production and properties of transplantable tumors of thyroid gland in Fischer rat. *Recent Progr. in Hormone Research* **19**:579-618, 1963.
15. Doniach, I. Comparison of carcinogenic effect of X-irradiation with radioactive iodine on rat's thyroid. *Brit. J. Cancer* **11**:67-76, 1957.
16. Kneeland, V., et al. Comparison of carcinogenic effect of internal and external irradiation of thyroid gland of male Long-Evans rat. *Endocrinology* **61**:574-581, 1957.
17. Lindsay, S., Sheline, G. E., Potter, G. D., and Chaikoff, I. L. Induction of neoplasms in thyroid gland of rat by x-irradiation of gland. *Cancer Research* **21**:9-16, 1961.
18. Goldberg, R. C., and Chaikoff, I. L. Development of thyroid neoplasms in rat following single injection of radioactive iodine. *Proc. Soc. Exper. Biol. & Med.* **76**:563-566, 1951.
19. *Idem.* Induction of thyroid cancer in rat by radioactive iodine. *Arch. Path.* **53**:22-28, 1952.
20. Potter, G. D., Lindsay, S., and Chaikoff, I. L. Induction of neoplasms in rat thyroid glands by low doses of radioiodine. *Arch. Path.* **69**:257-269, 1960.
21. Doniach, I., and Williams, E. D. Development of thyroid and pituitary tumours in rat two years after partial thyroidectomy. *Brit. J. Cancer* **16**:222-231, 1962.
22. Goldberg, R. C., Lindsay, S., Nichols, C. W., Jr., and Chaikoff, I. L. Induction of neoplasms in thyroid glands of rats by subtotal thyroidectomy and by injection of one microcurie of I-131. *Cancer Research* **24**:35-43, 1964.
23. Bielschowsky, F. Neoplasia and internal environment. *Brit. J. Cancer* **9**:80-116, 1955.
24. Shuster, R. C. Dark repair of ultra-violet injury in *E. coli* during deprivation of thymine. *Nature* (London) **202**:614, 1964.
25. Duffy, B. J., Jr., and Fitzgerald, P. J. Thyroid cancer in childhood and adolescence: report of 28 cases. *Cancer* **3**:1018-1032, 1950.
26. Simpson, C. L., Hempelmann, L. H., and Fuller, L. M. Neoplasia in children treated with x-rays in infancy for thymic enlargement. *Radiology* **64**:840-845, 1955.
27. Winship, T. W. Personal communication.
28. Warren, S., Alvizouri, M., and Colcock, B. P. Carcinoma of thyroid in childhood and adolescence. *Cancer* **6**:1139-1146, 1953.
29. Sheline, G. E., Lindsay, S., McCormack, K. R., and Galante, M. Thyroid nodules occurring late after treatment of thyrotoxicosis with radioiodine. *J. Clin. Endocrinol. & Metab.* **22**:8-18, 1962.
30. Lindsay, S., and Chaikoff, I. L. Effects of irradiation on thyroid gland with particular reference to induction of thyroid neoplasias: *review. Cancer Research* **24**:1099-1107, 1964.
31. Doniach, I. Experimental induction of tumors of thyroid by radiation. *Brit. M. Bull.* **14**:181-183, 1958.
32. Leblond, C. P., and Walker, B. E. Renewal of cell populations. *Physiol. Rev.* **36**:255-276, 1956.
33. Socolow, E. L., Hashizume, A., Neriishi, S., and Niitani, R. Thyroid carcinoma in man after exposure to ionizing radiation: summary of findings in Hiroshima and Nagasaki. *New Eng. J. Med.* **268**:406-410, 1963.
34. Astwood, E. B., and Cassidy, C. E. Treatment of simple goiters and thyroid nodules with thyroid hormone. In *Clinical Endocrinology.* Edited by E. B. Astwood. Vol. 1. 724 pp. New York: Grune, 1960. Pp. 152-159.
35. Nichols, C. W., Jr., Lindsay, S., Sheline, G. E., and Chaikoff, I. L. Induction of neoplasms in rat thyroid glands by x-irradiation of single lobe. *Arch. Path.* **80**:177-183, 1965.
36. Godwin, J. T. Personal communication.