World J. Surg. 16, 126–140, 1992

World Journal of Surgery

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

The Surgical Management of Benign and Malignant Thyroid Neoplasms in Marshall Islanders Exposed to Hydrogen Bomb Fallout

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On March 1, 1954, a serious fallout accident occurred during the United States atomic testing program at Bikini in the Trust Territory of the Pacific Islands. Following the detonation of a large thermonuclear device (known as Bravo) an unexpected shift in winds resulted in deposition of radioactive debris on several inhabited atolls in the Marshall Islands. During the early post-detonation period military, sea, and air surveys traced the hottest portion of the parabolic cloud as it drifted in an ever widening pattern of diminishing concentration eastward and southeast of Bikini. The center of the cloud passed North of the Rongelap Atoll, which was the nearest inhabited atoll. This report concerns the development of thyroid lesions, the special circumstances encountered during thyroid surgery, and the results of the surgical management of benign and malignant lesions that were subsequently encountered in this population.

After the fallout accident on March 1, 1954 (Fig. 1), attention was directed first toward the inhabitants of the Rongelap Atoll and the more peripheral island of Ailingnae (Sifo), lying 105 nautical miles east of Bikini, and then to Utirik Atoll, 300 miles eastward. The cloud arrived over Rongelap in 4 to 6 hours and over Utirik in about 22 hours. Sixty-three individuals on Rongelap Atoll and 18 Rongelapese on Ailingnae were evacuated about 51 hours after the explosion. There were 159 people removed from Utirik in 72 hours [1].

The calculated amount of radiation received by the Marshallese on the 3 atolls has been subject to considerable re-evaluation [2–4]. Table 1 lists the latest estimates of doses to the Marshallese population, based on: 1) the distance from Bikini, 2) the decay of the radioactivity with the passage of time, and 3) the dispersal of the cloud.

The day following the fallout the radiation effects became evident in the Rongelap people. Gamma radiation, though sublethal, caused early gastro-intestinal symptoms and later a transient depression of blood elements. The deposition of fallout material on the skin caused transitory spotty lesions (beta burns) and epilation. There was internal absorption of radioactive material from ingestion of contaminated food and water from catchments. Wide variations in levels of contamination were found in the people apparently due to differences in diet, drinking water, metabolism, and age [1]. The dose to the thyroid in children was larger than in adults [4].

After 3 1/2 months the people of Utirik, who had shown none of the symptoms described above, were returned to their atoll because the radiation levels on Utirik were considered safe. However, the Rongelap people were not returned to their atoll for 3 1/2 years.

Radioiodines absorbed from the fallout were primarily short lived (half life seconds to hours) and probably caused most of the effect to the thyroid. However, ^{131}I (half life 8 days), calculated to be 1/10 as abundant, also contributed some of the radiation effect on the thyroids [1, 2]. These effects on the thyroid and the development of thyroid growths have now been studied for many years.

Detailed annual medical examinations, including extensive laboratory observations, have been carried out on the exposed persons and on unexposed comparison populations by medical personnel from Brookhaven National Laboratory and their invited medical consultants [1, 5–7]. The Utirik people initially were examined only at 3 year intervals, but later annually as with those from Rongelap. One of us (BMD) has participated in 9 of these annual examinations in the Marshall Islands.

The Development of Thyroid Abnormalities

Nine years following exposure, thyroid nodularity was first detected. Reduced thyroid function was suspected as the cause. Consequently, on the advice of several leading thyroidologists, the prophylactic administration of 0.2 mg of thyroxine to all exposed Rongelap people was begun in 1965. This dose was later reduced depending on clinical findings. A constant supply was provided and its administration supervised at the time of each survey by the Brookhaven Medical Team.

The first nodules that were discovered in 3 Rongelap children, who had been exposed at ages 3, 3, and 4 years of age, were removed in 1964 at the U.S. Naval Hospital at Guam. At the time of surgery an initial presumptive diagnosis of carcinoma in 1 individual (diagnosis later revised) resulted in a near total thyroidectomy. The nodules in the remaining 2 patients were benign. Thereafter, nodules began to appear in young

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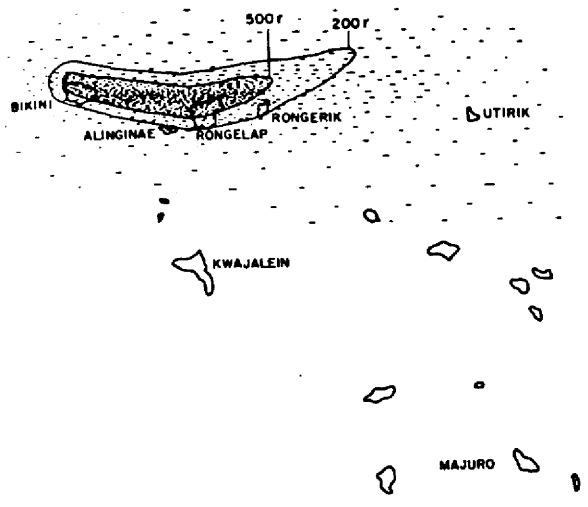

Fig. 1. A diagram of the fallout area from the detonation of a high yield thermonuclear device (Bravo) on Bikini on March 1, 1954 and the relationships of atolls of the Northern Marshall Islands [6].

adults from Rongelap, and particularly in those who were exposed as children <10 years of age at the time of the accident.

The decline in thyroid function was noted in 4 Rongelap children who showed gradual retardation of growth. This was most marked in 2 children, exposed at 1 year of age [5, 6]. Their thyroids gradually became atrophic with clinical signs of myxedema. Neither of the 2 children developed thyroid masses, then or since. As time passed some others among the more heavily exposed group showed a slight degree of reduced thyroid function, evident only on a biochemical basis and without clinical signs of hypothyroidism [7, 8]. Early in the study Micronesian people were found to have somewhat higher protein bound iodine (PBI) levels than most populations due to the presence of unusually high iodo-proteins, so that subnormal levels were not recognized until more refined tests for thyroxine were available. A number of the exposed Rongelap people have gradually over the years developed biochemical hypothyroidism [9–11].

Between 1965 and 1968, 12 more Rongelap people developed palpable thyroid nodules which prompted surgical exploration at New England Deaconess Hospital, Boston. Among the 12 patients there was 1 carcinoma with a positive lymph node found in 1965. This was the first frank carcinoma found up to that time.

It is noteworthy that of the 15 individuals undergoing surgery until 1968, 14 patients were <10 years of age when exposed and all were from the most exposed group (Rongelap). All had adenomatous changes in addition to the 1 carcinoma. Various pathologists have incidentally commented on the unusual degree of focal or nodular hyperplasia in the adenomas in 9 of the first 15 cases [8].

In 1969 on a single survey, 5 additional exposed persons were found to have small palpable nodules and were surgically explored by the author (BMD). Three of these persons proved to have carcinoma, 1 with extensive metastatic deposits in numerous cervical lymph nodes. One person with carcinoma had been exposed on Utirik. More masses then began to appear in the lesser exposed Ailingnae and Utirik groups. As time passed, between 1 and 13 persons developed nodules and were referred each year for surgery by the author (BMD). The peak occurrence of masses happened in 1979 (8 in 1978; 13 in 1979). Only 1 person underwent surgery in the period from 1986 to 1988. In the meantime the population base was diminishing from natural attrition but not from the effects of radiation.

Table 1. The most recent estimated dose of radiation to the thyroid in various groups of exposed Marshallese.[a]

Group	Age	External dose (rads)	Thyroid dose (rads) (avg-max)[b]
Rongelap (63 people)[c]	1 year	190	5,000–20,000
	9 year	190	2,000–8,000
	Adult	190	1,000–4,000
Ailingnae (19 people)	1 year	110	1,300–5,200
	9 year	110	540–2,200
	Adult	110	280–1,120
Utirik (159 people)	1 year	11	670–2,700
	9 year	11	300–1,200
	Adult	11	150–600

[a]From Lessard and coworkers [2].
[b]Does not include external dose.
[c]Includes 3 in utero exposures.

The Need for Controls

Since little was known of the natural occurrence of thyroid neoplasms in Micronesians, it was necessary to examine the population thought to have been unexposed [1, 6, 8]. Individuals to be described hereafter are difficult to define as distinct control groups because they represent a very diverse range of people and situations accumulated over the length of the study. The initial control group consisted of 86 Rongelap relatives who were living on Majuro Atoll, far remote from the fallout area at the time of the accident. They were matched for sex and age. Because of inadequate numbers, attrition from natural causes, and wanderings to other atolls, additional controls were needed. Therefore, the additional controls consisted of people of Rongelap origin, who were merely not on Rongelap at the time of the accident, and supplemented the initial control group. However, some of these controls may have been living on neighboring atolls (south of Rongelap and Utirik) where slight amounts of fallout may have occurred [3]. By 1979 this group had reached 227 people, most of whom had been available for multiple examinations [9–12]. Another group of Rongelap controls were individuals born after the accident of exposed and unexposed Rongelap parents. These young individuals were part of a group who were born after the accident and screened for possible inherited effects from exposed parents. Many were reaching an age comparable to those who had been exposed and developed nodules at an early age. The entire expanded group of registered Rongelapese eventually reached 668 people [1, 8].

Another group of controls consisted of 473 unexposed people, mostly of Utirik origin, who turned up on Utirik or other atolls during street surveys to examine thyroids during the annual examinations of exposed people. Finally because of the need for the largest possible control population, a one-time survey of some of the populations on neighboring atolls (Likiep and Wotje) was made to provide still another group of 354 controls. Some of those with a palpable mass were registered

and included in the operated group as were other controls found to have masses.

It should be emphasized that the number of controls referred to in previous publications varies. The controls were collected over a period of 23 years. Some, who had come to live on the 3 exposed atolls, were examined repeatedly, others only once. The Medical Team examined approximately 800 person each year. The number of available controls examined changed through loss of follow up, by death from natural causes, refusal for repeated examinations, or drifting in and out of the areas where the examinations are held.

The Changing Trend in Surgical Management

Early in the operative experience with the first 15 of the exposed Rongelap people, bilateral subtotal thyroidectomy was performed to remove the obvious multiple nodules. Only if a carcinoma was found during surgery was a total lobectomy done. With the discovery of malignancy in 3 of 5 exposed people undergoing surgery in 1969, it became more evident that radiation was the cause and the whole gland might be at risk. Therefore, any palpable irregularities were promptly explored. Furthermore, it was anticipated that the multiple minute atypical lesions found in some of the exposed might further develop or that new lesions might evolve in a remnant of thyroid that might be allowed to remain.

At the time of surgery, where there was a known history of radiation, the reasons for doing a total or a very near total thyroidectomy included: 1) the finding of a frankly malignant lesion, 2) an entire gland being replaced by adenomas, 3) histologic uncertainty on frozen section, but suspicion that an atypical lesion might be malignant, 4) gross features such as fleshy salmon pink tissue, scalloped capsular margins of a lesion, clusters of lesions radiating from a common encapsulated point, or puckering of the surface of the gland adjacent to a lesion in spite of a benign frozen section, and, (5) the finding of a spherical or tiny but firm lymph node adjacent to the thyroid, arousing suspicion of metastatic spread. On the other hand, depriving these particular people of all thyroid tissue could not be justified unless there was guaranteed availability of supplemental thyroxine for their life time on these tiny remote atolls. However, since the supply of thyroxine had been fully provided for the exposed Rongelap people this concern became less important.

In the past 20 or 30 years, the senior author has developed a philosophy that a clean total thyroidectomy with regional lymph node dissection should be done in any individual found to have carcinoma of the thyroid. It is important to emphasize that, when a total thyroidectomy is indicated, that procedure should be done without mutilation or disfigurement or any risk to the recurrent laryngeal nerves, or the possibility of permanent parathyroid injury. It has been the author's policy that all patients with palpable nodules should be routinely given a small trace dose of radioiodine pre-operatively, as an adjunct to management during surgery [12]. This permits an assay of the function of the tumor at surgery. If the ratio of radioiodine in a sample of tumor is <1 to 100, compared to an equal weight of normal thyroid tissue, experience has shown that the lesion will very likely prove to be malignant. Furthermore if a total thyroidectomy is done, the presence of ^{131}I in the patient permits a scan of the neck before the wound is closed. This is done to prove the removal of all functioning tissue. The purpose is to avoid the subsequent confusion that often arises when a scrap of normal tissue remains and later takes up ^{131}I. This leads to a suspicion of recurrence. Figure 2 shows how carcinomas do not take up radioiodine. Thus direct counting of tumor tissue at surgery may be supportive of a tentative diagnosis.

Surgery

It became gradually apparent that the circumstances encountered in this population were not identical with those found in most civilian populations. There were more carcinomas than might be expected and an unusual number of microscopic and macroscopic atypical adenomas were present.

The gross findings at surgery in the most heavily exposed Rongelapese often related to the degree of radiation exposure. In 8 patients operated by the author (BMD), the gland was shrunken and somewhat gnarled. Where these changes were most striking there were also fine tortuous venules on the capsule of the gland and the strap muscles were sometimes moderately adherent to the capsule. These gross findings were similar to thyroids that the author (BMD) had observed in some cases of Graves' disease that had been inadequately treated with ^{131}I and subsequently required surgery. These gross features varied from marked to a relatively normal gland in the Rongelap group. This indicates that there was considerable variation in radiation damage within the same group. In contrast, in the lesser exposed Utirik group, there were only occasional lobulations, in addition to the discrete nodule(s) that had led to exploration.

Frozen section diagnosis was of great value here, but there were some limitations among the irradiated thyroids. Some lesions were so small that capsular, blood vessel, or lymphatic invasion could not be determined yet an accompanying minute positive node was discovered. In some lesions there were aggregates of cells displaying papillary configurations that were presumably related to a decline in thyroid function, but large bizarre nuclear forms with excess chromatin were sometimes also seen. These resembled some nuclei found in malignant cells, but these nuclei also resembled some seen in thyroids of Graves' disease inadequately treated with ^{131}I [13–16]. Thus, the difficulty in distinguishing between small atypical adenomas and carcinomas in the frozen sections at the time of surgery prompted the pathologists (although very experienced in thyroid pathology) to be hesitant to make a firm diagnosis of malignancy in some cases. Therefore, the surgical approach that followed was usually based on the assumption that the final diagnosis might be carcinoma. Among the atypical lesions, the tentative report sometimes indicated that the lesion was benign but later it was called malignant or vise versa. It must be recognized that since there is sometimes a difference of opinion on final microscopic preparations, as there has been here, the difficulties on frozen section are obvious. Furthermore, the very small lesions, located with the naked eye in the surgical specimen (grossly millimeters in size), were not submitted for frozen sections but saved for fixed microscopic preparations

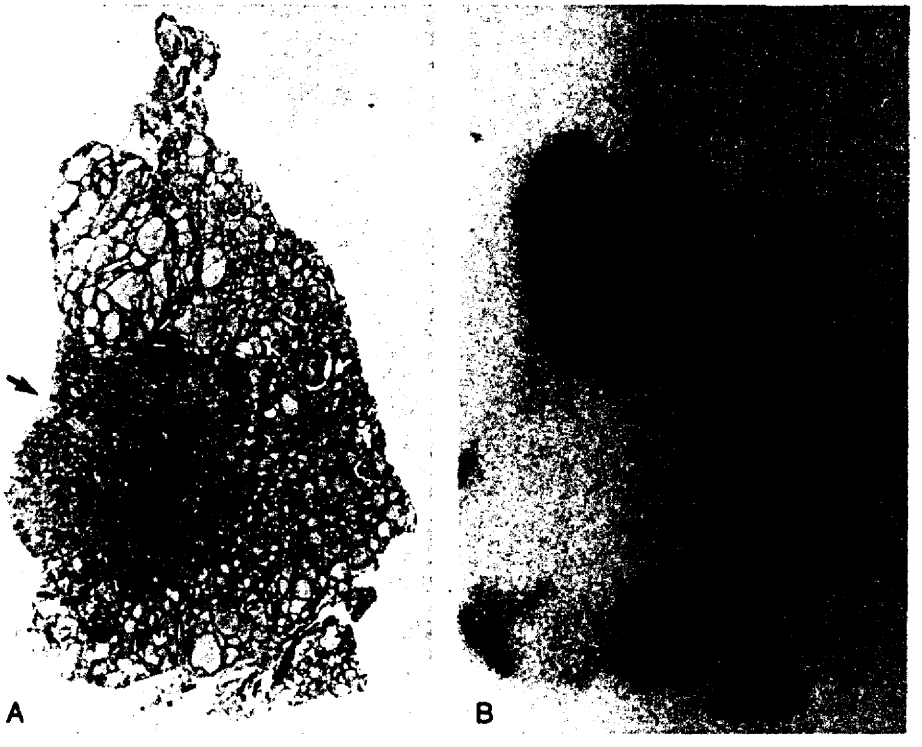

Fig. 2A. Tissue section (×75) of thyroid carcinoma (arrow). **B.** The radioautograph prepared from the tissue section shown in A, demonstrating no blackening on the film in the area corresponding to the position of the carcinoma. The normal tissue took up the isotope. There were several other minute carcinomas in both lobes.

Table 2. Histologic findings among the exposed and unexposed Marshallese.[a]

	Exposed						Unexposed								
	Rongelap & Ailingnae			Utirik			Controls Rongelap			Controls Utirik			More distant atolls		
Total Number operated	86[b] 30			159 25			668[c] 12			473 2			354 8		
Histology findings	Benign	Atyp	Ca	Benign	Atyp	Ca	Benign	Atyp	Ca	Benign	Atyp	Ca	Benign	Atyp	Ca
	19	5	6	14	1	10	6	2	4	0	1	1	2	4	2
% Ca of total			6.97%			6.28%			0.60%			0.21%			0.56%

[a]The atypical lesions listed here do not include the many atypical lesions associated with carcinoma in the same gland.
[b]Includes 4 exposed in utero.
[c]Among the Rongelap controls, 1 carcinoma was found in the original 86 matched controls who were known to have been on Majuro remote to the fallout. The remaining 3 carcinomas were found in Rongelapese who were from other atolls and not among those evacuated from Rongelap.
Atyp: atypical; Ca: carcinoma.

and therefore not reported until 24 hours after the operation was completed. Furthermore, it was clear that the first operation must be adequate because a second operation in the face of scar tissue is more hazardous than the first. Therefore, a very complete procedure was undertaken provided it could be done without risk.

Of 23 cases ultimately classified as carcinoma, a positive diagnosis was made on frozen section in 14 patients. In 3 cases a suspicion of carcinoma was reported at the time of surgery. In 6 patients the initial diagnosis was benign adenoma but later the lesion (or another less conspicuous one) was judged to be carcinoma.

There was a total of 80 thyroid explorations in 77 Marshallese natives because of palpable thyroid nodules; 55 patients were known to have been exposed and 22 patients were unexposed (Tables 2 and 3). A total of 23 cases of carcinoma were found (Figure 3).

In 14 cases the dominant mass was the carcinoma. In 9 patients the dominant mass was a benign mass that led to operation and an incidental finding of a carcinoma elsewhere in the gland. In 2 other cases multiple and very atypical lesions were found at second operations.

There have been 27 total or near-total thyroidectomies in the exposed and unexposed patients where there was a presumptive diagnosis of carcinoma at surgery. A near total thyroidectomy rather than total thyroidectomy was some times done because one or more of the parathyroids were intimately bound to the thyroid capsule. This made it necessary to preserve a

Table 3. Thyroid operations performed in the Marshallese (80 operations).

Diagnosis	Total thyroidectomy	Almost total	Bilateral subtotal	Single lobe	Local excision
Carcinoma[a]	10	6	4	3	0
Atypical[b]	2[c]	3[d]	2	4	0
Benign	1	5	23[e]	10	7
Total	13	14	29	17	7

[a]Based on the opinion of pathology panel.
[b]Does not include atypical lesions accompanying carcinomas.
[c]One patient was reoperated for regrowth following bilateral subtotal thyroidectomy 10 years earlier.
[d]Two patients were reoperated for regrowth following bilateral subtotal thyroidectomy 10 years earlier.
[e]Includes a previous bilateral subtotal thyroidectomy for benign adenomas.

minute adjacent piece of thyroid capsule to preserve the blood supply to that parathyroid. However, such a procedure was essentially a total removal of all thyroid tissue (Table 3). Among 77 cases operated only one lobe was removed in 17 patients. In 6 patients where carcinoma was suspected and in 3 patients where carcinoma was found only one lobe was totally removed because of advanced age, physical disability, or doubtful frozen section diagnosis. Among the remaining 29 cases where the presumptive diagnosis was adenoma(s) a bilateral subtotal thyroidectomy was done, preserving non-nodular tissue. Local excision was performed in 7 patients.

The more extensive dissections required individual variations in the management of the parathyroids. At least 3 parathyroids were identified in each case. Transplantation was required in 2 cases (2 in 1 case; 1 in another). It was customary to salvage for transplantation any parathyroids lying in close proximity to positive nodes on the surgical specimen. These were sliced very thin, leaving the capsule intact on one side, and placing it under the skin over the sternum where the site could be palpated thereafter. Among all of the operations by 3 different surgeons, there has been 1 case of permanent hypoparathyroidism directly attributable to the surgery and a second case in which asymptomatic hypocalcemia developed after the patient had been normocalcemic for 20 years following the surgery. Both cases were among the first 3 operated; carcinoma had been suspected and a total thyroidectomy had been undertaken. There have been no recurrent laryngeal nerve injuries. There have been no recurrences of carcinoma as of March 1991 (37 years following exposure and 27 years following the first surgery).

Precise direct measurement of the size of the carcinomas on the surgical specimen or on microscopic sections showed that the sizes ranged from microscopic to 3.4 cm. There were 12 patients in which the largest carcinoma was <1.0 cm in diameter, in 2 patients it was 1.0 cm, and in 8 patients it was >1.0 cm. In one patient the size of the lesion was not recorded.

Lymph Node Involvement

Where a diagnosis of carcinoma was made or strongly suspected after the initial total lobe was removed, an extensive lymph node dissection on the same side, including the upper anterior and posterior mediastinum, was performed. If positive a node was found on the first side, the regional nodes immediately adjacent to the contralateral lobe were also removed and inspected. There were 8 cases in which one or more lymph nodes were positive. In 3 cases there was but one positive node found and it was lying adjacent to the thyroid. In the remaining 5 cases multiple positive nodes were found in the jugular and or upper mediastinal areas. They were unilaterally abundant in 3 cases and bilateral in one case. In 5 of the 8 cases the primary lesion was 1.0 cm or less in diameter. In one unexposed individual from Utirik, born 1 year and 4 months following the accident, the initial mass had been excised elsewhere but it's diameter had not been recorded. At the second operation by the author (BMD), there were extensive lymph nodes involved. Under the circumstances the primary probably was >1 cm. It is very significant that of 14 cases where the primary carcinoma was 1 cm or less, in 5 patients the disease had already spread. There has been no evidence of distant metastases in any case. These findings show that, where surgery happened to have been

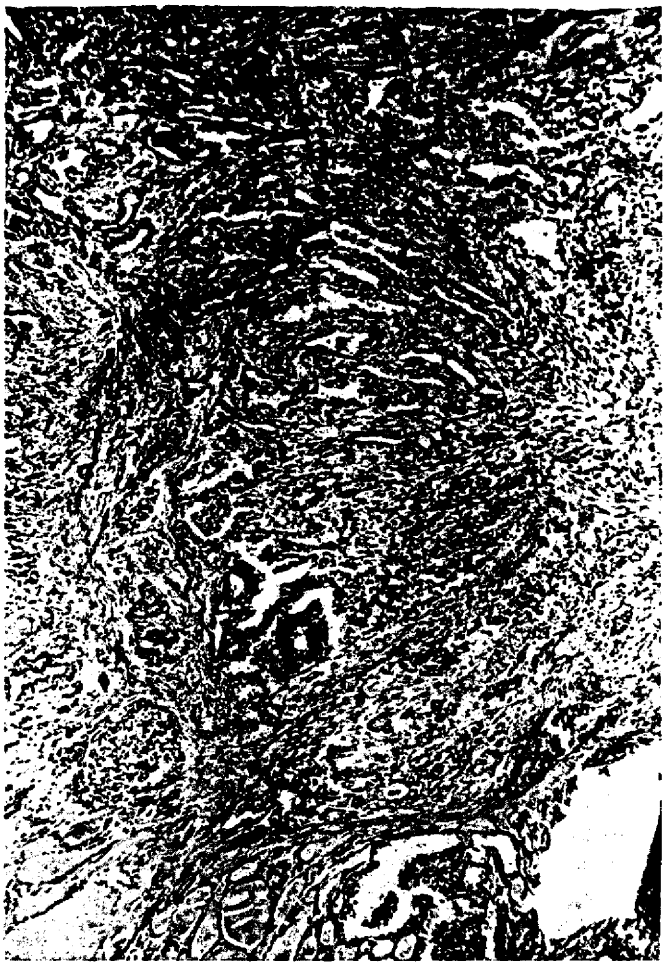

Fig. 3. An infiltrating (primarily) follicular carcinoma in a 38 year old female exposed on Rongelap at age 16. The primary lesion was 0.8 cm. Lymph nodes were involved. This represents 1 of 5 cases with one or more positive lymph nodes in which the primary lesion was 1 cm or less in diameter. (×75).

undertaken in this irradiated population and where the possibility of carcinoma was anticipated, minute carcinomas were found. Although the usual reaction might have been to show little concern for such occult carcinomas, this study shows that when positive lymph nodes were diligently sought, some of these minute primaries had already begun to metastasize. If exploration had not been undertaken until a mass had become conspicuous from outside of the neck, as is the usual clinical scenario, then many additional positive lymph nodes probably would have been found.

Pathology

The histologic preparations from all of the Marshallese thyroids after 1968 were examined by more than a dozen different pathologists in different medical centers and have been studied by the author (BMD). Due to difficulties encountered by pathologists in deciding just how many of these thyroid lesions should be classified as carcinoma, a panel of 6 pathologists, particularly interested in the thyroid, was assembled in 1981 to review the library of microscopic preparations. The panel consisted of: Drs. L.V. Ackerman, W.A. Meissner, D.E. Paglia, J.D. Reid, A.L. Vickery, and L.B. Woolner. The senior author, who had prepared detailed drawings of the surgical findings and had identified the selection of tissues for histological preparations, attended these sessions. During these sessions there were subtle differences of opinion as to whether a lesion should be classified as carcinoma or considered an atypical adenoma [17–19]. In 1 case there was debate concerning a metastatic deposit in a lymph node, although all of the lesions in the gland were thought to be benign. Even though gross thin serial sections had been made to find the very minute primary in this case, there was speculation that the primary had been missed. Unanimous opinion was obtained in most cases (Table 3).

Altogether there were 23 cases considered by all of the panel to contain at least one carcinoma. Among the 245 individuals known to have been exposed (excluding those in utero) on the 3 atolls, there were 55 operated upon (Table 2). In 16 patients there were malignant lesions and in 39 patients there were benign lesions. Among 668 unexposed Rongelap controls, 12 persons had or developed masses and underwent surgery. In 4 patients, carcinomas were found; in 6 patients, benign adenomas; and in 2 patients, atypical adenomas. Masses were found in 2 of 473 unexposed people of Utirik origin. One was a carcinoma; one was an atypical adenoma. Among 354 people whose thyroids were examined on "street surveys" on several atolls (primarily Likiep and Wotje), 8 people were found to have masses and were explored; 2 were carcinomas, 4 were atypical adenomas, and 2 were benign adenomas. These people were considered to have been outside of the high risk area according to the aerial surveys made the day of the accident (Table 2).

Most of the frank carcinomas (Fig. 3) were mixed papillary and follicular (19 cases). By most classifications these would all have been called papillary carcinomas [20]. The follicular component predominated in most cases. In 5 cases the lesion was almost exclusively follicular. Three cases were predominantly papillary and 1 case was solid cellular.

Atypical Lesions

In the final analysis it seemed important to make a separate category called "atypical adenomas". These small cytologically atypical hyperplastic lesions ranged from a few millimeters to several centimeters in diameter. At least one or more pathologists (but a minority) had originally considered some of these lesions to be carcinomas. They were found in the most heavily exposed individuals and frequently in glands that often contained a carcinoma. There were 13 cases in which no carcinoma was present (Table 2). Such an association suggested that the same factor that produced these atypical lesions also produced carcinomas.

The features of the cells in such lesions seemed to imply that with further growth, the lesion might display diagnostic features of carcinoma, as suggested by others [21, 22] who studied thyroids exposed to roentgen radiation (Figs. 4 and 5). These changes were found even though supplemental thyroxine had been given. Autoradiographs were done on all operative cases and showed that these lesions took up very little or no radioiodine, as occurs with most all carcinomas [12].

Ruling out malignancy in some of the larger atypical growths proved to be difficult (Fig. 6). In some of these lesions the finding of a mixed papillary and follicular pattern with crowding of cells, bearing bizarre nuclear forms with vacuolation and possible mitoses prompted a suspicion of a potential to metastasize (Figs. 4B, 6C, 7 and 8). However, without clear evidence of invasive qualities, such as capsular, blood vessel or lymphatic invasion, such a diagnosis was not possible. Still, this did not eliminate a suspected potential to become invasive with the passage of time.

Multiple Malignant Lesions in the Same Individual

Among the 23 patients with malignant lesions of the thyroid, 16 patients showed additional benign and or atypical adenomatous lesions. In 10 patients there were multiple carcinomas. In 8 patients a smaller carcinoma was found in the opposite lobe (Fig. 2). Although there is the possibility that the additional carcinomas could have represented intraglandular spread, it is much more likely that they represented multicentric sites of origin because the entire gland was at risk from radiation. However, 4 of the 10 patients with multiple carcinomas were among those persons considered to be unexposed. These observations of multiple carcinomas emphasize the importance of removing all thyroid tissue completely when a carcinoma is found following radiation exposure. It should be assumed that other subclinical carcinomas may be present in the same gland, even though at surgery gross nodularity does not appear to be present in other parts of the gland.

Re-Operations

Three exposed persons from Rongelap who had previously undergone bilateral subtotal thyroidectomy ultimately developed additional discrete growing masses 10 or more years after the first operation. All 3 patients had shown atypical adenomas at the first operation. Total or very near total thyroidectomy was done at the second operation. A new lesion in 2 cases

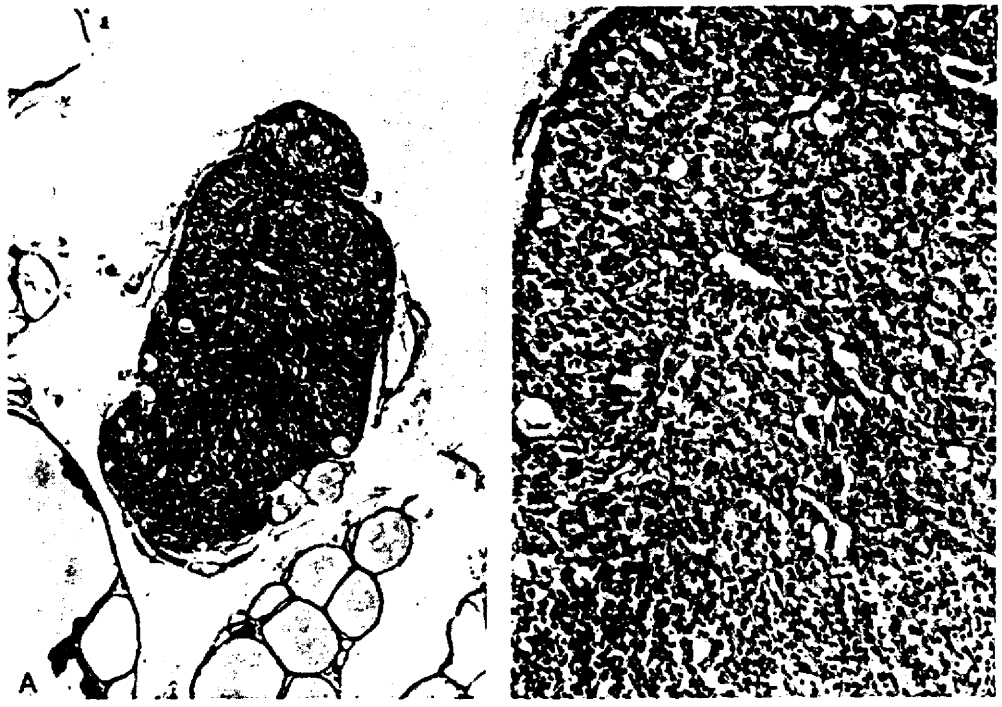

Fig. 4. An example of an atypical lesion in the thyroid of an 18 year old female exposed on Ailingnae at age 2. This atoll received less radioactive fallout than Rongelap. **A.** The size of this lesion maybe appreciated by comparison with the size of the normal follicles. Although the lesion is very small, its configuration suggests that the developing capsule around the lesion has already been breeched by proliferating cells forming a secondary lobulation at one end. (×75). **B.** Higher magnification of the lesion in A. to illustrate the detail of the cells. This lesion is composed of cells with many bizarre and giant nuclear forms with some prominant nucleoli and some mitotic figures. The lesion was considered an atypical adenoma by the panel. It would seem that this lesion was so small that it had not yet declared its potential to metastasize. It is classified as an atypical adenoma. (×255).

showed bizarre nuclear forms, hyperplasia, and what some considered to be capsular invasion; however, in view of the presence of scar tissue from previous surgery such lesions were not classified as carcinomas but atypical adenomas (Figs. 7 and 8). Figure 8B, for instance, shows probable capsular invasion with marked cellular atypia. Another lesion (Fig. 8C) from the same individual shows marked papillary structure. In the third reoperated case there were atypical lesions found (Fig. 9), as had been present 10 years before. Perhaps in retrospect, some of these operations should have been total thyroidectomies at the first operation.

There were 3 other cases (not reported here) which required a second operation, but for different circumstances. In 2 patients the removal the remnant of a lobe, 3 days and 3 months respectively, was indicated because a lesion was origionally thought to be benign at the time of surgery but later (with additional study and consultation) was judged to be carcinoma. The third case was reexplored because a lymph node had become palpable 5 years following wide removal of a carcinoma with positive lymph nodes. Fortunately there was no recurrence of carcinoma.

Discussion

From the Marshallese experience it seems clear that a spectrum of thyroid neoplasms, including carcinoma, have resulted from radiation fallout, comparable to cases reported by others [21–27] from roentgen rays. The fact that no lesions were palpated during annual examinations for 9 years following the fallout indicates that there was an extended latent period following exposure. It seems significant that the first lesions began to appear in the most heavily exposed population (Rongelap) and that it was in the children of that group that the lesions developed first. Later, lesions began to appear in the lesser exposed groups (Ailingnae and Utirik). Thus, the latent period seemed to be related to the degree of exposure.

Mention has been made of the nodular hyperplasia of the thyroid in 9 of the first 14 individuals operated [8]. All but one of these individuals were very young children (7 years of age or less) when exposed 10 to 15 years before. All of the neoplasms were benign except for a single carcinoma in a person exposed at age 30. As the latent period lengthened, carcinomas became numerous. The importance of the observations on the development of neoplasms in children is incidentally shown by an absence of any thyroid masses in 236 children and young adults born after the accident and examined later by the Brookhaven Medical Team for inherited defects in the next generation [8].

Thyroid hormone prophylaxis against the possible development of nodules had not been given during the first decade. During the next decade, benign and later malignant neoplasms began to appear increasingly. The occurrence of lesions reached a peak at 25 years. Even after the peak had passed, 9

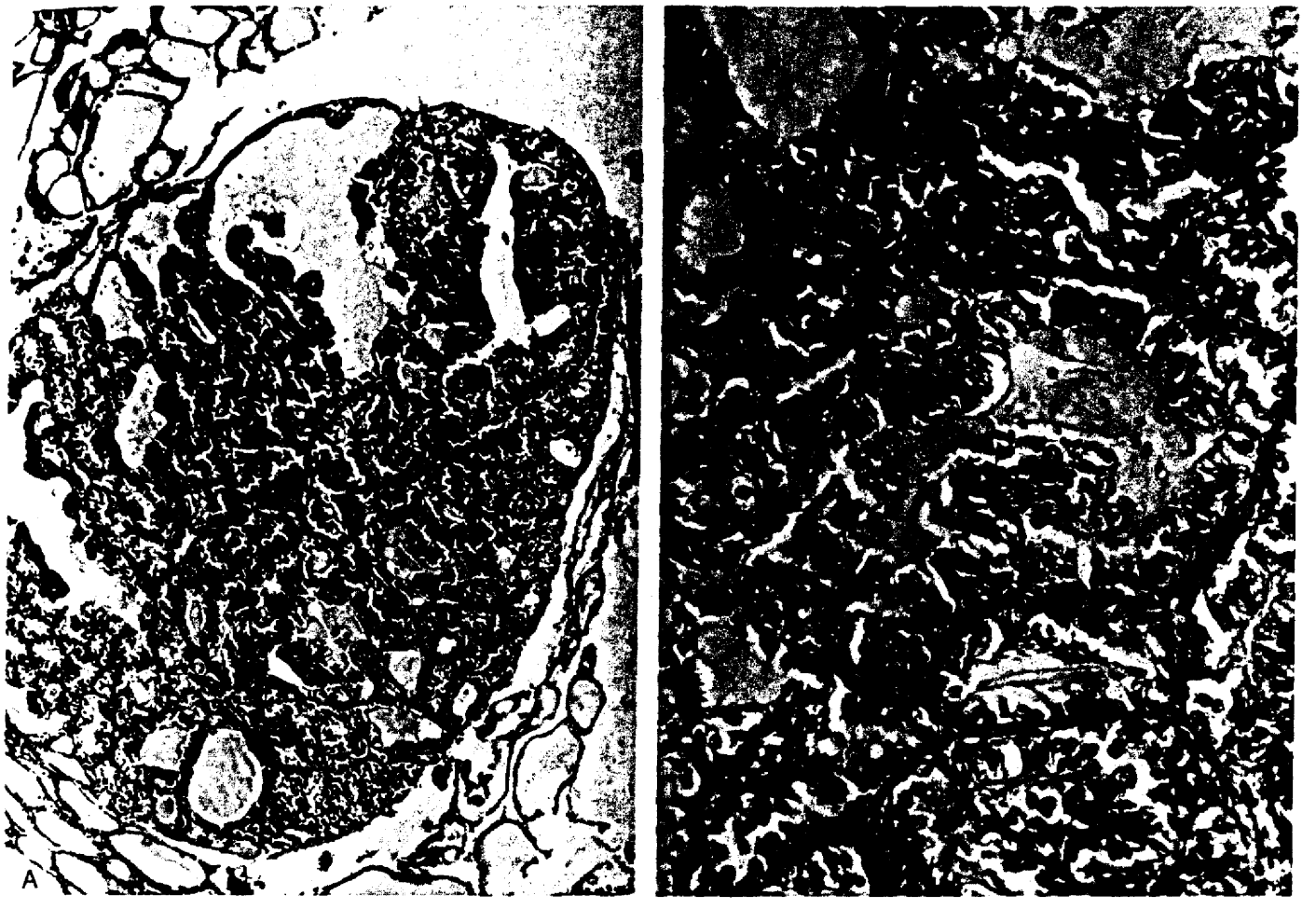

Fig. 5. A second small lesion (2 mm) in the same individual illustrated in Figure 4. **A.** Low magnification showing a papillary lesion. This lesion was enclosed by a very thin intact capsule. The parenchyma of this thyroid did not show microscopic evidence of radiation effect, as was seen in some thyroids from Rongelap where the dose was higher than on this atoll, Ailingnae. (×75). **B.** The same lesion shown in A. This lesion was considered an atypical adenoma (×255).

carcinomas were found among 19 cases operated. Eight of the 9 patients had been exposed and 6 of these were among the less exposed Utirik people. Thus the sequence of findings suggests that benign neoplasms begin to appear first and after a longer interval carcinomas were more frequently found. Thus, the interval between exposure and the development of carcinoma was longer particularly in the lower dose group. The peak occurrence has now clearly passed.

Hypothyroidism was not detected in the exposed Rongelap people for almost a decade following the accident [1, 5, 6]. More sophisticated studies on the stored blood samples (taken before any thyroid supplement was started) revealed that a few individuals had mild biochemical hypothyroidism but without the clinical signs, except for the 2 boys irradiated in infancy that developed myxedema [8]. Thus the mild hypothyroidism may have been a factor in producing the early hyperplasia. This raises the question whether a modicum of thyroid deficiency was related to the initiation of neoplasms. The majority of the Rongelap people took the thyroxine supplement regularly after this routine therapy was started in 1965. Although short intervals of non-compliance may have occurred in some individuals, the thyroid masses continued to develop in spite of the medication.

There are perhaps two factors operating in these people; one which initiates formation of neoplasms and another which promotes their growth. The radiation appears to be the initiator. A *low* thyroid hormone level in a few individuals might be the stimulant for growth. Thus the clinical appearance of lesions may have been delayed by giving supplemental thyroid hormone. Ultimately gross neoplasms appeared. This might explain why the lesions continued to become palpable. It might also explain the abundance of small atypical lesions and small carcinomas, some of which had already metastasized but had not become palpable.

It has been pointed out that the amount of exposure in the Rongelap group slowly produced frank thyroid failure in the 2 individuals who had been exposed at 1 year of age. Although 18 of 20 children exposed under the age of 10 developed neoplasms, the 2 individuals who ultimately displayed myxedema have not developed growths as of 1989. Thus, the masses

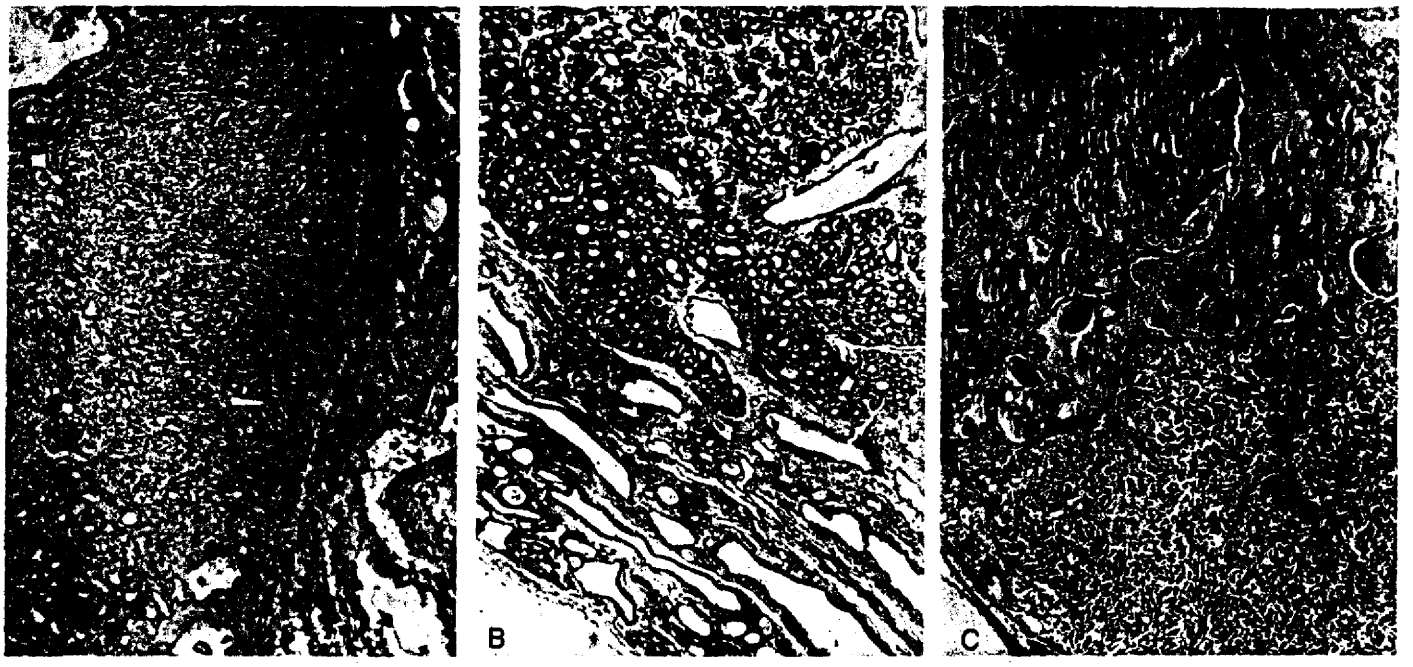

Fig. 6. This lesion was from a 78 year old male whose home was Utirik, but he was reported to have been off that atoll at the time of the accident. There was a large multinodular goiter. **A.** The largest tumor (10 cm) displayed a variety of histologic patterns. This illustrates an area of questionable capsular invasion in a microfollicular adenoma (×20). **B.** Another area of the same tumor, showing microfollicular structure and possible capsular invasion (×75). **C.** A third area of the same tumor showing pleomorphic cells arising next to the capsule (×100).

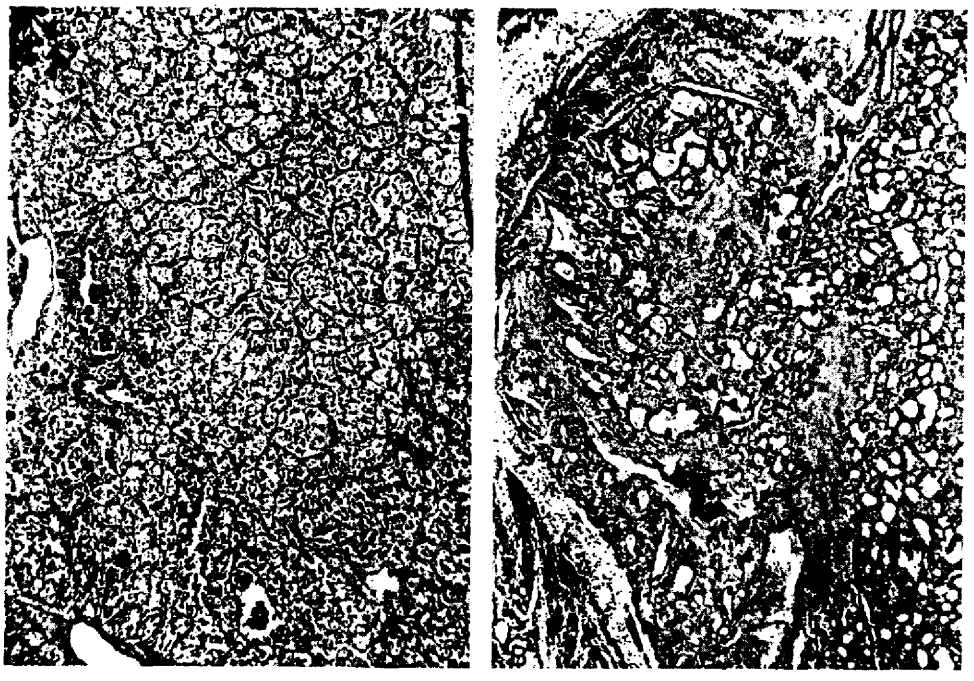

Fig. 7. Samples of thyroid tissue from a Rongelap man exposed at age 7. He had displayed acute beta burns of the skin and suppression of blood elements. A bilateral subtotal thyroidectomy was done at the first operation at age 22. A mass recurred and he underwent repeat surgery 13 years after the first operation. **A.** Tissue recovered at first operation in 1969. The thyroid contained a multitude of small nodules, the largest being 2.0 cm in diameter. Some grossly normal tissue was allowed to remain from both lobes. Diagnosis was adenomatous nodules with considerable radiation effect (×75). **B.** Tissue recovered at a second operation. Numerous masses up to 2 cm were found. This microscopic section came from the left upper pole where the largest previous lesion had been located. This shows what is believed by some to be penetration of the capsule which together with the cellular features suggested to some observers that it might be classified as a follicular carcinoma. The lesion is classified as an atypical adenoma. The presence of postoperative scar tissue confused the issue of capsular invasion (×75).

developed in those who had retained some thyroid function and who harbored cells that retained a capacity for mitosis.

The obvious differences in the effects on the thyroid in the Rongelap people in spite of equal exposure to fallout could be due to age, susceptibility to neoplastic change, or the amount of radioiodine in oral intake immediately after the accident. For instance, drinking rain water from catchments would provide a large amount of radioiodines while quenching thirst with uncontaminated coconut milk (a common practice) would provide none.

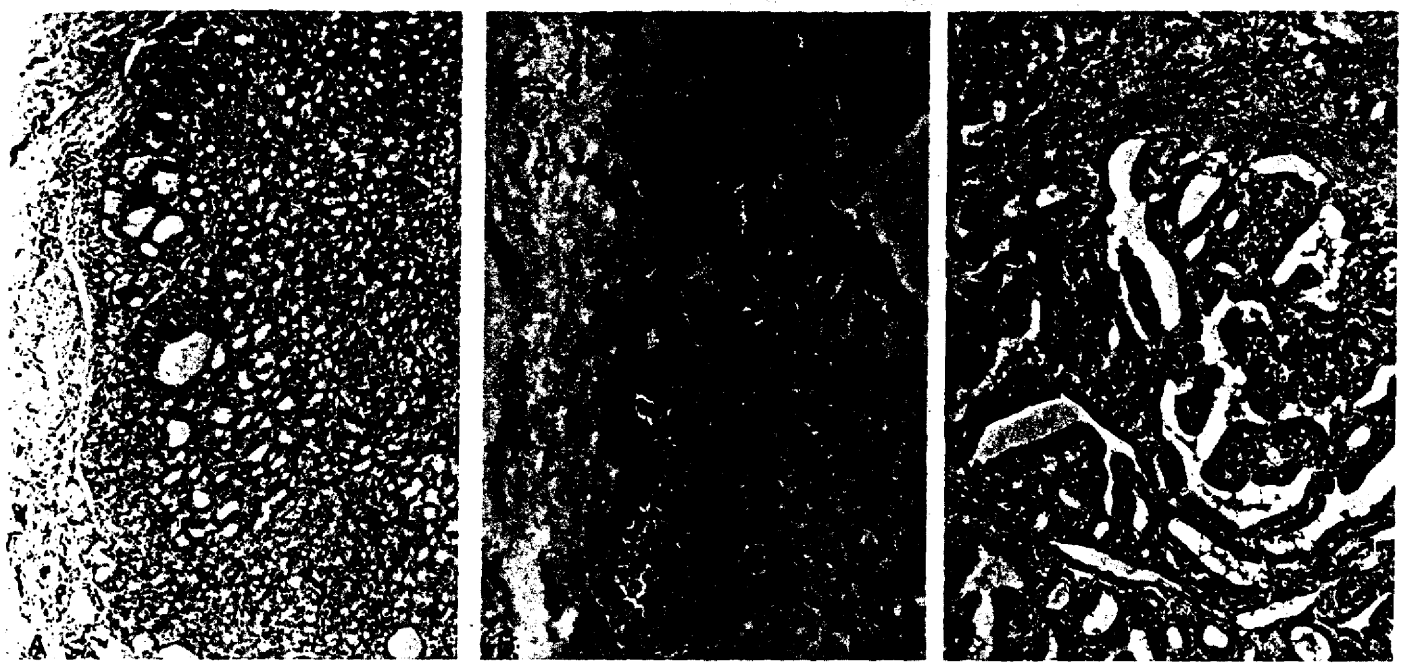

Fig. 8. This female was exposed on Rongelap at 1 year of age. She experienced marked beta burns of the skin, epilation, leukopenia, and thrombocytopenia. A bilateral subtotal thyroidectomy was done at age 12. The diagnosis at that time was adenomatous goiter. Further surgery was required in 1983 for a recurrent growth at age 29. Total left lobectomy (essentially all of the right lobe had been removed at the first operation). Diagnosis: Adenomatous goiter. At the second operation **A.** two pathologists considered one of the lesions to be mixed papillary and follicular carcinoma (×75). This shows a microfollicular lesion with debatable capsular invasion; however, postoperative scar confused the issue in this case. **B.** High magnification of cells composing the edge of one lesion (×200). **C.** A papillary lesion in another part of the lobe with the capsule intact (×75).

The early and frequent development of neoplasms in young Rongelap people who were exposed in the early part of the first decade of life is one of the most significant findings in these studies. Such lesions are very uncommon in the general population of the world; but is dramatically emphasized here by the failure to find masses in control children born after the accident of exposed Rongelap parents.

From a knowledge of the cultural habits of the Marshallese, it is known that the youngest exposed Marshallese (new born to age 2) were being almost exclusively breast fed. Thus, much of the iodine isotopes passed through the mother via the milk to the infant. Upon review of the findings in the mothers of the 6 children who had been exposed in infancy (5 Rongelap; one Utirik) and later were operated for masses, there were 3 of the mothers who have also been operated, 2 of which had carcinomas.

Two of 3 Rongelap children, who were exposed in utero during the first and second trimesters and subsequently were operated at ages 19 and 25 respectively, had adenomas with hyperplasia. At least one of these individuals, as a fetus at the time of the accident, should have developed sufficient thyroidal function to concentrate radioiodine [28]. In the younger fetus it is impossible to judge whether thyroidal uptake and retention took place at the time of the accident or lingered in mother's thyroid long enough to become available to the maturing fetus. The 2 mothers of the fetuses later developed masses that were operated. In one the lesion was a carcinoma; in the other the patient was operated twice for multiple atypical adenomas (Fig. 9). On Utirik where the fallout was much less than on Rongelap, 7 of 8 fetuses of pregnant women exposed are known to have developed no nodules.

Benign neoplasms and carcinomas have been found in some of the controls and in some of the Marshallese who presumably had been in the more remote areas (Table 2). What happened in the fringe areas beyond Utirik is not known; however, later there was detectable radioactivity in some wells on other nearby atolls [3]. The major proportion of radioiodines were short lived isotopes with half lives of seconds to minutes [2]. These caused most of the thyroid damage in people nearest to the point of detonation. The ^{131}I (half life 8 days) represented only about 1/10th of that of the shorter lived isotopes of iodine in the cloud [2, 9]. Thus, the short lived isotopes had decayed considerably before the cloud had reached the outer limits of known spread. However, the ^{131}I, although diluted by dispersion, would not have decayed significantly within the time frame of the drift of the cloud. It is possible that some of the supposedly unexposed people may have received small amounts of attenuated fallout at the fringes of the cloud, although it seems probable that such radiation would have produced minimal, if any, biological effects.

The uncertainty through out this study has been the question of the occurrence of spontaneous neoplasms in this population and its relationship to the occurrence of neoplasms in the fringe areas. From time to time efforts were made in this study to find a completely satisfactory group of controls. Even among the first group of matched Rongelap controls who were clearly

Fig. 9. This female was exposed on Rongelap at age 7. Bilateral subtotal thyroidectomy, removing all gross nodules, was done at age 22. The gland displayed many discrete lesions of various size and patterns, the largest being 1.0 cm. A palpable mass recurred 10 years later. Total thyroidectomy revealed many similar lesions, the largest being 1.5 cm. No malignant change had occurred in the interval. A variety of small papillary, solid cellular, and follicular patterns scattered throughout the gland at the first operation (×25).

outside the fallout area, there were 5 people in this group who developed masses over the years. One was carcinoma.

It seemed clear that neoplasms sometimes arise spontaneously in the Micronesians, as they do in other parts of the world. A review of the surgery logs at the Majuro Hospital (which receives patients from the entire Trust Territory) dating from the early 1960s to the late 1970s, revealed an occasional thyroidectomy and several carcinomas of the thyroid (personal review by BMD). Most of these surgical cases came from the Caroline and Marianna Islands, far west of the fallout area. None of these cases were being cared for by the Marshall Island Brookhaven Medical Team. Recently Hamilton and coworkers [29] reported finding thyroid masses in people living in more remote parts of the Marshall Islands. As of March 1989, a review of thyroid operations logged at the Majuro Hospital for the several years preceding and following the Hamilton report revealed only 4 thyroid operations. One of the 4 was said to have been a carcinoma (Dr Julian, the surgeon at Majuro Hospital, personal communication).

As emphasized in this report, there is sometimes difficulty drawing a distinction between benign and malignant thyroid neoplasms. The effect of radiation on the thyroid cells adds to the difficulty because of bizarre nuclear forms which may develop [13, 16]. Such nuclei may contain excessive amounts of chromatin not unlike malignant cells [14–16] (Figs. 4, 7 and 8). Furthermore, the radiation may damage the function of the gland, causing a decrease in production of thyroid hormone and a superimposed compensatory stimulus for cell division among the surviving cells [14]. This may result in cellular hyperplasia with the formation of papillary structures. It is therefore not surprising in the case of the Marshallese that pathologists might disagree about the diagnosis and the potential for some lesions to metastasize.

Many of the papillary and mixed papillary and follicular thyroid lesions grow very slowly. Once removed it is impossible to say what that lesion might have done. The Marshallese accident has given an unique opportunity to see these thyroid lesions develop after a single simultaneous event in multiple individuals. Some lesions were so small that they had not yet grown to the extent that there was overt invasion of the capsule or the wall of a blood vessel; yet, the cellular forms sometimes provided a basis for suspicion that some of these small lesions had not fully declared their pathophysiologic potential and spread to lymph nodes. As this experience has evolved, the occasional uncertainty of the diagnosis at surgery prompted this surgeon to remove all lymph nodes in the immediate drainage area of a lobe which contained a lesion in question. It was a fortuitous finding that in these cases there were 5 instances of spread to lymph nodes while the primary was only 1 cm or less in diameter, in 3 cases to only a single lymph node. Many writers consider such small lesions in the thyroid to be innocuous [17–19, 26, 30]. In this study the circumstances led to the discovery of carcinomas that seemed to be in an incipient stage of development. If these small lesions had not been discovered by the palpation of experts or found incidentally at surgery (undertaken for what proved to be a benign lesion), it is reasonable to speculate that the pathological process would probably have continued until the primary lesion had become obviously palpable and many nodes by then would have become positive. The latter scenario is the customary finding encountered in a general surgical experience, where a frank carcinoma is palpably obvious with many positive nodes discovered; just as occurred here in 3 cases where the primary lesion was large (easily palpable) and many nodes were involved.

Three or more decades ago many observers [24, 26, 31–35] reported on the multicentric nature of papillary carcinoma of the thyroid. At that time, the importance of the relationship of thyroid carcinoma to the previous use of radiation treatment for thymic hypertrophy and inflammatory disease of the neck had not been appreciated. Multicentricity was reported to be frequent when tiny sites were looked for. The occurrence of positive nodes was reported to be very high [31, 33, 35; 36]. These were usually more advanced cases in which a clinically evident mass had drawn attention; however, it was not always

the largest lesion that had given rise to the metastases. Emphasis on the occurrence of multicentricity seems to have passed with the decline in the use of external irradiation to the neck [40, 41]. Total thyroidectomy for multicentric papillary lesions was thought to be appropriate by some authors [32, 33, 37, 38, 41–43, 44], but the occurrence of complications in the hands of some surgeons and the indolent nature of the disease caused a decrease in interest in total thyroidectomy [34, 40, 41, 45]. Although 36 years have passed, the final story on these surgical cases and on the remaining exposed individuals has not been told. Most of these thyroid carcinomas, like those found elsewhere in the world, are a very low degree of malignancy. As shown by annual examinations and routine diagnostic chest x-ray films, there has been no recurrence of carcinoma thus far. Although wide removal of the deep jugular and upper mediastinal nodes was done in most cases of carcinoma, some positive lymph nodes may have been missed and are now inaccessible to physical examination. The fact that a lesion in question had been widely removed or thought not to have spread was no guarantee that the lesion did not have the potential to spread or might still appear. There has not been full agreement about the nature of the lesions in 2 of the 3 cases that were reoperated for regrowth. The lesions from the first operation in those cases were considered atypical adenomas and were probably not carcinoma. A minority considered the lesions from the second operations to be locally malignant. It seems that, where the irradiated thyroid tissue remains, neoplasms may still develop.

Summary

Radiation from radioiodines produced benign and malignant neoplasms in some Marshallese who were accidently exposed to fallout. Thorough annual study of each of 245 exposed person has been accomplished over 37 years or within their natural life time. More than 1000 other Marshallese have served as various controls. Seventy-seven irradiated and control cases have been operated for thyroid masses. In 8 of 23 cases of carcinoma, the disease had spread to lymph nodes. Five of the 8 primary lesions that spread were 1 cm or less in diameter. Minute multicentric carcinomas and atypical adenomas were found in addition to adenomas, presumably because the whole thyroid was at risk. Total or very near total thyroidectomy was the preferred procedure when carcinoma is present or suspected. There have been no recurrences of carcinoma; no disfigurement; no recurrent laryngeal nerve injuries; and no deaths related to surgery. There has been 1 case of postoperative hypoparathyroidism and another asymptomatic hypocalcemia which only became detectable 20 years after surgery.

When neoplasms might be expected from radioiodines in fallout, repeated meticulous examinations of the thyroid are required because some small lesions may metastasize early. Since multiple carcinomas have been found along with atypical adenomas in the irradiated glands and there has been difficulty distinguishing between the two, the observations in this study suggest that atypical lesions may eventually develop frank histological features of carcinoma and have a potential to metastasize. Furthermore, an interpretation of descriptive anatomical features of a thyroid neoplasm does not always reflect the physiological and behavioral processes going on in that tissue. Some lesions metastasize although they may appear to be benign. This series of observations over many years represent the sequential development of thyroid neoplasms, resulting from a single simultaneous exposure to radioiodines from fallout in a population.

Résumé

Le 1 mars 1954, un accident de retombée radio-active s'est produit pendant les essais atomiques à Bikini dans le Territoire Trust des Iles du Pacifique. Des débris radio-actifs sont tombés sur les atolls inhabités des Iles Marshall après la détonation d'un énorme appareil thermonucléaire, en raison d'un changement inattendu des conditions climatiques. Juste après la détonation, une surveillance militaire aérienne et maritime a permis de suivre les déplacements de la portion la plus chaude du nuage parabolique. Celui-ci s'est déplacé vers l'est et le sud-est tout en diminuant d'intensité et en se dispersant. Le centre du nuage radio-actif est passé au nord de l'atoll Rongelpa, atoll peuplé le plus près. Cet article rapporte le développement des lésions thyroïdiennes, les conditions particulières et les résultats de la chirurgie des lésions bénignes et malignes de la thyroïde rencontrées dans cette population dans les suites de cet accident.

Resumen

En marzo 1 de 1954 sucedió un grave accidente de contaminación en el curso del programa de ensayos atómicos de los EUA en Bikini en el Pacífico. Después de la detonación de un gran artefacto termonuclear, un inesperado cambio en la dirección de los vientos causó el depósito de desechos radioactivos en varios islotes habitados en las Islas Marshall. En la fase inmediatamente siguiente a la detonación, el seguimiento militar, marino y aéreo rastreó la porción más "caliente" de la nube parabólica en la medida que se movilizaba en un patrón de decreciente concentración hacia el este y hacía el sudeste de Bikini. El centro de la nube pasó al norte del islote Rongelap, que era el islote habitado más cercano.

El presente informe se refiere al desarrollo de lesiones tiroideas, las circunstancias especiales que fueron encontradas en el curso de la cirugía y los resultados del manejo quirúrgico de la lesiones benignas y malignas halladas en esta población.

Se realizó el estudio anual de 245 personas expuestas, en el curso de 37 años o en el curso natural de su vida. Se han operado 77 personas irradiadas y personas control por la presencia de masas tiroideas. En 8/23 casos de carcinoma se halló extensión ganglionar. También se encontraron pequeños carcinomas multicéntricos y adenomas atípicos, además de adenomas, presumiblemente debido a que toda la glándula estuvo en riesgo. Se realizó tiroidectomía total o casi total como procedimiento de elección, sin mortalidad ni complicaciones mayores. Se presentó un caso de hipoparatiroidismo postoperatoria y otro de hipocalcemia asintomática, detectada sólo 20 años después de la cirugía. Esta serie presenta el desarrollo secuencial de neoplasias tiroideas como resultado de una exposición única a radioyodos a partir de la contaminación de una población.

Acknowledgment

The laboratory support for part of the special studies was a grant from The US Atomic Energy Commission and its successors, including Brookhaven National Laboratory. The authors wish to acknowledge the assistance, suggestions and support of many friends and collaborators over the past 22 years with whom the senior author has participated in the care of the Marshallese: especially, Drs. Robert A. Conard, William H. Adams, Eugene P. Cronkite and Mr. William A. Scott of Brookhaven National Laboratory; and Drs. John D. Reid and Mary Petrelli of the Department of Pathology, Cleveland Metropolitan Hospital; and finally the many laboratory assistants and surgical residents who participated in the special studies and care of the patients.

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Invited Commentary

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"Radiation associated thyroid tumor" is a term well entrenched in the literature and usually refers to a patient having a thyroid neoplasm after known exposure to an irradiating source [1]. The irradiation has usually been part of a therapeutic program and was at its most common in the 1930's and 1940's, when infants and young children were treated by irradiation for thymic or tonsillar disorders. The time from irradiation to either presentation or detection of malignancy was approximately 20 years. The problem still persists as outlined in a recent report on thyroid disease following treatment of Hodgkin's disease [2]. Further information of this phenomenon was derived from the atomic experience in Hiroshima and Nagasaki, where it was demonstrated that thyroid cancer was significantly increased in the population heavily exposed to ionizing radiation in 1945 at the time of atomic bombing [2].

The thyroid pathology in local inhabitants following a serious fallout accident in the Marshall Islands in 1954 and reported by Dobyns and Hyrmer in this article has been carefully studied and provides what is perhaps the most complete study available in relation to the dosage, period of exposure, subsequent clinical progress, and management of those involved in radiation damage to the thyroid gland. It is assumed that most of the effects on the thyroid were due to short lived radioiodines with half lives of seconds to hours. It is also considered that I^{131} (half life 8 days) which was present at 10% of the level of short lived radioiodines but contributed some of the radiation effect on the thyroids. The intensity of the radiation and the predilection of radioiodines for the thyroid gland was mooted as causing reduction of thyroid function and the development of thyroid nodules. Those children whose thyroid function deteriorated to the level where clinical myxoedema was apparent had complete atrophy of the thyroid gland and no nodular growth followed. It is probable that the universality of stromal damage left it not able to respond to TSH. As for others, the drift to hypothyroidism was more in the vein observed after a standard dose of I^{131} in hyperthyroidism where 3.5% of patients per year develop deficient thyroid function. It was observed that patients with smaller goiters became hypothyroid before those with larger lesions [3]. It is significant therefore that in the population reported by Dobyns and Hymer that the children had a larger dose of I^{131} to the thyroid than did the adults [1] and although thyroxine was administered to the population in 1965, a significant time lead was already established before it was commenced.

In this very carefully studied group of patients the incidence of carcinoma was suspect in any person presenting with a clinically detectable, palpable thyroid abnormality. The surgeon who treated these patients was confronted with a serious problem and the solution adopted in the management of the patients was far seeing. The approach to total or near total thyroidectomy became established, based on sound grounds which ranged from finding grossly obvious malignancy to histological uncertainty on frozen section but suspicion that an atypical lesion might be malignant; the finding of firm lymph nodes near the gland which were suspected for malignancy were a further problem in operative decision making. A further factor had to be considered in taking the step of carrying out total thyroidectomy in an isolated population, namely, the supply of T4 and compliance in its taking had to be considered. As people exposed on Rongelap were well supplied with hormone, this was not of major concern.

The authors address the value of frozen section, a modality frequently rejected by histologists, but averred to as useful by many endocrine surgeons. The problem in the irradiated group related to small atypical lesions; these made the experienced thyroid pathologists a little diffident in diagnosing malignancy. An approach was taken therefore to clear as much thyroid tissue as possible and this overcame the need for secondary

surgery and had no adverse effect on the patient. There was a significant number (55%) of cancers <1.0 cm in diameter. In 5 (36%) of these cases a careful search revealed positive lymph nodes. This observation is of interest in view of the ongoing argument that prevails in calling total or near total thyroidectomy, radical therapy. As time passes more evidence accrues to endorse this "radical" approach in thyroid malignancy. In these patients with a low degree of malignancy there has been no recurrence, surely an accolade to the well recorded surgical clearance of the thyroid gland and nodal disease as outlined by the authors in this report.

References

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