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17 August 1979

Allen W. Mathies, M.D.
Dean, University of
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2025 Zonal Avenue
Los Angeles, CA 90033

BEST COPY AVAILABLE

Dear Dr. Mathies,

I must apologize for not responding more promptly to our very productive meeting on 25 July.

Your understanding and enthusiasm for the problems of field medicine were greatly appreciated. Relatively few physicians have a realistic perspective on the practice of medicine in such areas. It's a real challenge, but very rewarding. Both Susan and I have really been turned on to see these people moving from the 18th century to 20th century medicine.

One of the older Robert Wood Johnson programs (called the "Clinical Scholar" program) really intrigued me. Did Southern California work with that program? As you know the graduates had advanced training in sociology, economics, anthropology, systems analysis, health care planning, etc., in addition to their basic medical education. I think it really takes that type of Renaissance physician to deal effectively with medicine emerging in a third world nation. We find that we must constantly place ourselves in context with their indigenous medicine and work with it. Folk medicine still exists in the Marshalls, but it is very difficult to identify, particularly after 30 years of occupation and the credibility gap that has been generated by the accident in 1954. During the last year, by bringing more Marshallese into the program, in responsible positions, the culture has begun to open up to us. The whole social setting of medical care delivery is changing as we work together with traditional medicine.

I appreciate your offer to join one of the surveys (schedule permitting) and would like to give you the dates for the coming year:

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First Survey 1980

January 10 to Honolulu
January 12 to Majuro
January 20 to Kwajlein
January 27 board ship to outer islands (Rongelap, Utirik)
February 5 ship to Utirik
February 17 return to Kwajalein
February 20 return to Honolulu
February 21 return to home

Since this spans almost 6 weeks, we have been dividing consultants into two groups - the first group covers the islands of Majuro and Ebeye (unfortunately much like Tijuana) - leaving the U.S. on 10 January and returning on about the 30th, the second group will leave the U.S. about 23 January, returning on 21 February. This trip is really our basic adult screening program (please see the enclosed research plan). In addition we deliver primary care as needed at sick call - a very busy spot.

The May-June survey will be very similar but the emphasis is on pediatrics and will cover the period from 13 May to 27 June with about the same amount of time spent on each island.

September-October trip in 1980 will concentrate on dental problems, diabetes, and a variety of substudies. Again as well as primary care. The dates are tentatively set for 4 September through 10 October. I hope this will provide you with adequate information for advance planning. In respect to the possibility of establishing a formal affiliation between the Medical School of the University of Southern California and Brookhaven National Laboratory-Marshall Islands study, I have tried to present the advantages of such an arrangement to Southern California and then to BNL. These factors are included in the text of my letter to Brian Henderson (please see enclosure), but in addition, during our discussion we expanded the concept to encompass a broader training spectrum.

If the anticipated expansion and concomitant funding develop as all signs indicate, the Brookhaven National Laboratory/Department of Energy Marshall Islands study will be in a position to offer paramedical training scholarships to carefully screened Marshallese. In fact we have two excellent candidates for R.N. training identified already. A coordinated SC/BNL field program would offer a unique field training setting for a wide spectrum of students from a pre- to postgraduate levels. We would like to support a multidisciplinary approach, where the teams could see the synthesis of sociology, medical economics, and health care systems planning as it impacts upon medical practice.

I realize that this is a very sketchy outline of what would need to be a much more detailed presentation but I thought I should jot these ideas down and get them to you as soon as possible. I have discussed

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these ideas with the senior administrators of both BNL and the Department of Energy and they have indicated a sincere interest in further exploration of such an affiliation. You realize of course that the further development of these plans is contingent upon approval by the Department of Energy and adequate funding from Congress. All indications that we have at the present time encourage us to believe that both DOE and Congress would support such a concept. I am in frequent contact with Bruce Wachholz, Ph.D., who is the DOE coordinator for all Marshall Island programs, and will send a copy of this letter to Bruce. The next move is obviously up to the DOE and to the funding authorities to clear the way for all the plans we have outlined. I certainly hope that such an affiliation can be established. I think it would be tremendously productive for both institutions.

Thanks again for your warm reception and hospitality. Susan and I are looking forward to seeing you again in California.

Sincerely,

Hugh S. Pratt, M.D.
Principal Investigator,
Marshall Islands Programs
Brookhaven National Laboratory

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Enclosures:

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Research Plan

A. Introduction:

1. Objective:

The primary objective is the determination of the life-time effects of radioactive fallout on the Marshallese who were accidentally exposed on 1 March 1954.

2. Background:

This study focuses on the acute and long-term radiation effects on a population of Marshall Islanders inadvertently exposed to fallout.

The accident occurred on March 1, 1954, when an unexpected shift of winds, following detonation of a thermonuclear device at Bikini, caused radioactive fallout to be deposited on several inhabited islands to the east. Evacuation of the exposed group was accomplished within two days. The estimated whole-body gamma doses to the Marshallese on the three atolls were: Rongelap (64 people), 175 rads; Ailingnae (18 people), 69 rads; and Utirik (158 people), 14 rads.

Acute effects of gamma exposure were noted in the Rongelap and Ailingnae groups, but not in the Utirik group. Another source of exposure in all the island groups was due to internal absorption of radionuclides from inhalation and ingestion of contaminated food and water as determined by radiochemical urine analysis. Only the isotopes of iodine, strontium and barium were absorbed to any significant degree. No acute symptoms were noted from this internal absorption and by six months, urinalyses indicated these isotopes to have been virtually eliminated. Nevertheless, early exposure to radioiodines resulted in delayed but serious injury to the thyroid glands and hematologic depression for 15 years.

The thyroid dose was estimated to be considerably higher in the children due to the smaller size of the thyroid glands. In the Rongelap people, the thyroid dose from gamma radiation and radioiodines (principally I^{131}, 132, 133, 135) was estimated to be about 335 rads in adults. In small children, the doses ranged from 700 to 1400 rads.

Following the initial studies, annual examinations, and more recently, quarterly examinations, of the exposed people, as well as an unexposed comparison Marshallese population, have been carried out.

In the first ten years after the accident, few findings were noted that could be related to radiation exposure. During the second decade, however, serious late effects developed related primarily to the thyroid gland. In addition, a Rongelap man who had been exposed at 1 year of age died of acute myelogenous leukemia which was likely related to radiation exposure.

Nodules of the thyroid gland began to develop in Rongelap children, and to a lesser extent, in adults, beginning about nine years post exposure. These nodules have continued to appear over the subsequent fifteen years and virtually all of these have been resected surgically.

In 28 patients, benign nodules were found. Cancer was found in seven patients. All seven malignant tumors were of low grade malignancy. Localized metastasis were noted in several cases, but there were no distant metastasis.

The high incidence of thyroid nodularity in the irradiated subjects is in agreement with previous data linking irradiation of the gland with subsequent development of thyroid nodules or carcinoma. Since ^{131}I is considered much less tumorigenic for thyroid tumors than x rays, it is rather surprising that, in view of the large contribution of radioiodines to the thyroid dose of the Marshallese, the risk factor (risk/rad) is comparable to that noted following x-ray exposure. This ma be related to the presence of more potent short-lived isotopes of iodine present in the fallout which accounted for two to three times the dose from ^{131}I.

Two boys who developed myxedema received an estimated thyroid dose of 1150 rads. In addition, at least five of the Rongelap population who had appropriate testing prior to surgery had either biochemical hypothyroidism or decreased thyroid reserve. Because of the suspicion of possible hypothyroidism in individuals exposed to even lower calculated doses, a series of studies of thyroid reserve in previously unoperated exposed Marshallese was initiated in 1974.

Since the most sensitive index of impaired thyroid function is an elevation in serum TSH which occurs through the hypothalmic-pituitary-thyroid feedback axis, serum TSH concentrations and their response to thyrotropin-releasing hormones (TRH) were measured in both the comparison and the exposed Rongelap population.

On the basis of these studies, criteria were established for classification of patients as having biochemical evidence of impaired thyroid function.

In a control group of 115 who were not exposed to radiation, 10% had a serum TSH > 3 μU/ml (normal < 3 μU/ml, borderline 3-5 μU/ml, elevated > 5 μU/ml). In 9%, serum TSH was only minimally elevated (4 μU/ml or less). None of these patients had detectable clinical hypothyroidism or thyroid enlargement, but serum T4 concentrations were generally in the low normal range.

In the exposed Utirik population, 12% of the subjects tested had at least one basal serum TSH greater than 3 μU/ml, though none of these was in excess of 5 μU/ml. The prevalence of elevated TSH in this population is not significantly different from that of the unexposed group. In the Rongelap and Ailingnae population, 25% of the subjects were found to have at least a single elevated basal serum TSH greater than 3 μU/ml. In two cases, the serum TSH was in excess of 7 μU/ml. This is a significantly higher prevalence than in the other two groups pooled.

An association of thyroid nodularity and cancer with prior radiation of the thyroid gland, particularly in younger patients, is well-recognized and the association has recently been reviewed by Maxon et al. (Am.J.Med. 63: 967, 1977) and De Groot et al. (Radiation-Associated Thyroid Carcinoma, Grune & Stratton, N.Y., 1977). In addition, it has been recognized that radiation to the thyroid delivered in the course of treatment of patients with thyroid hyperfunction is associated with hypothyroidism in a significant fraction of the patients (as high as 50%) at the higher dose levels.

There is little data available in the literature relative to the possibility of hypothyroidism following ^{131}I dosages of less than 2500 rads. Preliminary results of Hamilton and Thompkins (Further Adv.Thy.Res., K.Fellinger, R.Hofer, Eds., Vienna 1971, p.60 indicated that eight of 443 subjects (1.8%) subsequently became hypothyroid after diagnostic ^{131}I tests at less than 16 years.

The present studies suggest that there is a significant risk of development of impaired thyroid function many years following estimated thyroid doses of less than 500 rads from the mixture of radioiodines and gamma radiation present in fallout from nuclear detonations. In the Rongelap and Ailingnae group, the effect has

apparently not been significantly severe to result in clinically evident hypothyroidism but by currently acceptable criteria, there is evidence of impaired thyroid reserve in these individuals. If left untreated, it would be anticipated that thyroid function would continue to decrease in this group to the point of clinical hypothyroidism. The data also indicate that the frequency of an elevated serum TSH, the earliest biochemical evidence of impaired thyroid function, is also significantly more common in the Rongelap population than in the control-unexposed group. There are several other exposed Rongelap individuals in whom results of basal TSH, and at least one TRH test, have suggested the possibility they may also have evidence of impaired thyroid function.

These data indicate that in addition to thyroid nodularity, which is a well-recognized manifestation of exposure to radioactive iodine or external radiation, biochemical evidence of thyroid dysfunction can appear 25 years or longer after an initial thyroid dose of as low as 350 rads. (Conard, R.A. et al. BNL Report 50424, Brookhaven National Laboratory, Upton, N.Y., December, 1975).

3. Rationale:

The exposed Marshallese constitute a unique population accidentally exposed to acute and long-term effects of fallout from a ground/sea level 15 MT thermonuclear weapon.

The radiation characteristics are different from those under observation in Japan and in other nuclear reactor or weapons-test accidents. This prospective study, now in its twenty-fifth year, has provided unique epidemiological data on 244 exposed individuals, particularly in relation to thyroid pathology. In recent years, we have seen an unusually high prevalence of biologic hypothyroidism, previously unsuspected.

Although a significant number of people suffered beta burns, no skin cancer has been detected, but continual monitoring is necessary.

One man, exposed at one year of age, died of acute myelogenous leukemia at age 19. Since pre-accident vital statistics are almost totally unreliable, one of the important goals of the study is to establish the incidence and/or prevalence of those pathologic conditions most frequently associated with radiation in a control/comparison group of Marshallese. Due to cultural, geographic and political problems, the accumulation of this type of data is proceeding very slowly. The lack of reliable vital statistics, coupled with the small size of the exposed group, makes the statistical analysis of the data very difficult.

In addition, one should recognize that with the Westernization of the Marshallese culture following the accident, consumption and/or exposure to a number of potent carcinogenic agents has occurred. These other independent variables, i.e., smoking, chemical carcinogens, etc., should not be underestimated in the analysis of selected cancers, for example, lung, GI, CU.

In the case of thyroid neoplasia, these carcinogens would have little effect. (Larsen, P.R., et al. Late Biologic Effects of Ionizing Radiation I. IAEA, Vienna, 1978, p. 101).

4. Comprehensive Progress Report

a. Period:

March 9, 1954 to present.

b. Summary:

Post-exposure surveys in the Marshall Islands have been conducted for 25 years In addition to the 244 people originally exposed, a group of 209 unexposed Marshalles are examined as a comparison population to assess late effects of radiation from fall out. The continuing development of thyroid neoplasms and biochemical hypofunction, and the appearance of one case of acute leukemia, indicate the need for frequent examinations. In addition to physical, hematological, and other laboratory examination the surveys involve special studies related to aging, malignancy reproduction and measurement of body burdens of radionuclides resulting from the slight contamination remaining on the islands. Thyroid patients are returned to the United States for hospitalization and surgical treatment. In view of the diverse medical problems and their management, a physician, nurse practitioner, and laboratory assistant are in residence at Kwajalein and make regular trips to Rongelap, Majuro and Utirik to supervise care and perform interim examinations of the exposed Marshallese. Medical surveys of these people are conducted at frequent intervals. The surveys are carried out jointly by Brookhaven National Laboratory under the auspices of the Department of Energy and the Trust Territory of the Pacific Islands.

c. Detailed Report:

The progress relative to the research objectives for this twenty-five-year follow-up is best presented in the 20 Year Report
There have now been 39 thyroid abnormalities (35 with surgery) among the 244 exposed Marshallese. The occurrence of three thyroid cancers in the exposed Utirik population (compared with four in the Rongelap group) appears to implicate radiation exposure in the etiology, but the high incidence is puzzling since it is greater than would be predicted based on Rongelap and Japanese data; there does not appear to be any increase in benign thyroid tumors in the group compared to the much greater incidence in the Rongelap group. Because of the uncertainty of the incidence of thyroid tumors in unexposed Marshall Islanders and in order to obtain better statistics, during the past two years thyroid examinations were included on all unexposed Rongelap and Utirik people on any of the Marshall Islands visited. This study has been extended to include thyroid surgery when indicated. Also, in order to help solve the Utirik dilemma, re-evaluation of radiation doses from fallout to the Utirik people, including the thyroid, has begun.

In 1977, a bill authorizing compensation to certain of the Utirik and Rongelap people for radiation injuries was signed by the President and in FY 1979 payments were completed.

A study of the high incidence of maturity onset diabetes in the study group was initiated several years ago and continues. During the past year an intestinal parasite survey was completed on Rongelap Atoll with studies of stool specimens and serological testing. Anthelmintic therapy (Vermox) was completed on nearly the entire population. A large percentage of the people had positive stools for parasites. The parasites have been virtually eliminated in this island group by the treatment regimen. A similar study is under way in Utirik, using a different agent (Parantyl Pamoate) (Personal Correspondence, W. A. Krotoski).

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During FY 1978 and 1979, a comprehensive health education program directed toward instructing the people of Rongelap and Utirik about the effects of radiation was carried out by Dr. Naidu of BNL (Safety and Environmental Protection Division). A booklet on radiation and its effects was developed and Dr. Naidu established a residence on each island for at least a month. His command of the language and integration into their society resulted in a significant transfer of information (judged by the sophistication of their questions to the medical group on subsequent visits). Radiological monitoring of people living on Rongelap, Utirik and Bikini, including radiochemical analyses of urine samples and whole body gamma-spectrographic analyses, has been intermittent, as indicated during the study. Evaluation of low levels of plutonium detected in the urines of Bikini and Rongelap people continues. It is still uncertain if contamination of urine samples may be a factor. A disturbing finding was a sudden increase in the Cs^{137} levels in the Bikini people, resulting in their resettlement.

Two new physicians were hired in 1978 for the program. Dr. W. Grant replaced Dr. K. Knudsen as the Resident Physician and Dr. H. Pratt replaced Dr. R. Conard after he retired (January 1, 1979).

The attitudes of the Rongelap and Utirik people toward the examinations has gradually improved in recent years due partly to a better understanding of the objectives of the medical team as a result of the increased educational program, and partly to an improved attitude of the Marshallese politicians. However, activist groups from Japan and agitation in the United States continue to cause unrest among the people.

Studies with Dr. Raymond A.Popp (Oak Ridge) for frequency of isoleucine substitution in hemoglobin of Marshallese as an index of somatic mutations associated with radiation exposure and aging were continued (Popp, R. A. et al., Interdiscipl. Topics Geront. 9: 209-18, 1976).

Studies of polymorphism and rare protein variants in the blood cells from children of exposed and unexposed parents by Dr. James Neel (University of Michigan) were reactivated and he has expanded his battery of tests for these variants in Marshallese children (Neel, J.V. et al., Amer. J. Hum. Genet, in press).

A small clinical laboratory has been established on Ebeye under the direction of the resident physician. A laboratory technician was hired as an assistant.

d. Publications:

Cronkite, E.P., et al., Some effects of ionizing radiation on human beings: A report on the Marshallese and Americans accidentally exposed to radiation fallout and a discussion of radiation injury in the human being. AEC-TID 5385, U.S.Governmen Printing Office, Washington, D.C. 1956.

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Cronkite, E.P., et al., Twelve-month post exposure survey on Marshallese exposed to fallout radiation. BNL 385 (T-71), August 1955.

Conard, R.A., et al., Medical survey of Marshallese two years after exposure to fallout radiation. J.A.M.A. 164: 1192, 1957; BNL 412 (T-80), March 1956.

Conard, R.A., et al., March 1957 medical survey of Rongelap and Utirik people three years after exposure to radioactive fallout. BNL 501 (T-119), June 1958.

Conard, R.A. et al. Medical survey of Rongelap people, March 1958, four years after exposure to fallout. BNL 534 (T-135), May 1959.

Conard, R.A. et al. Medical survey of Rongelap people five and six years after exposure to fallout. BNL 609 (T-179), September 1960.

Conard, R.A. et al. Medical Survey of Rongelap people seven years after exposure to fallout. BNL 727 (T-260), May 1962.

Conard, R.A. et al. Medical survey of Rongelap people eight years after exposure to fallout. BNL 780 (T-296), January 1963.

Conard, R.A. et al. Medical survey of the people of Rongelap and Utirik Islands nine and ten years after exposure to fallout radiation (March 1963 and March 1964), BNL 908 (T-371), May 1965.

Conard, R.A. et al. Medical survey of the people of Rongelap and Utirik Islands eleven and twelve years after exposure to fallout radiation (March 1965 and March 1966), BNL 50029 (T-446), April 1967.

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Robbins, J., Rall, J.E., and Conard,R.A. Late effects of radioactive iodine in fallout. Ann.Intern.Med. 66: 1214-42 (1967).

Conard, R.A., Sutow, W.W., Colcock, B.P., Dobyns, B.M., and Paglia, D.E. Thyroid nodules as a late effect of exposure to fallout, in Radiation-Induced Cancer (Proc. IAEA Symp., Athens, April 1969), pp. 325-36, IAEA, Vienna, 1969.

Sutow, W.W. and Conard, R.A. The effects of fallout radiation on Marshallese children, in Radiation Biology of the Fetal and Juvenile Mammal (Proc. 9th Annu. Hanford Biology Symp., Richland, Wash., May 1969) pp. 661-73, M.R. Sikov and D.D. Mahlum, Editors, CONF-690501, 1969.

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B. Specific Aims:

1. Continuation of medical survey (every four months) of exposed and comparison groups (see Methods).

2. Re-establishment of "cohort" control - first established in 1957.

3. Establish biochemical profile of nearest suitable Marshallese population living in ambient Micronesian radiation background.

4. Establish mechanism (via resident staff) for collection of more valid vital statistics on:

   a. cause of death, e.g., set up mechanism for autopsy, record review or limited cytologic studies (needle biopsy);

   b. morbidity - assist Trust Territory in new format for record review;

   c. birth/neonatal data - looking specifically for increased incidence of congenital abnormalities, abortions, miscarriages, etc.;

   d. collect data on immunizations.

5. Computerization - (after restructuring all clinical records) to improve availability and data reduction both in the field and at BNL.

6. Accelerated and expanded health education programs to attempt to place radiation risk in relation to other carcinogenic risks, e.g., smoking. The adverse effects of their diet should be emphasized in relation to diabetes, obesity, and severe periodontal disease. The relative impact of poor nutrition on their health should be placed in perspective with the morbidity and/or mortality from radiation.

7. Continued investigation in the following areas:

   a. diabetes per Dr. Field (Conard, R.A. et al. BNL Report 50424, Brookhaven National Lab., Upton, N.Y., December, 1975; letter from Dr. Field, 10/10/78).

   b. genetics per Dr. Neel (Am. J. Human Genetics 28: 262, 1976).

   c. aging per Dr. Popp (Interdiscipl. Topics Geront. 9: 209, 1976).

   d. intestinal parasites per Dr. Krotoski (Personal Correspondence, W.A. Krotoski).

8. Begin liaison with the newly-established "free association" government of the Marshall Islands.

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