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Late Biological Effects From Internal and External Exposure

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ABSTRACT

Information on late biological effects of radiation was obtained from the long-term medical followup of a small population of Marshallese accidentally exposed to radioactive fallout from a thermonuclear test in 1954. Endocrine data are compatible with a sequence of nonstochastic radiation effects. The ingestion of radioisotopes of iodine produced clinical thyroid hypofunction in children, biochemical evidence of thyroid dysfunction in some adults, thyroid adenomatous nodule formation, and, as a possible indirect effect of thyroid damage, at least two cases of pituitary adenoma. In contrast, the only evidence of a stochastic effect has been a real increase in thyroid cancers among the more highly exposed people of Rongelap, none of whom have evidence of residual disease. While three nonthyroidal cancers which are known to be inducible in humans by external irradiation have been documented in the exposed population, three similar cancers have occurred in an unexposed comparison population of Marshallese.

Nonstochastic effects of radiation exposure may be common but subtle. In the Marshallese experience the morbidity of delayed nonstochastic effects far exceeds that of the stochastic.

INTRODUCTION

In 1954, 253 Marshallese living on the remote Pacific atolls of Rongelap and Utirik were accidentally exposed to radioactive fallout from a thermonuclear test (Co80). The 167 residents of Utirik, who received approximately 11 rads of external gamma radiation, had no evidence of acute radiation injury. In contrast, the acute effects suffered by the 86 more highly exposed inhabitants of Rongelap, 19 of whom were on nearby Ailingnae atoll at the time of the fallout, included skin burns and blood count depression, effects commensurate with the 110-190 rads of external gamma radiation they received (Cr55). This presentation is a review of subsequent medical events to illustrate probable and possible residual somatic effects of internalized radionuclides resulting from fallout exposure. The details of that exposure have been discussed elsewhere (Le85).

NONSTOCHASTIC EFFECTS

Nonstochastic radiation-induced lesions are pathologic effects in which the severity is a function of radiation dose. Five years after the 1954 exposure growth retardation was documented in two young Rongelap boys. When newer tests of thyroid function became available it was determined that the growth retardation was due to hypofunction of the thyroid gland, with milder impairment being noted in several other children (Su65). The hypothyroidism had resulted from extensive thyroid destruction which followed ingestion of radioisotopes of iodine. Iodine is a component of thyroid hormone, and to make the hormone the thyroid gland concentrates iodine up to 500 times the plasma concentration. As a consequence it is now estimated that the two boys suffered an absorbed thyroid dose of 5000 rads (Le85). Such a dose effectively ablates the young thyroid gland. This serious condition has been and is being treated with lifetime thyroid hormone replacement. Had present-day knowledge been available at the time of fallout exposure, the diminished thyroid function that occurred might have been predictable because lethal damage to irradiated cells is in part a function of radiation dose, i.e., is nonstochastic. In the case of the young Rongelap children thyroid deficiency was evident within a few years of exposure. It is now apparent, however, that with smaller radioiodine doses from the fallout a milder and delayed form of thyroid hypofunction has occurred. A recent evaluation of the exposed individuals of Rongelap indicates that 16% have evidence of decreased thyroid function (La82). Most show only elevated levels of thyroid stimulating hormone, an indication that the pituitary gland is attempting to stimulate an impaired thyroid to maintain a normal thyroid hormone output (Fig. 1). The clinical significance of this residual somatic effect (diminished thyroid reserve) is not yet clear, but conceivably overt hypothyroidism may develop many years after exposure.

Clearly, the organ concentration of an internalized radionuclide will be a major determinant of the severity of its effect. Tissues or organs other than thyroid which are known to significantly concentrate fallout radionuclides include the liver, which can concentrate the actinides (Fig. 2). Abnormal liver function was noted in several Japanese fishermen of the Lucky Dragon 2-3 months after their exposure to the same 1954 fallout (Ts55). Bone, especially the endosteal surface, serves to localize plutonium, strontium and radium. Anatomic considerations also affect concentration; for example, the

poorly soluble plutonium oxide, upon inhalation, remains localized in the lung. The gastrointestinal tract, by containing ingested nonabsorbable radionuclides for the 42 hours or so required for transit of food, increases radiation to the bowel. It is estimated that the more highly exposed Marshallese received 50-75 rads to the gut by this mechanism, making the gastrointestinal tract second only to the thyroid in total absorbed radiation dose. If one acts promptly, it may be possible to minimize radiation dose from internalized radionuclides. In the particular case of radioiodine concentration by the thyroid, it has been argued that stable iodine should be administered to persons acutely exposed to radioiodines in an attempt to dilute the internalized radionuclide (NCRP77).

There may be indirect consequences of loss of tissue or organ function because of the interdependence of components of biological systems. Ten years after fallout exposure thyroid nodules were detected in three Rongelap girls. All exposed Marshallese are offered annual medical examinations, and, through 1983, 28 nodules had been surgically removed from the exposed persons of Rongelap. In an attempt to suppress nodule formation all of the latter were placed on suppressive doses of thyroid hormone beginning in 1965. The types of thyroid nodules found during 30 years of observation can be grouped into the adenomas, carcinomas, and adenomatous nodules (Table I). Most of the Marshallese nodules have belonged to the latter group. Adenomatous nodules are benign and are not properly categorized as neoplasms. Among the exposed population both benign adenomatous nodules and thyroid hypofunction display a positive correlation with radiation dose (Fig. 3). It is possible, therefore, that the initial thyroid damage resulted in low-grade thyroid dysfunction. This in turn led to chronic over-stimulation of the thyroid by the pituitary gland and subsequent adenomatous nodule production (Fig. 1). This hypothesis, if proven, would make adenomatous thyroid nodules an indirect but physiologic response of the thyroid to tissue injury, rather than a neoplastic effect of radiation. An alternative explanation is that thyroid hypofunction and radiation, when combined, are more effective in producing adenomatous nodules. Adenomatous nodules are usually of no clinical significance. They do not evolve into carcinomas, and surgical removal is necessary only to rule out that diagnosis. Nevertheless, the clinical evaluation involved is associated with its own morbidity, a factor of considerable import which has generally gone unmentioned. Prominent in this morbidity is thyroid surgery itself, a procedure which requires general anesthesia, results in the unavoidable removal of some normal thyroid tissue, and can damage the parathyroid glands.

Twenty-two years after exposure a nonfunctioning pituitary tumor was diagnosed in a Rongelap woman. Another pituitary tumor, a prolactinoma, has now been diagnosed in a Utirik woman. From retrospective blood tests for prolactin, a marker for prolactinoma, this tumor is known to have been present 21 years after exposure or even earlier. A third exposed woman who was on Utirik also has a mildly elevated prolactin level. Although a CT scan of the skull does not suggest the presence of a pituitary tumor, that diagnosis remains a possibility. Pituitary tumors are usually benign, but they can cause clinical problems because of their intracranial location or because of inappropriate pituitary hormone secretion. There is no prior evidence to suggest that pituitary tumors are induced in man by radiation. Nevertheless, experimental animals whose thyroids have been damaged with iodine-131 may

develop pituitary tumors (Fu73), and hypothyroidism in humans has been associated with proliferation of pituitary cells and adenoma formation (Ru55). We may be seeing another effect of nonstochastic radiation injury, a link in a chain of reactions stemming from radiation-induced thyroid dysfunction. However it is important to note that at the present time the association of the two diagnosed cases of pituitary tumor with radiation exposure is only statistical, not causal (Ad84).

Thyroid hypofunction may pose additional risks. If not treated, hypothyroidism can produce a dysbetalipoproteinemia, the clinical effect being an elevated blood cholesterol. An increase in the risk of coronary heart disease may be associated with certain types of mild thyroid dysfunction (Fo70,Ti81). However, serum cholesterol levels in the exposed Marshallese have not been elevated.

Harmful nonstochastic radiation effects may not end with apparent early recovery. There may be the initiation of a chain of pathologic events, each new link being more difficult to detect, thus more difficult to relate to the initial injury. Furthermore, the full range of residual somatic effects of acute radiation exposure in man is not known. For example, there is a suggestion of another residual lesion in Rongelap exposed. Peripheral blood neutrophil counts, lymphocyte counts, and platelet counts, when analyzed for trend over time (Fig. 4), have displayed a statistically significant decrease when compared to blood counts of an unexposed comparison Marshallese population. The degree of decrease is not great on an individual or collective basis, and in itself does not represent a clinical problem. No increase in susceptibility to infection has been noted. However, such a long-term depression detectable in a population has not been previously described (Bl66), and the data will receive a more detailed analysis. These findings, if confirmed, would add detectable hematologic effects to the late nonstochastic effects list. In this case acute external rather than internal radiation is the probable etiology. This is because chronic low-dose exposure from internalized long-lived bone-seeking radionuclides that can damage bone marrow have no clinical significance to the exposed Marshallese due to the low doses they received from these classes of radionuclides.

STOCHASTIC EFFECTS

Stochastic radiation-induced lesions are pathologic effects in which the probability of an effect, not its severity, is a function of dose. Radiation-induced neoplasms are such events, and their clinical presentations and the problems they produce are indistinguishable from spontaneously occurring neoplasms. Neoplasms are new growths of tissue in which the growth is progressive and not under normal control. If the neoplasm is invasive or can metastasize to other organs it is termed malignant. Carcinomas of various kinds are malignant; adenomas, on the other hand, are benign. Determining the excess incidence of radiation-induced malignant disease requires knowledge of the incidence of spontaneously occurring malignancies. The spontaneous incidence varies with age, sex, and ethnic background, genetic background and environment.

Malignant neoplasms inducible in man by acute external radiation, as revealed by statistics collected on atomic bombing survivors in Japan, include

leukemia, cancers of thyroid, breast, lung and stomach, and multiple myeloma (Wa83,Ic82,Be78). Other studies suggest brain tumors may be increased (Se80), and the list continues to grow. Eighteen years after the 1954 exposure, acute leukemia was diagnosed in a young Rongelap man who had been one year of age at the time of the fallout (Co75). The peak incidence of acute leukemia in the Japanese A-bomb survivors exposed at less than 15 years of age occurred about 5-10 years after their exposure. It is probable that the acute leukemia in the Rongelap man was a carcinogenic event due to his exposure. There has been a stomach carcinoma diagnosed in a Rongelap man 20 years after exposure, and 28 years after exposure, a meningioma was diagnosed in a Utirik woman. On the other hand, one death from breast cancer, one from lung cancer, and one from a spinal cord tumor have been recorded in the unexposed comparison population. There is a reasonable chance such tumors will occur spontaneously in any population over thirty years. Based on the dose, one would not expect to see an epidemic of radiation-induced malignant disease in the Marshallese. In Japan for example, among 82,242 atomic bombing survivors, an estimated 181 of the 3,842 cancer deaths were attributed to radiation exposure (Be78).

Four thyroid nodules in the exposed Rongelap group have been papillary carcinomas. About 90% of radiation-induced thyroid cancers are of this type (Ma81), and they require special mention. The relative importance of internal and external exposures in the induction of thyroid cancer is currently being debated. Three cases have been detected in the lower dose Utirik group and there have been two thyroid carcinomas found in the unexposed comparison population. The application of statistics to small numbers does not permit firm assumptions as to risk of thyroid carcinoma in the exposed Marshallese, but it is highly probable that the Rongelap group has had a true increase in incidence. Fortunately papillary carcinoma of the thyroid is a malignancy of low virulence, even if radiation-induced. Papillary carcinoma has a mortality rate of about 2-3% (Wo71). The type of thyroid carcinoma responsible for most deaths is the anaplastic variety, and this type has not been found in the exposed Marshallese. At the present time there is no definite evidence of residual thyroid carcinoma in any exposed Marshallese who has received treatment, nor has there been any mortality. In fact, when compared to an age and sex-matched unexposed Marshallese population selected in 1957, there has been no statistically significant difference in overall survival in the Rongelap group (Fig. 5). The same is true for the exposed group from Utirik. However, this may not have been the case if surveillance for thyroid nodules, their surgical removal, or thyroid hormone suppression had not been implemented in the early years following fallout exposure.

CONCLUSION

Despite the considerable attention accorded radiation-induced thyroid carcinoma, the documented morbidity from the nonstochastic effects of thyroid irradiation has far surpassed the morbidity from stochastic effects. It is true that radiation-induced thyroid hypofunction, in contrast to thyroid carcinoma, is easily treated and perhaps prevented. But the seriousness of nonstochastic effects, of which thyroid damage is only one, lies both in the large number of persons that could be affected, and in the subtlety of the development of those effects. It is recommended that more study be devoted to radiation effects whose severity is expressed as a function of absorbed dose.

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Table I. Thyroid Lesions Diagnosed at Surgery Through 1983

Exposure Group	Number of Persons	Adenomatous Nodules	Adenomas	Carcinomas
Rongelap	86	21	2	4
Utirik	167	10	2	3[b]
Comparison	227[a]	4	1	2

Not Included: are the following unoperated (and therefore unconfirmed) nodules: Rongelap - 1; Utirik - 1; Comparison - 5.

Included: are all consensus diagnoses of a panel of consultant pathologists; two different lesions were detected in one person each from Rongelap and Utirik.

[a] This number includes all persons who have been included since 1957 in an unexposed comparison group. Some have not been seen for many years; others have been added as recently as 1979.

[b] Equally divided opinion in one case; follicular carcinoma vs. atypical adenoma.

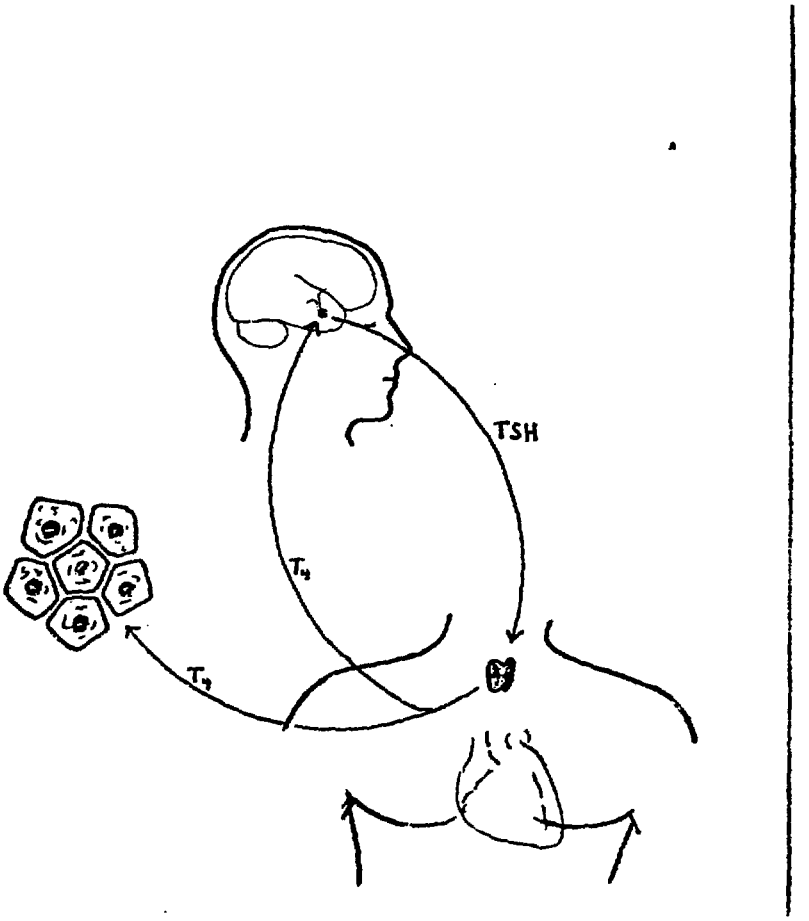

Figure 1. Thyroid-stimulating hormone (TSH) is produced by the pituitary gland. It stimulates the thyroid to produce and release thyroid hormone (T_4). T_4 regulates cell metabolism. It also regulates its own production through feedback inhibition of the pituitary. Thyroid hypofunction (with low T_4) impairs cell metabolism throughout the body. The low T_4 also results in chronic over-stimulation of the damaged thyroid by TSH, which could, in turn, result in the formation of benign adenomatous nodules.

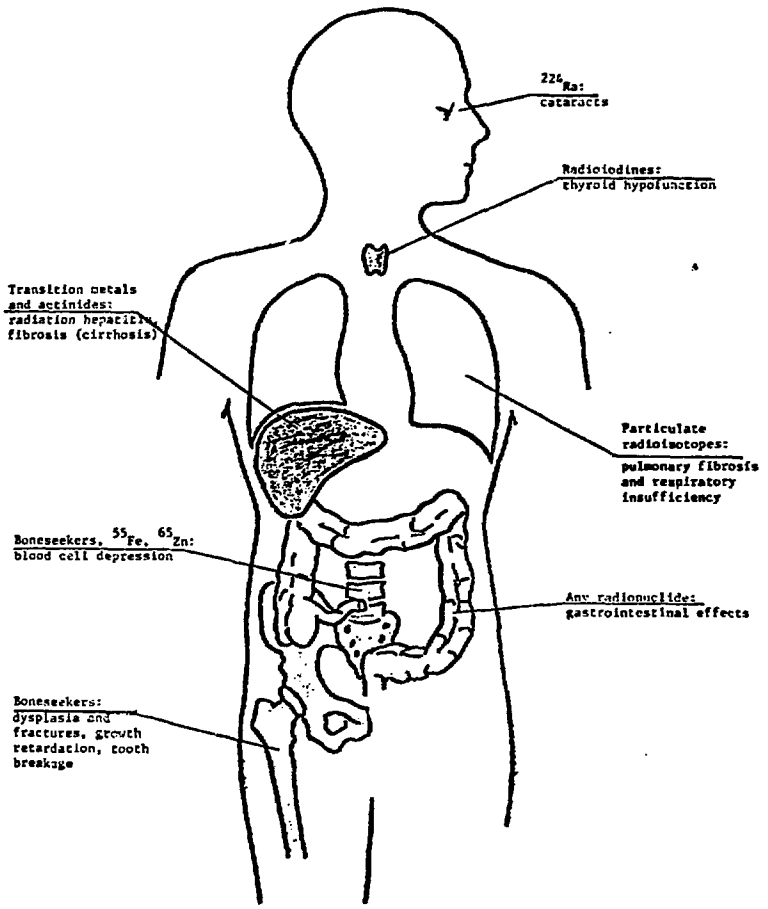

Figure 2. Examples of internal radionuclide concentration or localization and their potential pathophysiologic consequences.

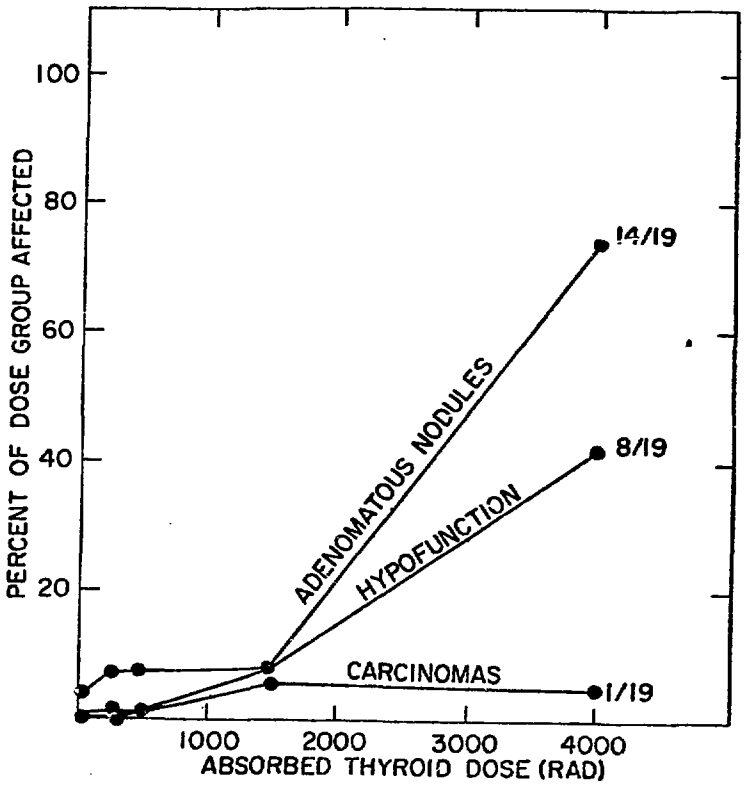

Figure 3. Prevalence of thyroid lesions as a function of absorbed thyroid dose in exposed and unexposed Marshallese. The 19 persons in the highest dose group were less than 10 years of age at the time of exposure.

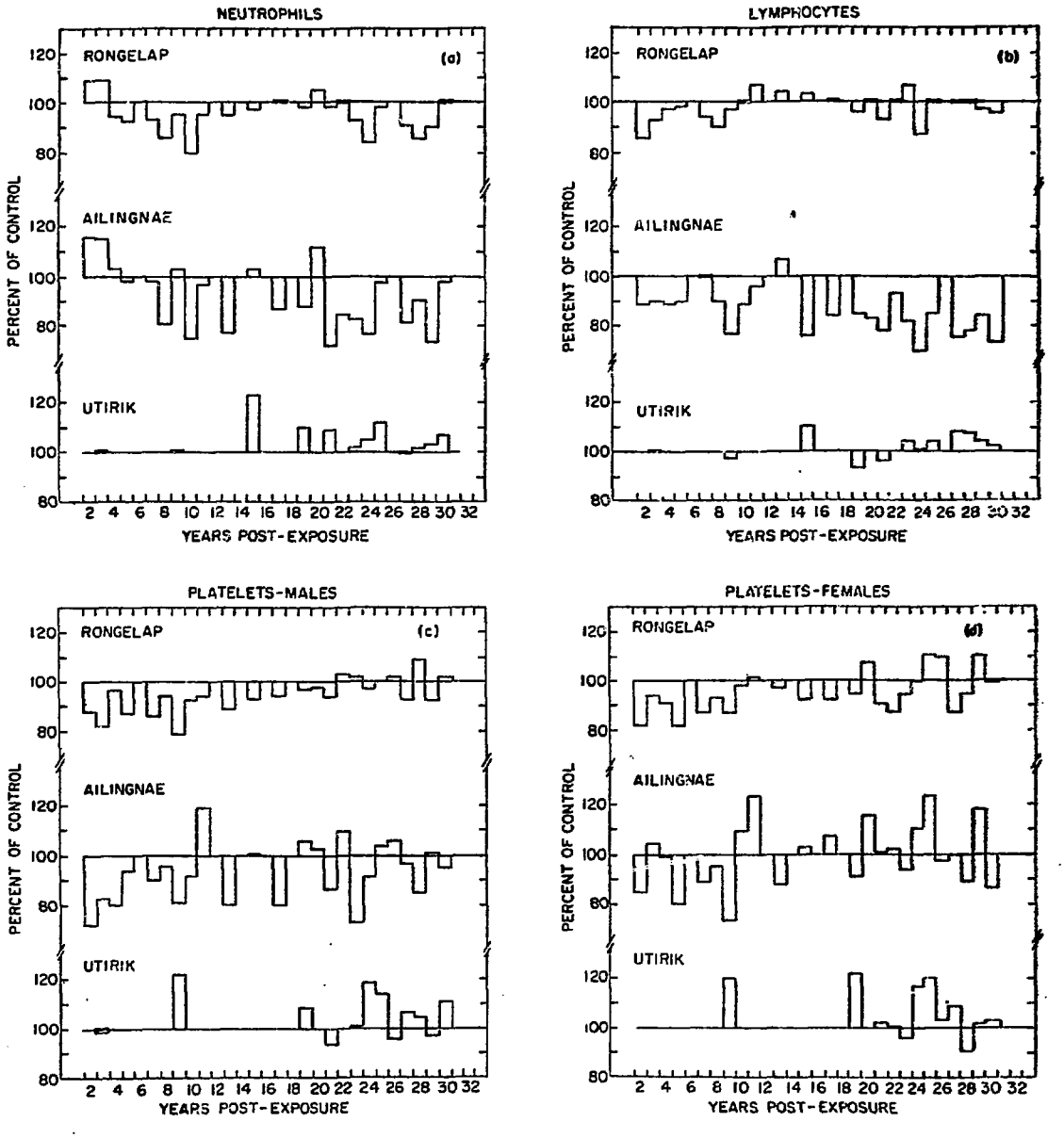

Figure 4. Mean annual blood counts of exposed Marshallese graphed as percent of control values. The Ailingnae subgroup (n = 19) is displayed separately from the Rongelap group (n = 67).

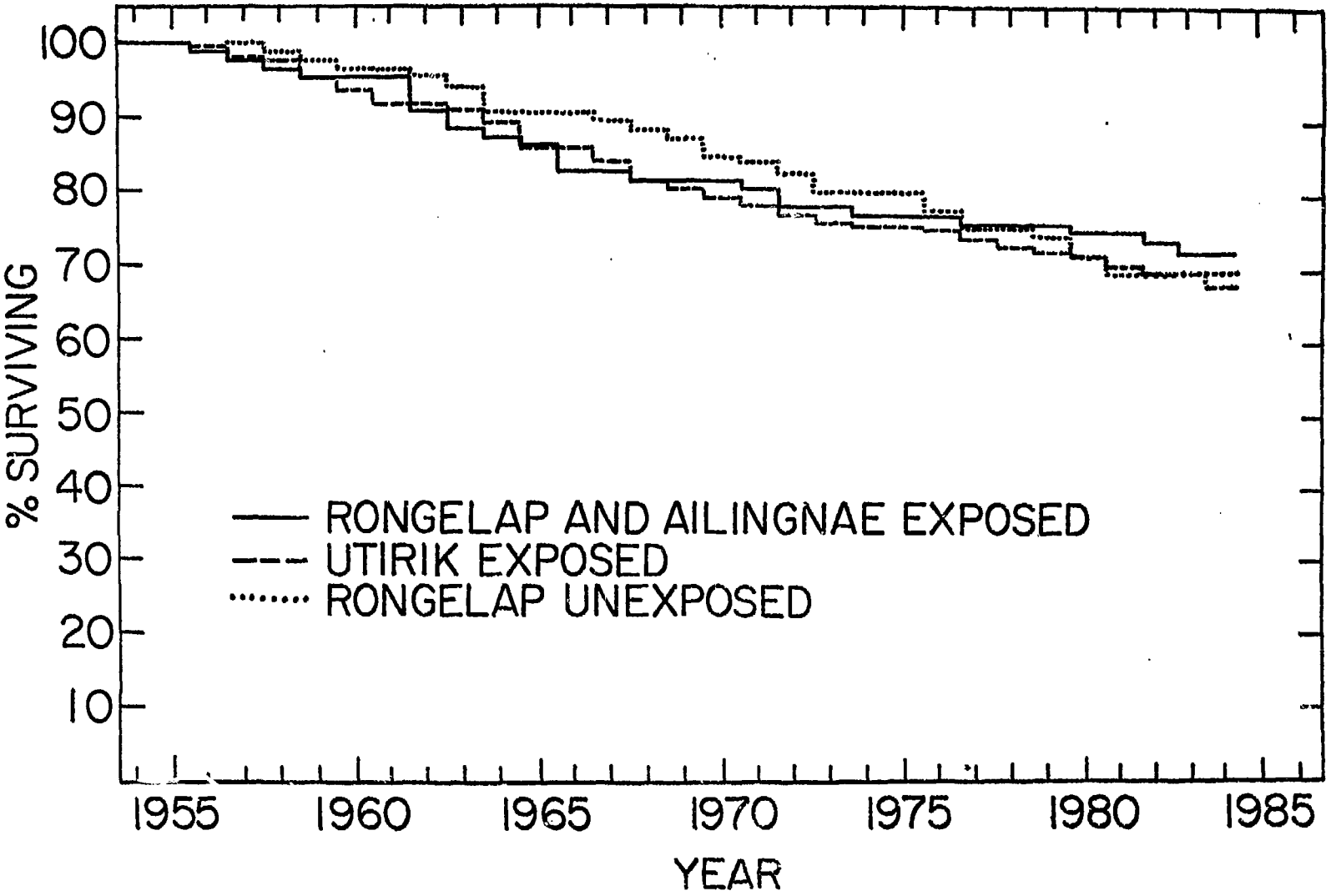

Figure 5. Survival curves of exposed and unexposed Marshallese populations.