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Elevation of the Serum Protein-Bound Iodine Level in Inhabitants of the Marshall Islands

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SOME years ago, in the course of follow-up examinations of some inhabitants of the Marshall Islands who had been exposed to fallout radiation from a 1954 hydrogen bomb explosion, a high incidence of unexplained elevation of the serum protein-bound iodine (PBI) level was found in both exposed and unexposed subjects [*1*]. The present report describes various studies of the kinetics of iodine metabolism in these subjects and some further work on the nature of the serum iodine.

MATERIAL AND METHODS

The people studied are all inhabitants of the Marshall Islands, most of them from the single atoll of Rongelap. To the best of our knowledge there has been little outbreeding. In some instances the results of radiated and control populations will be presented separately. All results reported in this article are from healthy persons who received no medication. Normal values for the fractionation of serum iodine by chromatography were obtained on blood drawn from normal volunteer subjects at the Clinical Center, National Institutes of Health.

The serum protein-bound iodine was determined by the method of Foss et al. [*2*] by Brookhaven National Laboratory, by the Boston Medical Laboratories and by Bioscience Laboratories. In addition, values for butanol-extractable iodine (BEI) of serum are available, obtained by Bioscience Laboratories. Column chromatography of the serum iodine was also performed by Bioscience Laboratories, using a modification of the method of Galton and Pitt-Rivers [*3,4*]. In this method the serum is adjusted to pH 10.0 with 0.8N NH_4OH and placed in a previously washed Dowex 1 by 2, 200 to 400 mesh column which had been treated with 0.8N NH_4OH until the pH of the eluate reached 10.9. A ratio of 4 ml. of serum to 8 ml. of resin is used. The first elution is with distilled water and yields the iodoprotein fraction. Experiments with labeled L-thyroxine added to serum showed that less than 5 per cent of the thyroxine appeared in this fraction. Thyroxine (T_4) and triiodothyronine (T_3) were eluted with 10 M acetic acid. Urinary iodine determinations were performed by the Boston Medical Laboratory. In several instances the capacity of thyroxine-binding alpha globulin (TBG) was measured by a method described previously [*5*].

Studies with I^{132} were performed using a well-collimated 1 inch sodium iodide crystal at 25 cm. for the patient's neck. The I^{132} was milked daily from tellurium^{132} bound to a resin by elution with 0.1M NH_4OH. It was calibrated against a Cs^{137} standard. The I^{132} was administered orally before breakfast. Counts were obtained over the neck at approximately ½, 1, 2, 3 and 4 hours, and a single 3 hour urine specimen was assayed for I^{132} content. In all instances a count of the neck was performed before the I^{132} dose was given since a small amount of what was presumed to be Cs^{137} increased the background slightly. Mathematical analysis of these data used an IBM 7094 computer and the program of Berman et al. [*6*]. No experimental correction for extrathyroidal radioactivity "seen" by the counter was made since the computer program adjusted the readings over the neck for this factor. A least squares best fit assuming exponential thyroid uptake and renal excretion of iodide produced a "best" value for this factor, termed σ_{21}. We are indebted to Dr. Mones Berman for this analysis.

RESULTS

The results of analyses for iodine in serum are shown in Table 1. It is apparent that throughout several years and with several different methods, the average serum protein-bound iodine level in the inhabitants of Rongelap is higher than normal and that the values in from 16 to 64 per cent of the natives are above the normal range by American standards. The first results showing an elevated PBI level were obtained in 1958 and since that time repeated efforts have been made to ensure that glassware and syringes were not contaminated with iodine. The absence of contamination can be seen by the fact that

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TABLE I
SERUM IODINE

Date	Group	Average	Range	No. Samples	Per cent Over 8 μg.
	Serum Protein-Bound Iodines				
1959	Marshallese	6.2	4.1– 9.2	12	16
1962	Marshallese	8.6	4.6–12.0	14	64
1964	Medical team	4.9	2.5– 6.9	10	0
1965	Marshallese exposed	7.6	4.1–11.9	31	42
1965	Marshallese controls	7.0	3.9–10.7	19	28
	Serum Butanol-Extractable Iodines				
1959	Marshallese	4.9	2.7– 8.7	12	

Serum Iodine Chromatography

Group	Total Iodine (av.)	Iodoprotein (av.)	$T_4 + T_3$ (av.)	No. Samples
Marshallese	6.98	2.22	4.53	19
Americans	5.09	0.80	3.76	25

All values are micrograms of iodine per 100 milliliters of serum.

the total iodine is not markedly greater than the PBI and by the normal levels obtained in 1964 on members of the medical team, whose blood was obtained at the same time and under the same conditions as that of the natives.

The increase in PBI could be due to several factors. It could be the result of a general increase in serum PBI in all of the population or it could be due to the occurrence of some genetic difference so that a substantial fraction of the population has abnormally high PBI levels and the rest of the population normal levels. In the first case, a distribution curve of level of PBI versus number would show a normal distribution except that the whole curve would be displaced about 2 μg. per cent upwards. In the second case, the distribution curve would be bimodal and a family tree would show familial clustering—the precise type depending on the manner of inheritance. Figure 1 shows a distribution curve of PBI level versus incidence at that level; there appears to be a single peak with

TABLE II
URINE IODINE*

Date	Method	Average	Range	No. Samples
1965	Boston Medical Laboratory	105	19.5–279	28

* Micrograms per day.

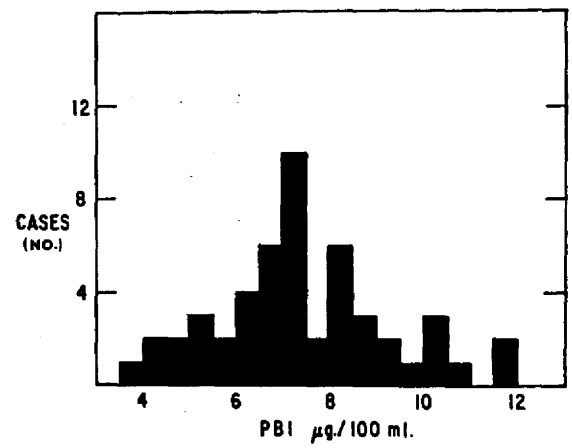

FIG. 1

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no evidence for a bimodal distribution. The low number of PBI values from 7.75 to 8.0 μg. per cent seems to be due to statistical variation from the small numbers of cases. Furthermore, the elevated values, defined as those above 8.0 μg. per cent, did not show a familial pattern of distribution. It appears, therefore, that the elevation in the PBI levels is a general phenomenon affecting all the population.

The difference between PBI and BEI in twelve cases was 1.6 μg. per cent, which is somewhat greater than an average value of 0.6 μg. per cent [7,8]. This was suggestive evidence for the presence of iodoprotein in serum. The results obtained by column chromatography substantiate this since an average iodoprotein level of 2.22 μg. per cent was found. The average value for the amount of thyroxine plus triiodothyronine in these serum samples was 4.53 μg. per cent. These data may be compared with results obtained on twenty-five normal North American control subjects residing temporarily in Washington, D. C., who showed an average serum iodoprotein level of 0.8 μg. per cent and an average $T_4 + T_3$ level of 3.76 μg. per cent.

The data on urinary iodine are shown in Table II and the average value of 105 μg. per day is quite similar to values found in the Eastern United States [9].

The results of studies with I^{132} are shown in Table III and are compared with normal values from the United States; the rate of thyroidal uptake and the rate of urinary excretion are both decreased. Since they are decreased more or less proportionately, the calculated

asymptotic uptake is normal or slightly elevated. These data together with the urinary iodine values, may be used to calculate the average daily secretion of thyroid hormone, assuming steady state conditions, by the formula $S = \frac{EU}{1-U}$, where

S = amount of iodine secreted by the thyroid (micrograms per day)
U = fractional thyroid uptake of iodine
E = urinary iodine (micrograms per day)

Using E = 105 μg. per day and U = 0.42, an average value for S may be calculated to be 76 μg. of iodine per day. This value is somewhat higher than similar ones calculated for other groups but is not extraordinarily high [*10–12*].

COMMENTS

It has not been possible to determine the basal metabolic rate in the inhabitants of Rongelap. However, the consensus of all physicians who have examined these people is that they are not hyperthyroid. The explanation for the large number of subjects with a high PBI level is, therefore, surely not an epidemic of hyperthyroidism. An elevation of thyroxine-binding proteins in serum could, as in the cases of congenital elevation of thyroxine-binding globulin described by Beierwaltes and Robbins, cause an increase in serum PBI without hyperthyroidism [*13*]. The serum levels of TBG in the Marshallese measured by Dr. J. Robbins were, however, within normal limits. The discrepancy between PBI and BEI, however, suggested the presence of an iodoprotein in serum. The chromatography of serum iodine showing an iodoprotein level in the Marshallese of 2.2 μg. per cent seems to implicate the iodoprotein as associated with the elevated PBI level.

Detailed data are not available on the calorigenic potency of serum iodoproteins but some results show that most of the iodinated amino acids in this protein are monoiodotyrosine and diiodotyrosine [*14,15*]. These iodoamino acids are devoid of physiologic activity. Hence an iodoprotein containing only these iodoamino acids is likely also to be physiologically inactive.

The reason these persons secrete such an iodoprotein into the blood is not at all clear. The data on normal control subjects from the Eastern United States, who showed 0.8 μg. per cent iodoprotein in their serum, suggest that it is a normal albeit minor constituent. The method of chromatography employed is such that well under 5 per cent of serum thyroxine (or 0.2 μg. per cent) appears in the unretarded or iodoprotein fraction. Therefore, the finding of iodoprotein does not appear to be a methodologic artifact.

TABLE III
KINETIC STUDIES WITH I^{132}

Cases	λ_{31}*	λ_{61}†	Theoretical Uptake	σ_{31}‡	No. Cases
Marshallese	0.72	0.97	42%	0.08	21
Normal	1.0	2.0	33%	...	...

* λ_{31} is the fraction of extrathyroidal iodide transferred to the thyroid per day.
† λ_{61} is the fraction of extrathyroidal iodide excreted in the urine per day.
‡ σ_{31} is the value derived by the computer for the fraction of extrathyroidal iodide "seen" by the counter.

The urinary iodine values were in the normal range. In general it had been expected that subjects who live close to the sea and who eat seafood and fish would have a relatively higher iodine intake. The inhabitants of the Marshall Islands have fish as one of their main sources of animal protein. Furthermore, these people are constantly exposed to sea spray since the highest point on the atoll is approximately 20 feet above high tide and the island at its widest is about a quarter of a mile across.

The data on urinary iodine were used with the results obtained with I^{132} studies to calculate the amount of iodine secreted daily by the thyroid. The value of 76 μg. is somewhat higher than the figures of 57 μg. per day found by Stanbury *et al.* [*10*] or 58 μg. per day found by Freinkel and Ingbar [*11*], but closer to the value of 70 μg. per day proposed by Riggs [*12*]. Unfortunately, nothing is known about the rate of turnover of the serum iodoprotein. If it has roughly the same rate of degradation and the same volume of distribution as thyroxine, we would expect the thyroidal secretion of organic iodine in the Marshallese to be proportional to the level of organic iodine in their serum. Adding iodothyronine values to iodoprotein levels for both Marshallese and Americans, and multiplying the ratio by the best value for iodine secreted by normal Americans we obtain:

$$\frac{2.22 + 4.53}{0.80 + 3.76} \times 58 = 86 \text{ μg. per day}$$

This agrees fairly well with the figure of 76 μg. per day calculated independently from urine and radioiodine studies and is compatible with the clinical picture of a euthyroid status despite an elevated PBI level and an increased thyroid iodine secretion rate.

The depressed thyroidal iodine uptake rate and renal excretion rate are puzzling and no explanation for them is available at this time.

SUMMARY

From 20 to 40 per cent of the people living on an atoll in the Marshall Islands have elevated serum protein-bound iodine levels without evidence of hyperthyroidism. The increase in serum protein-bound iodine (PBI) seems to be general throughout the population since the distribution curve of serum PBI is simple. Column chromatography of the serum iodine in twenty-five normal subjects in the United States shows average values of iodoprotein of 0.8 μg. per cent and of thyroxine plus triiodothyronine of 3.8 μg. per cent whereas in the Marshallese the average iodoprotein level was 2.2 μg. per cent and thyroxine plus triiodothyronine 4.5 μg. per cent. The high iodoprotein levels appeared to account for the increase in serum PBI in the Marshallese. The thyroidal iodide clearance and the renal iodide clearance in the Marshallese were both depressed to approximately one half of normal. The amount of iodine secreted by the thyroid in the Marshallese was estimated to be 76 μg. per day.

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