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Serologic Markers for Hepatitis B among Marshallese Accidentally Exposed to Fallout Radiation in 1954

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At least one serologic marker of prior hepatitis B infection (hepatitis B surface antigen, antibody to surface antigen, or antibody to core antigen) was found in 91.7% of 314 Marshallese tested. The prevalence of hepatitis B surface antigenemia (3.3%) in a subpopulation that had resided on Rongelap Atoll at the time of accidental exposure to radioactive fallout from a thermonuclear test in 1954 did not differ significantly from the prevalence in a selected unexposed population (10.5%).

A high prevalence of hepatitis B infection has been reported in Asia and the Western Pacific (*1–5*). Herein is documented another Pacific population, that of the Republic of the Marshall Islands, in which nearly universal serologic evidence of hepatitis B infection is present in adults. Against this background serologic markers of prior hepatitis B infection have been analyzed in a subpopulation of Marshallese which was accidentally exposed to radioactive fallout from a thermonuclear test in 1954. This was done because radiation-induced immunosuppression may determine, in part, the frequency and consequences of the chronic hepatitis B surface antigen (HBsAg) carrier state. Data reported by the Radiation Effects Research Foundation suggest such a deleterious effect among Japanese atomic bombing survivors (*6, 7*). The Marshallese hepatitis B experience does not reveal a similar pattern.

MATERIALS AND METHODS

The atolls of Enewetak and Bikini in the Marshall Islands were U.S. nuclear proving grounds from 1946 to 1958. In 1954, the populations of Rongelap and Utirik atolls, numbering 253 including those *in utero*, were accidentally exposed to radioactive fallout from a thermonuclear test on Bikini atoll (*8*). Inhabitants of Rongelap received a whole-body gamma radiation dose of 110 to 190 rad; those on Utirik received approximately 11 rad. The thyroid-absorbed dose due to radioiodines was much higher (*9, 10*). Since 1954 the exposed populations have voluntarily received periodic medical examinations and treatment carried out by the Medical Department of Brookhaven National Laboratory under contract to the Atomic Energy

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Commission (now the U.S. Department of Energy). To detect unsuspected medical consequences of their radiation exposure, a third group of Marshallese has also been followed with medical examinations. This population, composed of Rongelap people who were not on Rongelap Atoll at the time of the fallout, is identified herein as the "comparison" group, and the age and sex distribution of its current members is statistically similar to each of the two exposed groups (*9*).

In 1984, sera were collected from 268 persons in the exposed and comparison groups and tested for serological evidence of hepatitis B infection. In addition, 46 children of either exposed or unexposed parents were evaluated to obtain information on the age-specific prevalence of hepatitis B markers. Their ages ranged from 10 to 28 years, in contrast to those in the three exposure categories who were 29 years of age or older at the time of serologic testing. All but three persons tested were residents of one of four atolls: Rongelap and Utirik are the remote atolls which received the fallout, and Kwajalein and Majuro are larger population centers.

Tests for HBsAg, e antigen, and antibodies to HBsAg, core antigen, and e antigen were performed using commercially available radioimmunoassays (Abbott Laboratories, North Chicago, IL). The level of hepatitis B surface antigenemia was estimated by ratio units of the test samples as described in the test kits.

TABLE I

Summary of Positive Serologic Tests for Hepatitis B Surface Antigen (HBsAg), Antibody to Surface Antigen, and Antibody to Core Antigen among 314 Marshallese

	Number of persons tested	*Persons with one or more positive tests*	*Persons positive for HBsAg*
By sex			
Male	134	123 (91.8)[a]	20 (14.9)
Female	180	165 (91.7)	16 (8.9)
Combined	314	288 (91.7)	36 (11.5)
By age (years)			
10–28	46	43 (93.5)	3 (6.5)
29–39	127	115 (90.6)	14 (11.0)
40–49	48	43 (89.6)	6 (12.5)
>49	93	87 (93.3)	13 (14.0)
By atoll of residence[b]			
Kwajalein	100	89 (89.0)	10 (10.0)
Majuro	74	68 (91.9)	4 (5.4)
Rongelap	61	58 (95.1)	3 (8.5)
Utirik	76	70 (92.1)	19 (25.0)
By radiation exposure group			
Rongelap exposed	61	50 (82.0)	2 (3.3)
Utirik exposed	112	103 (92.0)	21 (18.8)
Rongelap comparison	95	86 (90.5)	10 (10.5)
By atoll of residence, excluding Rongelap exposed			
Kwajalein	69	63 (91.3)	6 (8.7)
Majuro	61	58 (95.1)	4 (6.6)
Rongelap	44	42 (95.5)	3 (6.8)
Utirik	76	70 (92.1)	19 (25.0)

[a] Percentage of the total population tested is shown in parentheses.
[b] Three persons resided outside the atolls listed.

TABLE II

Age Distribution of Hepatitis B Seronegative Persons in Rongelap Exposed and Comparison Groups

Group	Number of persons tested	Number of seronegative persons	Mean age (±SD) seronegative persons	Percentage seronegative		
				Age group (years): 29–39	40–49	>49
Rongelap exposed	61	11	39.7 ± 10.8	25.0 (7/28)	16.7 (2/12)	9.5 (2/21)
Rongelap comparison	95	9	41.7 ± 10.3	12.2 (5/41)	10.0 (2/20)	5.9 (2/34)
P value[a]				>0.30	>0.50	>0.30

[a] χ^2 analysis of Rongelap exposed versus comparison group.

Antibody to δ antigen was determined by a blocking enzyme immunoassay using human anti-δ IgG and δ antigen derived from chimpanzee liver.

Statistical testing of differences in the prevalence of HB markers was performed by χ^2 analysis of independence between two or more groups; the Kruskal–Wallis test was used for comparing HBsAg ratio units. Analysis by age was based on the groupings of <29, 29–39, 40–49, and >49 years. Since the adult prevalence of positive hepatitis B serology was reached during the second decade or earlier, it was judged probable that most persons >49 years of age had acquired hepatitis B prior to the 1954 fallout, whereas the younger groups would include those most likely to express an interaction between radiation exposure and acquisition of the infection.

RESULTS

Serologic evidence of prior hepatitis B infection was widespread by adulthood in the Marshallese population tested (Table I), with the sexes showing equivalent prevalences. No significant difference in the prevalence of at least one hepatitis B marker was detected when evaluated according to atoll of residence (χ^2 (3) = 1.86, $P > 0.50$), age group (χ^2 (3) = 1.10, $P > 0.70$), or radiation exposure group (χ^2 (2) = 4.36, $P > 0.10$). The prevalence of seronegativity did not differ significantly between the Rongelap exposed and the comparison group (χ^2 (1) = 1.88, $P > 0.10$), even when analyzed by age (Table II).

HBsAg was detected in 11.5% of the total population tested (Table I). The relatively low prevalance in the exposed Rongelap population was not significantly different from the comparison group (χ^2 (1) = 1.83, $P > 0.10$). All of the Utirik population tested were exposed, thereby precluding a comparison of their very high prevalence with unexposed Utirik inhabitants. Because the prevalence of HBsAg by atoll was also lowest on Rongelap (χ^2 (3) = 19.39, $P < 0.001$), prevalence by atoll was recalculated after excluding the exposed Rongelap group. A statistically significant variation among atolls remained apparent (χ^2 (3) = 14.18, $P < 0.01$), with Rongelap still having the lowest prevalence. When grouped by age, the oldest population had the highest prevalence of HBsAg (Table I), although group differences were not statistically significant (χ^2 (3) = 1.77, $P > 0.50$). The mean levels of HBsAg antigen (±SD) among

surface antigen-positive individuals were 187 ± 48 for the Rongelap exposed ($N = 2$), 177 ± 40 for the Utirik exposed ($N = 21$), and 179 ± 40 for the comparison group ($N = 10$). These values do not differ significantly ($P > 0.80$). Of 34 HBsAg-positive persons detected, 8 (23.5%) were also positive for e antigen, a correlate of infectivity.

Antibody against δ agent was not detected in any of the Marshallese tested.

DISCUSSION

It is now 31 years since radioactive fallout settled on Rongelap and Utirik. The number of Marshallese remaining in the radiation-exposed groups is small in comparison with the population of Japanese atomic bomb survivors being followed by the Radiation Effects Research Foundation. Nevertheless the high prevalence of serologic markers of hepatitis B infection in the Marshallese permits statistical inferences of differences among the three exposure groups. This analysis indicates (i) persons from Utirik, who suffered a relatively low radiation exposure, have the highest prevalence of HBsAg; (ii) persons from Rongelap who received a high exposure have the lowest prevalence of HBsAg; (iii) unexposed persons living on Rongelap also have a relatively low frequency of HBsAg; and (iv) the prevalence of at least one marker for HB was similar in all three groups.

There is reason for concern about a possible clinically significant depression in immune competence in the exposed people of Rongelap. Peripheral blood lymphocyte responsiveness to phytohemagglutinin has been reported as diminished in the heavily exposed Japanese population (*11*). Complement fixation tests performed in 1959 for several infectious diseases revealed most mean antibody titers to be lower in the Rongelap exposed than in the comparison population (*12*). There was, in addition, a lower primary antibody response to tetanus toxoid among the exposed Rongelap group when challenged 3 years after the fallout, although the difference between exposed and unexposed was not statistically significant (*13*). Despite these findings, immunoglobulin levels, phytohemagglutinin responsiveness, and tuberculin and *Candida* skin test responsiveness have been similar in the two groups (*9*, *14*, *15*). There has been no documented increase in any type of infection noted as a delayed consequence of radiation exposure in either the exposed Japanese or the Marshallese.

With regard to hepatitis B infection, HBsAg titers among the Japanese exposed to >100 rad are similar to those who received <10 rad, and the occurrence of antibodies to HBsAg is similar in the high- and low-dose groups (*7*). Nevertheless, studies by the Radiation Effects Research Foundation have revealed a suggestive association between radiation dose and prevalence of cirrhosis in atomic bomb survivors, and the prevalence of HBsAg is 3.4% in the high-dose and 2.0% in the low-dose groups, a statistically significant difference (*6*, *7*). These investigations have suggested therefore that HBsAg persistence, but not susceptibility to the infection itself, might be the consequence of immunologic impairment in the high-dose group.

With this background it is reassuring to note that the prevalence of HBsAg was relatively low among the exposed Rongelap group rather than elevated. It is unlikely that this finding is due to earlier attrition among HBsAg-positive exposed persons

because (i) the 30-year survival curves of the three exposure categories are virtually identical, and (ii) there has been only one exposed person, an 82-year-old Rongelap man, who is known to have died with a diagnosis of possible liver disease (*9*, *16*). There is evidence that lethal consequences of hepatitis B infection may be decreased in immunosuppressed persons, perhaps because cell-mediated immunologic reactions are minimized (*17*). However, patients who are immunologically suppressed may be at increased risk for developing a chronic HBsAg carrier state (*18*). An analysis of hepatitis B serology among the exposed Rongelap population does not indicate that they share that risk. In addition, the age distribution of exposed Rongelap individuals having no serologic evidence of prior hepatitis B infection did not differ from serologically negative persons in the comparison group. These findings do not suggest a clustering of immunologically impaired persons among those in the exposed Rongelap group who were young at the time of fallout exposure.

Since hepatitis B surface antigenemia in the comparison population and unexposed current inhabitants of Rongelap was not significantly different from the exposed Rongelap group, it is likely that the relatively low prevalence of HBsAg in present or past inhabitants of Rongelap and the high prevalence on Utirik are related to local factors rather than radiation dose. In such small isolated populations the factors affecting maternal–newborn (vertical) transmission, an important mode of hepatitis B virus infection, may vary significantly from island to island. Inhabitants of Rongelap were removed from their contaminated atoll between 1954 and 1957, and in the early years after the fallout the Rongelap exposed received greater medical attention than those on Utirik. However, no Rongelap individual 20 years of age or older at the time of exposure who was tested in this survey had HBsAg, thus suggesting that neither the temporary relocation nor the differences in medical attention following exposure account for the lower prevalence.

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