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EFFECTS OF CONTINUOUS IRRADIATION OF MICE ON THE IMMUNE RESPONSE TO LIVE LISTERIA MONOCYTOGENES VACCINE

by

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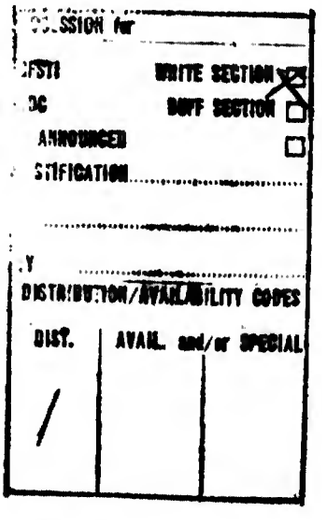

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ABSTRACT

Mice exposed continuously to radiatic delivered at 1.0-1.5 rad/hour were exposed to a respiratory infection with a midlethal dose of a live avirulent strain of Listeria monocytogenes immediately after accumulating either 1700-2200 rad or 2800-3000 rads. The surviving mice were challenged two weeks later with a second aerosol containing the organism in order to determine their immune state. All of the non-irradiated mice exposed to the two aerosol infections survived while 24% of the 1700-2200 rad irradiated mice and 54% of the 2800-3000 rad groups succumbed to the second infection. If the irradiated mice were immunized with two aerosol exposures at a two week interval both the irradiated (2200 rad) and the non-irradiated animals survived. Immunity following a single exposure was of short duration. If the challenge was postponed until 4 weeks after the immunizing exposure, 90% of the irradiated mice died.

Clearance of L. monocytogenes from the lungs, liver and spleen was rapid in the non-irradiated immune group. By the fourth day after challenge, few organisms could be isolated. If the mice were irradiated prior to immunization, clearance was delayed. Bacteria could still be found in all organs. Large numbers of bacteria could be isolated from both groups of non-immune mice.

NON-TECHNICAL SUMMARY

The Problem

Increasing interest is being focused on the possible use of airborne avirulent bacterial and viral strains as a possible means of immunization against a subsequent infection with virulent strains. This method of immunization is applicable in both clinical situations and in protection against biological warfare. Additional interest has been expressed regarding the possibility that exposure to low dose rate gamma radiation (such as might be encountered in a radiation fallout field) may decrease the individual's resistance to a live avirulent immunizing agent to the extent that serious illness or death might result from the immunization itself. Also the question has been raised as to whether a person's ability to acquire immunity might be impaired by exposure to low dose rate gamma radiation.

The Findings

These studies have shown that chronically irradiated mice are more susceptible to an immunizing exposure of Listeria monocytogenes than non-irradiated animals. In addition, the ability of the surviving irradiated mice to acquire immunity within two weeks appeared to be impaired. The immune response decreased as the total dose of radiation increased, as indicated by a smaller number of survivors

following respiratory challenge with a lethal dose of organisms. When the interval between aerosol immunization and challenge was increased to four weeks, a decrease in percent survivors was noted in both non-irradiated immunized and irradiated (2200 rad) immunized mice. It was more pronounced however, in the irradiated immunized group. Two immunizing exposures resulted in essentially 100% protection in both irradiated and non-irradiated mice.

Studies on the growth of the organisms in the irradiated animals indicated that both the irradiated and non-irradiated immune mice were able to destroy the invading bacteria more rapidly than the non-immune.

INTRODUCTION

It was shown previously (1) that exposure of mice to chronic gamma radiation delivered at 1.0-1.5 rad/hr resulted in a marked increase in susceptibility to airborne infection with Listeria monocytogenes. As the cumulative radiation dose increased the susceptibility to infection increased so that mice receiving a total of 2500 rad over a two month period were over 33 times as susceptible to fatal infection as those receiving no radiation.

The resistance of animals to L. monocytogenes can be enhanced by immunization with sublethal doses of the virulent live organism (2-7). Since protection is not afforded by passive immunization with antiserum (5,8,9) and since, as Seeliger (10) points out, no relationship exists between circulating antibody titers and the severity of infection or degree of immunity in humans, it has been concluded that resistance to L. monocytogenes is not mediated by by humoral factors. Thus, as in tuberculosis, brucellosis and tularemia, it has been claimed that an alternative mechanism, probably mediated by cells, plays a role in acquired resistance to Listeriosis. Related studies (12,13) have supported this concept of acquired cellular immunity, but have emphasized that the cellular resistance is non-specific in nature.

The studies to be reported here deal with the effects of prior exposure of mice to chronic gamma radiation on the development of acquired immunity following airborne challenge with L. monocytogenes.

MATERIALS AND METHODS

Mice *

Equal numbers of male and female LAF_1 (C57L ♀ x A/He ♂) mice from our laboratory colony were used in the experiment. Mice were 12 to 16 weeks old at the time of exposure to bacterial aerosols.

Irradiation of Mice

Mice were continuously exposed to γ radiation from a Co^{60} source at a dose rate of 1.0-1.5 rad/hour until the desired accumulated doses were obtained. Plastic mouse cages housing 10 mice each were placed on curved wooden racks so that the center of each was equidistant from the Co^{60} pellet. Initial studies employed a 2.5 curie Co^{60} source. Dose measurements were made with a Philips standard dosimeter. Later studies were done with a lead shielded 10.8 curie Co^{60} source. Dose measurements were made with TLD System Dosimeters. The Co^{60} source was in continuous operation except for

* In conducting the research described in this report, the investigators adhered to the "Principles of Laboratory Animal Care" as established by the National Society for Medical Research.

1 hour per week when the cages were changed. Fresh food pellets and water were also supplied at this time. No deaths occurred among the mice during the radiation exposure period or among animals held as long as six weeks after removal from the Co^{60} source.

Listeria monocytogenes

Media and growth conditions used in the cultivation of L. monocytogenes have been previously described (1).

Exposure of Mice to Bacterial Aerosol

Mice were infected by exposure to aerosols of L. monocytogenes in a modified Henderson apparatus (14). Irradiated mice were exposed within 2 hours after removal from the Co^{60} source. The aerosol was sampled with impingers simultaneously with exposure of the animals. Calculations of the dose inhaled by the experimental animals were made from the data obtained on the concentration of cells collected in the impinger fluid and from the respiratory rate and volume of the animal according to Guyton's formula (15).

Exposed animals were observed for deaths. Immunity was measured by challenging the survivors to a second respiratory infection 2 to 4 weeks later using a dose of organisms that was normally lethal for non-irradiated mice. Survival following the second exposure was used as an index of immunity. Animals were observed for 30 days after the last aerosol exposure. Most mice that succumbed were autopsied and

examined for gross pathological changes. Bacteriological studies showed that, with very rare exceptions, L. monocytogenes could readily be isolated from the lungs, livers and spleens of the dead mice.

Bacterial Enumeration in Lung, Liver and Spleen

Organs were removed, homogenized, and aliquots were plated on tryptose agar as previously described (1). Results were expressed as the number of viable organisms per organ.

RESULTS

Initial experiments were designed to determine if non-irradiated and irradiated mice could be immunized by means of an aerosol against a subsequent lethal aerosol challenge of L. monocytogenes. Both non-irradiated and irradiated mice were initially exposed to the same immunizing doses of the airborne Listeria. Since irradiated mice are more susceptible to an initial airborne infection (1), the immunizing exposure was adjusted so that fewer than 50% of the irradiated mice would die after primary exposure. This was a non-lethal dose for a non-irradiated population. Two weeks after exposure to the immunizing aerosol of Listeria the surviving mice were challenged with approximately 5 $LD_{50's}$ of the microorganism for a non-irradiated, non-immunized population. This dose was sufficient to kill all

irradiated non-immune mice and all but a few of the control group.

From the data presented in Table I, it was evident that exposure to continuous low dose rate gamma radiation resulted in some decrease in the immune response. Although essentially all the non-irradiated immune mice survived, 24% of all the mice immunized after exposure to 1700-2200 rad died, while 54% of the mice accumulating 2800-3000 rad succumbed to the challenge dose of L. monocytogenes. The majority of non-irradiated mice surviving the initial immunizing dose of $2.9\text{-}4.2 \times 10^4$ organisms manifested physical signs of infection after the challenge dose of L. monocytogenes. However, all except 2 of the 58 mice recovered.

A comparison of the effectiveness of two immunizing aerosol exposures on the ability of non-irradiated and irradiated mice to survive a challenge dose of 1.7×10^6 Listeria is presented in Table II. The primary immunizing aerosol was given four weeks before challenge and the second immunizing aerosol was given two weeks in advance of challenge. Mice were removed from the Co^{60} source two hours before the primary immunization and were not subjected to further radiation. The percent survival following challenge with 1.7×10^6 cells was comparable in non-irradiated and irradiated (2200 rad) mice when both groups had received two immunizing aerosols. In the group of mice which had only a single immunizing dose four weeks

TABLE I

SURVIVAL OF MICE IMMUNIZED BY AEROSOL EXPOSURE TO *LISTERIA MONOCYTOGENES*.

Group	Immunizing Dose	Challenge Dose	Dead Total	% Dead
Irradiated Immune				
1700 rad	4.2×10^4	3.7×10^6	8/40	20
1900 rad	2.9×10^4	2.6×10^6	11/37	30
2200 rad	3.5×10^4	2.6×10^6	6/28	21
2800 rad	1.9×10^4	1.7×10^6	18/28	64
2877 rad	7.8×10^2	7.6×10^6	7/17	41
2900 rad	1.3×10^5	5.5×10^6	9/19	47
2986 rad	5.4×10^4	6.3×10^6	11/19	58
Irradiated Non-Immune				
2200 rad	---	2.6×10^6	20/20	100
2877 rad	---	7.6×10^6	18/19	95
2900 rad	---	5.5×10^6	8/8	100
3000 rad	---	6.3×10^6	10/10	100
Non-Irradiated Immune				
	4.2×10^4	3.7×10^6	2/40	5
	2.9×10^4	2.6×10^6	0/9	0
	7.8×10^2	7.6×10^6	0/19	0
	1.3×10^5	5.5×10^6	0/20	0
	5.4×10^4	6.3×10^6	0/20	0
Non-Irradiated Non-Immune				
	---	1.7×10^6	50/58	86
	---	2.6×10^6	52/60	87
	---	3.0×10^6	17/20	85
	---	3.7×10^6	55/62	85
	---	4.2×10^6	30/31	97
	---	5.5×10^6	8/10	80
	---	6.3×10^6	7/10	70
	---	7.6×10^6	10/10	100

TABLE II

SURVIVAL OF CONTINUOUSLY γ-IRRADIATED MICE TO LISTERIA MONOCYTOGENES

FOLLOWING PRIMARY AND SECONDARY AIRBORNE IMMUNIZATION

Group	Primary Immunizing Dose	Secondary Immunizing Dose	Challenge Dose	Survival Total	% Survival
Irradiated *	2.6×10^4	1.6×10^4	1.7×10^6	17/18	95
	2.6×10^4	None	1.7×10^6	2/20	10
	None	None	1.7×10^6	0/10	0
Non-Irradiated	2.6×10^4	1.6×10^4	1.7×10^6	20/20	100
	2.6×10^4	None	1.7×10^6	15/20	75
	None	None	1.7×10^6	4/20	20

* 2200 rad γ Radiation at 1.5 rad/hour.

before challenge, 75% of the non-irradiated mice and only 10% of the irradiated mice survived. None of the irradiated non-immunized mice survived, although 20% of the non-irradiated non-immunized animals were able to do so.

Since it had been determined that both non-irradiated and irradiated mice could acquire immunity to L. monocytogenes following aerosol immunization, providing the total radiation exposure did not exceed approximately 2000 rad, an additional parameter was studied to supplement these findings. The distribution of Listeria was followed in the lung, liver and spleen of animals from the four groups over a four day period following a challenge of 1.5×10^6 bacteria, in order to determine the clearance of the organisms by these organs (Table III).

As expected, extensive bacterial proliferation was found in the organs of non-immune groups of mice following the challenge. With the exception of initial clearance by the lungs at four hours post infection, between 10^5 and 10^8 bacteria were found in all organs on the second and fourth days following aerosol exposure. On the other hand, although Listeria did spread to a slight extent from the lungs to the liver and possibly the spleen of non-irradiated immunized mice, it was quite evident that by the second day significant suppression of

TABLE III

THE RECOVERY OF LISTERIA MONOCYTOGENES FROM IRRADIATED AND NON-IRRADIATED, IMMUNE MICE

Group	Survivors Total	% Survivors	Colony Count Per Organ							
			Zero Hour Lung	4 Hours Lung	Day 2 Lung	Day 2 Liver	Day 2 Spleen	Day 4 Lung	Day 4 Liver	Day 4 Spleen
Irradiated immunized [a]	6/21	76	1.5×10^5	1.9×10^4	9.0×10^4	1.9×10^3	5.0×10^3	3.0×10^1	1.2×10^4	$< 2.0 \times 10^1$
			1.0×10^5	1.2×10^4	5.2×10^5	2.5×10^6	5.0×10^3	1.6×10^7	1.1×10^8	4.5×10^5
			1.3×10^5	3.0×10^4	3.9×10^4	2.4×10^4	2.2×10^3	8.4×10^2	4.2×10^2	$< 2.0 \times 10^1$
Irradiated non-immunized [b]	0/25	0	6.8×10^4	2.6×10^4	4.9×10^6	8.8×10^6	1.8×10^5	1.1×10^8	2.4×10^8	1.2×10^7
Non-Irradiated immunized [a]	16/16	100	1.6×10^5	3.4×10^4	6.0×10^2	7.8×10^3	$< 2.0 \times 10^2$	$< 3.0 \times 10^1$	6.0×10^1	$< 2.0 \times 10^1$
			9.0×10^4	contaminated	$< 3.0 \times 10^2$	$< 6.0 \times 10^2$	$< 2.0 \times 10^2$	$< 3.0 \times 10^1$	$< 6.0 \times 10^1$	$< 2.0 \times 10^1$
			1.2×10^5	1.5×10^4	3.0×10^2	1.0×10^4	$< 2.0 \times 10^2$	$< 3.0 \times 10^1$	$< 6.0 \times 10^1$	$< 2.0 \times 10^1$
Non-Irradiated non-immunized [a]	2/18	11	1.5×10^5	3.7×10^4	4.0×10^6	2.0×10^6	1.7×10^5	7.0×10^6	6.2×10^7	1.8×10^5
			1.4×10^5	2.6×10^4	3.3×10^6	4.5×10^6	3.1×10^5	1.2×10^8	1.3×10^8	3.3×10^6
			1.9×10^5	7.3×10^4	4.7×10^6	1.0×10^7	1.6×10^5	1.8×10^7	8.3×10^7	2.5×10^5

[a] Inhaled challenge dose = 1.5×10^6 Listeria Monocytogenes.

[b] Inhaled challenge dose = 8.0×10^5 Listeria Monocytogenes.

bacterial growth had occurred and by the fourth day no detectable bacteria were present in these organs.

Distribution of Listeria in the organs of irradiated immunized mice showed a variable response following the aerosol challenge. The number of microorganisms recovered was less than that encountered in both non-immunized groups of mice, but more than that observed in non-irradiated immunized mice. By the fourth day there was a wide variation in the numbers of recoverable bacteria. Suppression of bacterial growth was observed in the lungs, liver and spleen of two mice, whereas large numbers of Listeria were recovered from the third mouse.

DISCUSSION

These studies have shown that both non-irradiated mice and mice exposed to continous low dose rate γ radiation can be immunized by the respiratory route against a subsequent challenge of a normally lethal dose of airborne Listeria, providing the total dose of radiation is not too high.

Even though the immunizing aerosol dose of Listeria ($1.2\text{-}4.2 \times 10^4$ cells) was adjusted so that no deaths occurred in a non-irradiated population, the increased susceptibility of mice, exposed to Co^{60} γ radiation (1) caused deaths in some of the mice

after exposure to the immunizing dose of bacteria. From the data, it appeared that a difference existed in the response of non-irradiated immunized and irradiated immunized mice challenged with a comparable dose of the Listeria aerosol. This difference in percent survival, although apparent, may not have existed had the challenge aerosol doses for the two groups been based on a challenge dose consisting of a comparable multiple of the bacterial LD_{50} for each group. Mice which had been irradiated, immunized and challenged were more susceptible than were non-irradiated immune mice exposed to the same bacterial challenge. In view of these facts, the most valid comparisons are those between the immune and non-immune irradiated mice and between the immune and non-immune non-irradiated animals rather than between irradiated and non-irradiated groups. On the basis of these comparisons one can conclude from the available data that both immunized populations demonstrated a greater resistance to the high dose aerosol challenge than did the non-immune animals. However, the lower number of survivors among irradiated immunized mice indicates that impairment of their ability to acquire immunity had occurred.

Experiments in which non-irradiated and irradiated mice received two immunizing bacterial aerosol exposures at 14 day intervals before challenge indicated that both groups were quite resistant when challenged with an identical aerosol dose. However, irradiated mice immunized

with a single dose and held four weeks before challenge showed a very low percent survival compared to non-irradiated mice similarly handled. This undoubtedly was a reflection of both the short duration of immunity and remaining injury resulting from radiation. Non-irradiated mice challenged four weeks after a single immunizing aerosol, although more resistant than irradiated mice similarly treated, showed less resistance to the challenge than non-irradiated mice immunized at 28 and 14 days before challenge. These findings are in accordance with those of Mackaness (11) who suggested that immunity to listeriosis in the mouse, although strong, is of relatively short duration following immunization.

Comparison of the data obtained on bacterial numbers in the lung, liver and spleen homogenates of non-irradiated and irradiated groups of mice following challenge proved quite interesting in light of our previous data on percent survival following aerosol infection with large numbers of microorganisms. As expected, extensive bacterial growth was found in the organs of non-immunized irradiated and non-irradiated mice on days 2 and 4 following challenge. However, on the same days, bacterial counts from the organs of non-irradiated immunized mice indicated that the organism had failed to grow in the tissues of these mice. These findings are in agreement with the thesis that the antibacterial mechanism developed during the primary

infection is retained after recovery from the primary infection (11). It has been our experience that no bacteria can be found in the organs of surviving irradiated or non-irradiated mice 14 days after a primary infection. Thus, any bacteria recovered from the organs of mice challenged at this time can be attributed only to those inhaled at challenge. The clearance of bacteria from the organs of two irradiated immunized mice and the bacterial growth in another was undoubtedly a reflection of the variable survival rate (76 %) observed in this group following aerosol challenge.

Bensted (16) has reported that mice exposed to 1400 rad of γ radiation delivered at 50 rad/day were as fully capable of producing hemagglutinins to sheep red blood cells as were non-irradiated controls. Silverman (17) also found no inhibition of antibody formation to sheep red blood cells in mice receiving a total of 1200 or 2200 rad delivered at 36 rad/day. In addition, mice similarly irradiated were able to reject allogenic skin grafts as readily as non-irradiated controls. The inhibition of the immune response to Listeria monocytogenes may appear to be in contradiction to these results. The determination of an immune response to bacterial infection by challenge, however, is a measure not only of the response of the host to the immunization, but also its interaction with the challenge organism. We have shown previously (1) that resistance of continuously irradiated mice to

infection with this organism is considerably reduced. This is further borne out by the experiments which showed that the organism can proliferate in the lungs, liver and spleen of some of the irradiated immune animals. Thus, it might be expected that in some of these immune mice the balance between the immune response and the irradiation injury would be tipped in favor of the invading organism. Presumably, if the total radiation dose received was increased further, conditions would be even more advantageous to the organism.

If, as Mackaness states (11), immunity to Listeriosis in the mouse is a cellular response due to the increase capacity of the macrophage to resist intracellular growth of the organism, irradiation with a sufficiently high dose might be expected to prevent the development of the immune response. Donaldson, et al., (18) and Nelson and Becker (19) have shown that these cells lose their bactericidal properties following acute radiation in the mid-lethal range. Kornfeld and Greenman (20) have found a reduction in the numbers of peritoneal macrophages in mice exposed to continuous γ radiation delivered at about 1.4 rad/hour. Neither the phagocytic function nor bactericidal properties of the macrophages from the continuously irradiated mice were tested. However, the results of the experiments presented in this report would suggest a functional impairment.

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