VARIATION IN MORBIDITY AND MORTALITY OF MURINE TYPHUS INFECTION IN MICE WITH CHANGES IN THE ENVIRONMENTAL TEMPERATURE

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Experiments reported in the preceding paper have shown that murine typhus rickettsiae cause a uniformly fatal rickettsial peritonitis in the dba strain of mice, while in other strains, under identical environmental conditions, the mortality is less than 60 per cent. In the course of this work, it became apparent that relatively slight changes in room temperature had a marked influence on the course of the infection. Data showing this effect will be summarized in this paper.

EXPERIMENTAL

In all, 105 mice of mixed sexes were injected intraperitoneally with light, heavy, or massive doses of murine typhus rickettsiae, and maintained at different temperatures. Some animals were kept in an artificially cooled room in which the temperature varied between 65° and 73°F. The remainder of the animals were kept in a room in which the temperature was dependent on climatic variation. Some experiments were done during relatively cool spring weather, during which the temperature range was between 70° and 80°F. Other experiments were done during heat waves, with temperatures in the animal room ranging from 85–98°F.

Of the 105 mice included in this analysis, only 44 represent parallel experiments. Twenty-two of these were kept at 65–73°F. and the other 22, injected with identical inocula, (brain tissue from dba mice dead or dying after intraperitoneal inoculation), were kept at 85–98°F. (approximate). The mortality in the cooler room was 100 per cent while only 2 of 22 animals in the warm room died. The other 61 mice represent experiments which were not strictly parallel, since several different batches of inoculum were used.

Smears were made from the peritoneal cavity of each mouse dying, and animals in which huge numbers of rickettsiae were found, without evidence of secondary infection, were regarded as having died of typhus.

RESULTS

The results are summarized in Table I. With massive or heavy doses, intraperitoneally injected dba mice invariably died when kept at 70–80°F. (approximate). Even with light dosage, death occurred in all dba mice injected intraperitoneally and kept at 65–73°F. In a very warm room (85–98°F. approximate) 9 out of 13 mice survived following heavy dosage and 20 out of 22 following light dosage. A definite lengthening of the incubation period and prolongation of life was noted in animals dying in the warm room.

DISCUSSION

The favorable effect of low temperature on the intracellular growth of rickettsiae has long been recognized. The relatively low temperature of the scrotal sac in guinea pigs is directly or indirectly the cause of the well known scrotal reaction seen in murine typhus. The lower temperature of the skin may, in a similar way, explain the multiplication of rickettsiae in the cutaneous vessels, with the consequent production of a rash in humans.

Lillie *et al.* (1) noticed a seasonal variation in the intensity of the brain lesions produced in guinea pigs by murine typhus rickettsiae, the lesions being most numerous and most marked in the winter and least numerous and least marked

TABLE I

Mice Injected Intraperitoneally and Kept at Different Room Temperatures

Temperature range	Inoculum	No. and variety of mice	Mice showing illness	Mice dying	Time of death
85–98°F.	Mouse tissues (heavy dosage)	13 dba	13	4	7–9 days
		2 A albino	0	0	
	Brain from dba mouse injected intraperitoneally (light dosage)	22 dba	12 (mild in 10)	2	7–10 days
70–80°F.	Mouse and guinea pig tissues (heavy dosage)	18 dba	18	18	4–5 days
	Yolk sac suspension (massive dosage)	9 dba	9	9	3–4 days
65–73°F.	Brain from dba mouse injected intraperitoneally (light dosage)	42 dba	42	42	6–7 days

in the summer; they roughly paralleled an inverted environmental temperature curve. Artificially high environmental temperature also decreased the average intensity of the brain reaction as compared with that of other guinea pigs simultaneously inoculated with the same material.

Clavero and Perez (2) point out that the vaccine of Blanc (an attenuated live vaccine) gave very favorable results in North Africa, with febrile reactions in only 1 to 4 per cent of the individuals vaccinated, while in Chile febrile reactions occurred in 23 per cent, and 5 deaths occurred. These authors suggest that these discordant results may be explained by the different climatic conditions in the two countries. Similarly, they state that from the communications of Sparrow and Otto, it appears that the mortality in mice injected with a murine strain of typhus originating in Tunis was greater in Frankfort, Germany, than in Tunis itself.

Castaneda (3) was able to obtain a generalized rickettsial infection of the peritoneal cavity in irradiated guinea pigs, rabbits, and sheep, by keeping the body temperature of those animals below 38°C. He reduced the temperature of his animals by placing the cages on ice, by the use of barbiturates, or by shaving the skin of the animals and placing a fan in front of the cages. The temperature of his animals showed marked individual variations, but he found that the animals with the lower temperatures showed the more generalized peritoneal infections and also greater numbers of rickettsiae.

The favorable effect of high environmental temperature on the course of experimental typhus infection in mice is rather unexpected because none of the temperatures at which the work was done were outside the normal seasonal range of "room temperature." It is apparent that if mice are used to test the effectiveness of therapeutic agents in typhus infection, the external temperature must be carefully controlled.

Whether the observations made here could have any possible application to the treatment of typhus in man is problematical. Mice have a much less constant body temperature than human beings, and the febrile reaction manifested in the usual case of typhus in man would appear adequate to bring the temperature of the body as a whole to an optimal level. It is noteworthy, however, that rickettsiae are found microscopically in the cutaneous lesions in much larger numbers than in any other organ. Since the temperature of the skin, under usual environmental temperatures, remains relatively low even in febrile patients, high external temperatures would raise the skin temperature and might have the effect of inhibiting rickettsial growth in the capillaries of the skin.

SUMMARY

Murine typhus rickettsiae injected intraperitoneally in mice of the dba strain caused a uniformly fatal rickettsial peritonitis if the animals were kept at a room temperature ranging from 65–73°F. or from 70–80°F. With an environmental temperature range of 85–98°F., a mortality of less than 25 per cent was observed.

By utilizing different strains of mice and controlling the environmental temperature, conditions may be created under which murine typhus will have any desired degree of mortality. Such conditions have obvious advantages for the evaluation of therapeutic measures in typhus infection.

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