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Temperature Reactions in Mice Infected with Pneumococci.*

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White and Parker[1] have recently demonstrated that concentrations of sulfanilamide which had merely a bacteriostatic action on the streptococcus *in vitro* at temperatures below 39°C were bactericidal at 40°C. Since it is of importance to apply such findings to *in vivo* studies, a number of experiments were undertaken to determine the normal temperature of mice, the reason for variation if any existed, and lastly, the effect of temperature changes on the course of the pneumococcus infection in normal mice and those treated with sulfanilamide.

Walther[2] and Rolly and Meltzer[3] found that rabbits kept in a room warm enough to raise their body temperatures showed an increased resistance to pneumococcus infections. Loewy and Richter[4] raised the body temperature of rabbits by the Sachs-Aronson operation, or "heat puncture", and found that such animals were more resistant to pneumococcus infections than normal animals. Experiments on white mice have been reported by Ritzmann,[5] who found that mice kept for a period of weeks at a temperature of 95°F were less resistant to infections of streptococci and tetanus spores, and by Colvin and Mills,[6] who found that white mice kept at high temperatures were less resistant to streptococcus infections than animals kept at room temperature. McDowell[7] found that rats kept at a temperature of 83°F were more resistant to pneumococcus infections than rats kept at medium temperatures.

Temperature readings in our own experiments were made with a thermocouple attached to a Leeds and Northrup type K potentiometer. The warm junction was designed to penetrate the skin, and was inserted subcutaneously in making the temperature readings. The

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1 White, H. J., and Parker, J. M., *J. Bact.*, 1938, **36**, 481.

2 Walther, P., *Arch. f. Hyg.*, 1891, **12**, 329.

3 Rolly, F., and Meltzer, *Dtsch. Arch. f. Klin. Med.*, 1908, **94**, 335.

4 Loewy, A., and Richter, P. F., *Arch. f. path. Anat. und Phys.*, 1896, **145**, 49.

5 Ritzmann, O., *Arch. f. Hyg.*, 1907, **61**, 355.

6 Colvin, J. W., and Mills, C. A., *Science*, 1939, **90**, 275.

7 McDowell, C., *Am. J. Hyg.*, 1923, **3**, 521.

average temperature of 126 mice in a series of 268 readings taken at different times was 100.6°F, with a standard deviation of 1.1°.

In order to raise the temperature of the animals, they were placed in a chamber maintained at 98°F. It was found that mice placed in such a room showed a rise in temperature of about 2° to 3° in less than ½ hour, and that the temperature remained in this range during the entire period they were kept in the chamber. Eighty-one readings on 17 mice kept at 98°F over a period of 3 days yielded an average temperature of 104.1°F with a standard deviation of ±0.95°F. Twenty-four normal mice remained under these conditions for 3 days without showing any signs of injury. The food intake of these animals was normal, although the water intake was higher than usual.

To study the effects of different external temperatures on the progress of Type II pneumococcus infections in mice several parallel experiments were conducted. Equal numbers of control and treated mice were kept (1) at room temperature (approximately 70°F) throughout the experiment, and (2) at 98°F for 3 days immediately following the pneumococcal inoculations. The experiments were conducted on equal groups of from 6 to 10 mice per group. A total of 50 mice was used in each group. The technic of drug administration was the same as that used previously.[8]

TABLE I.
The Sulfanilamide Intake for Each Group, in g per kg of Body Weight.

Day	At room temperature	At 98° F
1	.50	.49
2	.76	.76
	Inoculation with pneumococcus Type II.	
3	.725	.81

TABLE II.
Time of Survival of Mice Treated with Sulfanilamide in Food and Inoculated Subcutaneously with 15,000 Lethal Doses of Pneumococcus Type II.

	Control Groups		Treated Groups	
	At room temperature	At 98° F	At room temperature	At 98° F
No. of mice	50	50	50	50
Survivors at 30 days	0	0	1	1
Range	18.5-52.5 hr	14-45.5 hr	20.5-252 hr*	20-60 hr
Mean	29.0 "	20.6 "	69.5 "	30.1 "
Standard error	1.08 "	0.9 "	5.7 "	1.3 "

* Figures for range, mean, and standard error in the treated groups are for those mice which died.

[8] Bieter, R. N., Larson, W. P., Levine, M., and Cranston, E. M., PROC. SOC. EXP. BIOL. AND MED., 1939, **41**, 202.

In an attempt to explain the apparent decrease in resistance of infected mice at 98°F, as compared to those kept at room temperature, readings were made on mice injected subcutaneously with the same dose of the pneumococcus as used above. These measurements were made on animals kept at room temperature after infection, and those kept at the higher temperature. In the former, the mice showed a steady decline in temperature, beginning about 14 hours after infection, and continuing until death. In some cases, the temperature immediately before death was as low as 84°F. At no time was there a rise in temperature above the normal range in any of the mice studied. In those mice kept at 98°F, the temperature remained above normal, and no drop was detected even in those examined shortly before death.

To eliminate the possibility of increased toxicity of sulfanilamide at the higher temperature, 24 mice were placed on the diet containing the same amount of drug used previously (0.5%) and were kept in the heated room. None of these mice showed any ill effects after 3 days, and the average intake of food was the same as in the animals infected with the pneumococcus.

In a recent communication from Perrin Long, we learn that he has measured temperatures of mice. His findings are in agreement with those here reported.

Summary. The body temperature of mice is markedly influenced by the surrounding temperature. Pneumococcic infections in mice are associated with a marked drop in temperature. Infected mice held at incubator temperature succumb more rapidly than those at room temperature. Incubator temperature promotes the infective processes in mice more than the protective action of sulfanilamide.