# Antagonism of Cortisone to Body Temperature Reducing Effect of Histamine.* (20884)

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Mice inoculated with *Hemophilus pertussis* vaccine are more sensitive to the lethal effects of histamine, of anaphylactic shock, of heterologous vaccines, and, of anoxia than uninoculated animals(1,2). Cortisone inhibits histamine death in pertussis-injected mice(3). It is believed that further work on the mechanism of cortisone-histamine antagonism will be facilitated by the use of a less complex endpoint than death. Fabinyi and Szebehelyi(4) have shown that histamine decreases the body temperature of mice at 18-20°C. The following experiments will demonstrate that pertussis-inoculated mice are more sensitive to the temperature-lowering effects of histamine than uninoculated animals, and, that cortisone will reduce the fall in rectal temperature of both pertussis-inoculated and uninoculated animals. It is hoped that this study will focus attention on the histamine-antagonizing ability of cortisone, since this property may be of some importance in the anti-allergic activities of this hormone.

*Materials and methods.* White, 17 to 25 g mice, bred in our laboratory from a strain originally purchased from Tumblebrook Farms, were employed. Since female mice have been reported to be more sensitive to histamine than males(5), either all females or all males were used in any one experiment. A group of female mice was injected with 0.2 ml of *H. pertussis* vaccine† containing 47.7 billion organisms per ml. Five days later, both pertussis-inoculated and uninoculated animals were placed in a room thermostatically controlled to 18°C. Rectal temperatures of all animals were taken by means of a copper-constantan thermocouple connected to a galvanometer. Pertussis-inoculated mice were then divided into 3 groups, each group consisting of 10 animals. The first batch of mice was injected subcutaneously with 5 mg/kg of histamine dihydrochloride; the second and third groups, with 10 mg/kg and 20 mg/kg, respectively. Eighteen uninoculated mice were separated into 3 equal groups, and each group was challenged with subcutaneous doses of either 25, 50, or 100 mg/kg of histamine dihydrochloride. Rectal temperatures of all animals were recorded at ½, 1, 2, and 4 hours after the administration of histamine. Twenty mg/kg of histamine killed 4 of 10 pertussis-inoculated animals, and 100 mg/kg of this amine was lethal to 1 of 6 uninoculated mice. Any temperature readings obtained from animals who subsequently succumbed were discarded. The data in Fig. 1 thus represent the average temperatures of survivors at various time intervals after histamine administration. In a *second experiment*, only male mice were employed. Ten pertussis-inoculated and 10 uninoculated animals were challenged with 25 mg/kg and 400 mg/kg of histamine respectively. These doses of histamine killed 4 of 10 pertussis-inoculated mice and 5 of 10 uninoculated animals. Only temperatures of

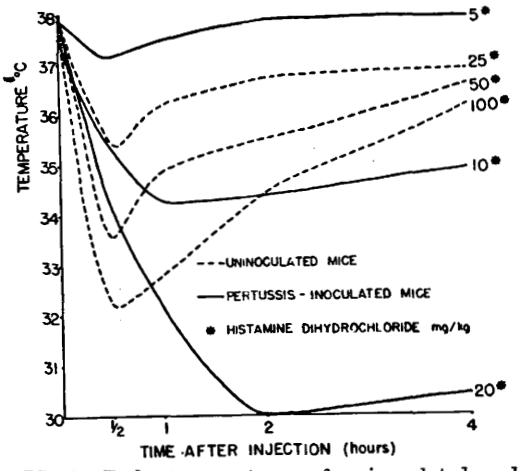


FIG. 1. Body temperatures of uninoculated and pertussis-inoculated mice after administration of varying doses of histamine dihydrochloride.

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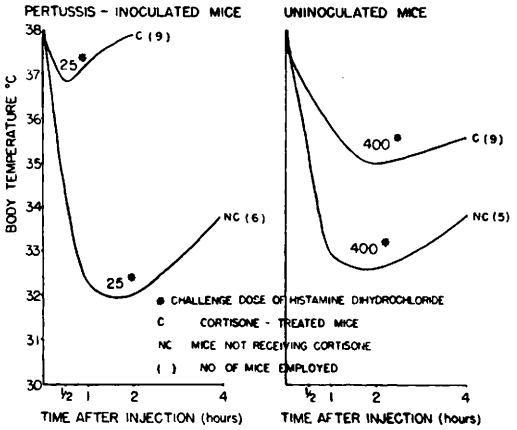


FIG. 2. Antagonism of cortisone to body temperature reducing effect of histamine in pertussis-inoculated and uninoculated mice.

survivors were averaged. In addition, 9 pertussis-inoculated and 9 uninoculated animals were injected intramuscularly with 2.5 mg of cortisone acetate (Upjohn) 18 hours before challenge doses of histamine were administered. All pertussis mice inoculated with cortisone survived 25 mg/kg of histamine, and all normal control animals injected with cortisone survived 400 mg/kg of this amine. Temperatures were recorded as described in the previous experiment.

*Results.* The effect of varying doses of histamine on the body temperature of pertussis-inoculated and uninoculated mice is shown in Fig. 1. It is evident that pertussis-inoculated mice are more sensitive to the temperature-reducing effects of histamine than uninoculated animals. Ten mg/kg of histamine in pertussis-inoculated mice resulted in approximately the same temperature drop as 50 mg/kg in uninoculated animals. Likewise, the data in Fig. 2 demonstrate that 25 mg/kg of histamine resulted in a fall in temperature in pertussis-inoculated mice comparable to that produced by 400 mg/kg in uninoculated animals. The data in Fig. 2 also indicate that cortisone reduces the fall in body temperature after histamine in both pertussis-inoculated and uninoculated mice. The maximum temperature drop in pertussis-inoculated mice without cortisone was 5.9 $\pm$ 1.3°C; in pertussis-inoculated, cortisone-treated mice, 1.0 $\pm$ .82°C. The difference between these values is a significant one, ($p = <.01$). The fall in temperature of uninoculated mice without cortisone was 5.2 $\pm$ 1.2°C; the temperature drop in uninoculated cortisone-treated mice was 2.3 $\pm$ .23°C. The difference between these values is a significant one, ($p = .05$).

*Discussion.* The body temperature reducing effect of histamine in mice appears to offer a convenient method for studies of cortisone-histamine antagonism. Gyermek believes that histamine lowers body temperature at 20°C by dilating skin capillaries thus increasing heat loss(6). Since cortisone has been reported to augment the vasoconstrictor action of epinephrine(7), its antagonism to histamine in our experiments may be due to a potentiation of the vasoconstrictor effect of endogenous epinephrine on skin vessels with a resultant decrease in heat loss.

*Summary.* Pertussis-inoculated mice are more sensitive to body temperature lowering effect of histamine than uninoculated animals. Cortisone reduces the temperature drop in both pertussis-inoculated and uninoculated mice.

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