ing resistance to infection. Because these small doses were shown to be non-toxic to the normal animal, it would seem that cortisone has some specific detrimental effect in mouse typhoid.

Summary. Cortisone, administered in single injections ranging from 0.25 to 5 mg, markedly decreased resistance of mice to *S. typhimurium*. Cortisone had the greatest effect on resistance when administered within 2 days before or after typhoid inoculation. Subcutaneous injections of two other steroids, progesterone and desoxycorticosterone acetate, in dosage range of 0.1 to 10 mg, had no effect on mortality in mouse typhoid.

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Cortisone and Mortality in Mouse Typhoid. II. Effect of Environmental Temperature.* (22985)

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In an investigation of effects of cortisone‡ on mice infected with *Salmonella typhimurium,* it was observed that during the hot summer months cortisone treatment was more effective in reducing survival. To determine the effect of environmental temperature on cortisone treatment, the following experiments were completed under conditions of controlled room temperature.

Procedure. Two mouse strains were used: an innately resistant strain (RI), and a strain (Z) of intermediate resistance to *S. typhimurium*. Of 280 untreated female RI mice, 100 to 400 days old, 77.9% survived a single dose of 200,000 11C *S. typhimurium,* whereas only 42.8% of 1440 Z females survived the same inocula. Evidence that this disease resistance is innate and not acquired has been reviewed by Gowen(1). Hormone-treated mice, 5½ to 7 months old, were given a single subcutaneous injection of cortisone acetate (Cortone, Merck) in saline with suspending agents (polyoxyethylene sorbitan monooleate and sodium carboxymethylcellulose) and benzyl alcohol as preservative. Control animals received an equal volume of Aqueous Vehicle No. 1 (Merck). Cortisone and aqueous vehicle injections were given 24 hours before typhoid inoculation. All mice were inoculated with $2X10^5$ viable cells of 11C strain of *S. typhimurium*. Throughout each 3 week experiment, cortisone-treated mice and their litter-mate controls were confined in the same cage; identification was by pedigree numbers. This investigation was conducted during the summer and an air conditioning unit was used to attain "moderate" temperature of 21° to

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TABLE I. Survival of Control and Cortisone-Treated Mice in 2 Environmental Temperatures after Inoculation with *S. typhimurium*.*

Exp.		Z females			Z males			RI males		
		Total	Survived	% survived	Total	Survived	% survived	Total	Survived	% survived
		Moderate environmental temp. (21° to 25°C)†								
A	C‡	40	34	85	71	52	73			
	T	40	21	52	71	43	61			
B	C	34	23	68	30	15	50	52	45	86
	T	34	0	0	30	3	10	52	41	79
		Warm environmental temp. (29° to 36°C)								
C	C	26	18	69	22	10	45	45	33	73
	T	26	0	0	22	0	0	45	0	0
D	C	63	33	52						
	T	63	0	0						
E	C				61	50	82			
	T				61	0	0			

* Each treated mouse received subcut. inj. of Cortone (Merck) and each control received Aqueous Vehicle No. 1 (Merck) one day before intrap. inoculation of 2×10^5 living cells of *S. typhimurium*. Treated mice of Z strain were given 1 mg cortisone; treated mice of RI strain were given 2 mg cortisone.

† Temperature ranges were: Exp. A, 23°-25°C; Exp. B, 21°-24°C; Exp. C, 29°-36°C; Exp. D, 31°-36°C; and Exp. E, 29°-31°C.

‡ C = Control; T = Treated.

25°C (70° to 78°F) in the Isolation Room. When the air conditioner was not in operation, the temperature in the Isolation Room varied according to outside environment. This "warm" room ranged from 29° to 36°C (85° to 96°F). These temperature ranges are minimum and maximum values. Temperatures were noted 4 times daily during each 3 week experiment. Because only one room was available for these experiments, temperature comparisons were made on mice inoculated at different times. To compensate for this lack of experimental control, the 3 inoculations at "warm" temperatures were alternated with the two at "moderate" temperatures.

Results. The 5 successive bacterial inoculations (Exp. A through E) are summarized in Table I. Only comparisons of cortisone-treated mice and their litter-mate controls are valid here. Because temperature comparisons were necessarily made with animals which were inoculated at different times, certain experimental errors may have arisen. Nevertheless, 2 trends were consistent throughout these 5 independent experiments. First, treatment with cortisone reduced natural resistance of both the RI and Z mice. Second, number of survivors was further reduced if cortisone-treated mice were maintained at the warmer temperature (29° to 36°C). Not included in this Table are additional data accumulated during these 5 inoculations from 26 pairs of male Z mice, given 2 mg cortisone. At this dosage, the effect of temperature on survival was not significant. It is evident that the effect of environmental temperature may be seen only at a critical hormone dosage.

In general, survival of controls was also lower at warmer temperature. However, this difference in survival of controls is not significant. In previous observations in our Laboratory, more than a thousand mice of Z strain were inoculated with $2X10^5$ cells of *S. typhimurium* (11C) and survival was 42%. In the present study, the survival values for Z controls ranged from 45% to 85%. These figures were a bit higher, but not exceptionally so, considering the numbers of animals used in each experiment. Therefore we must conclude that environmental temperature had no significant effect on survival of infected controls.

Fig. 1 illustrates the combined survival data of Z females during 3 weeks following inoculation. When pooled data of replicates A and B were compared with those of repli-

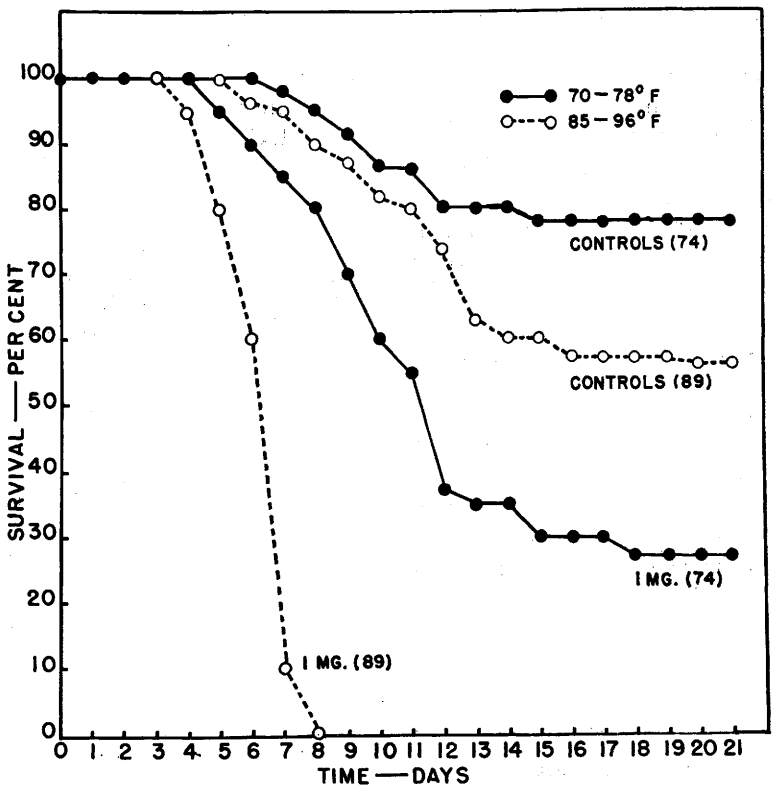

FIG. 1. Effect of environmental temperature on survival of control and cortisone-treated mice during mouse typhoid infection. Numbers in parentheses indicate No. of mice (Z females) in each group.

cates C, D, and E, the effect of temperature upon survival of cortisone-treated animals was evident by the fifth day after inoculation in both Z and RI strains.

Discussion. It has been shown that cortisone, in combination with its suspending agents and preservative, has a greater effect in reducing survival in mouse typhoid when the animals are maintained in a room temperature of 29° to 36°C than between 21° to 25°C. No data are available with which to evaluate the possible effect of the suspending agents and/or preservative. This lack makes insecure comparisons of survival of mice receiving Aqueous Vehicle with that of mice receiving no treatment at all. Scherr(2) has reported that in monilial infections, male mice treated with Aqueous Vehicle of cortisone showed higher mortality than untreated controls. This was not true of female mice he treated similarly. Scherr(3) has also shown that the toxic effect of cortisone for normal mice was greater at an environmental temperature of 35° to 37°C than at 25° to 29°C.

In studies of tourniquet shock, Moore(4) has shown that the mortality of injured mice is greater when maintained at temperature of 35°C instead of 25°C. Scherr(5) reported that mice infected with moniliasis have a higher death rate at 35° to 37°C than at 28° to 32°C. Therefore, it might be expected that mice injured by *Salmonella* endotoxins would show greater mortality in the warmer room temperature. In our study, however, infected mice, which did not receive cortisone, were not significantly harmed by maintenance at 29° to 36°C instead of 21° to 25°C. Moore(4) has reported that the mortality of tourniquet-injured mice maintained at 35°C was increased by high environmental humidity. In our experiments there was, however, no way of controlling humidity when air conditioner was not in use.

The reduced resistance, observed in in-

fected cortisone-treated mice in a warm environment, may be the result of the action of cortisone in decreasing capillary permeability (6). Also, it has been shown that cortisone blocks body temperature reducing effect of histamine(7). Weir(8) concluded that at moderate environmental temperatures (20°C) fever was not characteristic of mouse typhoid. He reported that rectal temperatures of infected mice were highly correlated with room temperature. Other studies have also shown that the mouse has little defense against increased environmental temperature(9,10). Hence, it is possible that the effect of temperature on toxicity of cortisone may be demonstrable only in the mouse.

Summary. Mice infected with *S. typhimurium* were maintained for 3 weeks either in a warm environmental temperature of 29° to 36°C or a moderate temperature 21° to 25°C. At the warmer temperature, subcutaneous injections of cortisone were more effective in reducing survival. Room temperature had no significant effect upon survival of those infected mice which received the Aqueous Vehicle of cortisone.

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Cortisone and Mortality in Mouse Typhoid. III. Effect of Natural and Acquired Immunity.* (22986)

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Cortisone may either increase or decrease resistance of infected animals, depending upon severity of the infection(1). Conversely, survival of animals infected by the same experimental inoculum may be either increased or decreased by cortisone treatment, depending upon hormone dosage(2). Most studies of hormone-infection relationship rely upon quantitative manipulation of either the hormone or the infectious inoculum. In the present investigation, a third experimental design was possible, by using host animals of varying genetic constitution. Seven strains of mice which differed in natural resistance to *Salmonella typhimurium* were given the same amount of cortisone and were inoculated with the same number of bacteria. It was then possible to establish the effect of cortisone on innate resistance to disease. The effect of cortisone on acquired resistance was determined by comparing mortality of normal and previously immunized mice during simultaneous treatment with cortisone and infection with *S. typhimurium.*

Materials and methods. All mice were between 5 and 7 months old. Seven inbred mouse strains were used: S, RI, Z, K, E, LGw, designated L, and BALB/Gw, designated Ba. These strains were chosen because of the wide range in their innate resistance to mouse typhoid. Inoculations of $2X10^5$ living bacteria of the 11C culture of *S. typhimurium* have established the following survival values: S, 95%; RI, 78%; K, 63%; Z, 43%; E,

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