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Effect of Adrenocorticotropic Hormone on Pneumococcal Infections in Rabbits. (20492)

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Many investigators have reported on the effects of large doses of cortisone and Compound F on the resistance of various animal species to a variety of infections(1-20). Shwartzman(21) has shown that adrenocorticotropic hormone (ACTH) and cortisone in combination, or cortisone alone, produced a marked acceleration of poliomyelitis infection in mice and an enhancement in the susceptibility of hamsters to this infection. He has reported, however, that ACTH alone failed to produce this effect and hence has postulated that the adrenals may elaborate an unknown factor capable of reversing the enhancing effects of cortisone on infection. It seemed important, in view of the possible widespread significance of these observations, to determine if Shwartzman's findings applied to other infections and to other species. The present report is concerned with the effect of ACTH on an experimental pneumococcal infection in rabbits.

Methods. Male albino rabbits, weighing between 2.0 and 2.5 kg each, were infected intradermally with a Type I pneumococcus by injecting into the shaved abdominal skin 0.1 cc of a 2 x 10^{-3} dilution of a 6-hour culture grown in nutrient broth containing 5% defibrinated rabbit blood. The virulence of the culture was such that 0.5 cc of a 10^{-9} dilution (1-3 organisms) was lethal for a mouse. The size of the skin lesion resulting from the injection of the pneumococci was measured by tracing the periphery of the lesion on transparent paper and the area of the skin lesion was subsequently obtained by retracing the paper outline with a planimeter. The blood culture studies were performed by plating 0.1 cc of blood obtained from the marginal ear vein in 5% blood agar. Serial 10-fold dilutions of the blood were plated in order to assure accuracy in determining the number of bacterial cells. The plates were then incubated for 24 hours at 37°C.

A sample of crude ACTH, equivalent to Armour Standard La-1-A, was given in doses of 0.25 mg to 2.0 mg every hour night and day. Treatment was initiated 18 hours before the bacterial injection and then continued for 96 hours or until death of the animal. Similar studies were repeated with a highly purified ACTH containing 200-300 units per mg (22) with essentially the same results.

Results. Survival studies. The data presented in Table I indicate that 76% of the control animals survived the infection. Animals treated with ACTH, in contrast, began to die within 24-48 hours after the bacterial injection, and only 17% of the animals receiving ACTH survived the 10-day observation period. These data indicate that ACTH is capable of decreasing the survival of rabbits

TABLE I. Survival of Animals Treated with ACTH and Infected Intradermally with *D. pneumoniae.*

	Dose ACTH in mg/hr				
	Saline	.25	.5	1.0	2.0
No. of animals	17	6	6	17	6
% survival	76	17	17	18	17

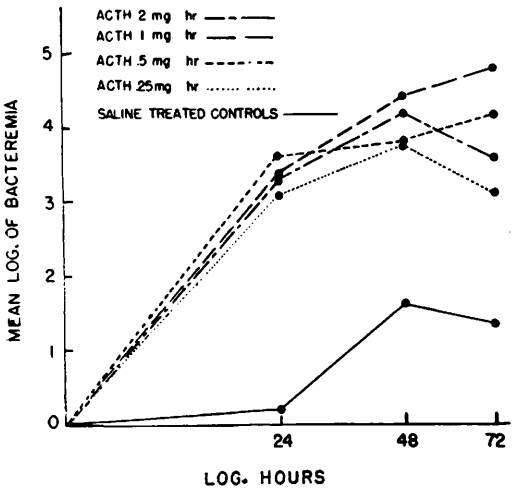

FIG. 1. Bacteremia in rabbits treated with ACTH.

infected with a Type I pneumococcus. Control studies performed with the same doses of ACTH in non-infected animals showed that these quantities of the hormone were not lethal. Animals that received ACTH, however, developed a marked lipemia and in some cases the total lipid content of the serum reached a value of 5 g %. Adrenal hypertrophy was observed in the animals which received ACTH.

Blood culture studies. The control rabbits developed a transient bacteremia which had its onset approximately 4 hours after the intradermal injection of the pneumococci and reached a peak at 48 hours after the injection (Fig. 1). The bacteremia then gradually subsided and the blood was sterile in most cases at the 120-hour observation period. The animals receiving ACTH, in contrast, developed an early onset of sepsis and within 24-48 hours large numbers of pneumococci were found in the blood. Overwhelming sepsis occurred, in most cases, within 72 hours. Occasionally, animals receiving ACTH died 6 hours after the bacterial injection and numerous pneumococci were found in the blood.

Skin lesions. There were marked differences in the size and character of the skin lesion in the control and ACTH treated animals (Fig. 2). In the control animals the lesion reached a maximal size of approximately 50 sq cm within 48 hours. It remained essentially the same size for the next 4 or 5 days and then gradually subsided over the ensuing 15-day period. The lesions in the animals receiving ACTH developed very slowly and appeared as small flat areas with little evidence of inflammation.

The microscopic picture of the skin lesions in the 2 groups of animals offered a striking contrast. In the control animals, there was an infiltration of polymorphonuclear leucocytes at the bacterial injection site within a few minutes after infection was initiated, and these cells accumulated rapidly within the next few hours. Relatively few pneumococci were observed and they were found mainly within the leucocytes in the saline treated controls.

In the ACTH treated rabbits the inflammatory reaction was markedly suppressed and relatively few polymorphonuclear leucocytes, and little edema fluid, were found even 18 hours after the bacterial injection. Numerous pneumococci were observed in the tissue and blood vessels surrounding the injection site and animals frequently died of overwhelming infection with little evidence of local inflammation.

Discussion. Under the conditions of this study, rabbits receiving ACTH show a low-

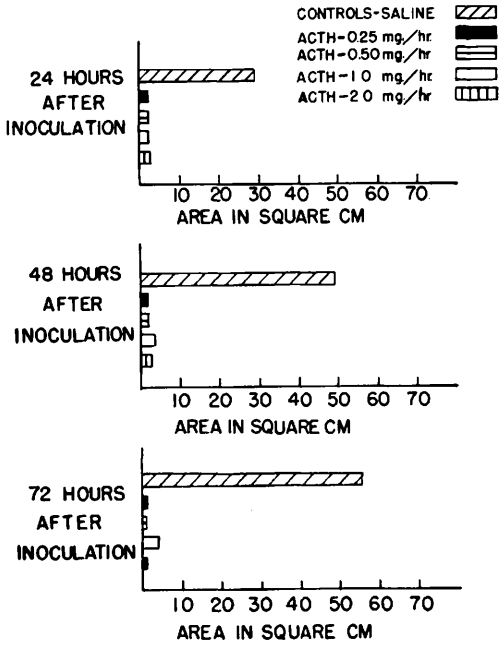

FIG. 2. Skin lesion size in rabbits treated with ACTH.

ered resistance to an experimental pneumococcal infection. The basic response of the animals receiving ACTH was essentially the same as that observed in rabbits treated with cortisone and Compound F(23). There was a marked suppression in both the cortisone and ACTH treated animals in the rate of mobilization of polymorphonuclear leucocytes at the injection site. The suppression of the inflammatory response, however, was greater and persisted for a longer period of time in animals receiving ACTH(23). Also there was essentially complete suppression of edema fluid formation under the influence of ACTH. It is not possible to state at this time whether these differences in response were related to variations in dosage and rate of absorption of the 2 materials, or to an actual difference in the effects of the hormones.

The data presented in this study do not support the hypothesis that ACTH in the rabbit can cause the secretion of a factor that counteracts the adverse effects of cortisone on pneumococcal infections, as Shwartzman has suggested for poliomyelitis in mice and hamsters(21). It is recognized that the experimental procedure used in the present study differed from that employed by Shwartzman, particularly with regard to the infectious agent and dosage schedules. Shwartzman's studies employed poliomyelitis while the studies reported here used a Type I pneumococcal infection. The ACTH was injected either once or 3 times a day in the studies reported by Shwartzman, and every hour, night and day, in our studies. This dosing schedule was undertaken in view of the findings of Ingle (24) that the effects of ACTH could best be demonstrated by maintaining constant tissue and blood levels. The adrenal cortices, in the present studies, were markedly hypertrophied and the hyperglycemia, lipemia, and atrophy of lymphoid tissue indicated a pronounced hyperadrenocorticism.

Summary. ACTH, given at frequent intervals and in large doses, lowers the resistance of rabbits to a Type I pneumococcal infection. ACTH appears to suppress inflammation at the bacterial injection site sufficiently to permit early and rapid invasion of the blood stream and surrounding tissues.

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