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THE INFLUENCE OF CORTISONE AND HYDROCORTISONE ACETATES ON THE COURSE OF *MYCOBACTERIUM LEPRAEMURIUM* INFECTION IN RATS

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Prolonged administration of cortisone acetate or hydrocortisone acetate produces a decrease in the rate of growth of treated rats. In this respect the effect of the latter steroid is the more pronounced. Lepromata in the steroid treated animals are significantly smaller than those in the control rats. This difference is more pronounced with the cortisone acetate treatment. However, whilst there is no appreciable difference in the distribution of organisms in the lepromata, the spread of infection is not increased by the steroid treatment, as the number of animals showing acid fast organisms in the spleen is no greater in the treated groups than in the controls.

It has been repeatedly demonstrated that corticotrophin (ACTH), cortisone acetate and some other adrenal steroids, when injected in large doses, will interfere with the host defence mechanism against bacterial infections (Foley, Morgan, and Greco, 1957a). It has also been suggested that the steroids interfere both with antibody formation and with the development of tissue immunity (Foley *et al.*, 1957a and b). In addition, other investigators have shown that cortisone will lower the resistance of laboratory animals to a wide range of bacterial, viral, protozoal and fungal infections (Kass and Finland, 1953).

The majority of experiments in this field reported in the literature have been of short duration. It was therefore thought of interest to investigate the effect of prolonged administration of cortisone and hydrocortisone acetates on the course of *Mycobacterium lepraemurium* infection in rats, which affords an excellent opportunity of studying the effect of administering the steroids in an infection of long duration.

MATERIALS AND METHODS

Male Wistar rats of the A.R.C. strain of body weights 120 to 160 g. were maintained on a cube diet and tap-water. All rats were inoculated subcutaneously in the right flank with *Mycobacterium lepraemurium.*

The inoculum was prepared from a rat leproma which was finely minced in Dubos medium. Each rat was injected with 0.4 ml. of the suspension. The infected rats were then randomly distributed into three groups of 10; the first group was treated with intramuscular injections of cortisone acetate, the second with hydrocortisone acetate, the third group remained untreated. The doses were 2.5 mg. of steroid/rat, three times a week for the first month, twice a week for the next three months and then once a week until the end of the experiment. During this time each rat was weighed weekly. All rats were killed at six months after inoculation, and the lepromata were removed and weighed. The lepromata, spleens and livers of all the rats were examined histologically for the presence of acid fast organisms.

RESULTS

Effect of Steroid Treatment on Animal Growth.—The first obvious effect of the steroid treatment was the retardation of growth in the treated animals. Within 1 to 2 weeks after the commencement of the experiment, a diminution of growth rate was observed; this continued for the duration of the experiment. It appeared that hydrocortisone acetate was more potent in its growth-retarding effects than cortisone acetate.

Because of this effect, the dose of steroid was gradually reduced since it was feared that if the retardation of animal growth became too drastic it might interfere with the study of the effects of the steroids on the course of infection.

Fig. 1 shows the effect of adrenal steroid treatment on body weight. The mean body weights at weekly intervals of the control and of the treated groups are plotted for the duration of the experiment.

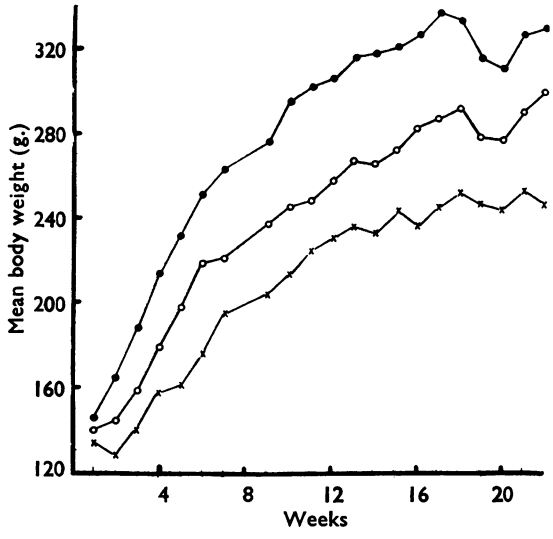

FIG. 1.—The effect of adrenal steroid treatment on body weight Each point represents the mean body weight of a group of 10 rats. The steriods were administered intramuscularly ; 2·5 mg. being given thrice weekly during the first month, 2·5 mg. twice weekly for the next three months, and then 2·5 mg. weekly until the end of the experiment. ●, Controls; O, cortisone acetate ; X, hydrocortisone acetate.

Effect of Steroid Treatment on the Growth of Lepromata.—Each of the rats infected with *Mycobacterium lepraemurium* subsequently developed a leproma at the original site of inoculation. As far as could be determined there was no significant difference in the time at which the lepromata appeared in the steroid treated and in the control groups. However, as the lepromata developed, it became apparent that they were very much smaller in the animals receiving steroids than in the untreated rats. Also several of the lepromata in the treated animals ulcerated and discharged before the end of the experiment, even though the lepromata were quite small when compared with those of the controls.

Six months after infection, the rats were killed and the lepromata removed. The lepromata were significantly smaller ($P<0.01$) in the rats receiving hydrocortisone acetate treatment, and in the rats treated with cortisone acetate ($P<0.001$). In this respect the effect of cortisone acetate was significantly more pronounced than that of hydrocortisone acetate ($P<0.01$). This difference in size was shown to be related only partially to the retardation of growth of the animals, since there is still a significant difference in weight ($P<0.01$) between the lepromata of the untreated and cortisone acetate treated animals when the results are expressed as g. of leproma/100 g. of body weight. These results are shown in Table I and Fig. 2.

TABLE I

THE EFFECT OF ADRENAL STEROID TREATMENT ON LEPROMA WEIGHT

The steroids were injected intramuscularly in doses of 2·5 mg./rat ; 3 times/week for the first month, twice a week for 3 months, and once a week until the end of the sixth month. The results of tests for significant differences between the mean weights of intact lepromata are shown.

Treatment	No. of Lepromata		Mean Weight of Intact Lepromata ± S.E.			
			g.		g./100 g. body wt.	
	Burst	Intact		P		P
Controls ..	1	9	13·46±2·14	—	4·04±0·68	—
Hydrocortisone acetate	4	6	5·94±0·86	<0·01	2·48±0·44	<0·1 >0·05
Cortisone acetate	3	6	2·44±0·70	<0·001	0·68±0·19	<0·01

Effect of Steroid Treatment on the Spread of Infection.—Smears and sections were made from the lepromata and spleens of all the rats, and sections only from the livers. There were innumerable acid fast organisms in all the lepromata, and as far as could be determined there was no appreciable difference in the distribution of organisms in the lepromata of either the treated or the untreated rats. However, the smears and sections of the spleens of the control animals showed a somewhat different picture from those of the treated rats. As shown in Table II, the number of animals showing acid fast bacilli in the spleen was smaller in the steroid treated groups than in the controls. This effect was most pronounced in the cortisone acetate treated group, in which only 1 out of 8 of the rats showed bacilli in the spleen. The results from the liver

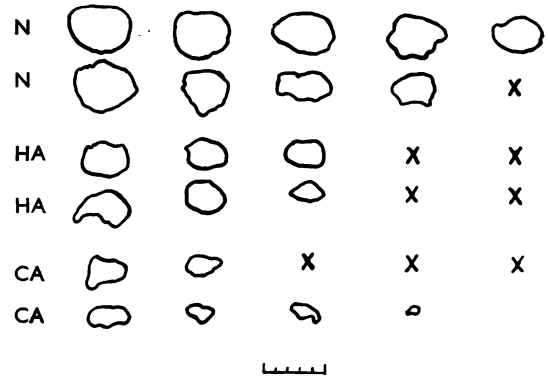

FIG. 2.—Lepromata from the normal untreated rats (N) and from the hydrocortisone acetate (HA) and cortisone acetate (CA) treated rats when removed 6 months after inoculation. The symbol X indicates lepromata which had burst and discharged before the end of the experiment. The scale is in cm.

sections were somewhat inconclusive, since only 4 rats from the control group of 10 animals showed acid fast bacilli.

TABLE II

NUMBER OF RATS SHOWING ACID FAST BACILLI IN LEPROMA, SPLEEN AND LIVER

Treatment	Smears		Sections	
	Leproma	Spleen	Spleen	Liver
Controls	10/10	9/10	7/10	4/10
Hydrocortisone acetate	7/7	6/10	3/10	4/10
Cortisone acetate	8/8	1/8	1/8	2/8

DISCUSSION

Prolonged administration of either cortisone or of hydrocortisone acetate does not increase the severity of the infection; indeed the smaller lepromata and the slight reduction in the spread of acid fast bacilli to the spleen in the steroid treated rats indicates that the reverse has taken place. The reduction in leproma size is not entirely related to the retardation of growth of the treated animals; it seems likely that the reduced leproma size is due mainly to the anti-inflammatory action of the steroids. The fact that cortisone acetate is more effective in this respect is not unexpected since other experiments performed in this laboratory have shown that cortisone acetate when injected intramuscularly into the rat is more potent than hydrocortisone acetate as an anti-inflammatory agent.

The results of this investigation are in agreement with the observations of Naguib and Robson (1956), who showed that prolonged administration of cortisone acetate in mice infected intracorneally with murine leprosy decreased the development of both macroscopic corneal and systemic lesions. However, these authors found that large numbers of acid fast bacilli were present in the livers and spleens, whereas in the present work the steroid treatment appeared to have reduced the spread of bacilli to these organs.

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