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# THE EFFECT OF CORTISONE ON EXPERIMENTAL CORNEAL TUBERCULOUS LESIONS

BY

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Experimental lesions induced by the intracorneal injection of tubercle bacilli into rodents have proved useful in assessing the anti-tuberculous effect of drugs (Gardner, Rees, and Robson, 1949; Rees and Robson, 1950). The method seemed likely to yield information regarding the effect of cortisone in experimental tuberculosis, and the results of such an investigation are presented here.

## METHODS AND MATERIAL

The intracorneal infection of the rabbit was produced by the method of Gardner *et al.* (1949). The bovine strain of *Mycobacterium tuberculosis* and the dosage employed were the same as used by these authors. The administration of cortisone was by the intravitreous route and, in the animals so treated, 0.1 ml. of a suspension containing 2.5 mg. of microcrystalline cortisone was introduced into the vitreous of the right eye twice weekly, while the same quantity of the suspending fluid only was similarly introduced into the left eye to act as a control. All rabbits were examined at weekly intervals and the extent of the lesion assessed with an arbitrary numerical scale similar to that used by Gardner *et al.* (1949).

Five rabbits were inoculated with tubercle bacilli intracorneally and divided into two groups, as follows:

*Group 1.*—Three rabbits—cortisone commenced on day of inoculation and discontinued on the 38th day.

*Group 2.*—Two rabbits—control group—untreated.

This experiment was continued over a period of 56 days, and the findings are shown in Fig. 1.

A further 12 rabbits were divided into three equal groups which were inoculated with tubercle bacilli intracorneally and treated as follows:

*Group 3.*—Cortisone commenced on day of inoculation.

*Group 4.*—Cortisone commenced 14 days after inoculation.

*Group 5.*—Control group—untreated.

The cortisone was given as in the first experiment. Observation was maintained over a period of 42 days; the animals were then killed and the eyes removed for histological examination. The results of this experiment are shown graphically in Fig. 2. Histological examination revealed, in both cortisone-treated and control eyes, ulcerated and caseating corneal lesions in which numerous tubercle bacilli were present. The cellular reaction in both treated and control eyes was predominantly polymorphonuclear and of similar degree in both groups.

Four more rabbits were then subjected to experimental corneal infection and treated with the antihistamine substance promethazine (phenergan). The dosage was 5 mg./kg./day given in two equal subcutaneous injections. The results of this experiment are shown in Fig. 4.

## RESULTS

The administration of cortisone to the animals inoculated intracorneally with tubercle bacilli leads, as is shown in Figs. 1 and 2, to depression of the severity of the ensuing lesion. The lesions appear, as in the control animals, between the 7th–14th days, but progress much less rapidly. This effect, however, is limited to the period of cortisone administration, for after discontinuance of therapy a rapid increase in the severity of the lesion follows.

Delaying the administration of cortisone until a lesion is established at 14 days after experimental infection also produces a depression of the severity of the lesion, but to a lesser degree than that shown after immediate therapy (Fig. 2).

Illustrations of typical corneal lesions produced during these experiments are shown in Fig. 3.

The experiment with promethazine, which was investigated since, like cortisone, it has anti-allergic effects, shows quite clearly that this substance has no effect on the development of the corneal tuberculous lesion, such as was produced by cortisone (Fig. 4). It must be noted, however, that the antihistamine was given subcutaneously and that there are no data available to show whether effective concentrations of promethazine could be produced in the cornea with this method of administration, though experience with other drugs, e.g. the sulphonamides and penicillin, suggests that systemic administration of drugs is a highly effective method of reaching the cornea.

Promethazine 5 mg./kg. was injected subcutaneously into one rabbit, and three hours later the plasma and anterior chamber fluid were tested on the guinea-pig ileum for antihistamine content: both fluids contained similar small amounts of antihistamine, of the order of rather less than 1 $\mu$g./ml.

## Discussion

Cortisone affects inflammation by actions on the cellular or humoral responses to the organisms involved. There is some doubt what part is played by the inhibition of antibody (Germuth and Ottinger, 1950) or of sensitization mechanisms (Long and Miles, 1950; Woods and Wood, 1950; Long, Miles, and Perry, 1951), but the effects of cortisone on lymphoid tissue (Molomut, Spain, and Haber, 1950), granulation tissue (Ragan *et al.*, 1949), macrophage and fibroblast activity (Dougherty and Schneebeli, 1950; Spain and Molomut, 1950), and hyaluronidase action (Seifter, Baeder, and Begany, 1949; Benditt, Schiller, Wong, and Dorfman, 1950) have been clearly demonstrated. These effects are, in general, inhibitory. Lymphoid tissue is reduced in mass and appears less active histologically. The formation of granulation tissue is depressed and the macrophage and polymorph reactions are less than in control animals with either allergic or traumatic inflammations. The action of hyaluronidase on blood vessels and connective tissue is prevented. These are some of the actions of cortisone which may operate in any inflammatory situation. They may all depend, as Green (1950) has suggested, on an interference with the carbohydrate metabolism of the cells, those in a state of proliferative activity being most affected.

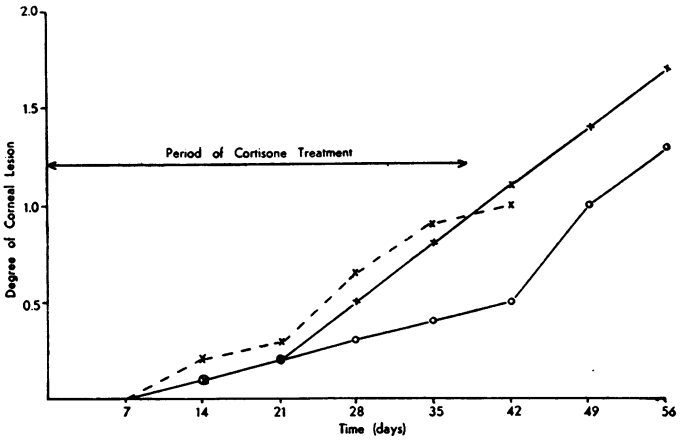


FIG. 1.—Showing the effect of cortisone treatment, started immediately after inoculation, on the progress of corneal tuberculosis in rabbits. ×——×——× Control eyes of treated animals. O——O——O Treated eyes of treated animals. × - - - × - - - × Untreated animals. Note sudden increase in rate of development of lesions on cessation of treatment.

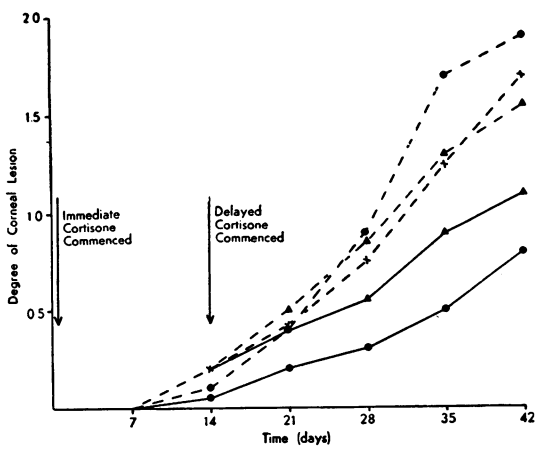


FIG. 2.—Showing the effect of cortisone treatment, started immediately after inoculation and after an interval of 14 days, on the progress of corneal tuberculosis in rabbits. ●- - -●- - -● ▲- - -▲- - -▲ Control eyes of treated animals. ●——●——● ▲——▲——▲ Eyes of animals treated immediately after inoculation. Eyes of animals in which treatment was started 14 days after inoculation. × - - - × - - - × Untreated animals.

Work on experimental tuberculous infection has suggested that the sum total of the action of cortisone is usually an enhancement of the infection. Thus Hart and Rees (1950) describe an extension of previously fibrotic and static tuberculous lesions in mice following cortisone administration. Similar chronic lesions in rats were not usually fatal, but there was a considerable mortality among a cortisone-treated group (Michael, Cummings, and Bloom, 1950). Bunn and Drobeck (1952), using rabbits infected with tubercle bacilli by inoculation of organisms into the anterior chamber of the eye, found that A.C.T.H. and, to a lesser extent, cortisone, administered at, or shortly after, the time of infection, produced a rapid enhancement of the subsequent lesion.

Enhancement of experimental infections by cortisone has also been reported in poliomyelitis (Shwartzman, 1950).

There is, however, evidence that cortisone can be of considerable value in decreasing the extent and inflammatory reaction of acute tuberculous lesions, notably in the larynx (Le Maistré and Tompsett, 1951). In man, local treatment with cortisone has produced beneficial effects in a number of inflammatory ocular conditions (Gordon and McLean, 1950; Olsen *et al.*, 1950;

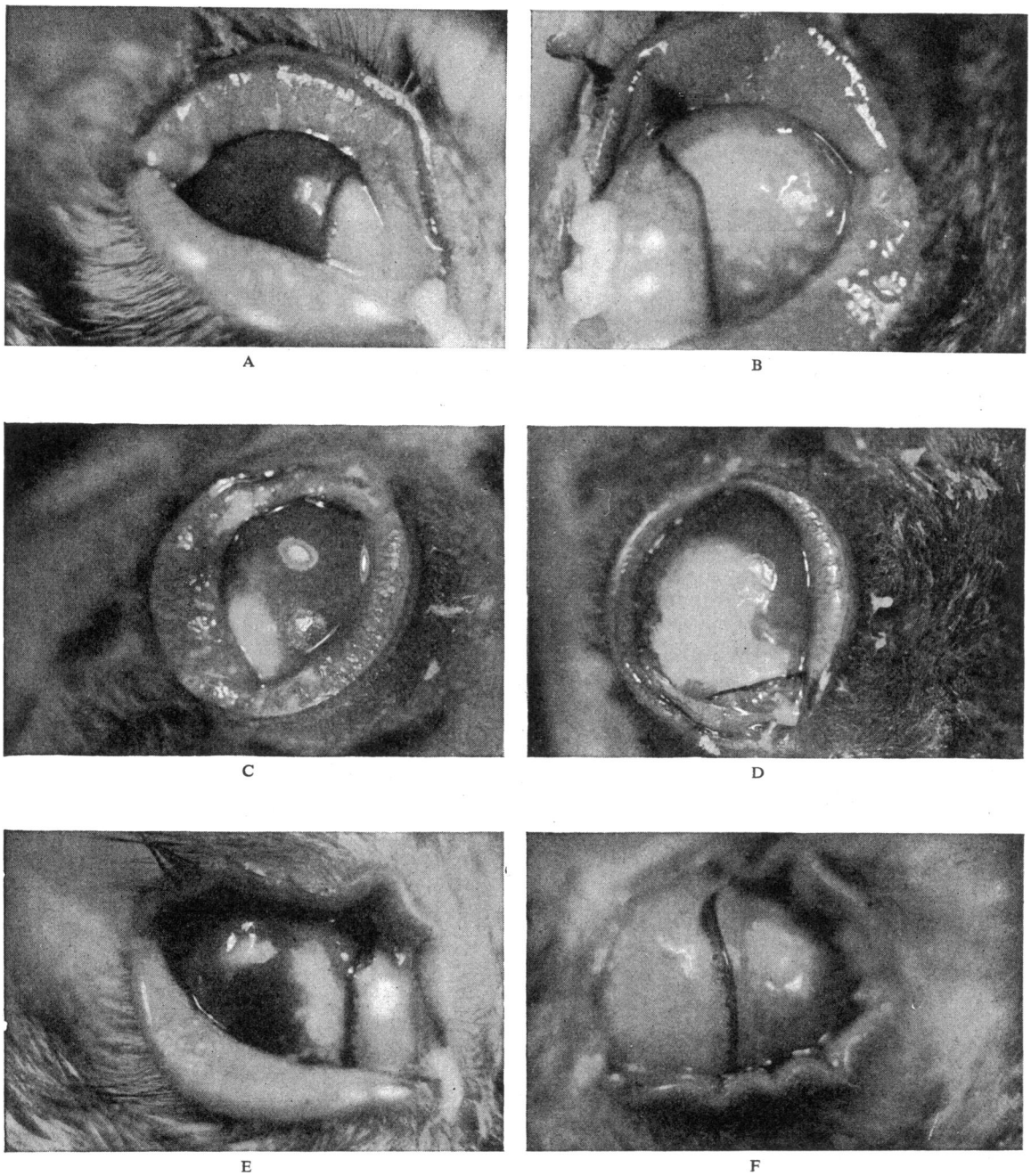


FIG. 3.—Illustrating the effects of cortisone treatment on the development of corneal tuberculosis in rabbits. A and B, Condition of treated eye (A) and control eye (B) 35 days after the beginning of treatment started immediately after inoculation. C and D, Condition of treated eye (C) and control eye (D) 45 days after the beginning of treatment started immediately after inoculation. E and F, Condition of treated eye (E) and control eye (F) 21 days after the beginning of treatment which was started 14 days after inoculation.

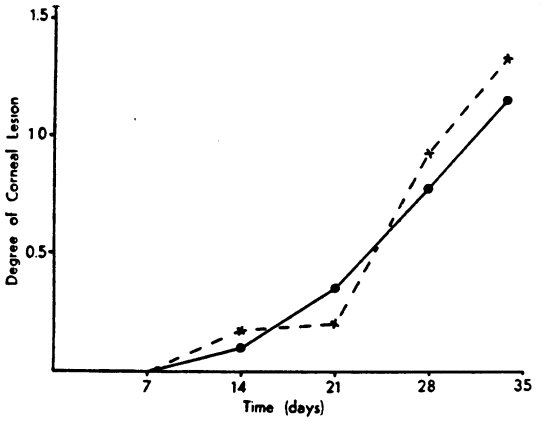


FIG 4.—Showing the absence of effect of promethazine on the development of corneal tuberculosis in rabbits. ●——●——● Eyes of animals treated with promethazine. ×---×---× Eyes of untreated animals.

Harvey, Howard, and Kattus, 1950). Here, however, there were somewhat different circumstances in that most of them were inflammatory states not associated with the presence of specific organisms in the tissues. In a few tuberculous cases there was temporary "improvement" as assessed largely by the degree of vascularity of the parts (Harvey *et al.*, 1950), but Jones and Meyer (1950) have demonstrated experimentally that cortisone will also inhibit post-traumatic vascularization of the cornea.

A great diversity in the results of the investigation on the effects of cortisone in experimental tuberculous infections is shown in the literature. Thus Spain and Molomut (1950) showed an increase in the number and extent of tuberculous lesions in guinea-pigs treated with cortisone, while Le Maistré and Tompsett (1951), also investigating experimental tuberculous lesions in these animals, found no evidence of the enhancement of such lesions by large doses of cortisone or A.C.T.H.

The evidence regarding the effect of cortisone and A.C.T.H. in experimental tuberculosis is reviewed by Dye *et al.* (1952). It is apparent that the data are rather contradictory and that no clear conclusion can be reached at this stage.

The present report of an inhibitory effect by cortisone on experimental tuberculous infection is apparently opposed to many of the results of similar work, but there are important differences in the experimental conditions. Many reports quoted deal with visceral infections often with markedly granulomatous lesions. We produced a slowly progressive local primary infection.

Histological examination of the corneae in both cortisone-treated and control animals revealed no differences in the appearances of the inflammatory reactions in these groups. Local necrosis and a moderate, predominantly polymorphonuclear, cellular response was seen in all the animals. The depression of the extension of the lesion in the cortisone-treated animals would therefore appear to result from the fact that in the cornea, a tough and avascular tissue, limitation of the extent of the infective lesion depends much more upon the plasticity of the ground substance than upon a granulomatous reaction. The spread of organisms will require increased plasticity if not liquefaction. Cortisone, by rendering the ground substance resistant to enzymatic action, may thus restrict the size of the lesion.

We believe that this is a reasonable, if at present speculative, explanation of our findings. Its consideration has at least stressed the importance of the tissues involved in deciding the effect of cortisone on experimental lesions.

## SUMMARY

The effects of cortisone upon experimental infection with bovine tubercle bacilli of the rabbit's cornea has been studied, and a depressant effect upon the severity of the lesion has been observed. Such a depressant effect is not produced by the systemic administration of an antihistamine (promethazine).

The possible mechanisms of this action are discussed.

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