Thrombin clotting times, at 16° C. and pH 7.5, of human citrated plasma containing 0.25 units/ml. heparin; effect of 2×10^{-4} M dinitrophenol; 50 mgm. per cent aureomycin; 0.25 gm. per cent mapharside (*m*-amino *p*-hydroxyphenylarsinic acid); 5×10^{-4} M atebaine

but this requires more critical study⁵. Negative results have been obtained with azide, iodoacetate and *l*-thyroxine.

Attempts to demonstrate an inorganic phosphate requirement for the action of heparin have so far failed, but arsenite at 2×10^{-2} M is inhibitory. It seems possible, therefore, that the anti-thrombic action of heparin is mediated by a coupled phosphorylation.

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¹ Green, J., *Proc. Scot. Soc. Exp. Med.* (June 1951).

² Loomis, W. F., and Lipmann, F., *J. Biol. Chem.*, **173**, 807 (1948).

³ Loomis, W. F., *Science*, **111**, 474 (1950).

⁴ Waisbren, B. A., and Glick, D., *Proc. Soc. Exp. Biol. and Med.*, **75**, 476 (1950).

⁵ Edsall, J. T., and Lever, W. F., *J. Biol. Chem.*, **191**, 735 (1951).

Cortisone and *Plasmodium berghei* Infection in Mice

THERE is considerable clinical evidence to show that in persons infected with malaria various stimuli may precipitate an acute attack. These stimuli include surgical operations, the injection of vaccines, exposure to cold, and possibly, for persons who have not become acclimatized, ascent to high altitudes. There is also evidence, both clinical and experimental, to show that injections of cortisone increase the virulence of bacterial and virus infections. Trypanosome infections also, including Chagas's disease, are intensified in animals given cortisone^{1,2}.

In mice infected with *Plasmodium berghei*, cortisone appears to act in a similar manner. When mice are inoculated subcutaneously with 0.1 ml. of mouse blood, infected with *P. berghei*, and showing approx-

imately 300 infected red blood cells per 1,000 red cells, parasites appear in very small numbers in the peripheral blood stream in about twenty-four hours and death occurs in nine to eleven days. In two experiments, twelve mice weighing 20 gm. were inoculated intramuscularly with 5 mgm. cortisone acetate; 30 min. later, these and twelve control mice were injected subcutaneously with 0.1 ml. of mouse blood in which counts showed that approximately 330 red cells per 1,000 were infected with parasites. The same dose of cortisone was repeated six hours after infection with the parasites, while the mice not receiving cortisone were given 0.1 ml. of physiological saline intramuscularly. The same doses of cortisone and physiological saline were given intramuscularly four days later to the two sets of mice. Normal mice given cortisone in this manner have remained healthy. Smears were made of blood from the tails of cortisone-treated and saline-treated mice six hours after infection and thereafter morning and evening until death. The smears were stained by Giemsa's method and 1,000 red cells were counted from each film, a note being made of the number of red cells infected with *P. berghei*.

In the cortisone-treated mice, it was noticeable that parasitized red cells were already present in the peripheral blood stream in the proportion of 10–16 per 1,000 at six hours after infection, whereas control mice failed to show any parasites in the peripheral blood stream at this period. At twenty-four hours after infection the control mice began to show four or five parasitized red cells per 1,000 red cells, whereas the cortisone-treated mice had eighteen to thirty-six infected cells per 1,000. The majority of the cortisone-treated mice, in seventy-two hours after infection, showed 300 per 1,000 red cells infected, whereas seven to eight days were required for the same level of parasitaemia to be attained in the control mice.

Death occurred in an average of just over five days in the cortisone-treated mice as against 9.5 days in the control mice. At death the spleens of cortisone-treated mice were smaller than those of control mice, suggesting that, as in other types of infection, the cellular reaction to infection was inhibited by the cortisone. Although results obtained in the mouse, which is highly susceptible to the effects of cortisone, cannot be directly transferred to man, these experiments suggest that cortisone may have to be used with caution in regions where malaria is prevalent.

Experiments with toxoplasma infections in mice also suggest that cortisone gives rise to a more fulminating infection than that seen in control mice.

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¹ Wolf, A., Kabat, E. A., Bezer, A. E., and Fonseca, J. R. C., *Fed. Proc.*, **10**, 375 (1951).

² Jarpa, A., Agosin, M., Christen, R., and Atías, A. V., *Bol. Inform. parasit., Chile*, **6**, 25 (1951).