Influence of Cortisone on Natural Course of Malaria in the Pigeon.*(19344)

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Experimental infections of tuberculosis in rabbits(1), guinea pigs(2), rats(3), and mice (4) have been found to react adversely to treatment with cortisone. Enhancement of the bacteremia(5) and earlier death of mice infected with Group A streptococci and of albino rats infected with Type I pneumococci have been reported. In the blood of mice experimentally infected with *Trypanosoma cruzi*(6) the number of parasites was increased three to fourfold by cortisone. The extent of cutaneous infections with *Trichophyton metagrophytes,* vaccinia virus and *Staphylococcus aureus*(7) has been increased, but skin sensitivity was not affected by cortisone treatment. Schmidt and Squires(8) have just reported the results of studies on malaria infections in monkeys treated wtih cortisone. No significant effect was noted on the parasite count previous to the crisis. Following the crisis the parasitemia persisted for a much longer period of time, but at a parasite level well below the initial peak count.

Attempts to determine the reactions of the hosts tissues to the administration of cortisone have revealed an interference in the production of granulation tissue in wounds of rabbits(9), a reduction in spleen size in mice(10), inhibition of tissue reactions to bacterial filtrates(11), and depression of the total cellular response to intraperitoneal injections of sterile mineral oil(12). Results of cortisone treatment in many kinds of experimental infections and the increased activity of certain macrophages produced by adrenal cortical extract reported by Gordon and Katsh(13) suggested studies on the action of cortisone on malaria infections and on immunity to reinfection. This report is concerned with the host-parasite relationship in pigeons infected with malaria and treated with cortisone.

Materials and methods. Infections of the 1P strain of *Plasmodium relictum* in pigeons were treated with cortisone (cortone acetate, Merck) in doses of 5 mg daily injected intramuscularly. The pigeons were inoculated by intravenous injection of blood from an infected bird. A comparable number of parasites was inoculated into each bird. Cortisone dosage was initiated 2 or 3 days before infection, or during the decline or at the termination of parasitemia. In one experiment in which the effectiveness of paludrine on the cortisone treated infections was studied the paludrine was administered by oesophageal tube in daily doses of 2 mg, the minimal effective dose. Thin blood films were made daily and stained by the Giemsa method. The results are recorded as the number of parasites per 10,000 R.B.C.

Results. Eleven pigeons have been given cortisone beginning treatment one to 3 days prior to inoculation. In 8 of these birds the initial peak infection was within the "normal" range and in the other 3 the peak was considerably higher than in any of the infected controls (Fig. 1).

The peak in the parasite number occurred at approximately the same time as observed for untreated infections. The decline in the parasitemia parallels that of the untreated infections for the first 2 or 3 days after which the parasite number abruptly begins a marked increase. The birds frequently die at this stage of infection. In untreated birds the parasite decline continues until none are found by the 9th or 10th day.

When cortisone treatment was withheld until 2 or 3 days following the peak parasite number the same effect was noted on the parasitemia. The number of parasites increased immediately and in most cases remained high until the bird died. Few of the pigeons were able to survive the period of prolonged high parasitemia. One bird of this series was able to reduce the infection following the second

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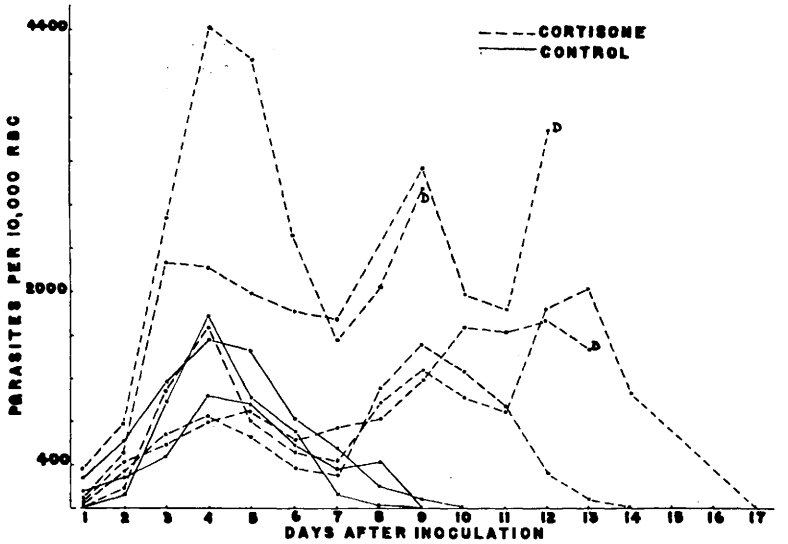

FIG. 1. Effect of cortisone on the parasitemia of pigeons infected with *P. relictum*. Cortisone dosage initiated 2 or 3 days before inoculation. D — bird died.

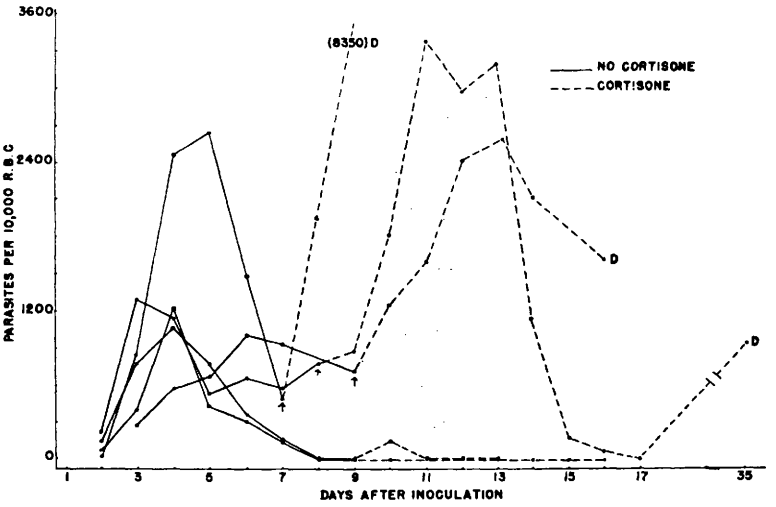

FIG. 2. Effect of beginning cortisone administration after the initial peak in parasitemia. Arrows indicate parasitemia on day of initial cortisone dosage. D — bird died.

peak to almost no parasites but continued cortisone dosage produced a third increase which resulted in death on day 35 of the infection. Cortisone had been reduced to 2 mg daily on day 26 and terminated on day 30. The infection was still on the increase at the time of death (Fig. 2).

In order to determine whether or not cortisone has a direct stimulating effect on the parasites, paludrine in 2 mg doses daily (minimal effective dose) was administered to 3 cortisone-treated birds. The infections were controlled with only an occasional parasite being found.

Daily injections of cortisone into 2 birds with latent infections failed to produce relapse. The physical condition of these birds appeared not to be affected. They remained healthy during the treatment in contrast to the cortisone treated birds with patent infections. Three birds with latent infections were given heavy superinfecting injections of para-

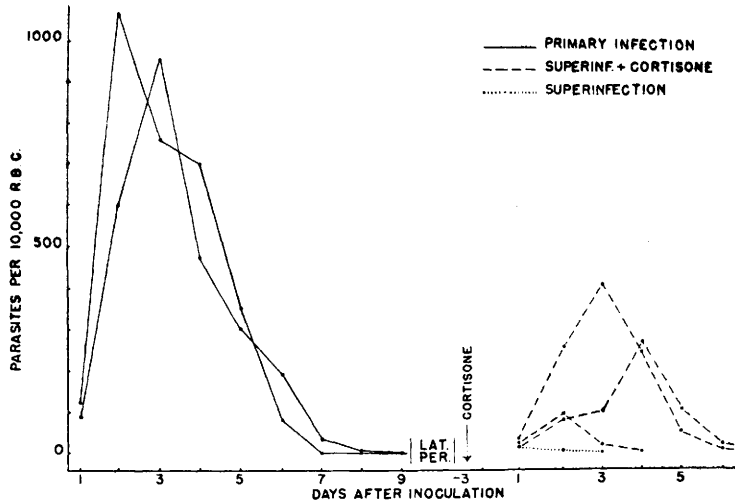

FIG. 3. Effect of cortisone on superinfections. Cortisone dosage was initiated 3 days before superinfection.

sites on the third day of cortisone therapy. The parasites increased in number attaining a peak count of approximately 30% of the initial peak infection on the 3rd or 4th day. A few parasites persisted through the 6th and 7th days (Fig. 3).

Discussion. The results of treating pigeons infected with *P. relictum* with cortisone suggests an interference with the action of the immune mechanism. The development of the immunity apparently is stopped short of full effectiveness before the parasites are reduced to the latent condition. The large number of parasites destroyed following the peak infection may act as somewhat of a blockade of the phagocytes of an impaired system giving the parasites a renewed opportunity to increase and accumulate in the blood. The effectiveness of the entire immune mechanism may be reduced, or some one or more factors of its system prevented from completing its function. Once the immunity is established and the infection assumes the latent condition cortisone apparently is without significant effect. A slight impairment in the function of the immune mechanism appears to result from the cortisone when a heavy inoculum of highly infected blood is injected. There is no indication that the increase in the parasite number in these birds is due to the action of the cortisone on the parasites. This strain of malaria in the pigeon has never been observed to relapse. With other strains which have a tendency to relapse it would appear that cortisone could possibly reduce the protective mechanism of the host to the extent that the infection would relapse. In monkeys infected with *P. cynomolgi* in which relapses are frequent Schmidt and Squires(8) have found that cortisone increases the number and intensity of relapse. Further studies are being made in an attempt to elucidate the mechanism of action of cortisone on humoral and cellular factors which may be concerned with resistance to malaria.

Summary. Cortisone has been found to increase markedly the parasitemia in pigeons infected with *P. relictum*. The increase is most apparent following the primary crisis. In this strain of malaria in which no relapse occurs normally cortisone was without effect on the latent infection.

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Pharmacologic Dissociation of Behavior and EEG "Sleep Patterns" in Dogs: Morphine, N-Allylnormorphine, and Atropine. (19345)

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Clinical experience has demonstrated that alterations in the state of consciousness are usually associated with changes in the electroencephalogram(1). In particular, characteristic changes in the electroencephalogram occur during natural sleep or after the administration of certain hypnotic drugs, notably the barbiturates(2,3). However, there is evidence that the mechanisms which subserve sleep may be dissociated from those which subserve synchronization and desynchronization of the electroencephalogram. Thus, Magoun(4) has shown that after destruction of the posterior hypothalamus in the cat, afferent sensory impulses may produce "arousal" patterns in the electroencephalogram, while the animal remains quite somnolent. The reverse has also been noted in a few instances. Thus, Andrews(5) observed that in one human subject, a single "analgetic" dose of morphine produced "sleep waves" in the EEG while the patient was wide awake. Cahen and Wikler(6) noted that in the rat, morphine produced "burst" and slow activity in the EEG, although the animal had to be restrained to permit recording. In this species, the "burst and slow wave" pattern produced by morphine was indistinguishable from that produced by pentobarbital, although in the latter case, the animal was anesthetized.

The purpose of the present report is to demonstrate that such dissociations between "sleep patterns" in the EEG and behavior can be produced regularly by administration of a number of drugs under certain experimental conditions, and to discuss the significance of these phenomena in relation to the mechanisms of sleep and the regulation of spontaneous rhythmic cortical electrical activity.

Methods. Twenty-three experiments were made on 12 mongrel adult dogs, in which permanent "mercury-platinum cup" dural electrodes had been implanted in the anterior, middle and posterior portions of the skull (corresponding roughly to the "frontal," "parietal" and "occipital" regions of the cerebral cortex) on both sides of the head symmetrically, according to the method of Wikler and Altschul(7). For recording, the animals were trained to lie quietly on a table in an electrically shielded room, without anesthesia or curarization. "Unipolar" tracings were obtained by pairing leads from each mercury-platinum electrode with a needle electrode inserted in the ipsilateral ear. Various "bipolar" tracings were also made. An eight-channel Grass ink-writing electroencephalographic apparatus was employed throughout.