

Increased Susceptibility of Rats to Plasmodium berghei after Treatment
Designed to Induce Immunologic Tolerance

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OBJECTIVE: Immunity to Plasmodium berghei infections in rats is conferred by prior experience with the infection, but little information is available concerning the antigenic substances which provoke the protective immune response. Most antigenic materials can produce immunologic tolerance when administered under appropriate conditions. The present experiment was designed to determine whether or not susceptibility to infection could be enhanced by techniques used to induce tolerance.

DESCRIPTION: Tolerance to heterologous erythrocytes can be induced by the simultaneous administration of large doses of antigen (erythrocytes) and the nitrogen mustard derivative cyclophosphamide.¹ This technique was adopted for use with P. berghei antigens by allowing parasitemia to build up, thus providing a large antigenic mass, and then administering the drug. A single experiment was performed using weanling albino rats randomly assigned to three groups (8 rats per group). Group I and II were infected intravenously with 1×10^7 P. berghei parasitized erythrocytes per 100 gm body weight and the parasitemia monitored by thin blood films. Eleven days later the animals in group I were given 27 mg of cyclophosphamide per 100 gm body weight intraperitoneally, white rats in groups II and III received saline. On days 15, 16 and 17 all rats received 10 mg sulfadiazine per 100 gm body weight. Reticulocyte counts were performed until the three groups were at comparable levels; all rats were then injected intravenously with 4×10^7 parasitized erythrocytes per 100 gm body weight, and the course of parasitemia monitored by thin blood films.

PROGRESS: Death of all but three of the group I rats (malaria plus drug treatment) between day 15 and day 22 limited the amount of data obtained. However, the results on the survivors are striking. Figure 1 summarizes the course of parasitemia in all three groups. With the exceptions cited below, each symbol represents the mean parasitemia in eight rats. It can be seen that cyclophosphamide quickly suppressed parasitemia (circles); further, sulfadiazine abolished the infection in the remaining infected rats (squares). The animals recovered quickly, the group I rats showing a reticulocytosis of 67-89% as compared with 7-26% in the group II animals on day 25. By day 36, six days prior to challenge, reticulocyte counts were 7-9% in group I, 4-6% in group II, and 5-7% in group III (normal controls). Individual reticulocyte counts in the group III animals ranged from 3-8% during the observation period. On rechallenge, little parasitemia developed in the previously uninfected rats (group III, triangles; maximum individual parasitemia, 9 parasites/100 erythrocytes) and even less in the sulfadiazine treated animals (squares; maximum individual parasitemia, 0.3 parasites/100 erythrocytes). These results were to be expected in view of the relatively low susceptibility of rats of this age (greater than 3 months) to the infection and to the well known phenomenon of acquired immunity. The three rats which had received cyclophosphamide, however, (plotted individually, circles) sustained higher parasitemias and, in fact, one animal died with an overwhelming infection.

Although no evidence is offered relevant to the specificity of the enhanced susceptibility, there was no gross evidence of generalized debility and erythropoiesis was essentially normal as judged by the pattern of reticulocyte counts. We therefore feel that the phenomenon is best explained in terms of induction of tolerance in the drug treated animals. Obviously, more work is needed to explore this hypothesis. This is the final report on this project.

SUMMARY: 1. Rats treated by a combined P. berghei malaria cyclophosphamide, regimen exhibited abnormally high susceptibility to rechallenge with P. berghei. It is suggested that immunologic tolerance to protective antigens was induced.

2. Incidental to the experiment was the observation that cyclophosphamide rapidly depresses P. berghei parasitemia in rats.

REFERENCE: Aisenberg, A.C., J, Exptl. med. 125: 833, 1967.

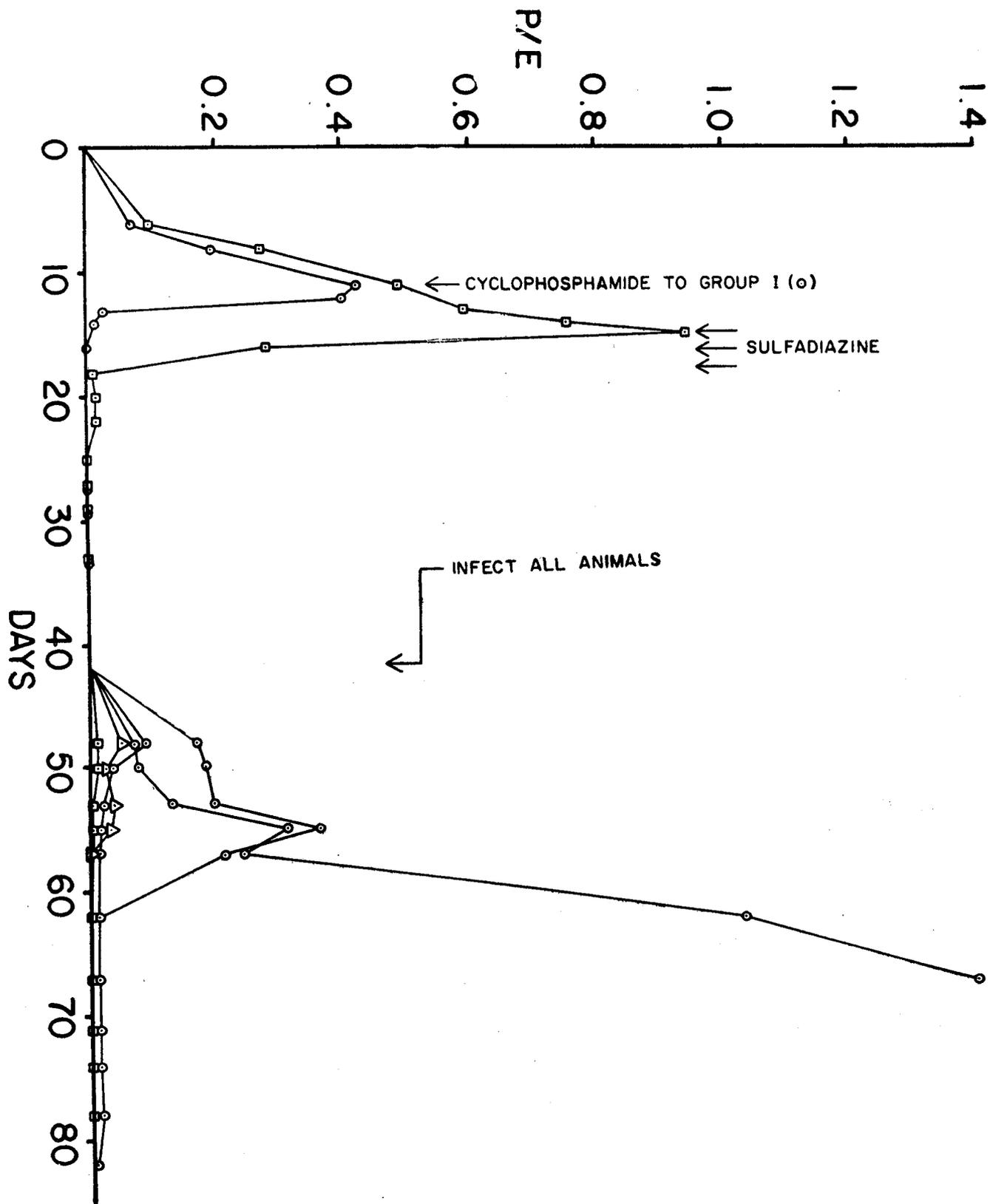


Fig 1. *Plasmodium berghei* parasitemia in rats expressed as ratio of total parasites to erythrocytes during drug treatment and rechallenge (see text for explanation).