Suppression of adjuvant arthritis by infection with a strain of the rodent malaria parasite *Plasmodium berghei*

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Hospital data (Greenwood, 1968) and a population survey (to be published) suggest that rheumatoid arthritis is an uncommon disease in Western Nigeria. Furthermore, Nigerian patients satisfying the American Rheumatism Association criteria for a diagnosis of definite or probable rheumatoid arthritis (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959) have a clinically milder disease than European patients with the condition (Greenwood, 1969) and rarely show any of the immunological changes associated with the disease (Greenwood and Herrick, 1970). The limited literature available suggests that rheumatoid arthritis is uncommon in some other parts of tropical Africa and also in New Guinea. However, rheumatoid arthritis is seen frequently in American Negroes (Engel, Roberts, and Burch, 1966), many of whom are of West African origin. It thus seems probable that environmental factors play some part in determining the infrequent occurrence of clinical cases of rheumatoid arthritis in some parts of tropical Africa. It has been suggested (Greenwood, 1968) that the effects of repeated parasitic infections from childhood might be one of these factors. In order to investigate this hypothesis we have studied the effects of malaria infection on adjuvant arthritis in the rat, a widely used animal model for human rheumatoid arthritis.

Materials and methods

Adjuvant arthritis was induced in inbred black-hooded rats, 3 to 6 months old, by an injection into the foot-pad of the right hind paw of 0.05 ml. of a suspension of steam-killed *Mycobacterium tuberculosis* in paraffin oil, made up at a concentration of 5 mg./ml. (Newbould, 1963). The extent and the severity of the ensuing arthritis in joints excluding those of the injected foot was assessed to give a numerical joint score. Changes in body weight were also followed.

Rats were infected with malaria by intraperitoneal injection of a small volume of parasitized blood containing 1×10^6 parasites obtained from an infected rat of the same strain. Control animals were injected with a similar volume of normal blood. Two strains of the rodent malaria parasite *Plasmodium berghei* were used: *P. berghei yoelii* (Landau and Killick-Kendrick, 1966) and *P. berghei Anka* (Bafort, Timperman, and Delbar, 1968).

Results

Rats infected with *P. berghei yoelii* at the time of adjuvant injection developed a milder arthritis than the controls (Fig. 1). The mean joint score at Day 26 of fifteen infected rats was significantly lower than the mean joint score of 26 controls ($P = 0.01$). The mean weight loss of the malaria infected rats (3.5 per cent. of their initial body weight) was also significantly less ($P = 0.02$) than the mean weight loss of the control animals (14.5 per cent. of their initial body weight). Infection with *P. berghei yoelii* one week before adjuvant injection had some inhibitory effect on the ensuing arthritis but infection one week after adjuvant injection was without effect (Fig. 2). *P. berghei yoelii* gave mild infections lasting for only a few days with peak parasitaemias of less than ten parasites/ 10^4 red blood cells.

In contrast to the findings with *P. berghei yoelii* it was found that infection with *P. berghei Anka* at the time of the injection of adjuvant did not prevent the subsequent development of severe arthritis (Fig. 1). *P. berghei Anka* gave rise to severe infections lasting for several weeks with peak parasitaemias of 500 to 1,000/ 10^4 red blood cells. Marked splenic hyperplasia was found in rats killed one month after infection with this parasite.

Two groups of ten rats were given intraperitoneal injections of 4×10^9 sheep erythrocytes and 0.3 ml. of a suspension of carbon particles respectively at the

FIG. 1 Effect of infection with two strains of malaria parasite on the development of adjuvant arthritis.
 ●—● 26 controls
 ○—○ 15 rats infected with *P. berghei yoelii* at the time of adjuvant injection
 △—△ 11 rats infected with *P. berghei Anka* at the time of adjuvant injection

time of the adjuvant injection. The course of the arthritis was not altered by injection of sheep erythrocytes; animals receiving carbon particles developed severer arthritis than the controls but the difference was not statistically significant.

Discussion

Induction of adjuvant arthritis in rats of a susceptible strain is highly reproducible and it thus seems probable that suppression of arthritis seen in the group of animals infected with *P. berghei yoelii* was associated with inoculation of the parasite. We have found that this parasite is also capable of suppressing the autoimmune diseases of NZB and NZB/NZW F₁ hybrid mice (Greenwood, Herrick, and Voller, 1970). The failure of *P. berghei Anka* to show a similar inhibitory effect can be accounted for in a number of possible ways. It is possible that the strain of *P. berghei yoelii* used in our experiments had become contaminated with a virus during passage. A number of rodent viruses are known to have immunosuppressive properties (Salaman, 1970) and it is possible that the suppression of the arthritis that we observed was due to a contaminating virus rather than to the malaria parasite itself. It would be of interest to know whether deliberate infection with viruses known to have immunosuppressive properties would modify the course of adjuvant arthritis. It is also possible that any inhibitory action of *P. berghei Anka* was overcome by the marked stimulatory effect of this parasite on the reticuloendothelial system. Thus it has been shown that ovalbumin inhibits the development of adjuvant arthritis when mixed with adjuvant and given as a single injection, but that it enhances the severity of the arthritis when given by repeated intramuscular injections in saline, thus stimulating the immunological system (Pearson and Wood, 1969). Our finding that stimulation of the reticulo-

FIG. 2 Effect of infection of rats at different times with *P. berghei yoelii* on the development of adjuvant arthritis.
 ●—● 6 controls
 ○—○ 5 rats infected 7 days after injection of adjuvant
 △—△ 5 rats infected at the time of injection of adjuvant
 ▲—▲ 5 rats infected one week before injection of adjuvant

endothelial system by injection of carbon particles enhanced the severity of adjuvant induced arthritis gives some support to this view.

Pearson and Wood (1969) have shown that a number of antigens can suppress the development of adjuvant arthritis when mixed with the injected adjuvant. However Currey (1970) has shown that, with the exception of tubercle bacilli, a number of antigens were without any inhibitory effect when injected intraperitoneally. Our observation that intraperitoneal injection of sheep erythrocytes was without effect is in keeping with these observations. These findings suggest that the inhibitory effect of intraperitoneal injection of *P. berghei yoelii* was not the result of a nonspecific form of antigenic inhibition.

Kapusta and Mendelson (1967, 1969) have reported that the interferon inducers statolon and a pyran copolymer have an inhibitory effect on the development of adjuvant arthritis. It has also been recently reported that production of interferon occurs during the course of rodent infections with *P. berghei* (Huang, Schultz, and Gordon, 1968). It thus seems possible that production of interferon may have played some part in the suppression of adjuvant arthritis produced by *P. berghei yoelii*.

The results of these experiments, together with our findings in NZB and NZB/NZW F₁ hybrid mice, indicate that under certain circumstances the presence of a parasitic infection can modify the course of an immunologically-mediated joint and connective tissue diseases in experimental animals. Extrapolation of these findings to considerations of human disease must be made with great caution but they do give some support to the hypothesis that a background of repeated parasitic infection may have some influence on the course and development of human connective tissue diseases.

Summary

Infection of rats with the rodent malaria parasite *P. berghei yoelii* at the time of an injection of adjuvant reduced the incidence and severity of the ensuing adjuvant arthritis. This strain of malaria parasite produced only a mild infection in rats. Infection with a more virulent strain of parasite, *P. berghei Anka*, which produced marked stimulation of the reticuloendothelial system, was without any inhibitory effect.

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RÉSUMÉ

La suppression de l'arthrite causée par l'adjuvant par l'infection avec une souche du parasite paludéen des rongeurs, *Plasmodium berghei*

L'infection des rats avec la parasite paludéen des rongeurs *P. berghei yoelii* au moment de l'injection de l'adjuvant avait réduit l'incidence et la gravité de l'arthrite qui avait lieu après l'adjuvant. Cette souche de parasite paludéen avait seulement produit une infection bénigne des rats. L'infection par une souche de parasite plus virulent, *P. Berghei Anka*, qui avait produit une stimulation marquée du système réticulo-endothélial, était sans aucun effet inhibiteur.

SUMARIO

Supresión de la artritis adyuvante con una variedad del parásito palúdico de los roedores *Plasmodium berghei*

La infección de ratas con el parásito plaúdico de roedores *P. berghei yoelii* al tiempo de aplicar una inyección de adyuvante redujo la incidencia y severidad de la artritis adyuvante consiguiente. Esta variedad de parásito del paludismo produjo tan solo una leve infección en ratas. La infección con una variedad más virulenta del parásito, la *P. berghei Anka*, que produjo un notable estímulo en el sistema reticuloendotelial, no tuvo ningún efecto inhibitorio.