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On the Influence of High Altitudes on the Course of Infection of Chicken Malaria (*P. gallinaceum*).*

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(Received April 14th, 1954.)

It has been known for a long time that the influence of high altitudes on malaria patients may give considerable relief during the course of infection.

As *v. Neergard* observed in 1920, cases of chronic tertian malaria showed a rapid decline of parasitemia and clinical symptoms as well as a marked improvement of the general state of health. *v. Neergard* concludes from this evidence that the influence of high altitudes must be an indirect one through an increase of the host resistance.

Anderson, v. Deschwanden and others made similar observations and found, with the disappearance of parasites from the blood, simultaneously an increase of the colour index up to 1.0-1.3. They therefore put the question whether hyperhemoglobinemia or other climatically induced changes of the blood have a direct action on the malaria parasites.

v. Deschwanden 1947 believes that the influence of high altitudes is mainly due to an increased activity of the reticulo-endothelial cells induced by meteorotropic factors that may provoke an intensified liberation of the merozoites into the blood stream, where the parasites are more accessible to therapeutics. At the same time he considers the possibility that it may rather be an improvement of the defence mechanism of the reticulo-endothelial system.

In 1948 *Garnham* was able to show that the nonexistence of malaria at high altitudes is due only to the temperature which is either too low for the breeding of the transmitting mosquitoes or for the development of the sporogonic cycle of the plasmodia concerned. The plasmodia, on the other hand, do not lose their virulence for man, if, under special local conditions, the other requirements for the plasmodial cycle are fulfilled. This suggests the hypothesis that the influence of high altitudes is caused by a reaction of the vertebrate host itself.

The problem of the influence of high altitudes is now being studied experimentally by a team of workers of the Swiss Tropical Institute. Animal experiments at different altitudes (Basle, Jungfrau Joch Station), recently combined with similar experiments in a low pressure chamber, should give us some detailed insight into the behaviour of a malaria parasite (*P. gallinaceum*) and its respective host (*Gallus gallus* L.).

In 1953 *Herbig* already reported that the infection in young chicks with *P. gallinaceum* can be moderated by keeping the birds at Jungfrau Joch Station (JJS). The development of the exoerythrocytic stages is delayed and there may even be a postponement of parasitemia. Cases of complete climatical adaptation of the erythropoietic system of the host before inoculation show no manifestations at all. *Herbig* draws the conclusion that this is due to an improvement of the unspecific host defence mechanism; but the question remains

* Our researches have been carried out partly at Jungfrau Joch Station. We wish to express our gratitude to Professor A. von Muralt, President of the Hochalpine Forschungsstation Jungfrau Joch, for allowing us to work in the laboratories of Jungfrau Joch Station.

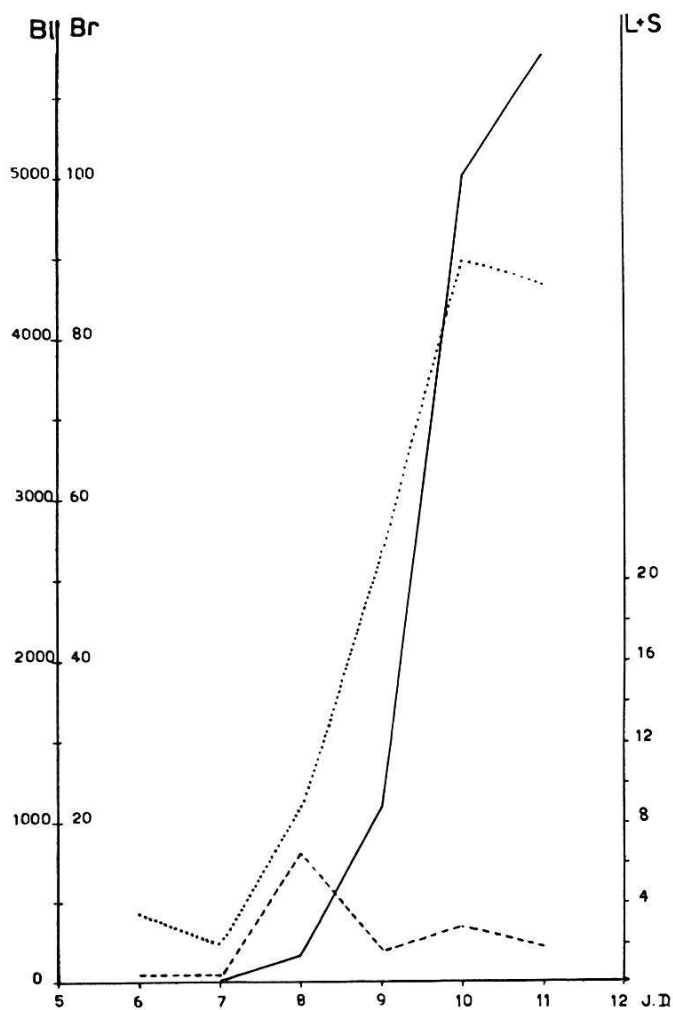


Fig. 1. *P. gallinaceum*: course of infection in chicks, 8 days old. Herbig 1951.

———— = Blood, - - - - = Liver, - - - = Spleen, = Brain.

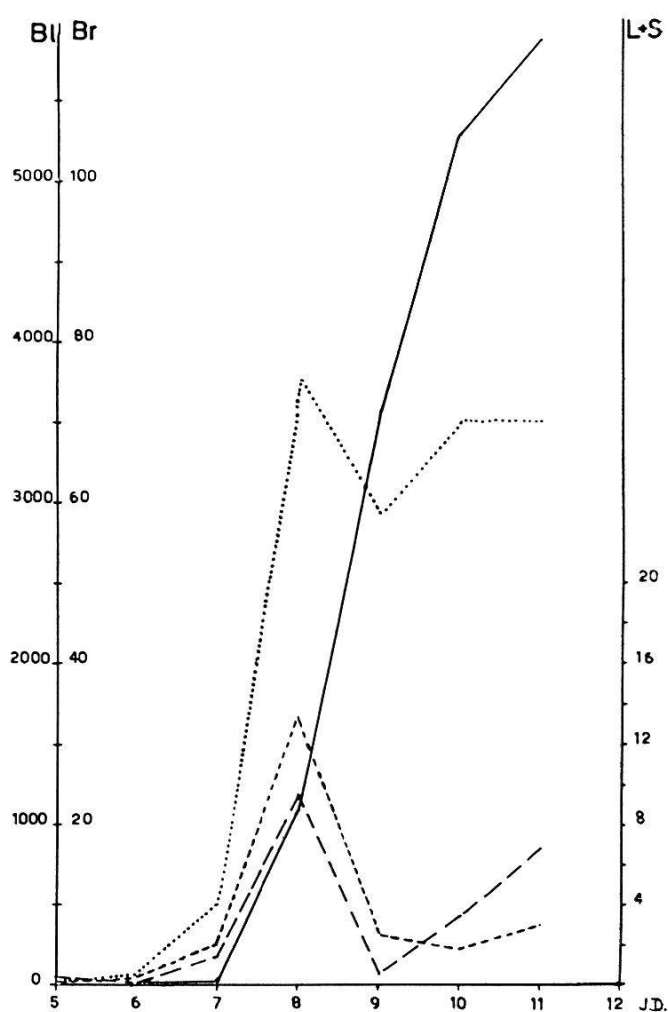


Fig. 2. *P. gallinaceum*: course of infection in chicks, 8 days old. 1953/4.

open whether a direct influence by the climatically induced changes might occur or not.

Our own investigations deal with acute infections of young chicks by sporozoite inoculation with *P. gallinaceum*. The strain of *P. gallinaceum*—already used by Herbig—has been maintained at the Swiss Tropical Institute for many years by cyclical passages through *Aedes aegypti* and *Gallus gallus* L. The sporozoite inoculation, the preparation of tissue smears and touches as well as the counting of these preparations are carried out as described by Herbig in 1953.

Identical series of experiments were made in Basle (280 m.), Jungfrau Joch Station (3457 m.) and in a specially constructed low pressure chamber with the same atmospheric pressure as JJS (490 mm. Hg).

To be able to compare our recent results with the data obtained by Herbig, we have to consider the fact that our strain of *P. gallinaceum*, the same as previously used by Herbig, has increased its virulence during the last 2 or 3 years (see diagrams in Figs. 1 and 2). This alteration occurred despite the fact that the strain has frequently been passaged through mosquitoes and that the strains of *Aedes aegypti* and *Gallus gallus* L. as well as the techniques used for inoculation have been exactly the same for many years. This suggests a certain amount of adaptation of the intermediate and definitive host—or may

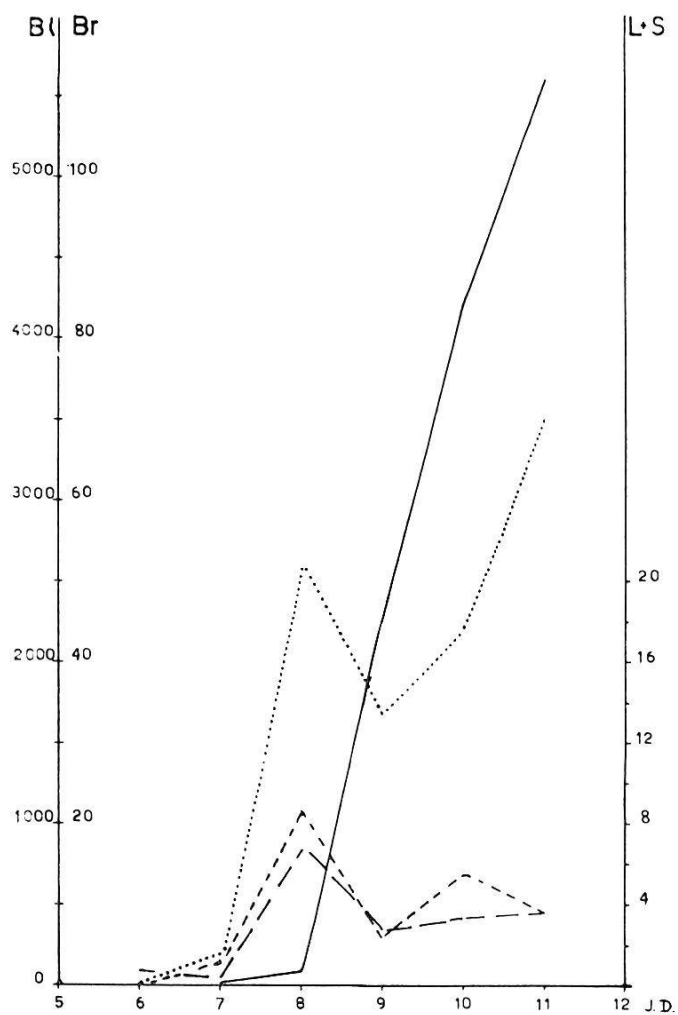


Fig. 3

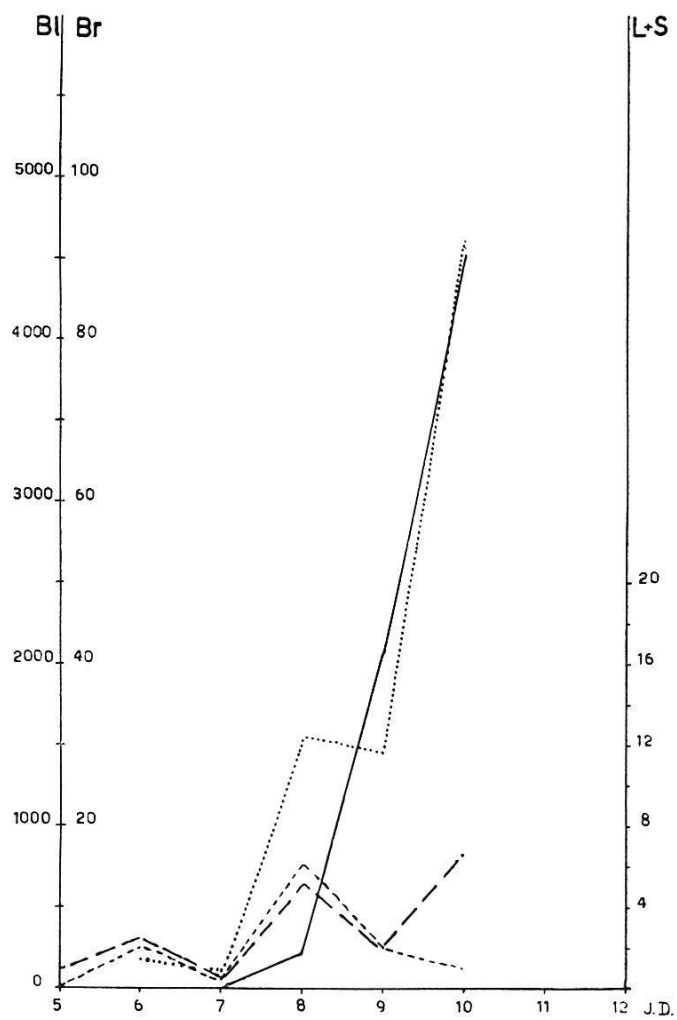


Fig. 4

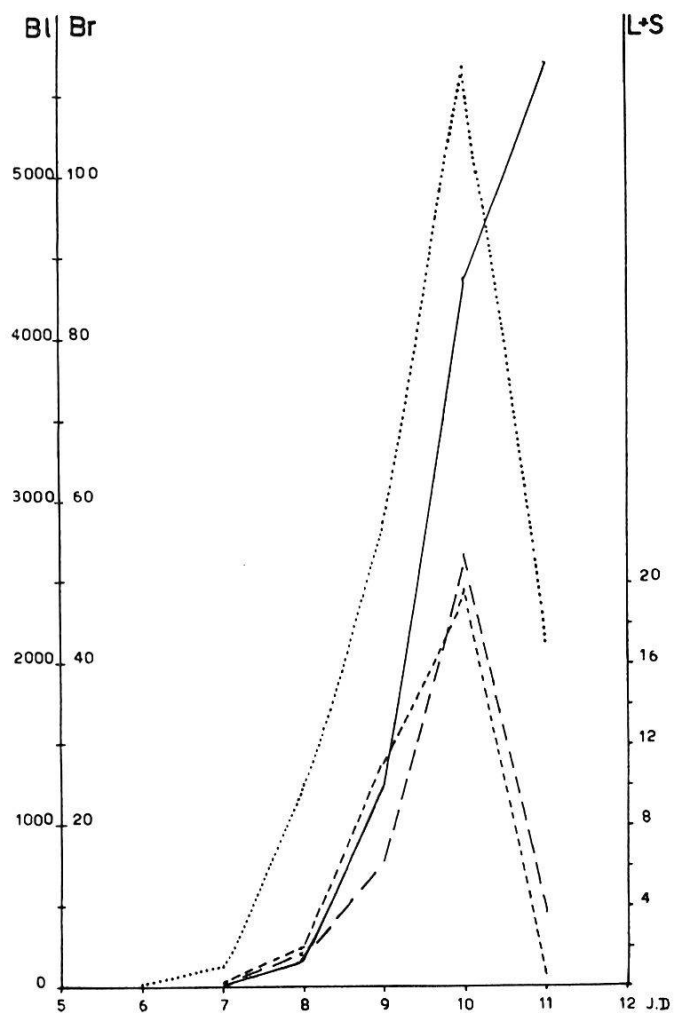


Fig. 5

Fig. 3. *P. gallinaceum*: course of infection in chicks, 30 days old. Basle (280 m.).

Fig. 4. *P. gallinaceum*: course of infection in chicks, 30 days old. Low pressure chamber at 490 mm. Hg corresponding JJS.

Fig. 5. *P. gallinaceum*: course of infection in chicks, 30 days old. JJS (3457 m.).

be one of them—to *P. gallinaceum* through the course of time, which manifests itself by the observed increase of its virulence.

We shall now discuss the relevant results of our recent studies. In the following paragraph we are first comparing the data of *Herbig* (Fig. 1) with our own (Fig. 2).

To facilitate comparison of the results, the data concerning the various organs (blood, brain, liver, spleen) are drawn on a different scale. The figures can be found under the headings Bl (blood), Br (brain), L (liver) and S (spleen) on the y-axes of the diagram. The values on graph 2 represent the mean values of two series of experiments which showed corresponding results. One rather interesting fact had to be neglected, namely that in the case of 3 among 15 chicks of one of this series the beginning of the infection was again advanced by one day.

Without considering the last mentioned fact, the curves on figs. 1 and 2 have a similar form but with a marked increase of virulence: the mean values for the first day of parasitemia in the 1951-series was the 8.0th day of infection (ID), whereas in the 1953/54-series the first parasites in the blood were found on the 6.6th ID. Another feature is the much steeper "flooding effect"¹ in 1953/54. The flattening out of the blood-schizont curve begins on the 9th day in 1953/54, in 1951 not before the 10th day of infection. The slope representing the schizonts found in the brain capillaries is also much steeper. The maximum is reached 2 days earlier than in 1951. The time relationship of the appearance of pre-erythrocytic stages in the liver remains the same, but the number of schizonts found is doubled. Spontaneous death occurs on the 10/11th ID in 1951, in 1953/54 on the 9/10th ID.

Diagrams in Figs. 3, 4, and 5 represent the main results obtained in 1953/54 in Basle, in our low pressure chamber (also in Basle) and at Jungfrau Joch Station. Comparing diagram 3 and 4 we scarcely find any difference between the course of a normal control infection in Basle and a corresponding series in the low pressure chamber. The first parasites in contact tissue preparations of liver and spleen were found on the 6th day in both cases, reached their maximum on the 8th ID, followed by a decline on the 9th ID and by an irregular increase up to the 10/11th ID. The comparatively small quantitative discrepancies on the 8th ID have to be neglected, as the data for the low pressure chamber were rather scarce and the ones for the control experiments in Basle for this day were obtained during the winter season, when the chicks are not quite as resistant as in summer. Liver, spleen and brain reach their maximum simultaneously with the "flooding effect" in the peripheral blood. The course of parasitemia is the same in both experiments.

In the low pressure chamber as well as at high altitudes the partial oxygen pressure declines with the atmospheric pressure, causing an increase of the red blood cells and even more so of the hemoglobin content which results of course in a marked rise of the colour index of the host. As the course of infection is the same for control experiments in Basle and the low pressure chamber, we must conclude that the decrease of the oxygen tension is not the factor responsible for the influence of high altitudes on the malaria parasites. It follows that the climatically induced changes of the blood system have no direct influence on the plasmodia.

The diagram in Fig. 5 shows a similar progress of the parasitemia in the experiments carried out on Jungfrau Joch Station. The beginning of the parasitemia is only slightly delayed, which confirms the hypothesis that the

¹ "Flooding effect" see *Huff, C. G. & Coulston, F.* (1944). — J. Inf. Dis. 75, No. 3.

erythrocytic adaptation itself is irrelevant for the course of infection. The case of the organs investigated is quite different: the first exoerythrocytic stages in contact tissue preparations can be revealed only one day later than normal. The high amount of schizonts is very striking, we found nearly twice as many as in the control experiments. The peak is reached on the 10th ID, on the 11th day we find a marked decrease.

The experiments and results discussed above show that no increase of the defence mechanism of the reticulo-endothelial system can be demonstrated during the later stages of the exoerythrocytic cycle in liver, spleen, and brain capillaries. On the other hand, the primary delaying of the development of the sporozoites and/or the first generation or generations of the preerythrocytic schizonts can be explained only if we assume that at high altitudes the unspecific host resistance becomes markedly improved and that the RES is activated. Probably the macrophages are enabled to deal more effectively with the phagocytosed parasites than at ordinary altitudes. It remains to be investigated—by using different methods and concentrating on the first days of infection—if the sporozoites, or rather the cryptozoites or metacryptozoites, are more readily open to attack. We hope to deal with this problem more thoroughly at a later date.

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