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The Influence of Malaria Chills on the Trypanocidal Action of the Serum.

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During their experiments on the natural immunity of man against the trypanosomes, which are pathogenic to animals, Laveran and Mesnil[1] discovered the trypanocidal action of the human serum. The serum does not destroy the trypanosomes *in vitro*, but it protects mice for from 1 to 2 weeks against an infection, which otherwise would cause death within a few days. It delays, therefore, only the development of the trypanosomes in the mouse. A complete protection is rare.

The trypanocidal substances are scanty in or absent from the serum of the newborn (Rosenthal and Nossen,[2] Platau,[3] Leichtentritt,[4] Neumark and Pogorschelsky[5]). In healthy children they appear after the 11th to 15th week and persist throughout life, although individual differences as to their strength exist. According to Rosenthal and Kleeman[6] the trypanocidal substances are increased in the later part of pregnancy. Under certain abnormal conditions they disappear more or less completely. Leichtentritt and Zielaskowsky[7] found a marked decrease in Barlow's disease, Grunwald and Leichtentritt[8] in xerophthalmia and infantile scurvy. Much attention has been given to the fact that diffuse diseases of the liver cause a very distinct reduction of the trypanocidal power of the serum (Ehrlich and Wechsberg,[9] Rosenthal and Krueger,[10] Mignoli,[11] Peutz,[12] Platau,[3] Munter[13]). Since the accumulation of the

bile pigment and the bile acids in the blood has nothing to do with this reduction, the liver is believed to be the source of the trypanocidal substances. Several authors tried to use the trypanocidal titer of the serum as a liver function test.

Plaut[14] studied the trypanocidal action of the serum in various mental diseases and observed that highly active sera were very common among patients with general paralysis. Neumark and Pogorschelsky[5] found an early appearance of the substance under discussion in congenital syphilis.

Whether infections affect the trypanocidal titer of the serum has not yet been definitely determined. Leichtentritt[4] did not see any influence especially in mild infections of early childhood. Mignoli[11] saw no changes in septicemia, but a diminution in cases of severe tuberculosis. Neumark and Pogorschelsky[5] observed a decrease in infectious diseases with fever. Barlowi[15] described a low titer during infections and a restoration to normal during convalescence.

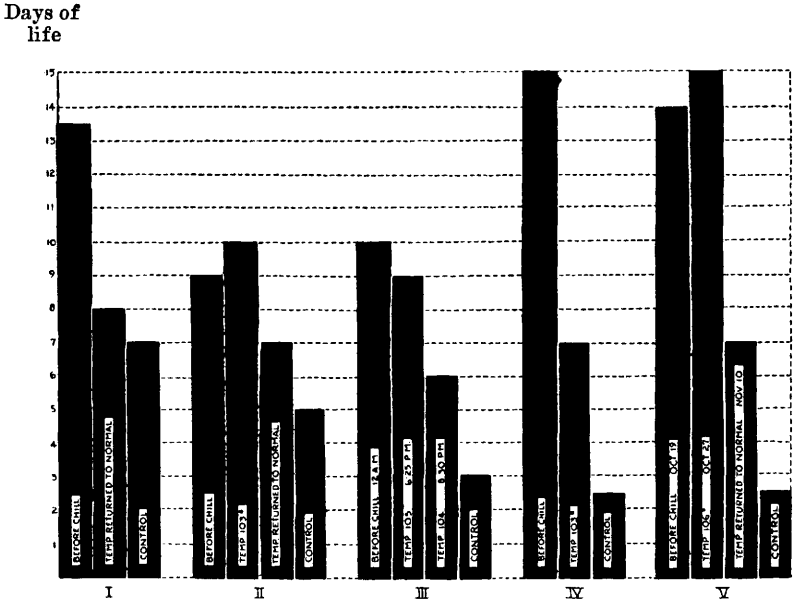
The use of malaria treatment in general paralysis offered the possibility of following more closely the effect of the malaria chills on trypanocidy of the serum.

A strain of *Trypanosoma equiperdum* obtained through the courtesy of Dr. Taliaferro was used. The intraperitoneal injection of 0.1 cc. of a suspension containing about one trypanosome in a high power field killed mice, 17 to 20 gm. in weight in from 2 to 5 days. The sera were used within 24 hours after they were drawn and were injected subcutaneously. In preliminary experiments with sera of normal individuals, and of patients suffering from various diseases except those of the liver, it was found that the average length of protection produced by 0.1 or 0.2 cc. serum was 11 days. Seven per cent of the mice were completely protected. In the beginning 0.05, 0.1, 0.15 and 0.2 cc. of serum were injected. In these experiments paradoxical results were sometimes obtained, in so far as smaller doses protected more than larger ones. Similar observations were made by previous investigators. There exist apparently individual differences as to the susceptibility of mice to the trypanosome infection. These differences are revealed only by the simultaneous injection of the protecting human serum. Sometimes trypanosomes appeared in the serum mice at the same time as they did in the untreated controls. But they disappeared after a few days, to come back and to increase rapidly in number until the animal died.

To overcome these complications only two doses of serum, namely 0.1 and 0.2, were finally given. Six mice were used in each

series. The blood was tested daily for trypanosomes. The average length of life after the infection of all the mice of each series was used as trypanocidal titer.

The frequent occurrence of highly protecting sera in cases of general paralysis mentioned by Plaut[14] was also seen in our experiments. Especially complete protection of mice was more common than in the other cases, namely 20 per cent against 7 per cent.



In case I blood was drawn immediately before and after the third chill. The highest temperature during this chill was 105[6]. A very mild infection was used as shown by the long survival of the controls.

In case II the samples were taken 2 hours before the 8th chill, 4 hours after the temperature had reached the peak which was 106, and 2 hours after the temperature had returned to normal.

In case III the blood samples were obtained during the 5th chill. The highest temperature in this chill was reached at 5:30 p. m. and was 105[4].

In case IV blood was drawn 2 hours before the 6th chill and 6 hours after the peak of the temperature rise (105[6]).

In case V the first sample was taken a few hours before the first chill started. The second sample was obtained at the peak of the 4th chill, and the last sample was secured the morning after the 16th chill.

These experiments show that the malaria chills cause a marked reduction of the trypanocidal titer of the serum. At the height of the fever there may be a slight increase of the titer, to be followed soon by a sharp drop. This drop is most pronounced shortly after the temperature has reached the normal level and is transient. The normal power of the serum is restored before the next chill starts. It makes no difference during which chill the blood samples are taken, since in each chill the same changes take place.

We do not know whether the liver cells during the malaria chills are injured. If the liver is really the source of the trypanocidal substances, their disappearance after the chills may point towards such a possibility. Other immune substances like the opsonins increase with each malaria chill (Hoff and Silberstein[16]).

Conclusions: During the malaria chills the trypanocidal action of the serum is distinctly diminished. This decrease is most pronounced shortly after the temperature has returned to normal. Before the next chill starts the normal titer is restored.

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