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COMPARATIVE STUDY OF ATEBRIN AND QUININE IN INFECTION INTENTIONALLY INDUCED WITH P. FALCIPARUM.

by

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In a paper on our earlier research* we confirmed the findings of other authors regarding the resistance of the sporozoite to anti-malarial drugs and we showed, on the strength of experimental evidence, that the efficacy of a prophylactic method in the case of persons who have undergone only one experimental infection depends on the length of the period of treatment with effective therapeutic doses: treatment for at least ten days after infection was necessary. It appeared to us - in the conditions under which our observations were made - that the drugs had no effective action until they began to affect the schizogonic forms.

In the course of our present investigations we have endeavoured to amplify these data by making the drugs act at different stages of evolution (?) of the sporozoite and the schizogonic forms.

In order to eliminate certain factors of variation inherent in infection by mosquito bite, we employed intravenous inoculation with a suspension of sporozoites.

Our patients therefore received only one inoculation (in a large dose) of sporozoites intravenously.

The treatment lasted for 5 days.

The date on which the drug to be studied - atebrin or quinine hydrochloride - was first administered varied in the different groups as follows**: one day prior to infection;

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* Archives Roumaines de Pathol. expérim. et de Microbiologie, 1932. V. 5. page 204.

** Transactions of the Royal Society of Tropical Medicine, V. 31, No. 2235, 241.

3rd, 5th and 7th day of incubation. This, despite its imperfections, was the only method whereby we could make the drugs take effect during the first stages of evolution of the parasite in the organism.

a) Single intravenous inoculation with sporozoites of P. falciparum.

Administration of atebrin or quinine hydrochloride one day prior to infection and during the four following days.

Controls.

Of eight paralytics inoculated but not treated, seven showed clinical symptoms of the disease after an incubation period varying from 8 to 13 days. Only one proved immune. This latter case was kept under observation for 15 months.

Quinine:

Seven paralytics treated with quinine hydrochloride - one gramme x 5 days - all showed clinical symptoms of the disease; the incubation period varied from 7 to 14 days.

Atebrin:

Of 22 patients treated with atebrin - 0.30 x 5 days - only one showed clinical symptoms of the disease after 28 days' incubation.

In the case of 5 patients parasitic infection alone developed three months after inoculation.

Sixteen patients were not infected. The observation period was as follows:

Over 8 months: 3; less than 8 months and as a rule over 2 months: 12; less than 6 weeks: 1.

The sporozoite and the first transitional (?) forms evolving towards trophozoites appear to be more susceptible to atebrin; this product did not, however, prevent infection in 6 out of 22 cases. The incubation period of positive cases was prolonged. Quinine administered under these conditions had no effect on the sporozoites; the incubation period was the same as in the case of the untreated controls.

b) Single intravenous inoculation with sporozoites. Drugs administered from the third day of incubation for five days.

Controls:

Three untreated paralytics showed clinical symptoms of the disease after an incubation period of 15 and 10 days, respectively; the parasites appeared on the 6th and 7th day of incubation.

Quinine:

Of three patients treated two showed clinical symptoms on the 18th and 22nd day of incubation; the third developed parasitic infection only, after 37 days of incubation.

Atebrin:

Of three patients treated with atebrin, two developed a parasitic infection after incubation periods of 20 and 104 days respectively; the third was not infected.

After an observation period of six months we are able to state that atebrin, administered from the third day of incubation, affects the parasite, the virulence of which it reduces to some extent: the incubation period was prolonged; the first stage of afebrile infection revealed itself only by the presence of the parasite in the blood, followed by its spontaneous disappearance.

During this period no gametocytes were found in the blood.

c) Cases infected under the same conditions.* Early treatment starting from the fifth day of incubation.

Quinine:

Of three patients treated with quinine hydrochloride - one gramme x 5 days - two showed clinical symptoms of the disease after an incubation period of 9 and 12 days, respectively. One of these cases was of a severe nature. The third case developed a parasitic infection three months later.

Atebrin:

The three paralytics infected and treated under the same conditions developed mild clinical symptoms after incubation periods of 10 and 30 days, respectively.

The action of atebrin on the first generations of trophozoites appears to be more marked than that of quinine; it is reflected in a prolonged incubation period and in very mild clinical symptoms. All the cases recovered spontaneously without any further treatment course.

d) Cases infected under the same conditions. Drugs administered from the seventh day of incubation.

Controls:

Two untreated paralytics developed the disease after an incubation period varying from 8 to 10 days. In one of these controls severe clinical symptoms appeared.

Quinine:

Of three paralytics treated, one showed mild clinical symptoms after a long incubation period; the fever and parasites disappeared spontaneously. No parasites were present in the other two cases during the three months they were kept under observation.

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* The controls of Group b), inoculated under the same conditions, may be compared with Group c).

Atebrin:

Two patients treated developed a parasitic infection with a slight sub-febrile condition; the third showed very mild clinical symptoms. The incubation period varied from 37 to 36 days. All three recovered spontaneously.

It is difficult in this group to distinguish between the action of quinine and that of atebrin. At this stage of infection treatment does not appear to hamper the immunisation of the patient, which shows itself in a tendency towards spontaneous recovery. The appearance of gametocytes was exceptional in these cases.

The drugs appear to have a strongly marked effect on the young forms of trophozoites.

CONCLUSIONS.

These investigations show that the "debilitating" action of atebrin, administered in therapeutic doses, on the sporozoite and its first transitional (?) forms (Group I) is sufficiently marked to deserve careful attention. If infection is not in every case prevented by atebrin the clinical symptoms or parasitic infection are very mild. Quinine, on the other hand, has no effect during this first stage of infection. The action of atebrin on the virulence of the parasite, which is greater than that of quinine, is obvious in the second and third group of patients (drug administered from the third and fifth day of incubation). It is only in the fourth group of patients, when the drugs (from the seventh day of incubation) have a marked effect on the schizogonic forms that the differences between the action of the two schizontocidal substances disappear.

These results provide an experimental basis for numerous prophylactic observations in this sphere and, we think, confirm the fact that this method does not impede the immunisation process.
