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STUDY OF EXPERIMENTAL MALARIA AND ELEVATED BODY TEMPERATURE IN A CONDITION SIMILAR TO BUERGER S DISEASE*

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Hyperthermice therapy has been quite frequently used in the past for treatment of progressive paralysis, and that of adnexitis; occasionally it is still administered, yet its mode of action is not completely understood. Thus it has so far remained undecided wheither artifical malaria induced by inoculation with *Plasmodium vivax* — the best known therapeutic procedure of this kind, introduced by Wagner-Jauregg in 1917 acts unspecifically, or involves some specific effect. More recently hyperthermic therapy has been used, with variable success, in the treatment of Bürger s disease (Thromboangiitis obliterans), a disturbance of peripheral circulation leading to obliteration of blood vessels. We have attempted this treatment in several instances and tried to assess its relative merits in comparison with other therapeutic measures. Following a procedure reported by Corelli (2) we induced malaria in our patients, and we obtained fairencouraging results even in difficult cases[3] (to be published elswhere).

On the other hand we were interested in the mechanism by which malaria might influence the pathological process in Bürger s disease. In order to study this question we had to find a suitable method, since neither the ethiopathology of Bürger s disease is completely clarified, nor have attempts to produce an analogous condition in animals been successful. It is possible, however, to produce ischemic gangrene in the rat s tail by inflictiong severe damage to the blood circulation in this organ, and this condition is similar to the final symptoms of Bürger s disease. We therefore adopted this method to produce Bürger-like conditions and to study the effects of hyperthermic treatment in this model.

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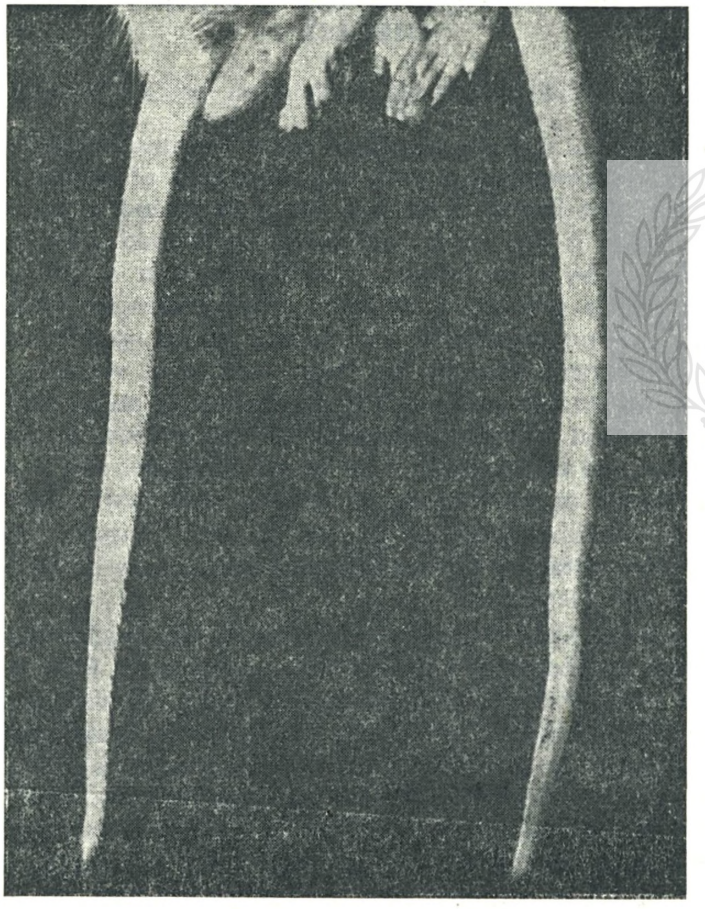
METHODS

Adult rats, both sexes, weighing 150—200 g were placed on a pellet diet (»Kalinovica« brand pellets) with unlimited access to water. Gangrene was induced in the animal s tails according to Ratschow and Strecker (5) by subcutaneous administration of a saline solution of ergotamine and adrenaline close at the tail root. During a seven-day period the animals repeatedly received doses of 0,5 mg ergotamine bitartrate and 5 micrograms adrenaline bitartrate. Injections were made on the first and second, and fourth and fith days, and finally on the seventh day. Controls received saline alone in the same manner. A few days after this treatment cyanosis appeared in the animal s tails, and was followed in due course by necrosis.

Artificial malaria was induced by inoculation with Plasmodium berghei,* an organism known to cause malaria in small rodents (6).



Left control rat Right treated rat with PV. Treatment from the first day of induced changes in the fail.

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The inoculation of the rats was carried out by transferring a few drops of blood from a previously infected mouse. Incidentally, rats usually survived the infection, and only a few animals died about 12 do 20 days after inoculation, whereas mice invariably succumbed the 5—6 th days after inoculation. Parasitemia in rats following inoculation was low, only about 3 per cent of the erythrocytes were affected, and it vanished completely after 20 days.

An unspecific elevation of body temperature was carried out by intravenous injection of pertussis vaccine according to Mewxould (4). In these experiments only male rats were used. Animals weighing 200 g were injected daily with 0,2 ml pertussis vaccine (Immunologic Institute, Zagreb) containing 2×10^{10} germs per ml, after having been kept at 25°C ambient temperature for six hrs prior to injection. Two separate groups were run. The first received vaccine starting simultaneously with the ergotamine-adrenaline treatment, the vaccine injections extending over a period of sixteen days, the second group started receiving vaccine on the day ending the ergotamine-adrenaline, and was injected on each of the following eight days.

RESULTS

Inoculation of rats with *P. berghei* did not elicit any rise in body temperature. Animals in this group did not show any alleviation of symptoms as compared to untreated controls. The symptoms observed ranged from cyanosis to fragmentation of the tail. In no animal was the severity of symptoms less than in the control group (Table 1).

Table 1.

RESULTS OF TREATMENT OF PERIPHERAL CIRCULATORY DAMAGE IN THE RAT S TAIL

Number of animals in group	Kind of treatment	Observed pathological changes*	Remarks
12	Inoculation with P. berghei	****	Inoculation carried out the same day as first administration of ergotamine-adrenaline
12	Inoculation with P. berghei	****	Inoculation carried out eight days after first administration of ergotamine-adrenaline
18	Intravenous injection of pertussis vaccine	*	Treatment started the same day as first administration of ergotamine-adrenaline
12	Intravenous injection of pertussis vaccine	**	Treatment started eight days after first administration of egotamine-adrenaline
18	Controls no treatment	****	—

* The serverity of symptomes was assessed for the whole group:
**** severe
** slight
* very slight

In view of these results another method for elevation of body temperature had to be tried. We succeeded in this by applying intravenous injections of pertussis vaccine. Table 2 shows that body temperature in these animals was above normal for at least one hour after injection. In this series of experiments there was a distinctly observable protective effect, viz. all animals exhibited symptoms less severe than untreated controls. The protective effect was especially obvious in the group starting treatment the same day as circulatory damage was being induced for the first time (Table 2).

Table 2.

BODY TEMPERATURE CHANGES* IN RATS TREATED WITH PERTUSSIS VACCINE

	Temperature			
	Before injection	After injection		
Day of treatment		1 hr	2 hr	3 hr
1.	38.1	39.1	38.6	38.3
2.	38.0	38.8	38.3	38.0
3.	37.6	38.9	38.2	37.8
4.	37.7	38.8	38.2	38.1

* Each figure represents the average from twelve animals.

DISCUSSION

It appears from these experiments that protection against the consequences of peripheral blood circulatory damage in the rat s tail is strictly correlated with hyperthermic response. Agents incapable to raise body temperature do not exert any protective action. The effectiveness of *P. vivax* in human therapy is, therefore, very probably due to its temperature-raising capacity, in that elevated body temperature somehow lessens the final symptoms of Bürger s disease. There still might be some additional specific action exerted by *P. vivax* taking part in the overall therapeutic effect, but there is no way to decide on this point from results obtained in the present experiments.

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UTICAJ EKSPERIMENTALNE MALARIJE I POVIŠENE TJELESNE TEMPERATURE PRI STANJIMA SLIČNIM BIRGEROVOJ BOLESTI

KRATAK SADRŽAJ

Gangrenozne promjene na repu štakora izazvane pomoću ergotamina i adrenalina poboljašavaju se pod uticajem pertussis vakcine, koja

izaziva povišenje temperature. Infekcija takvih štakora malarijom ne poboljšava cirkulatorne promjene na repu. To je vjerovatno u vezi s tim što malarija štakora (plasmodium berghei) ne izaziva povišenu temperaturu kod tih životinja.

Diskutira se o značenju ovih eksperimenata za terapiju Bürgerove bolesti pomoću malarije.

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