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**MALARIA AT HUMAITA COUNTY, AMAZONAS STATE, BRAZIL  
XVII — IMMUNE RESPONSE IN PATIENTS WITH PLASMODIUM FALCIPARUM  
ACCORDING TO GAMETOCYTES**

Domingos Alves MEIRA (1), Paulo Roberto CURI (2), Jussara MARCONDES (3), Elinda Satie MATSUOKA (4), Marina A. FAVRIN (4), Albert Boutros EL-KHOORY (5) and Norma Gerusa da Silva MOTTA (6)

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**S U M M A R Y**

In August 1983 the Authors studied 36 patients with *Plasmodium falciparum* malaria and 14 normal individuals born in Humaita region who had never had malaria, had no spleen enlargement and had negative parasitemia as well as passive hemagglutination. Medical histories were obtained and complete physical examination were performed in all of them just as blood tests, parasite density and lymphocyte typing. The lymphocytes were separated and then frozen in liquid nitrogen for later typing by rosette formation. The patients were divided in two groups according to the presence (13 patients) or absence (23 patients) of gametocytes before treatment. Severe malaria was predominant in the group without gametocytes. The results showed a decrease in the T-cell numbers in *Plasmodium falciparum* acute malaria patients both with or without gametocytes before the treatment, while B-cell numbers were normal only in the patients with gametocytes. These observations as like as those previously reported by the Authors, permit to associate the presence of gametocytes in peripheral blood and normal number of B-cells in patients with mild *Plasmodium falciparum* malaria.

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**I N T R O D U C T I O N**

The association between the amount of circulating lymphocytes and the presence of gametocytes in *Plasmodium falciparum* malaria patients<sup>11,12</sup> has suggested the need to investigate the eventual relations among such events and the immune response of the patients.

In this way in previous study the Authors<sup>11</sup> had showed that: 1) there is an association

among gametocytes, trophozoites, severity of clinical picture and amount of circulating lymphocytes in patients with *Plasmodium falciparum* malaria; 2) *Plasmodium falciparum* gametocytes probably come to the peripheral blood when the host's conditions become adverse to the asexual blood stage parasite survival; 3) when they appear in the peripheral blood during the disease, *Plasmodium falcipa-*

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Research accomplished in the School of Medicine — Botucatu — UNESP, with support of National Council of Scientific and Technological Development — CNPq (Proc. 40.3705/82) and presented in "The Fourth Japan-Brazil Symposium on Science and Technology" in Botucatu, São Paulo, Brazil, 1984.

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- (6) Doctor of the Department of Microbiology and Immunology of Basic Institute of Medical and Agricultural Biology — UNESP

rum gametocytes probably are an important index for the evaluation of prognosis and may be used to indicate the therapeutic schedule.

In posterior study the Authors<sup>12</sup> reported peripheral levels of leucocytes and lymphocytes in patients with *Plasmodium falciparum* malaria showing lower results in the patients without circulating gametocytes before the treatment and values next to normal in those with circulating gametocytes just as in prior investigations<sup>11</sup>.

CLYDE<sup>5</sup> and REILEY & BARRETT-JR<sup>14</sup> studied the behaviour of leucocytes in inhabitants of endemic regions and in patients with malaria and did not observe any relation between severity of illness and circulating leucocytes.

Otherwise, WILLIAMS et al.<sup>21</sup> studying various severe acute human infections noted that poor prognosis was often associated with depression in total numbers of T-cells as well as of T lymphocyte subpopulations as measured with OKT<sub>4</sub> (helper-inducer).

WYLER & OPPENHEIM<sup>22</sup> also suggested the importance of lymphocyte and its relation with immune response in malaria.

The studies of lymphocyte function in malaria patients with low blood stage asexual parasites<sup>10</sup> show that blastogenic responsiveness of peripheral blood mononuclear cells after stimulation with mitogens on cell surface antigen remains intact.

These findings seem to be in connection with the prior observations of the Authors<sup>11,12</sup> suggesting that as often as the asexual parasitemia is low, sexual blood stage parasites are present in a high proportion and the clinical picture is mild. In the same way, TROYE-BLOMBERG et al.<sup>20</sup> reported no response in lymphocyte function in about 50% of all the acutely ill *Plasmodium falciparum* malaria patients. In some of these, the tests turned into positives two weeks later, when the asexual parasitemia was already absent.

DRUILHE et al.<sup>8</sup> concluded that mild human malaria infection does not modify the cell-dependent immune responses markedly, contrasting with suppression of delayed cutaneous reactions in severe *Plasmodium falciparum* malaria.

The purpose of this investigation was to demonstrate the behaviour of leucocytes, total lymphocytes and T and B cells in *Plasmodium falciparum* malaria patients before and after the treatment, according to gametocyte presence and its eventual association with immune response.

## MATERIAL AND METHODS

In August 1983 the Authors studied 36 patients with *Plasmodium falciparum* malaria and 14 normal individuals born in Humaita region who had never had malaria, with no spleen enlargement and negative both parasitemia and passive hemagglutination. Medical histories were obtained and complete physical examinations were performed in all of them as well as blood tests, parasite density<sup>11</sup> and lymphocyte typing. The lymphocytes were separated and then frozen in liquid nitrogen<sup>9</sup> for later typing by rosette formation<sup>13</sup>.

The patients were treated with clindamycin, 20 mg/kg/day alone or in association with chloroquine for 3 to 5 days. None of them received primaquine.

The degree of parasitemia was determined daily during the treatment<sup>11</sup> but blood tests and lymphocyte typing were performed only before the treatment and at the end of it.

The patients were divided in two groups according to the presence (13 patients) or absence (23 patients) of gametocytes before treatment. Severe malaria was predominant in the group without gametocytes.

The results were analysed by "F" statistical method and paired and unpaired "t" test<sup>17</sup>.

## RESULTS

Table I shows that there was not significant difference between leucocyte and lymphocyte average in patients with gametocytes before the treatment and normal individuals. However, there was a significant difference between the leucocyte and lymphocyte averages in the patients without gametocytes and in those with gametocytes before the treatment as well as normal individuals. The leucocyte and the lymphocyte average were higher when the gametocytes were found in peripheral blood.

TABLE I

Comparison of leucocyte and lymphocyte average between normal individuals and *Plasmodium falciparum* malaria patients before the treatment according to the presence of gametocytes before the treatment

Groups	No. of individuals	Leucocyte average/mm <sup>3</sup>	Statistical analysis	Significance level	Comments	Lymphocyte average/mm <sup>3</sup>	Statistical analysis	Significance level	Comments
G <sub>1</sub>	14	5679	F = 13.21*	P < 0.001	(G <sub>1</sub> = G <sub>2</sub> ) > G <sub>3</sub>	2095	F = 14.17*	p < 0.001	(G <sub>1</sub> = G <sub>2</sub> ) > G <sub>3</sub>
G <sub>2</sub>	13	5100				1708			
G <sub>3</sub>	21	3671				1101			

G<sub>1</sub> = Normal individuals      G<sub>2</sub> = Patients with gametocytes before the treatment      G<sub>3</sub> = Patients without gametocytes before the treatment

TABLE II

Comparison of leucocyte and lymphocyte averages between normal individuals and *Plasmodium falciparum* malaria patients after treatment according to the presence of gametocytes before treatment

Groups	No. of individuals	Leucocyte average/mm <sup>3</sup>	Statistical analysis	Significance level	Comments	Lymphocyte average/mm <sup>3</sup>	Statistical analysis	Significance level	Comments
G <sub>1</sub>	14	5679	F = 4.79*	0.01 < p < 0.05	G <sub>1</sub> > G <sub>3</sub>	2095	F = 0.59	p > 0.50	The groups don't differ
G <sub>2</sub>	11	4873			G <sub>2</sub> is intermediate	2013			
G <sub>3</sub>	23	4352				1836			

G<sub>1</sub> = Normal individuals      G<sub>2</sub> = Patients with gametocytes before the treatment      G<sub>3</sub> = Patients without gametocytes before the treatment

MEIRA, D. A.; CURI, P. R.; MARCONDES, J.; MATSUOKA, E. S.; FAVRIN, M. A.; EL-KHOURY, A. B. & MOTTA, N. G. da S. — Malaria at Humaita County, Amazonas State, Brazil. XVII — Immune response in patients with *Plasmodium falciparum* according to gametocytes. Rev. Inst. Med. trop. São Paulo 27:229-237, 1985.

Table II shows that leucocyte average in *Plasmodium falciparum* malaria patients after the treatment, who had had no gametocytes before the treatment, was significantly different from leucocyte average in normal population.

Table III shows that there was significant difference between T lymphocyte average in patients with or without gametocytes before treatment and normal individuals. It also denotes that, when B-cell average was considered, the difference between normal individuals and patients with gametocytes before the treatment was not significant. However, B lymphocyte amount in patients without gametocytes before the treatment had a tendency to low levels.

In Table IV it can be noted that T and B lymphocyte averages in *Plasmodium falciparum* malaria patients after the treatment did not differ from those found in normal individuals.

When lymphocyte and leucocyte averages obtained before and after treatment were compared in patients with gametocytes before the treatment, the values did not differ significantly, as it is shown in Table V. However, patients who had no gametocytes before the treatment showed leucocyte and lymphocyte averages before and after the treatment differing significantly, since values obtained after the treatment were higher.

Table VI shows that B-cell average in patients who had gametocytes before the treatment was not significantly different before and after the treatment. In other hand, *Plasmodium falciparum* malaria patients with gametocytes before the treatment, T cell averages obtained before and after treatment differed significantly. This also was the pattern followed by T and B cell averages in patients without gametocytes before the treatment. It is important to notice that in all these cases the amount of T and B lymphocytes was higher after the treatment.

Figure 1 shows the different behaviour of leucocytes, total lymphocytes and T and B lymphocytes in normal individuals and in patients before and after treatment, according to the presence of gametocytes before the treatment. The leucocytes, total lymphocytes and T and B cell amounts were very low before treatment, in patients who had no gametocytes. It also shows that T lymphocytes were very low before the treatment even in patients with gametocytes. However, B lymphocyte amount was higher before treatment in patients with gametocytes. Finally, after treatment there was a trend to normal amount of leucocytes, total lymphocytes and T and B cells in all patients.

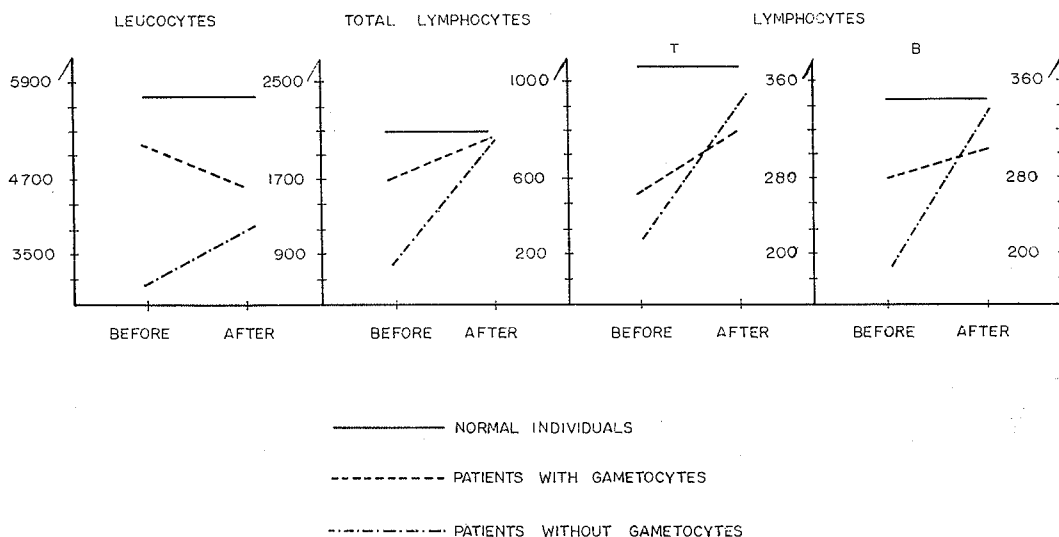


Fig. 1 — Leucocyte, total lymphocyte and T and B lymphocyte follow-up in normal individuals and in *Plasmodium falciparum* malaria patients, before and after treatment, according to the presence of gametocytes before the treatment.



T A B L E III

Comparison of T and B lymphocyte averages between normal individuals and *Plasmodium falciparum* malaria patients before treatment, according to the presence of gametocytes before treatment

Groups	No. of individuals	T lymphocyte average/mm <sup>3</sup>	Statistical analysis	Significance level	Comments	B lymphocyte average/mm <sup>3</sup>	Statistical analysis	Significance level	Comments
G <sub>1</sub>	14	1064	F = 14.88*	p < 0.001	G <sub>1</sub> > (G <sub>2</sub> = G <sub>3</sub> )	346	f = 2.58	p > 0.05	[(G <sub>1</sub> = G <sub>2</sub> ) > G <sub>3</sub> ] "Trend"
G <sub>2</sub>	13	529				284			
G <sub>3</sub>	20	357				220			

G<sub>1</sub> = Normal individuals      G<sub>2</sub> = Patients with gametocytes before the treatment      G<sub>3</sub> = Patients without gametocytes before the treatment

T A B L E IV

Comparison of T and B lymphocyte averages between normal individuals and *Plasmodium falciparum* malaria patients after the treatment, according to the presence of gametocytes before the treatment

Groups	No. of individuals	T lymphocyte average/mm <sup>3</sup>	Statistical analysis	Significance level	Comments	B lymphocyte average/mm <sup>3</sup>	Statistical analysis	Significance level	Comments
G <sub>1</sub>	14	1034	F = 1.51	p > 0.10	The groups don't differ	346	F = 0.10	p > 0.80	The groups don't differ
G <sub>2</sub>	10	786				306			
G <sub>3</sub>	20	869				332			

G<sub>1</sub> = Normal individuals      G<sub>2</sub> = Patients with gametocytes before the treatment      G<sub>3</sub> = Patients without gametocytes before treatment

MEIRA, D. A.; CUBI, P. R.; MARCONDES, J.; MATSUOKA, E. S.; FAVRIN, M. A.; EL-KHOURY, A. B. & MOTTA, N. G. da S. — Malaria at Humaita County, Amazonas State, Brazil XVII — Immune response in patients with *Plasmodium falciparum* according to gametocytes. Rev. Inst. Med. trop. São Paulo 21:229-237, 1985.

T A B L E V

Comparison of leucocyte and lymphocyte averages of *Plasmodium falciparum* malaria patients before and after treatment, according to the presence of gametocytes before the treatment

Groups	No. of individuals	Leucocyte average/mm <sup>3</sup>		Statistical analysis	Significance level	Comments	Lymphocyte average/mm <sup>3</sup>		Statistical analysis	Significance level	Comments
		Before	after				Before	after			
G <sub>2</sub>	11	5136	4873	t = 0.44	p > 0.50	Before = After	1724	2013	t = 1.03	p > 0.30	Before = After
G <sub>3</sub>	23	3578	4365	t = 1.75	0.05 < p < 0.10	Before ≅ After	1015	1836	t = 6.30*	p < 0.001	Before < After

G<sub>2</sub> = Patients with gametocytes before the treatment

G<sub>3</sub> = Patients without gametocytes before the treatment

T A B L E VI

Comparison of T and B lymphocyte averages of *Plasmodium falciparum* malaria patients before and after the treatment, according to the presence of gametocytes before the treatment

Groups	No. of individuals	T lymphocyte average/mm <sup>3</sup>		Statistical analysis	Significance level	Comments	B lymphocyte average/mm <sup>3</sup>		Statistical analysis	Significance level	Comments
		Before	after				Before	after			
G <sub>2</sub>	10	490	786	t = 2.41*	0.02 < p < 0.05	Before < After	299	306	t = 0.52	p > 0.50	Before = After
G <sub>3</sub>	17	357	812	t = 5.34*	p < 0.01	Before < After	203	325	t = 2.27*	0.02 < p < 0.05	Before < After

G<sub>2</sub> = Patients with gametocytes before the treatment

G<sub>3</sub> = Patients without gametocytes before the treatment