Am. J. Trop. Med. Hyg., 75(6), 2006, pp. 1195–1199

IMPORTED *PLASMODIUM FALCIPARUM* MALARIA: ARE PATIENTS ORIGINATING FROM DISEASE-ENDEMIC AREAS LESS LIKELY TO DEVELOP SEVERE DISEASE? A PROSPECTIVE, OBSERVATIONAL STUDY

RICHARD M. JENNINGS, J. BRIAN DE SOUZA, JIM E. TODD, MARGARET ARMSTRONG, KATIE L. FLANAGAN, ELEANOR M. RILEY, AND JUSTIN F. DOHERTY*

Hospital for Tropical Diseases, London, United Kingdom; London School of Hygiene and Tropical Medicine, London, United Kingdom

Abstract. Just more than 2,000 cases of *Plasmodium falciparum* malaria are reported in the United Kingdom annually, with a mortality rate of approximately 1%. Some studies suggest that patients with malaria who originate from disease-endemic areas are less likely to develop severe disease; such patients are often treated at home. We have prospectively examined 99 patients with imported *P. falciparum* malaria and categorized them according to severity as defined by World Health Organization criteria. There was no significant difference between those who developed severe disease and those who did not in terms of their ethnicity, residence in a malaria-endemic area, or history of previous episodes of malaria. To assume a patient has clinical immunity to malaria simply because they originate from or have lived for a long time in a malaria-endemic area may be inappropriate and unsafe.

INTRODUCTION

Plasmodium falciparum malaria accounts for 1–2 million deaths each year, and more than 95% of these occur among young African children.[1] However, with increasing travel, malaria is becoming a growing problem in temperate areas. More than 2,000 cases of *P. falciparum* malaria are reported in the United Kingdom each year, with a mortality rate of approximately 1%;[2] approximately 10% of these cases are managed at the Hospital for Tropical Diseases in London. Management of *P. falciparum* malaria varies widely in temperate countries, and there has been considerable debate recently about whether every patient with malaria should be admitted to hospital.[3] Patients with malaria may develop serious complications;[1] assessing the likelihood of development of severe disease should be an important part of their initial clinical management. People in malaria-endemic areas who experience repeated malaria infections develop a degree of immunity that confers some protection from clinical disease.[4] Some patients with imported malaria may be expected to have some degree of immunity, and others will be travelers who have never previously been infected. It is often assumed that people with imported malaria who have lived in malaria-endemic regions may be less likely to develop complications. Data from some previous studies have supported this assumption.[5–7] We have conducted a prospective study examining the clinical, parasitologic, and immunologic characteristics of *P. falciparum* infection in patients coming to the Hospital for Tropical Diseases in London to determine whether those factors theoretically associated with immunity, namely residence in a malaria-endemic area, previous infection with malaria, and ethnicity, are associated with protection against severe disease.

MATERIALS AND METHODS

Subjects. Patients coming to the Hospital for Tropical Diseases between July 2000 and August 2002 with an episode of confirmed *P. falciparum* malaria were invited to participate. The study protocol was reviewed and approved by the Ethics Committee of University College London Hospitals and signed informed consent was obtained from each subject.

Study design. All subjects were admitted to hospital and treated according to standard protocols, using oral or intravenous quinine followed by a second anti-malarial agent (usually sulfadoxine/pyrimethamine). Demographic and clinical data were recorded at admission and daily thereafter onto a standard pro-forma. Twenty milliliters of blood was taken before any anti-malarial treatment was given for routine hematologic (full blood count) and biochemical (urea and electrolytes and liver function tests) analyses, and repeated as clinically indicated. Sera were stored from this admission sample for immunoglobulin and cytokine assays. Malaria films were taken daily, stained with Field's stain, and examined at 1,000× magnification with the density of asexual infection expressed as a percentage.

Outcome measures. There is no generally accepted definition of what constitutes immunity to malaria, nor is there any laboratory marker that consistently predicts protection from disease.[4] As a result, we made no attempt to classify these subjects as semi-immune or naïve. Rather, we divided the study population into two groups, mild versus severe disease, using modified World Health Organization criteria[1] and then looked for any differences between the groups in terms of ethnicity, residence in a malaria-endemic area, previous history of malaria, or immunologic parameters that might be expected to be associated with less severe disease.

Subjects were classified as having severe disease if any of the following were present at any time: asexual parasitemia > 2%, schizonts on the blood film, bilirubin > 20 IU/L, creatinine >130 mmol/L, hemoglobin < 9 g/dL, platelet count < 50×10^9/L, or disease of sufficient severity to warrant admission to the intensive therapy unit (ITU). The decision to admit to the ITU was taken by attending physicians who were not otherwise involved in the study. Patients with severe disease had an average of 3.8 markers of severity, and their median parasitemia was 3.9%. All patients were monitored for hypoglycemia while receiving quinine but hypoglycemia *per se* was not taken as a marker of severe disease. Blood gas and lactate measurements were not routinely made.

* Address correspondence to Justin F. Doherty, Hospital for Tropical Diseases, Mortimer Market, Capper Street, London WC1E 6AU, United Kingdom. E-mail: tom.doherty@uclh.org

Axillary temperature was measured at admission and every four hours thereafter. The fever experienced by each subject during their admission was expressed as a cumulative sum around a value of 37.0°C.[8] As an example, a temperature of 39°C scored +2 and a second reading of 36.5°C scored -0.5; the final figure therefore represents the summation of each temperature reading taken during the admission. Duration of fever was taken as the number of days from the first recorded fever to the beginning of the first 24-hour period without fever (axillary temperature ≤ 37.5°C) irrespective of acetaminophen usage.

Immunologic parameters. Pro-inflammatory and anti-inflammatory cytokines (tumor necrosis factor-α [TNF-α], interleukin-10 [IL-10], interferon-γ [IFN-γ], and transforming growth factor-β [TGF-β]) and antibodies against *P. falciparum* schizont extracts (Pfse) were measured by an enzyme-linked immunosorbent assay (ELISA). *Plasmodium falciparum* schizonts obtained from Percoll purification were used for preparing an antigen to detect antibody to *P. falciparum* by standard capture ELISA as previously described.[9] Plasma concentrations of TNF-α and TGF-β were determined by DuoSet ELISA (R&D Systems, Abingdon, United Kingdom) according to manufacturers' instructions. Monoclonal antibody pairs (Pharmingen-BD, Oxford, United Kingdom) were used for determining the levels of IL-10 and IFN-γ as previously described.[10] Plasma samples were tested in duplicate at 1:12 dilution for TGF-β and at a dilution of 1:5 or 1:10 in all other cytokine assays; cytokine concentrations were then calculated per milliliter of undiluted plasma. All samples were tested in duplicate and assays were repeated at least once on different aliquots of each sample.

Statistical methods. The frequency and percentages for categorical variables were shown and differences between the mild and severe groups were tested using the chi-square distribution. For continuous variables, means and standard deviations were shown for normally distributed data, and for non-normal data (cytokine concentrations and duration data) geometric means and ranges were presented. For the comparison of continuous data across mild and severe patients, the T-test was used (on the log transformed data if necessary). With 25 patients with severe disease and 75 patients with mild disease, the study had 80% power to detect as significant an odds ratio of 4.0 for common categorical exposures, a 70% increase in IL-10 and IFN-γ, a 40% increase in TNF-α, and a 30% increase in TGF-β.

RESULTS

Ninety-nine patients with an average age of 39 years agreed to take part in the study. None were pregnant. Thirty-seven had taken anti-malarial prophylaxis and 19 had taken some anti-malarial treatment before coming to the hospital. The time between leaving a malaria-endemic area and coming to hospital averaged 13 days. Of the 99 patients, all but four acquired their infections in sub-Saharan Africa, and 53 of these infections were acquired in either Nigeria or Ghana. The other four patients acquired their infections in Cambodia, India, Pakistan, and Vanuatu. Twenty-five patients had severe disease as defined above. Of these 25, 24 acquired their infection in sub-Saharan Africa and one in India. Patients with severe disease each had on average 3.8 markers of severity and a median parasitemia of 3.9% (Table 1). Twenty-one had an asexual parasitemia >2%, 17 had schizonts on the blood film, 24 had hyperbilirubinemia, 6 had an elevated creatinine levels (4 of whom required dialysis), 7 had a hemo-

TABLE 1
Characteristics of patients classified as having severe malaria*

Ethnic origin	Schizonts	Maximal parasitemia, %	Bilirubin > 20 μmol/L	Creatinine > 130 μmol/L	Hemoglobin < 9 g/dL	Platelet count < 50×10^9/L	ITU	Dialysis	Exchange transfused	Died
Caucasian	Yes	25	Yes	No	Yes	Yes	Yes	No	Yes	No
Caribbean	Yes	2.2	Yes	No	No	Yes	No	No	No	No
Caucasian	Yes	7.3	Yes	No	No	Yes	No	No	No	No
Caucasian	Yes	1.7	Yes	No	No	No	No	No	No	No
Caucasian	No	2	No	No	No	No	No	No	No	No
Caucasian	No	8.4	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Asian†	Yes	2.1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Asian†	Yes	0.5	Yes	Yes	No	Yes	Yes	No	Yes	No
Caucasian	Yes	3.9	Yes	Yes	No	Yes	No	No	No	No
African	Yes	2.9	Yes	No	Yes	No	No	No	No	No
African	Yes	25	Yes	No	No	No	No	No	No	No
African‡	Yes	0.01	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
African	No	0.3	Yes	No	No	No	No	No	No	No
African§	Yes	25	Yes	Yes	Yes	No	Yes	Yes	No	No
African	No	2	Yes	No	Yes	No	No	No	No	No
African	Yes	3.9	Yes	No	No	Yes	No	No	No	No
African	Yes	2.5	Yes	No	No	No	No	No	No	No
African	Yes	17	Yes	No	No	Yes	No	No	No	No
African	Yes	3.2	Yes	No	No	No	No	No	No	No
African	No	4.5	Yes	No	No	Yes	No	No	No	No
African	No	4.8	Yes	No	No	Yes	No	No	No	No
African	Yes	18	Yes	No	No	Yes	No	No	No	No
African	No	3	Yes	No	No	No	No	No	No	No
Caucasian	No	30	Yes	No	No	No	No	No	No	No
African	Yes	4.2	Yes	No	No	No	No	No	No	No

* ITU = intensive therapy unit.
† Asian patients from the Indian subcontinent.
‡ Patient with Glasgow coma score < 15 and requiring ventilatory support.
§ Patient required ventilatory support.

globin concentration < 9 g/dL, and 13 had a platelet count < 50×10^9/L. Six required admission to the ITU, four of whom had a history of previous exposure to malaria.

One patient, a 21-year-old Nigerian woman, died despite admission to the ITU. She was born in Nigeria and lived there until the age of 13. She made her first trip back to a malaria-endemic area (Lagos) for eight years, and four days after returning was admitted to hospital with cerebral malaria, renal failure, and acute respiratory distress syndrome (ARDS).

As expected, the group with severe disease had a higher maximal temperature, were febrile for longer, and required a longer hospital stay, but there were few other differences between the two groups. There was no difference between those with severe disease compared with those with mild disease in terms of ethnicity, residence in a malaria-endemic area, or previous history of malaria (as shown either by the stated history of previous malaria or by the level of IgG antibody to Pfse). These results are shown in Table 2. A higher percentage of patients with mild disease reported taking antimalarial prophylaxis, and this difference was even greater among those who reported taking prophylaxis in the last 28 days, although not reaching statistical significance ($P = 0.10$). Although IgG, IgM and IFN-γ levels tended to be lower in severe cases than mild cases, these differences were not statistically significant. However, as expected, TNF-α concentrations were significantly higher in severe cases than mild cases; there was also a tendency (although not statistically significant) for IL-10 concentrations to be higher among severe cases. Conversely, there was a significant inverse relationship between the IgG antibody concentration to Pfse and highest recorded parasitemia (correlation = -0.24, $P = 0.023$) and highest recorded temperature (correlation = -0.26, $P = 0.016$). This suggested that individuals with previous exposure to malaria (i.e., those with anti-malarial antibodies) did have some degree of anti-malarial immunity. Furthermore, IL-10 concentrations were significantly correlated with highest recorded parasitemia (n = 41, correlation = 0.30, $P = 0.05$) and temperature (n = 39, correlation = 0.36, $P = 0.025$), and TNF-α concentrations were significantly associated with highest recorded parasitemia (n = 90, correlation = 0.49, $P < 0.001$) but not temperature (n = 85, correlation = 0.04, $P = 0.75$).

DISCUSSION

The purpose of this study was to prospectively compare patients with severe imported *P. falciparum* malaria with patients with mild disease in terms of their residential history, ethnic origin, and history of previous malaria, factors assumed to be associated with at least some degree of immunity to the disease. We anticipated that adult patients who were born and usually resident in sub-Saharan Africa (where almost all the malaria infections in this study were acquired) might have fewer parasites, less of an inflammatory response, and less severe disease than individuals who had not previously been exposed to malaria. However, there were no differences between the two groups in terms of any of these factors.

It is commonly believed that immunity to malaria is rapidly lost once an individual moves away from a malaria-endemic area, leaving previously immune individuals at high risk of severe disease should they become re-infected.[4] The one death in this study, that of a Nigerian woman who was re-exposed to malaria after eight years in Europe, could be seen as an example of this. However, systematic surveys of malaria in immigrants and during epidemics where malaria was rein-

TABLE 2
Demographic, clinical, and immunologic characteristics of patients with *Plasmodium falciparum* malaria, United Kingdom*

Characteristic		Malaria		
		Mild n = 74	Severe n = 25	Statistical value
Sex	Male	50 (68%)	18 (72%)	$\chi^2 = 0.17$, $P = 0.7$
	Female	24 (32%)	7 (28%)	
Age (years)	Mean (SD)	39.8 (13.2)	37.9 (13.3)	t = 0.6, $P = 0.6$
Ethnic background	White	21 (28%)	7 (28%)	$\chi^2_{df=2} = 3.42$, $P = 0.18$
	Black African	51 (69%)	15 (60%)	
	Other	2 (3%)	3 (12%)	
Born in sub-Saharan Africa		50 (68%)	14 (56%)	$\chi^2 = 1.09$, $P = 0.3$
Lived in malaria-endemic area		56 (76%)	20 (80%)	$\chi^2 = 0.19$, $P = 0.7$
Reported previous malaria		44 (59%)	11 (44%)	$\chi^2 = 1.81$, $P = 0.2$
Took malaria prophylaxis		30 (41%)	7 (28%)	$\chi^2 = 1.26$, $P = 0.3$
Duration of symptoms before admission (days)	Geometric mean† (range)	4.29 (1–60)	3.08 (1–10)	T = 1.63, $P = 0.11$
Temperature at admission (°C)	Mean (SD)	38.0 (1.16)	38.2 (1.19)	T = 0.69, $P = 0.5$
Data from hospital stay				
Length of admission (days)	Geometric mean (range)†	2.69 (0–8)	5.18 (2–20)	T = 5.97, $P < 0.001$
Highest temperature (°C)	Mean (SD)	38.4 (1.03)	38.9 (1.17)	T = 1.93, $P = 0.06$
Cumulative sum	Mean (SD)	6.05 (5.29) n = 67	9.09 (5.26) n = 23	T = 2.15, $P = 0.03$
IgG (arbitrary units)	Mean (SD)	1.15 (0.73)	0.91 (0.57)	T = 1.51, $P = 0.13$
IgM (arbitrary units)	Mean (SD)	0.75 (0.63)	0.53 (0.30)	T = 1.59, $P = 0.11$
IFN-γ (pg/ml)	Geometric mean (range)	n = 62, 4.39 (0.05–1244)	n = 20, 3.44 (0.3–37.1)	T = 0.53, $P = 0.6$
IL 10 (pg/ml)	Geometric mean (range)	n = 31, 33.37 (0.9–284)	n = 10, 77.21 (34.2–331)	T = 1.96, $P = 0.06$
TNF-α (pg/ml)	Geometric mean (range)	n = 67, 29.56 (3.7–299)	n = 23, 58.3 (10.1–356)	T = 3.61, $P < 0.001$
TGF-β (pg/ml)	Geometric mean (range)	(n = 67), 4.86 (1.24–13.5)	(n = 23) 4.89 (1.67–19.8)	T = 0.01, $P = 0.95$

* df = degrees of freedom; IFN-γ = inferferon-γ; IL = interleukin; TNF-α = tumor necrosis factor-α; TGF-β = transforming growth factor-β.
† Differences in geometric means tested on the natural log of the data.

troduced after many years of effective control showed that previously immune individuals, although they do become sick, have significantly lower parasite densities and a lower risk of severe and fatal outcomes than comparable, previously naive individuals.[11] Thus, our observation that a significant proportion of visitors and recent immigrants to the United Kingdom from malaria-endemic countries develop severe malaria suggests that they have (or had) little or no pre-existing functional immunity to malaria.

There is no marker that has reliably been shown to correlate with immunity to malaria, although there are inherent resistance traits such as sickle-cell trait or other hemoglobinopathies[4] that are known to be associated with protection against severe disease. Precisely what constitutes immunity to malaria is still much debated, but however it is defined, it is mediated in part by pro-inflammatory and anti-inflammatory cytokines, and there is evidence that these cytokines have a prognostic role.[12] In accordance with previous findings,[13–16] high serum concentrations of TNF-α and IL-10 were associated with higher parasite counts and more severe symptoms. However, although anti-malarial antibody levels (which can be viewed as a marker for previous exposure to malaria)[17] were inversely correlated with maximal parasitemia, there was no clear indication that antibody levels differed between those with mild disease and those with severe disease. This is consistent with the notion that malarial symptoms are in part immune-mediated and that individuals with considerable previous exposure to malaria can still have severe disease.[18]

The prevalence of severe disease among malaria-exposed adults in this study (26% of those who had ever lived in a malaria-endemic area and 22% of those born in sub-Saharan Africa had severe rather than mild malaria) might be considered rather high, given that most non-pregnant adults who become infected with malaria in malaria-endemic areas develop only trivial clinical disease and many people in malaria-endemic areas have parasites in the blood without developing any symptoms. However, the patients included in the present study may not be representative of adult malaria infections in general. Our patients are self-selected by virtue of the fact that they have symptoms of sufficient severity to seek medical care; it is possible that some cases of imported malaria in immune individuals go unrecognized and unreported because they have few clinical symptoms. Furthermore, African and Asian patients who come to London with malaria will, by definition, have access to sufficient resources to have traveled to Europe and, by inference, may have previously lived in more affluent areas and may not have had as much exposure to the parasite as their less-advantaged compatriots. Both of these considerations support the notion that most malaria patients, wherever they originate from, who come to hospitals in non-endemic countries are likely to have little effective anti-malarial immunity.

This study raises some important points for the management of imported *P. falciparum* malaria. First, malaria is not a trivial disease. Six percent of our patients required admission to the ITU and one patient died after developing cerebral malaria complicated by ARDS and renal failure. Second and more unexpectedly, severe disease was no less common among patients who might be assumed to have a degree of protective immunity than among previously malaria-naive patients. Many physicians managing cases of *P. falciparum* malaria in temperate areas may assume that complications are less likely to arise if the patient has lived in a malaria-endemic region, as a result of some degree of acquired immunity. Our study suggests that this assumption may not be valid.

Received May 24, 2006. Accepted for publication August 2, 2006.

Acknowledgments: We are grateful to the following clinicians for recruiting patients to this study: Kazeem Aderogba, Jim Buckley, Alex Bunn, Anna Checkley, Rod Escombe, Matthew Hamill, Damien Hatton, Damien Mack, Fabiola Martin, Elinor Moore, Baz Nadjm, Richard Stümpfle, Sonali Sudarshi, and Jenny Whetham. We thank Professor Peter Chiodini and laboratory staff in the Department of Parasitology at the Hospital for Tropical Diseases for processing blood samples and examining malaria blood films. We are also grateful to Liz King for performing the cytokine assays and to Suzanna MacDonald for assisting with these assays.

Financial support: This study was supported by the Special Trustees of the Hospital for Tropical Diseases.

Authors' addresses: Richard M. Jennings, Margaret Armstrong, and Katie L. Flanagan, Hospital for Tropical Diseases, Mortimer Market, Capper Street, London WC1E 6AU, United Kingdom. J. Brian de Souza, Jim E. Todd, and Eleanor M. Riley, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom. Justin F. Doherty, Hospital for Tropical Diseases, Mortimer Market, Capper Street, London WC1E 6AU, United Kingdom and London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom.

REFERENCES

1. Severe falciparum malaria. World Health Organization, Communicable Diseases Cluster, 2000. *Trans R Soc Trop Med Hyg 94* (Suppl 1): S1–S90.
2. Bradley DJ, Warhust DC, Blaze M, Smith V, Williams J, 1998. Malaria imported into the United Kingdom in 1996. *Euro Surveill 3:* 40–42.
3. D'Acremont V, Landry P, Darioli R, Stuerchler D, Pecoud A, Genton B, 2002. Treatment of imported malaria in an ambulatory setting: a prospective study. *BMJ 324:* 875–877.
4. Marsh K, 2002. Immunology of malaria. Warrell DA, Gilles HM, eds. *Essential Malariology.* Fourth edition. London: Arnold, 252–267.
5. Kain KC, Harrington MA, Tennyson S, Keystone JS, 1998. Imported malaria: prospective analysis of problems in diagnosis and management. *Clin Infect Dis 27:* 142–149.
6. Jensenius M, Rønning EJ, Blystad H, Bjørneklett A, Hellum KB, Bucher A, Haheim LL, Myrvang B, 1999. Low frequency of complications in imported falciparum malaria: a review of 222 cases in south-eastern Norway. *Scand J Infect Dis 31:* 73–78.
7. Bouchaud O, Cot M, Kony S, Durand R, Schiemann R, Ralaimazava P, Coulaud J-P, Le Bras J, Deloran P, 2005. Do African immigrants living in France have long-term malarial immunity? *Am J Trop Med Hyg 72:* 21–25.
8. Chaput De Saintonge DM, Vere DW, 1974. Why don't doctors use cusums? *Lancet i:* 120–121.
9. Rhee MS, Akannmori BD, Waterfall M, Riley EM, 2001. Changes in cytokine production associated with acquired immunity to *Plasmodium falciparum* malaria. *Clin Exp Immunol 126:* 503–510.
10. Dodoo D, Omer F, Todd J, Akanmori BD, Koram KA, Riley EM, 2002. Absolute levels and ratios of pro-inflammatory and anti-inflammatory cytokine production *in vitro* predict clinical immunity to *P. falciparum* malaria. *J Infect Dis 185:* 971–979.
11. Struik S, Riley EM, 2004. Does malaria suffer from lack of memory? *Immunol Rev 201:* 268–290.
12. Day NP, Hien TT, Schollaardt T, Loc PP, Chuong LV, Chau TT, Mai NT, Phu NH, Sinh DX, White NJ, Ho M, 1999. The prognostic and pathophysiologic role of pro- and antiinflammatory cytokines in severe malaria. *J Infect Dis 180:* 1288–1297.
13. Grau GE, Taylor TE, Molyneux ME, Wirima JJ, Vassalli P, Hommel M, Lambert PH, 1989. Tumor necrosis factor and

disease severity in children with falciparum malaria. *N Engl J Med 320:* 1586–1591.
14. Kwiatkowski D, Hill AV, Sambou I, Twumasi P, Castracane J, Manogue KR, Cerami A, Brewster DR, Greenwood BM, 1990. TNF concentration in fatal, non-fatal cerebral and uncomplicated *Plasmodium falciparum* malaria. *Lancet 336:* 1201–1204.
15. May J, Lell B, Luty AJ, Meyer CG, Kremsner PG, 2000. Plasma interleukin-10:tumor necrosis factor (TNF)-alpha ratio is associated with TNF promoter variants and predicts malarial complications. *J Infect Dis 182:* 1570–1573.
16. Kwiatkowski D, Bate CA, Scragg IG, Beattie P, Udalova I, Knight JC, 1997. The malaria fever response – pathogenesis, polymorphism and prospects for intervention. *Ann Trop Med Parasitol 91:* 533–542.
17. Drakeley CJ, Corran PH, Coleman PG, Tongren JE, McDonald SLR, Carneiro I, Malima R, Lusingu JP, Manjurano A, Nkya WMMM, Lemnge MM, Cox J, Reyburn HG, Riley EM, 2005. Estimating medium and long terms trends in malaria transmission using serological markers of malaria exposure. *Proc Natl Acad Sci USA 102:* 108–113.
18. Artavanis-Tsakonas K, Tongren JE, Riley EM, 2003. The war between the malaria parasite and the immune system: immunity, immunoregulation and immunopathology. *Clin Exp Immunol 133:* 145–152.