Deficient Spontaneous Cell-Mediated Cytotoxicity and Lectin-Induced Cellular Cytotoxicity by Peripheral Blood Mononuclear Cells from Thai Adults Naturally Infected with Malaria

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To assess general cytotoxic effector cell capabilities by peripheral blood mononuclear cells from patients with active malaria infections, we examined antibody-dependent cellular cytotoxicity, spontaneous cell-mediated cytotoxicity, and lectin-induced cellular cytotoxicity by using human and chicken erythrocyte, Chang cell line, and K562 cell line targets. By using human erythrocyte and Chang cell line targets, we found that Thai adults normally infected with malaria exhibit an almost normal lectin-induced cellular cytotoxicity. In addition, spontaneous cell-mediated cytotoxicity was marginally impaired with K562 but not with Chang cell line targets. Finally, no change in antibody-dependent cellular cytotoxicity was observed when chicken erythrocyte or Chang cell line targets were used. These observations, coupled with our previous observations of a physical loss of peripheral blood T cells, the presence of lymphocytotoxic serum antibodies, and defective T suppressor cell generation in patients with malaria, indicate that major alterations in the cellular immune system occur in patients with active malaria infections.

A detailed understanding of the response of the host immune system to malaria infection will result in clarification of the normal human response to parasitic infection as well as elucidation of the ways in which a parasite modifies the host immune response to avoid neutralization or destruction. We have therefore undertaken a series of experiments designed to determine the immunological alterations which occur during parasitic infection with *Plasmodium falciparum* and *Plasmodium vivax* in naturally infected Thai adults. Our studies to date have demonstrated that patients with malaria have a true decrease in circulating T cells but no real change in null or B cell number (33), antilymphocyte antibodies in their sera (32), a decrease in suppressor T cell generating capability (M. J. Gilbreath et al., submitted for publication), and serum factors capable of inhibiting normal lymphocyte blastogenesis (23). Because the studies which we carried out to date have not assessed cellular effector functions, we chose in the present study to begin examination of peripheral blood mononuclear cell-mediated cytotoxicity, using mononuclear cells from Thai adults naturally infected with *P. falciparum* and *P. vivax*. The results of the present experiments indicate that patients with malaria have defective T cell and natural killer (NK) cell cytotoxic capabilities in some systems but do not exhibit defective killer cell function. These abnormalities may be induced by the malaria parasite to allow continued replication.

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**MATERIALS AND METHODS**

**Patients.** Serum and peripheral blood mononuclear cells were obtained from 52 male patients with naturally acquired *P. falciparum* (33 patients) or *P. vivax* (19 patients) malaria. The patients were diagnosed by the medical staff of the Malaria Eradication Center, Phra-buddhabat, Thailand. All of the patients had low levels of parasitemia (<0.05%) as determined by examination of both thin and thick blood smears (mean parasitemia ± standard error [SEM] = 0.029 ± 0.004; mean age ± SEM = 25.6 ± 1.9 years), and all denied being on any medication at the time of testing. All patients were subsequently treated as outpatients by the medical staff. An age- and sex-matched healthy Thai volunteer who had not previously had malaria served as a control donor for each patient and was bled at the same time of day so that the cells could be tested simultaneously with the cells of the patients. Thus,
different normal fresh controls were used concurrently in all assays. Concurrent matched controls were necessary because of day-to-day variations in the assays. These variations can be appreciated by comparing the control values within the different figures (i.e., Fig. 2a versus 2b, Fig. 3a versus 3b, and Fig. 4a versus 4b), and they may be due to differences in the number of patients examined, the cycle or condition of the target cells, or seasonal variations in effector cell function.

Isolation and "fractionation" of peripheral blood mononuclear cells. Effector cells were obtained from 15 ml of heparinized peripheral blood (10 U of heparin per ml) and isolated by using Ficoll-Hypaque density gradient centrifugation (7) as previously described (33). Briefly, mononuclear cells were washed three times and suspended in final medium, RPMI 1640 (GIBCO Laboratories, Grand Island, N.Y.) containing 2 mM glutamine, 25 mM N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) buffer, 50 U of penicillin, 50 μg of streptomycin per ml, and 20% heat-inactivated fetal bovine serum. Some mononuclear cell preparations were "fractionated" into adherent and nonadherent cell populations by being passed over a Sephadex G-10 column as previously described (22). Cells were suspended in final medium and counted, and viability was determined by using the eosin dye exclusion technique. Nonheparinized blood was also obtained from the patients for use in serum regulatory studies.

Preparation of antisera. Anti-Chang cell antibody was prepared by injecting intravenously, without adjuvant, adult male rabbits (3 kg each) with 4 × 10⁸ Chang liver cells every 2 weeks for 3 months. The rabbits were bled 2 weeks after the last injections, and serum was collected from the clotted blood. Commercial rabbit anti-chicken erythrocyte antibody was obtained from Cappel Laboratories, Downingtown, Pa. (lot no. 11871). Before use, all antisera were heat inactivated for 60 min at 56°C.

Preparation of ⁵¹Cr-labeled target cells. The human myeloid cell line K562 was maintained in suspension culture. Chang liver cells (Microbiological Associates, Bethesda, Md.) were maintained in minimal essential medium, and fresh chicken erythrocytes were obtained daily from our laboratory animal facility. Fresh allogeneic human erythrocytes were obtained daily from normal human donors. Labeled target cells were prepared by washing the cells in assay medium three times and suspending the Chang liver cells or erythrocytes at 1 × 10⁸ or 4 × 10⁸ cells per ml, respectively. Then 0.1 ml of each cell suspension was incubated for 1 h at 37°C with 0.1 ml of chromium isotope (Na₂⁵³CrO₄ in saline; specific activity, 425 mCi/mg; New England Nuclear Corp., Boston, Mass.). The target cells were washed three times in medium and resuspended to a final concentration of 1 × 10⁸ Chang cells per ml, 1 × 10⁹ K562 cells per ml, 1 × 10⁷ chicken erythrocytes per ml, or 5 × 10⁷ human erythrocytes per ml.

Cytotoxicity assays. To carry out K562 spontaneous cell-mediated cytotoxicity assays, dilutions of unfractionated, nonadherent, or adherent effector cells (0.1 ml) and ⁵¹Cr-labeled K562 target cells (0.1 ml) were incubated for 4 h at 37°C in a humid environment of 5% CO₂ and 95% air as described previously by MacDermott et al. (19, 21). The antibody-dependent cellular cytotoxicity, lectin-induced cellular cytotoxicity, and spontaneous cell-mediated cytotoxicity assays with Chang or chicken erythrocyte targets were performed as previously described (19, 21). In brief, 50 μl of antibody, phytohemagglutinin, or medium was added to the well containing 0.05 ml of the labeled chicken erythrocytes or Chang target cells.

The optimal dilutions of anti-chicken erythrocyte serum, 10⁻⁵; anti-Chang serum, 1/3,000; and phytohemagglutinin, 1 μg/ml, were determined in preliminary experiments and were used throughout the study. Samples (50 μl) of unfractionated or fractionated (macrophage-depleted cells or macrophages) mononuclear cell populations were then added (at a concentration ranging from 1 × 10⁶ to 25 × 10⁶ cells per ml) to the wells. The Chang and chicken erythrocyte cytotoxicity assays were incubated for 18 h before being harvested and counted. The human erythrocyte lectin-induced cellular cytotoxicity assays were performed as previously described (19-21) and modified as follows. Dilutions of unfractionated, nonadherent, or adherent effector cells (0.05 ml) and ⁵¹Cr-labeled human erythrocytes (0.05 ml) were incubated with wheat germ agglutinin, 8 μg/ml, in round-bottom microtiter plates for 18 h at 37°C in 5% CO₂. The wheat germ agglutinin concentration used throughout the study was determined from preliminary experiments and was not cytotoxic to human erythrocytes in the absence of effector cells. All cytotoxicity tests were performed in triplicate using 96-well round-bottom microtiter plates (Flow Laboratories, Inc., Rockville, Md.). Maximal ⁵¹Cr release was determined by adding 5% Triton X-100 to incubation mixtures containing labeled target cells. The spontaneous release of isotope by the labeled target cells was essentially the same in cultures with mononuclear cells as in cultures without mononuclear cells. After the incubation period, the culture mixtures were harvested with a Titertek harvester (Flow), and the amount of radioactivity released from the cells was determined with a Packard model 3004 gamma counter (Packard Instrument Co., Inc., Rockville, Md.). Data were calculated for the assays by the following formula: (E - S/ max - S) × 100 = ³¹Cr specific release, where E = counts per minute (cpm) released from target cells plus effector cells, S = cpm released spontaneously from target cells, and max = cpm released after the addition of 0.5 ml of 5% Triton X-100.

Serum regulatory studies. A series of experiments was carried out to assess the effect of the serum of malarious patients on the ability of mononuclear cells to function as effector cells in the spontaneous cell-mediated cytotoxicity, antibody-dependent cellular cytotoxicity, and lectin-induced cellular cytotoxicity assays. In the experiments examining spontaneous cell-mediated cytotoxicity and lectin-induced cellular cytotoxicity, the inhibitory effect of autologous serum on the mononuclear cells of the patients was assessed as previously described (30). Briefly, the mononuclear cell spontaneous cell-mediated cytotoxicity and lectin-induced cellular cytotoxicity activities were studied before and after overnight incubation in serum-free medium. After overnight incubation, 5 × 10⁶ mononuclear cells per ml were incubated for 2 h at 37°C with an equal volume of 20% (vol/vol) heat-inactivated autologous or allogeneic serum or medium. Pooled serum from healthy male donors and fetal bovine
serum served as serum controls in these experiments. In the experiments examining antibody-dependent cellular cytotoxicity, a modification (25) of the antibody-dependent cellular cytotoxicity inhibition assay described by Perlmann and Perlmann (29) was used. Human effector lymphocytes from healthy donors were preincubated for 1 h at 37°C with a 20% (vol/vol) pool of either heat-inactivated patient sera, normal human control sera, or normal human sera before the suspension was added to the target cells.

**Statistical significance.** The statistical significance of the results was assayed by the Student t test and the paired-sample test or the Spearman rank correlation analysis for concordance.

**RESULTS**

Spontaneous cell-mediated cytotoxicity, antibody-dependent cellular cytotoxicity, and lectin-induced cellular cytotoxicity with cell line cells as targets. We first examined spontaneous cell-mediated cytotoxicity in which the effectors were NK cells. Spontaneous cell-mediated cytotoxicity against K562 targets by peripheral blood mononuclear cells from malarious Thai adults was significantly lower ($P < 0.05$) than with cells from healthy controls at 5:1, 25:1, and 50:1 effector-to-target cell ratios (Fig. 1). Patients with malaria had deficient NK cell activity when K562 cell line cells were used as targets, but when Chang cell line cells were used as targets, normal levels of spontaneous cell-mediated cytotoxicity were seen (Fig. 2). Thus, the NK cell deficiency was present only with certain targets. Furthermore, antibody-dependent cellular cytotoxicity, a killer cell-mediated event, was unchanged in peripheral blood mononuclear cells from malaria patients when Chang cell line cells were used as targets (Fig. 3; Table 1). However, use of the lectin phytohemagglutinin to induce killing of Chang cell line targets (Table 1) revealed that malaria patients exhibited significantly decreased lectin-induced cellular cytotoxicity compared with normal controls when 50:1

![FIG. 1. Spontaneous cell-mediated cytotoxicity by unfractionated mononuclear cells (MNC) from malarious Thai adults against K562 target cells. Values are expressed as mean percent of cytotoxicity ± SEM for the number of patients and concurrent controls studied (N). Symbols: *, level of statistically significant difference between patient and control cell cytotoxicity; ———, control MNC; ---, malarious patient MNC.](http://jcm.asm.org/)

![FIG. 2. Spontaneous cell-mediated cytotoxicity against Chang cells expressed as mean percent cytotoxicity ± SEM for the number of patients and concurrent controls (N) studied. Effector cells were from *P. vivax* patients (a) and *P. falciparum* patients (b). Open bars show the control data, and crosshatched bars show the data from the patients.](http://jcm.asm.org/)
significant difference was seen between controls and patients in antibody-dependent cellular cytotoxicity at any of the effector-to-target cell ratios when unfractionated mononuclear cells, macrophage-depleted lymphocytes, or macrophages were used as effector cells. Mononuclear cells did not cause cytotoxicity in the absence of rabbit anti-chicken erythrocyte antibody. Thus, normal antibody-dependent cellular cytotoxicity activity against chicken erythrocytes was seen, similar to the findings described above (Fig. 3; Table 1) for antibody-dependent cellular cytotoxicity with Chang cell line cells as targets. When lectin-induced cellular cytotoxicity was examined, using wheat germ agglutinin to induce killing of allogeneic human erythrocyte targets, significantly decreased lectin-induced cellular cytotoxicity ($P < 0.05$) was seen with patient mononuclear cells in comparison with control mononuclear cells in experiments performed at a 25:1 effector-to-target cell ratio (Fig. 5).

Because lectin-induced phagocytosis of erythrocytes by guinea pig and mouse macrophages has been reported (26) and we examined only unseparated peripheral blood mononuclear cells, the next question which arose was wheth-

![Graph](image-url)  

**FIG. 3.** Antibody-dependent cellular cytotoxicity against Chang liver target cells expressed as mean percent cytotoxicity ± SEM for the number of patients and concurrent controls studied (N). Cytotoxicity observed with cells alone (SCMC) was subtracted from that seen with cells plus rabbit anti-Chang antibody. Effector cells were from *P. vivax* patients (a) and *P. falciparum* patients (b). Solid bars indicate unfractionated mononuclear cells; crosshatched bars indicate control unfractionated mononuclear cells.

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Cytotoxicity measurement</th>
<th>% $^{51}$Cr release from cells$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>50:1</td>
<td>Spontaneous (SCMC)</td>
<td>33.2 ± 8.0</td>
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<tr>
<td></td>
<td>PHA$^c$ (LICC)</td>
<td>55.1 ± 11.2</td>
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<tr>
<td></td>
<td>Anti-Chang Ab$^d$ (ADCC)</td>
<td>58.4 ± 5.8</td>
</tr>
<tr>
<td>25:1</td>
<td>Spontaneous (SCMC)</td>
<td>23.9 ± 5.4</td>
</tr>
<tr>
<td></td>
<td>PHA (LICC)</td>
<td>45.7 ± 8.3</td>
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<tr>
<td></td>
<td>Anti-Chang Ab (ADCC)</td>
<td>51.2 ± 7.4</td>
</tr>
<tr>
<td>10:1</td>
<td>Spontaneous (SCMC)</td>
<td>14.1 ± 3.8</td>
</tr>
<tr>
<td></td>
<td>PHA (LICC)</td>
<td>29.2 ± 2.9</td>
</tr>
<tr>
<td></td>
<td>Anti-Chang Ab (ADCC)</td>
<td>23.2 ± 4.4</td>
</tr>
</tbody>
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$^a$ Effector-to-target cell ratio.
$^b$ Expressed as mean ± SEM for six individuals.
$^c$ Final concentration of phytohemagglutinin (1 μg/ml).
$^d$ Final dilution of 1:3,000 rabbit anti-Chang serum.
$^e$ Antibody.
$^f$ Statistically significant difference ($P < 0.01$).
$^g$ Statistically significant difference ($P < 0.05$).
er the deficiency of cytotoxic effector cell capability was greater in the lymphocytes or the macrophages of the patient or was the same in both cell subpopulations. Defective lectin-induced cellular cytotoxicity (wheat germ agglutinin-human erythrocyte) capacity existed in both the nonadherent mononuclear cell (lymphocyte) population and the adherent mononuclear cell (monocyte-macrophage) population (Fig. 6). In contrast, defective spontaneous cell-mediated cytotoxicity (K562) capacity existed only in the nonadherent mononuclear cell (lymphocyte) population, with the adherent mononuclear cell (monocyte-macrophage) population not exhibiting much killing with either control or patient mononuclear cells.

**Effect of patient sera on antibody-dependent cellular cytotoxicity, spontaneous cell-mediated cytotoxicity, or lectin-induced cellular cytotoxicity assays.** The next question was whether sera from patients with malaria could induce a defect in antibody-dependent cellular cytotoxicity, spontaneous cell-mediated cytotoxicity, or lectin-induced cellular cytotoxicity, using normal peripheral blood mononuclear cells as the effector cells. That is, in the assay systems in which patient mononuclear cells functioned normally, it was hypothesized that removing the mononuclear cells of the patient from their sera would result in loss of inhibition. Furthermore, in the assay systems in which patient mononuclear cells exhibited decreased cytotoxic capability, serum factors might account for the deficit. No statistically significant difference in antibody-dependent cellular cytotoxicity was seen in either the chicken erythrocyte or Chang assay systems, in which mononuclear cells incubated with 14 patient sera or healthy donor sera were tested at three different effector-to-target cell ratios (data not shown).
The spontaneous cell-mediated cytotoxicity and lectin-induced cellular cytotoxicity responses of mononuclear cells from malarious patients did not increase when the mononuclear cells were incubated overnight in serum-free medium at 37°C. Incubation of the mononuclear cells with autologous serum had little effect on the mononuclear cell spontaneous cell-mediated cytotoxicity response. The lectin-induced cellular cytotoxicity of the mononuclear cells incubated overnight was lower than the lectin-induced cellular cytotoxicity of fresh isolated mononuclear cells, and incubation of the mononuclear cells with autologous serum had little effect on lectin-induced cellular cytotoxicity. Finally, experiments in which nonadherent mononuclear cells from healthy donors were incubated for 2 h with malarious patients' sera that were known to contain cold-reactive lymphocytotoxic antibodies (single serum or pooled patient sera) failed to demonstrate any spontaneous cell-mediated cytotoxicity or lectin-induced cellular cytotoxicity inhibitory factors in the serum of malarious patients.

**DISCUSSION**

We have undertaken a series of studies to examine the immunological capabilities of naturally infected Thai adults who have *P. falciparum* and *P. vivax* malaria. The naturally infected human host presents a unique and important opportunity to examine the mechanisms by which the malaria parasite attempts to evade recognition and destruction. Our studies suggest that due to the infection with the malaria parasite, a number of immunological changes occur which may prevent the host from mounting a completely effective immune response which would lead to elimination of the *P. falciparum* or *P. vivax* organisms. In our previous studies, the changes we have observed include a loss of circulating T cells (33), a loss of functional concanavalin A-inducible T suppressor cells (Gilbreath et al., submitted for publication), antilymphocyte antibodies (32), and serum suppressor factors (23). However, our previous studies did not examine mononuclear cell effector functions, in particular, cell-mediated cytotoxicity. It is conceivable that mitogenic substances (11) present in one or more of the parasites stages, upon reaching an optimal concentration in the circulation, activate nonspecific effector cells. Parasitized erythrocytes may be more susceptible to destruction by these activated cells and could thus be eliminated. If cytotoxic cells function in clearing the malaria parasite, then interference with normal cytotoxic effector mechanisms, as suggested by our present findings, could be one way in which malaria parasites avoid destruction by the host immune system.

Greenwood and co-workers (12) and Brown and Smalley (8) have reported increased nonspecific and specific antibody-dependent cellular cytotoxicity by peripheral blood cells from Gambian children with malaria, which was felt to
correlate with an increase in the number of Null cells also present in these patients (35). Our finding of no difference in antibody-dependent cellular cytotoxicity effector function between patients and controls may be explained in part different antibodies, different target cell types, or the different types of patients examined.

Current evidence indicates that antibody-dependent cellular cytotoxicity, spontaneous cell-mediated cytotoxicity, and lectin-induced cellular cytotoxicity effector cells belong to subsets of T as well as Null lymphocytes. Spontaneous cell-mediated cytotoxicity and antibody-dependent cellular cytotoxicity effector cells include nonadherent, nonphagocytic, surface membrane immunoglobulin-negative, Fc receptor-positive, and E rosette-positive lymphoid cells (4, 14, 21, 34); spontaneous cell-mediated cytotoxicity but not antibody-dependent cellular cytotoxicity can be mediated by an E-rosetting subset which lacks detectable receptors for Fc (4); and both spontaneous cell-mediated cytotoxicity and antibody-dependent cellular cytotoxicity can be mediated by a subset of Null cells (21). T cells with Fc receptors for immunoglobulin G, i.e., Tε cells (27), are known to be capable of mediating spontaneous cell-mediated cytotoxicity against K562 cells (13), whereas adherent monocytes and B lymphocytes appear not to be directly involved in spontaneous cell-mediated cytotoxicity cell lysis (4, 21, 34). Depending on the lectin used and the target cell type, lectin-induced cellular cytotoxicity effector cells also belong to the Fc receptor-positive population (5, 6), the T cell subclass (28), Fc receptor-negative populations in the presence of phytohaemagglutin (31), and T, B, and Null cell subclasses (21). However, lectin-induced cellular cytotoxicity is also critically dependent upon the lectin used and the species from which the target cells are obtained (20). Furthermore, the subpopulations of human lymphocytes that respond to wheat germ agglutinin may be quantitatively minor. Indeed, Boldt (3) demonstrated that approximately 50% of the wheat germ agglutinin bound to the surfaces of human lymphocytes can be

FIG. 6. Lectin-induced cellular cytotoxicity with wheat germ agglutinin and human erythrocyte targets (a) and spontaneous cell-mediated cellular cytotoxicity with K562 target cells (b) of unfractonated, nonadherent, or adherent mononuclear cell populations from malarious Thai adults. Effector cells were from both P. falciparum and P. vivax patients. Cytotoxicity is expressed as mean percent cytotoxicity ± SEM for the number of patients and concurrent controls studied (N). Asterisk indicates the level of statistically significant difference in cytotoxicity between the patient and control cell populations at the respective effector-to-human erythrocyte target cell ratio. Patient and control adherent mononuclear cells were routinely >80% esterase positive, <5% E rosette positive, and <5% Slg positive; nonadherent cells were <5% esterase positive, >60% E rosette positive, and >16% Slg positive. Solid bars indicate control cells; dotted bars indicate cells from patients. MNC, Mononuclear cells.
localized to only 10% of the cells. This finding is also consistent with the data of Gordon et al. (10) in that early blast transformation and DNA synthetic responses caused by wheat germ agglutinin seem to involve only 10 to 15% of the T cells present.

There are several possible mechanisms to account for the decrease in lectin-induced cellular cytotoxicity and spontaneous cell-mediated cytotoxicity with normal antibody-dependent cytotoxicity as observed in the present study. First, as discussed above, different lymphocyte subclasses mediate each of the different types of cell-mediated cytotoxicity. Thus, a physical deletion or regulatory suppression of the appropriate subclasses could account for the results. It is also possible that specific lymphocytotoxic antibodies block or lead to deletion of the relevant T cells and a subgroup of NK cells but not killer cells if the Fc receptor is not blocked. Alternatively, antigens released from the malaria parasites themselves could block the effector lymphocyte receptors involved in target cell recognition or lead to deletion of the lymphocyte subclass by antigen-antibody complex formation on the surfaces of mononuclear cells, followed by removal in the reticuloendothelial system.

Because serum factors or immunoglobulins might account for our findings, it is of importance that no increase was seen in either spontaneous cell-mediated cytotoxicity or lectin-induced cellular cytotoxicity activity when mononuclear cells from malarious patients were incubated overnight. These results suggest that membrane binding serum factors, such as lymphocytotoxic antibodies or immune complexes, which have been reported to exist in sera from some malaria patients (1, 32), were not inhibiting spontaneous cell-mediated cytotoxicity or lectin-induced cellular cytotoxicity. Furthermore, the finding that sera from patients with malaria do not inhibit spontaneous cell-mediated cytotoxicity or lectin-induced cellular cytotoxicity effector cell functions by mononuclear cells from healthy individuals supports the conclusion that sera from malarious individuals have little or no in vitro effect on nonspecific effector functions. The presence of immune complexes (16) and other substances (18) in sera that bind Fc receptors and inhibit antibody-dependent cellular cytotoxicity in vitro, as well as the demonstration of immune complexes in malarious monkey plasma (15), suggested a serum regulatory mechanism capable of altering normal antibody-dependent cellular cytotoxicity activity in vivo. Using the antibody-dependent cellular cytotoxicity inhibition technique, however, we failed to detect immune complexes or any inhibitory factor in sera from patients. Since the antibody-dependent cellular cytotoxicity inhibition technique is a sensitive method for detecting small immune complexes (25) in serum, our results indicate either that soluble immune complexes are rarely present in malarious sera or that the immunoglobulin G subclasses responsible for the antibody-dependent cellular cytotoxicity blocking phenomenon differ from those found in immune complexes of malarious sera.

Reduced lectin-induced cellular cytotoxicity activity by macrophages from malarious humans is consistent, in part, with the report by Frankenberg et al. (9) of decreased phagocytosis throughout the malaria infection by cells from lethally infected mice (nonimmune). Furthermore, impaired macrophage lectin-induced cellular cytotoxicity in malarious individuals may be associated with the decrease in T cell numbers known to exist in malarious individuals, since animal studies have demonstrated that T cells mediate the activation of macrophages (17, 24).

The defects observed in the present study have also been described in diseases with possible autoimmune bases, such as multiple sclerosis (2) and systemic lupus erythematosus (30). The implication of this observation in our understanding of autoimmune disease is that changes such as those observed in the present study can occur secondary to a parasitic agent as well as in autoimmune processes such as systemic lupus erythematosus. On the other hand, the implication for the study of malaria is that the changes in immune function induced by parasitic infestation may allow or contribute to the autoimmune phenomena sometimes seen in these illnesses. Further studies on the mechanisms by which the malaria infection alters human immune function are of importance so that we can learn how parasites avoid or protect themselves from destruction or elimination by the host.

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