Studies of the Neutropenia of Acute Malaria

Neutrophil kinetics were studied in seven patients with acute malaria. Six patients with *Plasmodium vivax* had a mean neutrophil count of 1651 ± 282/ cu mm (range 360–2340); the neutrophil count in one patient with *P. falciparum* malaria was normal (4600/cu mm). In all of these patients, the numbers of circulating nonsegmented neutrophils were increased, neutrophil half-disappearance times were prolonged, and the total blood granulocyte pools were normal or increased. The marginal granulocyte pools were greatly enlarged but circulating pools were reduced, indicating that the apparent neutropenia was due to an altered intravascular granulocyte distribution. These patients had reduced numbers of mature marrow granulocytes and decreased marrow granulocyte reserves. These data provide a model for one mechanism of neutropenia in man: premature release of marrow granulocytes with a shift of the circulating cells into the marginal pool.

A NEMIA, THROMBOCYTOPENIA, AND NEUTROPENIA are frequently seen in acute malarial infections in man. The anemia and thrombocytopenia are attributable to splenic sequestration and shortened survival of erythrocytes and platelets, but the mechanism of the neutropenia is not known. In fact, in only a few clinical situations can the mechanism of neutropenia be characterized as a failure of production, alteration of distribution, or abnormality of neutrophil (PMN) lifespan in a manner analogous to the mechanisms of anemia and thrombocytopenia. Therefore, we have investigated neutrophil kinetics in acute malaria in an attempt to identify the mechanism of the neutropenia associated with this disorder and to define perhaps one kind of general pathophysiologic process that can lead to neutropenia in man.

MATERIALS AND METHODS

Patients

Seven male patients, ages 20–58 yr, with untreated acute malaria were referred to the NIH Clinical Center where the diagnoses were confirmed, and consent for these investigations was obtained. All of the patients had acquired their infections during recent travel in Southeast Asia. None of the patients had significant illnesses at the time of these studies other than malaria, although one man had had unexplained splenomegaly for...
several years prior to the acute malaria. In all patients the bone marrow aspirates, marrow reserve tests, and neutrophil kinetic studies were performed during the first 3 days of hospitalization. Antimalarial therapy with chloroquine was initiated before these studies were completed in five patients. Two patients with milder illnesses were studied prior to the institution of therapy.

**Blood Counts**

White blood cell (WBC) counts and differential leukocyte counts were made using an electronic particle counter (Coulter Counter, Model FN, Coulter Electronics, Hialeah, Fla.) and air-dried, Wright's-stained smears. Band PMNs were defined as those PMNs without definitely segmented nuclei but with nuclear chromatin more condensed than the usual "C-shaped" metamyelocyte. By this definition, metamyelocytes are very rarely observed in normal individuals, but bands account for 0%-5% of normal circulating PMNs.

**Bone Marrow Examinations**

Bone marrow aspirates were obtained from the iliac crest under local anesthesia, and 300-500 cell differential counts were made on Wright's-stained smears. An over-all interpretation of the marrow histology was also made from scanning the entire specimen.

**Bone Marrow Neutrophil Reserves**

The total PMN count was measured on venous blood samples obtained before and 12, 15, and 18 hr after the intramuscular injection of etiocholanolone (0.1 mg/kg) in all of the patients, and the maximum change from the baseline was used as a measure of marrow PMN reserves. Marrow neutrophil reserves were also measured in two patients using intravenously administered endotoxin (Lipexal, 0.8 mg/kg) as previously described. Studies of the neutrophil reserves were performed on ten normal volunteers of both sexes to compare with the responses of the patients.

**DF₃²P Leukokinetic Studies**

Neutrophil half-disappearance times (PMN t_1/2) and distribution were measured with a modification of the methods of Athens et al. Approximately 500 ml of blood were collected in a plastic bag containing 67.5 ml of ACD (acid citrate dextrose) anticoagulant (Fenwal Laboratories, Morton Grove, Ill.). Following the addition of 100 μCi of diisopropylfluorophosphate (DF₃²P, Radiochemical Centre, Amersham, England) the blood was gently mixed for 1 hr at room temperature and then reinfused over 15 min. Twenty milliliters heparinized blood samples were obtained from the bag before reinfusion and from the antecubital veins of the patients at 1, 3, 6, 12, and 24 hr after the reinfusion. Granulocytes were isolated from these blood samples by the ficoll-sodium diatrizoate (Hypaque) method of Boyum. This method regularly yields granulocytes virtually free of platelets and with less than 5% contamination by monocytes and lymphocytes. Each blood sample was mixed with 60 ml of phosphate-buffered saline and was then carefully layered over 3 ml of a mixture of five parts of 9% ficoll (w/v in distilled water) and 12 parts 33.4% Hypaque (w/v in distilled water) in 13 × 150 mm glass test tubes and centrifuged at 400 g for 40 min at 20°C. The layers (platelets, lymphocytes, and monocytes) above the erythrocyte-granulocyte pellet were discarded. The pellet was suspended in a mixture of 1.0 ml autologous fresh, ACD-anticoagulated plasma and 0.4 ml of 4.5% dextran (w/v in normal saline) and was allowed to settle at 1 g at room temperature. After approximately 20 min, most of the erythrocytes had settled. The supernate was removed, and the granulocytes and remaining erythrocytes were sedimented by centrifugation at 400 g for 10 min at 20°C. The remaining erythrocytes were lysed with two 30-sec exposures of the cell preparation to 0.20 normal saline at 4°C. The leukocytes of the final cell preparation in these patients were regularly greater than 95% PMNs with less than a 1:1 erythrocyte to PMN ratio. Both segmented and nonsegmented PMNs were present in the final preparations in the same relative numbers as in the blood, and the over-all
recovery of PMNs was usually 40%-60% of the number of cells in the original sample. After counting an aliquot of cells with an electronic particle counter, they were digested with 0.2 N NaOH for at least 2 hr at 60°C. The digested material was acidified with 10% acetic acid and solubilized in a Biosolv (BBS-3) (Beckman, Fullerton, Ga.)-Liquifluor (New England Nuclear, Boston, Mass.)-toluene cocktail (Biosolv 10%, Liquifluor 3.6%, toluene 86.4% by volumes) and the sample radioactivities measured with a liquid scintillation counter (Beckman liquid scintillation spectrometer, Model LS-250, Beckman Industries, Fullerton, Ga.). The specific activity for each sample was expressed as cpm per cell, and the decay curves were plotted on semilog paper. The specific activities for samples of the DF32P-labeled cells isolated by the Hypaque-ficoll technique were slightly higher than for duplicate samples of cells isolated by the more conventional dextran sedimentation procedure. These results were regarded as indicating that the DF32P label is not eluted by this separation procedure. Although most of the decay curves of PMN specific activity did not appear to be straight lines but rather showed a slight downward curvature (Type C curves),11 the slope and 1 ½ for the specific activity decay curve were calculated by the method of least squares.12 The total-body neutrophil pool, marginal and circulating neutrophil pools, and neutrophil turnover rates were measured by extrapolating the specific activity decay curves to time zero and applying the formulae as reported.9

RESULTS

Clinical Data

The patients' WBC and PMN counts at the time of hospitalization, as well as the type of malarial infection, spleen size, and other hematologic data, are shown in Table 1. Only one patient with Plasmodium falciparum infection was studied. He had only minimal splenomegaly, was not leukopenic, and showed a slightly different derangement of neutrophil kinetics from the other patients with P. vivax infections. For the acutely ill P. vivax patients, the mean WBC count was 3000 ± 167/cu mm and the mean PMN was 1651 ± 282/cu mm. In all of these patients there was a definite "left shift" toward immature neutrophil forms (i.e., increased numbers of bands and occasional metamyelocytes) in the peripheral blood (Table 1).

<table>
<thead>
<tr>
<th>Patient</th>
<th>WBC (cells/cu mm)</th>
<th>PMN (PMN)</th>
<th>Nonsegmented PMN</th>
<th>Hb (g/100 ml)</th>
<th>Platelets (per cu mm)</th>
<th>Spleen Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2900</td>
<td>1680</td>
<td>Left shift</td>
<td>10.5</td>
<td>164,000</td>
<td>2+</td>
</tr>
<tr>
<td>2</td>
<td>3500</td>
<td>1900</td>
<td>Left shift</td>
<td>9.6</td>
<td>39,000</td>
<td>2+</td>
</tr>
<tr>
<td>3</td>
<td>3000</td>
<td>1560</td>
<td>670</td>
<td>11.6</td>
<td>71,000</td>
<td>2+</td>
</tr>
<tr>
<td>4</td>
<td>3300</td>
<td>2340</td>
<td>830</td>
<td>14.7</td>
<td>118,000</td>
<td>2+</td>
</tr>
<tr>
<td>5a‡</td>
<td>2300</td>
<td>360</td>
<td>180</td>
<td>9.7</td>
<td>58,000</td>
<td>4+</td>
</tr>
<tr>
<td>5b‡</td>
<td>4400</td>
<td>2970</td>
<td>180</td>
<td>12.0</td>
<td>114,000</td>
<td>3+</td>
</tr>
<tr>
<td>6a</td>
<td></td>
<td></td>
<td>3000</td>
<td>2070</td>
<td>950</td>
<td>13.9</td>
</tr>
<tr>
<td>6b</td>
<td></td>
<td></td>
<td>4600</td>
<td>2500</td>
<td>125</td>
<td>14.5</td>
</tr>
<tr>
<td>7</td>
<td>5000</td>
<td>4600</td>
<td>2440</td>
<td>16.0</td>
<td>116,000</td>
<td>+</td>
</tr>
</tbody>
</table>

*Patients 1–6 had P. vivax and patient 7 had P. falciparum.
†(Including nonsegmented PMN).
‡Spleen size as estimated by palpation. 0, not palpable; +, tip palpable; 2+, palpable to 2 cm below left costal margin; 3+, palpable 3–4 cm below left costal margin; 4+, palpable more than 4 cm below left costal margin.
§5a, data when acutely ill; 5b, data 6 wk after initial study.
||5a, data when acutely ill; 6a, data 3 wk after initial study.
Bone Marrows

The bone marrow differential counts of the five patients from whom satisfactory specimens were obtained are compared with the normal data of Wintrobe in Table 2. In general, these patients' marrows contained a smaller than normal percentage of mature neutrophils, bands, and metamyelocytes with a near normal or increased percentage of neutrophil precursor cells. This abnormality is expressed by the decreased "maturation ratio" of these marrows (Table 2). Except for the patient with P. falciparum, the myeloid to erythroid ratios were also decreased. Biopsies were not obtained, but all of the marrows appeared hypercellular. Mild megaloblastic erythroid hyperplasia was noted in all of the P. vivax patients. Folate and vitamin B12 levels were not done.

Table 2. Bone Marrow Examination in Acute Malaria

<table>
<thead>
<tr>
<th>Cells</th>
<th>Normal*</th>
<th>Patients†</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Myeloblasts</td>
<td>2.0</td>
<td>0.3†</td>
<td>0.3</td>
<td>0</td>
<td>0.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Promyelocytes</td>
<td>5.0</td>
<td>2.0</td>
<td>3.3</td>
<td>0</td>
<td>2.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Myelocytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>12.0</td>
<td>33.0</td>
<td>19.6</td>
<td>14.5</td>
<td>39.0</td>
<td>34.0</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>1.5</td>
<td>2.0</td>
<td>0.3</td>
<td>1.8</td>
<td>4.0</td>
<td>3.4</td>
</tr>
<tr>
<td>Basophilic</td>
<td>0.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Metamyelocytes</td>
<td>22.0</td>
<td>19.0</td>
<td>12.0</td>
<td>8.6</td>
<td>10.0</td>
<td>16.0</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>20.0</td>
<td>12.0</td>
<td>7.0</td>
<td>2.1</td>
<td>10.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>2.0</td>
<td>0.6</td>
<td>1.0</td>
<td>1.2</td>
<td>6.0</td>
<td>7.1</td>
</tr>
<tr>
<td>Basophilic</td>
<td>0.2</td>
<td>0</td>
<td>0</td>
<td>0.2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>10.0</td>
<td>5.0</td>
<td>13.0</td>
<td>11.9</td>
<td>1.0</td>
<td>6.8</td>
</tr>
<tr>
<td>Plasma cells</td>
<td>0.4</td>
<td>0.6</td>
<td>0</td>
<td>1.2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Monocytes</td>
<td>2.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Megakaryocytes</td>
<td>0.2</td>
<td>0.3</td>
<td>0</td>
<td>0</td>
<td>0.4</td>
<td>—</td>
</tr>
<tr>
<td>Pronormoblasts</td>
<td>4.0</td>
<td>1.6</td>
<td>6.2</td>
<td>12.6</td>
<td>3.0</td>
<td>4.9</td>
</tr>
<tr>
<td>Normoblasts</td>
<td>18.0</td>
<td>23.0</td>
<td>37.2</td>
<td>46.2</td>
<td>23.0</td>
<td>14.0</td>
</tr>
<tr>
<td>Myeloid/erythroid ratio</td>
<td>3.6</td>
<td>2.9</td>
<td>1.0</td>
<td>0.5</td>
<td>2.8</td>
<td>3.9</td>
</tr>
<tr>
<td>Maturation ratio§</td>
<td>2.2</td>
<td>0.88</td>
<td>0.82</td>
<td>0.74</td>
<td>0.48</td>
<td>0.51</td>
</tr>
<tr>
<td>Interpretation</td>
<td>Hypercellular, megaloblastic, erythroid hyperplasia</td>
<td>Hypercellular, mild megaloblastic, erythroid hyperplasia</td>
<td>Hypercellular, maturation arrest, erythroid hyperplasia</td>
<td>Hypercellular, megaloblastic, granulocyte dyspoiesis with left shift</td>
<td>Left shift with maturation arrest</td>
<td></td>
</tr>
</tbody>
</table>

*Data from Wintrobe.
†Patients 2, 3, 5, and 6 all had acute P. vivax malaria; patient 7 had P. falciparum malaria.
‡Per cent of 300–500 marrow nucleated cells.
§Ratio of the percentage of metamyelocytes, bands, and PMNs to the percentage of myeloblasts, promyelocytes, and myelocytes.
Fig. 1. Marrow reserve tests in malaria. Maximum granulocyte increase from baseline following etiocholanolone (0.1 mg/kg) in acute and convalescent (11–15 days and 22–32 days) malaria. Numbers in parenthesis are the studies done. Bars are the means, and brackets represent 1 SEM.

Marrow Neutrophil Reserves

The bone marrow reserves as measured by the responses to etiocholanolone (Fig. 1) were strikingly abnormal in all of the patients at the time of their hospitalization. The mean response was 692 ± 261/cu mm (normal 4250 ± 550/cu mm). The two patients tested with endotoxin also had diminished responses, with a mean increase in PMNs of 411 ± 208/cu mm compared to the normal response of 7880 ± 900/cu mm. This abnormality was followed

Table 3. Leukokinetic Studies in Malaria

| Patient* | PMN $^{1/2}$ (hr) | TBGP† (cells $\times 10^7$/kg) | CGP† (cells $\times 10^7$/kg) | MGP§ (cells $\times 10^7$/kg) | GTR|| (cells $\times 10^7$/kg/day) |
|----------|-------------------|-------------------------------|-----------------------------|-----------------------------|---------------------------------|
| 1        | 22.0              | 230.0                         | 20.9                        | 209.1                       | 174.0                           |
| 2        | 28.3              | 60.0                          | 14.0                        | 46.2                        | 35.5                            |
| 3        | 14.8              | 154.0                         | 9.9                         | 145.1                       | 173.0                           |
| 5a       | 14.3              | 55.6                          | 2.5                         | 53.1                        | 64.8                            |
| 5b       | 7.6               | 119.0                         | 20.6                        | 98.4                        | 261.0                           |
| 6a       | 23.3              | 193.0                         | 13.7                        | 179.3                       | 134.0                           |
| 6b       | 7.7               | 62.0                          | 29.5                        | 32.5                        | 133.0                           |
| 7        | 13.4              | 221.0                         | 32.9                        | 179.0                       | 263.0                           |

Mean P. vivax when acutely ill

||||t| Mean ± 1 SD derived from patients 1, 2, 3, 5a, and 6a.|||From Wintrobe;13 mean ± 1 SD.

*Patients 1, 2, 3, 5, and 6 all had P. vivax malaria; patient 7 had P. falciparum.
†Total blood granulocyte pool ($\times 10^7$/kg).
‡Circulating granulocyte pool ($\times 10^7$/kg).
§Marginal granulocyte pool ($\times 10^7$/kg).
||Granulocyte turnover rate ($\times 10^7$/kg/day).
‡‡5a and 6a, data when acutely ill; 5b and 6b, data when well.
††Mean ± 1 SE derived from patients 1, 2, 3, 5a, and 6a.
Neutrophil half-disappearance time curves in malaria. Solid dots are PMN specific activities of acutely ill patients. Open circles are PMN specific activities of patients after recovery. Solid and dashed lines connect mean values for specific activity for each time point.

by serial testing in three patients. The response to etiocholanolone was still abnormally low at 2 wk after initiating therapy but was normal or possibly above normal by 3–4 wk after beginning therapy (Fig. 1).

Neutrophil Kinetics

The PMN $t_{1/2}$ total blood neutrophil pool, circulating and marginal pools, and neutrophil turnover rates for the six patients in which these studies were performed are shown in Table 3, and the PMN $t_{1/2}$ curves are shown in Fig. 2. Several abnormalities were observed: (1) the PMN $t_{1/2}$ for all of the acutely ill patients was remarkably prolonged compared to normal individuals. $^{14}$ (2) The distribution of cells between the circulating and marginal pools was very abnormal; the average marginal pool was four times larger than normal and the average circulating pool was about half the normal size. The mean total blood neutrophil pools were therefore about twice normal. The neutrophil turnover rates, however, were not significantly different from normal ($p > 0.1$, t test). For both patients in whom follow-up studies were possible, the PMN $t_{1/2}$ had returned to normal when the marrow reserve responses had returned to normal. One patient had at that time a normal total blood neutrophil pool and abnormal circulating and marginal pools; the other had a persistent abnormality of these pool sizes but also had had unexplained splenomegaly for some time. The patient with *P. falciparum* malaria also had a prolonged PMN $t_{1/2}$ and the same shift to an enlarged marginal pool.

DISCUSSION

These studies indicate that a shift of neutrophils from the circulating pool to an enlarged marginal pool is one mechanism for the reduced neutrophil counts seen in patients with malaria. The data from the neutrophil kinetic studies, marrow examinations, and marrow reserve tests also permit construction of a diagrammatic model of the effect of this infection on neutrophil distribution and turnover. As shown in Fig. 3, neutrophil production is
Fig. 3. Kinetic model for neutropenia of acute malaria. Normal model is adapted from Boggs and Winkelstein.\(^4\) Note that in the malaria model the marrow granulocyte reserves ("storage") are diminished, and total blood granulocyte pool ("circulation") is expanded as is marginal pool, but circulating pool is decreased, thus leading to peripheral neutropenia. Size of the proliferative compartment may not be accurately represented in this schematic diagram since it was not measured.

Conceptually divisible into the periods of proliferation, maturation, and storage.\(^4\) The mature cells are released into the circulation and are normally distributed between two compartments, the circulating and marginal pools. These pools are considered to be in dynamic equilibrium and are generally regarded to be of near equal size, although considerable individual variation has been observed.\(^9\) Neutrophils are normally lost from the circulation with a half-disappearance time of about 6 hr.\(^4\)

In these patients with malaria, there was an increased percentage of circulating band PMNs and an enlarged marginal pool that was accompanied by a striking prolongation of the PMN half-life. A long PMN half-life has been observed previously in chronic myelogenous leukemia,\(^15\) polycythemia vera,\(^11\) some patients with myelofibrosis,\(^11\) some infections,\(^11\),\(^16\) and normal volunteers given prednisone.\(^14\) In the first three of these patient groups, the long PMN half-life has been attributed to the relative immaturity of the circulating PMN population, as well as to the increased total blood granulocyte pool and recirculation of cells.\(^11\),\(^15\) It has been thought that the increase in PMN half-life in infections and in steroid-treated subjects is due to some regulatory relationship of PMN half-life to the blood granulocyte pool, since these parameters are usually directly correlated.\(^11\) The influence on PMN half-life of a shift to the left of the blood PMN series has not been clearly established.\(^1\) The data from these patients with malaria and a marked shift to the left suggest that prematurely released PMNs may have a longer than normal half-life like the cells in chronic myelogenous leukemia and analogous to the prematurely released "shift" reticulocyte.\(^17\) The influence on PMN half-life of the complex of other factors present in the patients with malaria, including the increased mean granulocyte pool size, the altered cell distribution, and the enlarged spleen, cannot be quantitatively evaluated.

As is indicated in Fig. 3, the mild neutropenia of these patients was a spurious one, since the total blood neutrophil pools were normal or increased and the neutropenia could be attributed to a shift of PMNs from the
circulating to an enlarged marginal pool. It has been previously reported that a "masked granulocytosis" may occur, i.e., the marginal granulocyte pool may be increased under circumstances in which the circulating pool is normal.\textsuperscript{18} Moreover, some patients with chronic neutropenia have large marginal but reduced circulating pool sizes.\textsuperscript{19} In neither of these circumstances, however, has a marked shift to the left been described, and in both circumstances the PMN half-life was normal. In normal individuals it is possible to measure the marginal pool by the response of the leukocyte count to exercise or parenteral epinephrine administration.\textsuperscript{9} Although confirmation of the increased size of the marginal pool by such methods was considered, the risk to these patients seemed too great to warrant their use.

These patients also had a decrease in the per cent of marrow cells in the maturational pool (metamyelocytes, bands, and mature PMNs), a morphologic situation often called "maturation arrest." Similar marrow histologic changes in malaria have been reported in great detail previously. In this pathologic situation it seems very probable that the marrow maturational pool has been shifted to a considerable degree into the circulation without the usual storage period, as indicated in Fig. 3, and that maturation is, indeed, not "arrested" at all.

The observation of a diminished bone marrow reserve could be explained by at least two mechanisms. The cells normally released by etiocholanolone or endotoxin may have been released prematurely as a consequence of the malaria infection, as proposed above. It is also possible that, since the marrow reserve tests measure only the increase in the size of the circulating neutrophil compartment,\textsuperscript{21} the cells released from the marrow immediately marginate and are, therefore, not counted. The slowness with which the marrow reserve test returns to normal was surprising and indicates that some influence of the infection on neutrophil kinetics persists for a prolonged period in the absence of overt parasitemia. Further definition of this abnormality may be possible by combining the marrow reserve test with neutrophil kinetic studies.

It cannot be ascertained from these studies how the enlarged spleen influences the neutrophil distribution and half-life. It is noteworthy, however, that splenomegaly has previously been associated with a shortened PMN half-life\textsuperscript{19} in the "hypersplenism" of cirrhosis. The prolonged half-life of PMNs in these patients indicates that this association does not always obtain and is more consistent with the concept that leukocytes, as well as platelets and erythrocytes, may be sequestered but not necessarily destroyed by the spleen. It is also possible that the PMN kinetics were influenced by the anemia and thrombocytopenia as mediated through an intramedullary process such as stem cell competition,\textsuperscript{22} but it is difficult at present to quantify these effects.

Recently, considerable interest has been focused on the similarities of many features of acute malaria and experimental antigen-antibody complex disease.\textsuperscript{3} Since anemia, thrombocytopenia, and neutropenia are also observed in this experimental situation and since the experimental thrombocytopenia appears...
to involve the interaction of the complexes with complement, platelets, and neutrophils, it is possible that studies of neutrophil kinetics in experimental complex disease may help to elucidate a more basic mechanism for the altered neutrophil kinetics observed here. It is also possible that a similar mechanism of altered intravascular distribution of PMNs may explain the neutropenia associated with many other acute infections.

ACKNOWLEDGMENT

The authors gratefully acknowledge the expert technical assistance of Mr. Stanley B. Ward. We thank Dr. Lay Fox, Chief, Department of Medicine, U. S. Naval Hospital, Bethesda, Md. for referring some of these patients for study. The lipexal and etiocholanolone were kindly prepared by the Pharmaceutical Development Service, Pharmacy Department, Clinical Center, NIH, Bethesda, Md.

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