Quantitative Relationships Between Circulating Leukocytes and Infection in Patients with Acute Leukemia

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Infection is currently the major fatal complication of acute leukemia (1). Previous studies have indicated a relationship between leukopenia and the presence of infection in patients with acute leukemia (2-4) and various types of agranulocytosis (5-7). Chemotherapeutic agents with bone marrow toxicity are being used with increasing frequency in malignant and other chronic diseases. Also, a high incidence of infection has accompanied the use of these agents as immunosuppressive therapy in patients receiving organ transplantation (8). The present study examines the quantitative relationships between the presence of infection and the degree and duration of leukopenia in patients with acute leukemia. The effect of changes in the level of circulating leukocytes on the occurrence, type and outcome of infections is also considered.

METHODS

The 52 patients selected for this study were first admitted to the Clinical Center of the National Institutes of Health during the period from August, 1959, to April, 1963.

The diagnosis of acute leukemia was confirmed by bone marrow examination in every patient. Thirty-four patients received similar initial antileukemic therapy consisting of 6-mercaptopurine and prednisone according to protocol of a study of the Leukemia Co-operative Study Group B (Protocol V) (9). The remaining patients received treatment with methyl glyoxal bis-(guanylhydrazone) (Methyl GAG) (10).

The clinical record of every patient was examined and all determinations of granulocytes, lymphocytes, and abnormal cells were tabulated. When the leukemic process was active, blood counts were obtained three times a week. When the leukemia was in remission, and the patients were otherwise healthy, the blood counts were recorded every 1 to 4 weeks. On days when no blood counts were available, the values were assumed to be the same as those next recorded. Patients were followed from initial admission at the onset of leukemia to death or until July 31, 1964.

White blood cell counts were determined by the Coulter counter technique. Twenty lambda of blood were diluted with 10 ml normal saline 1% saponin solution. The standard error for the procedure is 7.56% with a 1 to 2% error in the machine (11). Differentials were obtained by counting 100 cells, unless the white blood cell count was less than 1,000/mm³ blood, when only 25 or 50 cells were counted. Absolute levels of these blood cells were calculated from the white blood cell count and differential.

The absolute values of granulocytes and lymphocytes were grouped as: less than 100 cells/mm³ blood, 100 to 500 cells, 500 to 1,000 cells, 1,000 to 1,500 cells, 1,500 to 2,000 cells, and greater than 2,000 cells. Granulocytopenia and lymphopenia, when used in this paper, include all values less than 1,000 cells/mm³.
Severe granulocytopenia and severe lymphopenia indicate values less than 100 cells/mm$^3$ blood.

The clinical history and other laboratory data were carefully examined to determine the type, onset and duration of infection. This information was obtained independent of the hematological data to prevent any bias in dating onset and duration of infection. Infections were classified as: no infection; fevers without proven infection—this category includes fevers of unknown origin, fever which may have been due to the leukemic process itself, viral upper respiratory infections, and a few episodes of childhood exanthems; local infections—bacterial or fungal pharyngitis, tracheobronchitis, otitis media, skin abscesses, and cellulitis are included in this category; organ infections—this category includes pneumonia of any type, pulmonary and brain abscesses, and urinary tract infections; disseminated infections—septicemia, disseminated fungal, and disseminated viral infections (herpes simplex, cytomegalic inclusion disease) were included in this category. The term severe infection, when used herein, refers to the combination of organ and disseminated infections. Identified infection includes all types of proven infection.

RESULTS

Thirty-four patients with acute lymphocytic leukemia and 18 patients with acute myelogenous leukemia were included in the study.

The patients' ages varied from 1 to 77 years. The total time considered was 17,743 patient days. Survival ranged from 6 to 791 days (average, 329 days). Patients with acute myelogenous leukemia had a shorter survival time (average, 227 days) than patients with acute lymphocytic leukemia (average, 402 days). Five patients with acute lymphocytic leukemia were still living at the end of the study (July, 1964), having an average survival time of 426 days.

During 38% of the time studied (6,768 patient days) the patients had active acute leukemia as evidenced by a bone marrow category of A2 or A3 according to the criteria of the Acute Leukemia Co-operative Study Group (12). The patients were in bone marrow remission during the remaining 62% of the time. The patients with acute myelogenous leukemia spent less time in remission (43%) than the patients with acute lymphocytic leukemia (68%). Ten patients with acute myelogenous leukemia and four patients with acute lymphocytic leukemia never achieved a remission.

The patients spent approximately 50% of the time with granulocyte and lymphocyte levels less than 1,500/mm$^3$. Severe granulocytopenia (less than 100/mm$^3$) occurred more frequently than severe lymphopenia. Granulocytopenia occurred much more frequently during relapse than during remission. Granulocyte levels greater than 2,000/mm$^3$ were more common during remission but still were present less than one half of the time. The distribution of lymphocyte levels was very similar during relapse and remission.

LEUKOCYTE DISTRIBUTION

The patients with acute myelogenous leukemia had a different distribution of leukocytes than the patients with acute lymphocytic leukemia. Granulocytopenia (less than 1,000/mm$^3$) occurred more often in the patients with acute myelogenous leukemia, during both relapse and remission. Patients with acute lymphocytic leukemia spent much more time with granulocyte levels greater than 2,000/mm$^3$, but this difference was present only during remission. Lymphopenia was more prevalent in patients with acute myelogenous leukemia during remission and in patients with acute lymphocytic leukemia during relapse. During remission, lymphocyte levels greater than 2,000/mm$^3$ occurred three times more frequently in patients with acute lymphocytic leukemia.

GRANULOCYTES AND INFECTION

The effect of granulocyte levels on the presence of infection is illustrated in Figure 1. Since the relationship was similar for all types of proven infection, they have been combined. However, fever without proven infection was not closely related to the level of granulocytes. At less than 100 granulocytes/mm$^3$, 53% of the patient days were spent with identified infection. The
LYMPHOCYTES AND INFECTION

The effect of lymphocyte levels on the presence of identified infection is illustrated in Figure 3. This figure is very similar to the figure of granulocyte levels (Figure 1). As with granulocytes, fever without proven infection was not related to lymphocyte levels. The proportion of time spent with identified infection of all types decreased with increasing lymphocyte levels. However, identified infection continued to decrease with increasing lymphocyte levels above 1,500/mm$^3$, which was not true for granulocyte levels. Infection was always present more frequently in relapse than in remission at any given level of lymphocytes. This difference was even greater for lymphocytes than for granulocytes at every level.

The risk of infection at various lymphocyte levels was also examined (Figure 4). Severe lymphopenia (less than 100/mm$^3$) was not considered separately since the figures were unreliable, being based on only a few days (138 days for the entire study). The risk of developing severe in-

![Figure 1: The effect of granulocyte level on the presence of identified infection.](http://annals.org/)

![Figure 2: The frequency of infectious episodes related to the granulocyte level.](http://annals.org/)
Infection decreased with increasing lymphocyte levels, but the decrease was more gradual than it was for granulocytes (Figure 2). Again, severe infectious episodes occurred more frequently during relapse than during remission at every lymphocyte level.

**LEUKOCYTE LEVELS DURING INFECTIONS**

The granulocyte levels recorded during infectious episodes were examined next. The proportion of time spent with low granulocyte levels (less than 500/mm$^3$) increased with increasingly severe types of infection. Conversely, the proportion of time spent with higher granulocyte levels (greater than 1,500/mm$^3$) decreased with increasingly severe types of infection. Figure 5 illustrates this relationship for low granulocyte levels. During remission, the proportion of time spent with low granulocyte levels was relatively constant for all types of identified infection.

A similar analysis was made for lymphocyte levels. While the same general patterns existed for lymphocytes as were present for granulocytes, the relationships were less striking. Figure 6 illustrates the frequency of low lymphocyte levels (less than 100/mm$^3$) during infection.

**FIGURE 3.** The effect of the lymphocyte level on the presence of identified infection. The percentage of days spent with infection is plotted at each level of circulating lymphocytes. This percentage decreased with increasing lymphocyte level and was always higher during relapse than during remission.

**FIGURE 4.** The frequency of infectious episodes related to the lymphocyte level. The number of episodes of severe infection/1,000 days without severe infection is plotted for each lymphocyte level. The figures for < 100 lymphocytes/mm$^3$ and 100 to 500 lymphocytes/mm$^3$ are combined. The incidence figures for lymphocyte levels < 100/mm$^3$ were not statistically reliable because there were only a few days when such low lymphocyte levels were observed. The risk of developing infection decreased with increasing levels of circulating lymphocytes.

**FIGURE 5.** The frequency of granulocytopenia (<500 granulocytes/mm$^3$ blood) during infection. The percentage of days with granulocyte levels less than 500/mm$^3$ is plotted for each type of infection. In general, the more severe the infection, the greater the proportion of time spent with granulocytopenia. However, this relationship did not apply during remission.
FIGURE 6. The frequency of lymphopenia (<500 lymphocytes/mm$^3$ blood) during infection. The percentage of days with lymphocytes less than 500/mm$^3$ is plotted for each type of infection. The same curve for granulocytes (obtained from Figure 3) is included for comparison. The more severe the infection, the greater the proportion of time spent with lymphopenia. However, this relationship is not as pronounced for lymphocytes as for granulocytes. Since the figures were similar for lymphocytes during relapse and remission, they are not included.

Patients with acute lymphocytic leukemia had no infection during 82% of the time compared with 63% for patients with acute myelogenous leukemia. Each type of infection occurred more often in patients with acute myelogenous leukemia and this was true both during relapse and remission. Table 1 compares the time spent with severe (organ and disseminated) infections in patients with acute myelogenous and acute lymphocytic leukemia. While severe infection was much more prevalent at low levels of granulocytes (less than 1,500/mm$^3$) in patients with acute lymphocytic leukemia, this was not true for patients with acute myelogenous leukemia. Furthermore, this finding applied for both relapse and remission.

### Table 1. Time Spent with Severe Infections*

<table>
<thead>
<tr>
<th>Group</th>
<th>Granulocytes $&lt;1,500$</th>
<th>Lymphocytes $&lt;1,500$</th>
<th>Total Incidence</th>
<th>Incidence During Relapse</th>
<th>Incidence During Remission</th>
</tr>
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<tbody>
<tr>
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<td>19</td>
<td>14</td>
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<td>37</td>
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<tr>
<td>4</td>
<td>27</td>
<td>12</td>
<td>3</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

* Expressed as percentage of patient days.

### Table 2. Relationship Between Granulocytes and Lymphocytes During Severe Infection

<table>
<thead>
<tr>
<th>Group</th>
<th>Granulocytes $&lt;1,000$</th>
<th>Lymphocytes $&lt;1,000$</th>
<th>Total Incidence*</th>
<th>Incidence During Relapse*</th>
<th>Incidence During Remission*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
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<td>6</td>
<td>13</td>
<td>3</td>
<td>10</td>
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</tr>
</tbody>
</table>

* Expressed as number/1,000 days without severe infection.
RISK OF INFECTION (GRANULOCYTES VERSUS LYMPHOCYTES)

Table 2 indicates the relative importance of granulocytopenia and lymphopenia in the risk of developing severe infection. When both granulocytopenia and lymphopenia (Group 1) were present, the incidence of severe infection was highest. When granulocytopenia was present alone (Group 2), the incidence of severe infection was greater than when lymphopenia was present alone (Group 3). The lowest incidence of infection was observed when both granulocytopenia and lymphopenia were absent (Group 4). These relationships were very similar during relapse and remission, but again, the incidence of severe infection was always higher during relapse.

GRANULOCYTE FLUCTUATIONS RELATED TO INFECTION

The fluctuations in granulocyte levels during the week preceding severe infection were also examined (Table 3). This information was available in 115 of the 129 episodes of severe infection. Thirty-six per cent of the episodes were preceded by a fall in granulocyte level and in one half of these episodes the fall was greater than 500/mm$^3$. In one half of the episodes of severe infection, the granulocyte level either rose or remained greater than 1,000/mm$^3$.

Table 4 indicates the relationship between episodes of falling granulocytes and the occurrence of severe infection. The granulocyte level fell during 331 1-week periods. This does not include the episodes of falling granulocyte levels that occurred during severe infections. Twelve per cent of all episodes of falling granulocyte levels terminated in severe infection. The incidence was slightly higher if the granulocyte count fell more than 500/mm$^3$. When granulocytopenia was already present, any further reduction in the granulocyte count resulted in a 28% incidence of infection.
FIGURE 7. The effect of duration of granulocytopenia on the frequency of infection. The duration of granulocytopenia is plotted against the percentage of episodes resulting in infection. Along the abscissa are recorded the number of episodes of granulocytopenia (<1,000/mm$^3$) and severe granulocytopenia (<100/mm$^3$) for each time interval. The curves illustrate the percentage of episodes at both granulocyte levels resulting in any infection and in severe infection. The risk of developing infection increases the longer granulocytopenia is present and this risk is consistently greater at the lower granulocyte level.

If the granulocyte count was greater than 1,000/mm$^3$ at the beginning of the week and subsequently fell to less than 1,000/mm$^3$, there was a 14% incidence of severe infection. Very few severe infections occurred if the granulocyte count fell but remained greater than 1,000/mm$^3$. The final granulocyte count was the best index of the risk of developing severe infection. Regardless of the magnitude of the fall, the risk of developing infection increased as the final granulocyte count decreased. One of every four episodes during which the granulocyte count fell to less than 100/mm$^3$ terminated in severe infection. When these events were compared during relapse and remission, only a few differences were apparent. Although the risk of developing infection with any fall in granulocyte count was greater during relapse (16% versus 8%), if the fall exceeded 500 granulocytes/mm$^3$ the risk was the same for relapse and remission. If the granulocyte count fell to less than 100/mm$^3$ severe infection occurred in 24% of the episodes during relapse and 60% during remission.

Figure 7 depicts the risk of developing infection with increasing duration of granulocytopenia. Any episode of granulocytopenia, regardless of its duration, had a 39% chance of resulting in identified infection. As the duration of granulocytopenia lengthened the risk increased. Persistent granulocytopenia of 12 weeks' duration resulted in identified infection 100% of the time. The curve for severe infection was similar...
but at any given time, the risk of developing severe infection was less. When only episodes of severe granulocytopenia (less than 100/mm$^3$) were considered, the risk of developing infection was always greater and the slope of the curve was steeper. One hundred per cent of the episodes of severe granulocytopenia lasting 3 weeks or more were accompanied by identified infection.

RESPONSE TO INFECTION

The granulocytic response to severe infection was then analyzed. The changes in granulocyte level during the first week of the 129 episodes of severe infection are listed in Table 5. The granulocyte level fell or remained in the same category as often as it rose. When the granulocyte level changed in response to infection, the rise or fall was greater than 500/mm$^3$ in one half of the episodes. There was no difference in the granulocytic response to infection when relapse and remission were compared. The fatality rate of severe infection was related to changes in the granulocyte level during the first week of infection (Table 6). The fatality rate was highest for patients who had persistent severe granulocytopenia (less than 100/mm$^3$). When the granulocyte count fell to less than 100/mm$^3$ regardless of the initial level, the fatality rate was 72%. Patients had a lower

| TABLE 5. Changes in Granulocyte Levels During First Week of Severe Infection |
|--------------------------|------------------|
| Change in Granulocyte Level | Total |
| /mm$^3$ | no. | % |
| Any fall | 40 | 31 |
| Fall >500 | 19 | 15 |
| Any rise | 44 | 34 |
| Rise >500 | 27 | 21 |
| No change | 45 | 35 |
| Total | 129 |

<table>
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<th>Granulocyte Level</th>
<th>Episodes</th>
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</thead>
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<td>Initial</td>
<td>Change</td>
</tr>
<tr>
<td>/mm$^3$</td>
<td>no.</td>
</tr>
<tr>
<td>&lt;100</td>
<td>None</td>
</tr>
<tr>
<td>&lt;1,000</td>
<td>None or fall</td>
</tr>
<tr>
<td>&lt;1,000</td>
<td>Rise, but still &lt;1,000</td>
</tr>
<tr>
<td>&lt;1,000</td>
<td>Rise to &gt;1,000</td>
</tr>
<tr>
<td>&gt;1,000</td>
<td>Rise</td>
</tr>
</tbody>
</table>

The fatality rate if the granulocyte level rose regardless of the final level. The fatality rate was only approximately 30% if the final granulocyte level was greater than 1,000/mm$^3$, regardless of the initial level. In general, these relationships applied both during relapse and remission.

TYPES OF INFECTION

The severe infections considered above included 45 episodes of urinary tract infection, 43 of pneumonia, 27 of septicemia, and 10 of disseminated fungus. The fatality rate for all of the 129 episodes of severe infections was 41%; during relapse it was 47% and during remission 23%. Eighty per cent of disseminated fungus infections were fatal, 63% of septicemia, 35% of pneumonia, and 20% of urinary tract infection. The fatality rate was similar during relapse and remission for all types of infection except pneumonia (47% versus 13%). The mean duration of infection was similar for fatal and nonfatal episodes. However, if pneumonia persisted beyond 2 weeks, the fatality rate increased to 78%.

Ninety per cent of disseminated fungus infections and 78% of septicemia arose when the granulocyte level was less than 500/mm$^3$. However, only 15% of septicemia and 10% of disseminated fungus occurred when the granulocyte count was greater than 2,000/mm$^3$. Forty per cent of pneumonia and 38% of urinary tract infection occurred in the absence of granulo-
cytopenia. As might be expected, septicemia and disseminated fungus accounted for 58% of severe infections associated with severe granulocytopenia (less than 100/mm$^3$), and for only 25% of severe infections associated with a granulocyte level greater than 2,000/mm$^3$. Thirty-five per cent of pneumonia occurred during remission, accounting for 56% of all severe infections in remission. Only 18% of urinary tract infection, 10% of disseminated fungus infection, and 7% of septicemia occurred during remission.

**DISCUSSION**

The presence of infection in patients with acute leukemia is related to the level of circulating granulocytes and lymphocytes. All types of infection, ranging from a localized cellulitis at a venipuncture site to a disseminated fungus infection, are more likely to be present when the levels of granulocytes and lymphocytes are low. Furthermore, the lower the level of these leukocytes, the more likelihood that infection will be present. Not only is infection more likely to be present at low levels of granulocytes and lymphocytes, but when severe infection is present the leukocyte level will usually be low. Conversely, when infection is minimal or absent, the leukocyte level is more apt to be high. The great frequency of leukopenia with severe infection is not surprising, since it has been demonstrated that overwhelming infection may cause leukopenia (13). Leukopenia occurring during infection has been reported in alcoholics (14). Furthermore, one third of all severe infectious episodes in this study were accompanied by a fall in granulocyte count. Other observers have noted an even higher incidence of falling granulocyte levels associated with infection occurring in patients with acute leukemia (15, 16).

Infection was present more often during relapse at every leukocyte level. This suggests that other factors play a role in disposing to infection. Patients are apt to receive higher doses of antileukemic agents during relapse, and steroids are seldom administered as maintenance therapy during remission. Hersh, Carbone, Wong, and Freireich (17) have demonstrated that antileukemic agents depress antibody response to primary antigens. These agents are often toxic to the gastrointestinal tract, thus allowing infection to develop at sites of tissue damage. Methyl GAG frequently causes phlebitis, conjunctivitis, balanitis, and otitis media and these complications often predispose to bacterial infections. This may be one of the factors responsible for the higher incidence of infection in patients with acute myelogenous leukemia, irrespective of the granulocyte level. Other factors must also be involved since infection was more common in these patients with acute myelogenous leukemia during remission as well, at a time when Methyl GAG was not being administered.

The proportion of time spent with infection at higher granulocyte levels during relapse could be affected by patients having large numbers of circulating abnormal cells. Under these circumstances there may be a spuriously high absolute granulocyte count, since small errors in the differential, in the presence of a very high leukocyte count, would result in large errors in the absolute granulocyte count. In this study, very high numbers of circulating abnormal cells were seldom encountered, and had a negligible effect on any of these results.

Since the level of circulating leukocytes may be altered by the presence of infection, their effect on the risk of developing infection is best assessed by eliminating those days when infection is present. When this was done in the current study, the risk of developing identified infection was found to decrease with increasing levels of granulocytes and lymphocytes. It is interesting that no further reduction in the incidence of infection occurred above the level of 1,500 granulocytes/mm$^3$. Very low
levels of circulating granulocytes probably reflect complete absence of granulocyte reserves since there is such a striking decrease in the incidence of infection when the granulocyte level increases from less than 100 to greater than 500 granulocytes/mm³. These relationships were similar when the first, second, third, and fourth episodes of infection per patient were considered separately. Consequently, it can be concluded that the risk of developing infection is not influenced by preceding episodes of infection, if they have been completely eradicated.

Other investigators have also found a high incidence of infection associated with leukopenia in patients with leukemia. Boggs, Winthrop, and Maxwell (15) found that patients with low granulocyte levels on admission had a higher incidence of infection. However, this analysis failed to consider the intervening changes in granulocyte levels. The experience of this study indicates that leukocyte levels may fluctuate greatly from day to day, especially when patients are receiving antileukemic therapy. Miller and Shanbrom (2) found a high incidence of granulocytopenia associated with the onset of infection in patients with leukemia and lymphomas. A similar relationship was reported by Baker (5) in an autopsy series of disseminated fungus infection in acute leukemia.

The reason for this relationship between leukocyte level and occurrence of infection may be found in studies of the inflammatory response of patients with leukemia. Jaffe (18) concluded from an autopsy study that if granulopoiesis is completely exhausted, there is no defense reaction to infection. If some myeloid tissue capable of maturation remains, the patient with leukemia can react normally to infection. Braude, Feltes, and Brooks (19) discovered from phagocytic studies that the extreme susceptibility of patients with acute leukemia to bacterial infection is due to the marked decrease in total number of mature granulocytes rather than to a decrease in function of these mature granulocytes. Several studies using the skin window technique in patients with leukemia have demonstrated a deficiency of granulocytes in the inflammatory exudates if the number of granulocytes in the peripheral blood is reduced (20-22). Page and Good (23) found similar results in a patient with cyclic neutropenia and also in rabbits made granulocytopenic with nitrogen mustard.

Not only is the incidence of infection related to the granulocyte level, but also the outcome. The highest percentage of deaths occurred among patients with persistent severe granulocytopenia (less than 100/mm³). Those patients having initial granulocytopenia (less than 1,000/mm³) who experience a further fall in granulocyte level, also had a high fatality rate. Patients who could respond with any increment in granulocyte level had a more favorable prognosis. This experience differs from that of Raab, Hoeprich, Wintrobe, and Cartwright (24) who concluded that the outcome of infection was not related to granulocyte level. Obviously, the outcome of infection is influenced by the type of organism involved. Fungus infections are usually fatal, due to the inefficacy of currently available antifungal agents against Candida and Aspergillus species. On the other hand, staphylococcal infections are seldom fatal since the semisynthetic penicillins have become available (1).

While the onset of infection is related to the presence of lymphopenia, it is clear that granulocytes are of more importance. It is possible that the level of circulating lymphocytes does not reflect accurately the lymphocyte reserve. However, when there are few circulating granulocytes, the bone marrow is also usually deficient in granulocytes. Another possible explanation for the lesser importance of lymphocytes may be found in the experiments of Page and Good (23). They discovered that lymphocytes did not appear in inflammatory ex-
udates unless granulocytes were first present. Therefore, if the granulocyte level is low perhaps neither cell type will function adequately, but if the lymphocyte level is low, the granulocytes will still perform their functions.

Several aspects of granulocyte dynamics in patients with acute leukemia are useful in predicting risk of infection. A fall in granulocyte level carries a 12% risk of infection. Regardless of the magnitude of the fall, the risk is greater the lower the final granulocyte level. These results differ somewhat from those obtained by Silver, Beal, Schneiderman, and McCullough (3). They found that the median granulocyte count during periods without infection could not be correlated with the frequency of infection. However, 17 of 18 episodes of bacterial infection were preceded by a fall in granulocyte count. Since the time intervals are not mentioned, it is not possible to relate the results of their study to the present one. The most important factor in predicting risk of infection is the duration of granulocytopenia. There is a 60% risk of developing infection if granulocytopenia persists for 3 weeks. If the level of granulocytes is less than 100/mm$^3$, the risk increases to 100%. This fact must be taken into consideration when patients are undergoing cancer chemotherapy with agents that are able to depress the circulating granulocyte level.

Of course, the level of circulating granulocytes and lymphocytes is not the only factor predisposing to infection. As previously mentioned, antileukemic therapy may damage organs such as those of the gastrointestinal tract and allow infection to develop. The level of immune globulins and the ability to form antibodies are also very important. Furthermore, the reticuloendothelial system plays a crucial role in the body's response to infection (25, 26). Nevertheless, a knowledge of these relationships between leukocyte levels and infection may be very useful in understanding the infectious complications of acute leukemia and related hematological disorders.

**SUMMARY**

Granulocytopenia and lymphopenia occurred frequently in patients with acute leukemia, even during remission. The presence of infection was related to the level of circulating granulocytes and lymphocytes. The prevalence of all types of identified infection decreased with increasing levels of these leukocytes. However, fever without proven infection was not related to leukocyte levels. Furthermore, the proportion of time spent with granulocyte and lymphocyte levels less than 500/mm$^3$ increased with increasing severity of infection.

The incidence of infectious episodes also decreased with increasing levels of granulocytes and lymphocytes. A critical level existed for granulocytes (1,500/mm$^3$), above which level there was no further decrease in the incidence of infection. At every level of granulocytes and lymphocytes, the frequency of infectious episodes was greater during relapse. Infection occurred most commonly when both granulocytopenia and lymphopenia were present. However, the incidence of infection was greater in the presence of granulocytopenia alone than in the presence of lymphopenia alone.

Only 36% of severe infectious episodes were preceded by a fall in granulocyte level. Twelve percent of all episodes of falling granulocyte levels terminated in severe infection. However, if granulocytopenia was already present, a further fall in granulocyte level resulted in a 28% incidence of infection. The best indicator of the risk of infection was not the magnitude of the fall in granulocyte level, but rather the final granulocyte count. The risk of developing infection increased with increasing duration of granulocytopenia.

Although there was no characteristic granulocytic response during infection, the fatality rate for infection was related to the granulocyte level. The highest rate oc-
curred among patients with persistent severe granulocytopenia, but those patients with low granulocyte levels who were able to respond to infection with an increment in granulocyte level had a more favorable prognosis.

ACKNOWLEDGMENT

The authors wish to express thanks to Mrs. Grace Ensminger for assistance in preparing this manuscript.

SUMARIO IN INTERLINGUA

Le nivellos de granulocytos e de lymphocytes de 52 patientes con leucemia acute eseva tabulate durante le complete curso de lor morbo. Esseva includite in le studio un total de 17.743 dies/patiente. Le patientes se trovava in remission osseo-medullari de lor leucemia acute durante 62 pro cento del tempore. Granulocytopenia (minus que 1000 per mm³) e lymphopenia occurreva frequentemente, mesmo durante periodos de remission. Le procentage del tempore durante le qual le patiente habeva un identificate infection declinava con le alitamento del nivellos de granulocytos. Iste relation valeva tanto durante recidivas como durante periodos de remission, sed le proportion del tempore associate con infection a omne nivello de granulocytos esseva plus grande durante recidivas. Simile relations existeva pro lymphocytes. Le pro­portion del tempore con basse nivellos de granulocytos o de lymphocytes (minus que 500 per mm³) cresceva con le crescimento del severitate del infections.

Ben que le risco de contraer infections eseva relationate tanto con le nivellos del granulocytos como etiam con illos del lymphocytes, le nivellos de granulocytos eseva claramente plus importante. Infections occurreva plus frequentemente in granulocytopenia sol que in lymphopenia sol.

Treinta-sex pro cento del episodios de infection sever (pneumonia, infection del vias urinari, septicemia, infection fungal constitutional, etc.) eseva associate con un declino del nivello de granulocytos durante le septimana anterior. Dece-duo pro cento del omné episodios de descendent nivellos de granulocytos observate individualmente pro le varie septimanas se terminava in infection sever. Omné episodio de granulocytopenia, sin reguardo a su duration, habeva un probabilite de 39 pro cento de resultar in un infection identificabile. Como le duration del granulocytopenia se prolongava, assi le risco se elevava.

Infection sever causava un declino sub­sequente in le nivello de granulocytos tanto frequentemente como illo causava un augmento de ille nivello. Le responsa granulocytic a infection eseva simile durante recidivas e periodos de remission. Le mortalitate in consequentia de infection sever eseva plus alte inter patientes qui habeva nivellos granulocytic persistentemente infra 100 celular per mm³. Le mortalitate eseva plus basse pro patientes respondente a infection con un aug­mento de lor nivellos granulocytic.

REFERENCES


