According to classical morphological criteria, peripheral blood mononuclear cells are composed of two major populations of cells: the monocytes and lymphocytes. More recently, lymphocytes, by use of a variety of surface markers, could be further divided into B cells and T cells. These two lymphocyte subsets and the monocytes account for approximately 90% of peripheral blood mononuclear cells. Careful morphological analysis of the remaining cells has more recently enabled the delineation of another population of circulating mononuclear cells. These cells, according to their two most prominent morphological characteristics, were designated as large granular lymphocytes (LGL). LGL originate from the bone marrow, as suggested by their mode of reappearance after total body irradiation and autologous or allogeneic bone marrow transplantation. It has also been shown that diseases or irradiation of the bone marrow lead to severely depressed natural killer (NK) activity. LGL reside primarily in blood and spleen, sparing the thymus and lymph nodes.

LGL also differ from conventional lymphocytes with respect to their surface antigen patterns: only a subset exhibits reactivity with T cell-specific monoclonal antibodies such as OKT3, OKT8, and OKT4, but most of them express other surface antigens not shared by the majority of B or T cells. LGL also reveal a unique buoyant density, which enabled purification for further functional analyses. These investigations indicated that LGL contain virtually all effector cells capable of lysing the human tumor line K562 in a natural killer cell-like fashion, moreover, LGL-enriched suspensions were found to be highly effective in mediating antibody-dependent cellular cytotoxicity (ADCC). It thus appears the LGL represent a new subset of mononuclear cells controlling self-integrity by virtue of their capacity to exert NK lysis and ADCC. Although various aspects of LGL have extensively been studied in healthy individuals, very little is known about their frequency and their relationship to natural killing in disease states. Such data are presented here.

Materials and Methods

Patients

In this study, peripheral blood mononuclear cells from 171 patients (89 male, 82 female; age range 16–87 years) and 42 healthy controls (27 male, 15 female; age range 14–80 years) were assessed in parallel for the numbers of LGL and for NK lysis. Patients' diagnoses comprised a variety of nonmalignant states, such as severe aplastic anemia (4 cases), myelodysplasia (6 cases), cadaveric kidney transplant recipients (32 cases), and autoimmune diseases (34 cases); the latter group was composed of 6 cases with systemic lupus erythematosus, 8 with rheumatoid arthritis (RA), and 20 cases with immune cytopenias, panarteritis nodosa, or Sjögren's syndrome. Treatment of patients with severe aplastic anemia and with myelodysplasia consisted of transfusions with red blood cells or platelets, respectively; none of the cases suffering from autoimmune disorders, except four of the lupus patients, at the time of investigation received immunosuppressive drugs; all cadaveric kidney allograft recipients were under prophylactic medication with cyclosporin A or azathioprine and prednisone. Patients studied with malignant diseases suffered from malignant lymphomas (non-Hodgkin's lymphomas, 6 cases; Hodgkin's lymphomas, 15 cases), solid tumors (38 cases) or leukemias (ALL, 8 cases; CML, 11 cases; AML, 8 cases). Eleven of the Hodgkin's disease patients and three with AML, at the time of investigation, were in complete clinical remission subsequent to treatment with cytotoxic drugs and/or radiotherapy; 14 of the...
patients with solid tumors and all multiple myeloma cases had previously been treated with chemotherapy and/or surgery plus radiotherapy. Follow-up data on LGL and NK lysis of a further patient who underwent autologous bone marrow transplantation after high-dose cyclophosphamide and total body irradiation with 1,000 rad subsequent to allogeneic liver transplantation for treatment of metastatic breast cancer are also included in this series. Also presented are data from seven breast cancer patients with malignant effusions who underwent local instillation of alpha-interferon (1 case) or beta-interferon; 5 x 10^6 U of interferon (Virogen, Basel, Switzerland) were injected every alternate day, and the numbers of LGL and NK lysis were evaluated on peripheral blood mononuclear cells before and 1, 4, 24, and 48 hours after each instillation (details of this study will be reported elsewhere).)

**Separation of Cells**

Mononuclear cells were separated from heparinized venous blood samples by means of flotation on Ficoll-Isopaque (Lymphoprep, Nyegaard, Oslo, Norway). Cells were washed three times in tissue culture medium RPMI 1640 (GIBCO, Grand Island, NY), supplemented with 20 mmol/L HEPES buffer (GIBCO). Some 2 x 10^6 viable cells were then resuspended in 1.0 mL of the above medium, which was further supplemented with 10% heat-inactivated (56°C, 30 minutes) fetal calf serum (Gibco Europa, Glasgow, UK).

**Evaluation of LGL**

Smears from 5 x 10^6 cells were performed using a cytocentrifuge (Shandon Southern Products Ltd, Cheshire, UK). Slides were stained with May-Grünwald-Giemsa. They were read blind at a magnification of 800 x, using oil immersion, by three independent investigators. Per slide, at least 600 cells were investigated. LGL were defined as large lymphoid cells with three or more azurophilic granules contained in a pale and abundant cytoplasm. Morphological examples of this cell type are given in Fig 1 (see Gast et al) . In certain disease states, such as myeloproliferative syndromes, large numbers of myeloid precursor cells were present in mononuclear cell suspensions obtained by fractionation on Ficoll-Isopaque. Here, particular efforts were made to discriminate between LGL and granulated myeloid precursor cells. This was achieved by parallel evaluation of slides stained for acid phosphatase and unspecific esterases, respectively.

Results are expressed as the mean of the percentages of LGL counted by three independent investigators. Morphological evaluation of LGL, in our hands, represented a reliable and reproducible mean. Based on the evaluation of three independent investigators in the present series, the coefficient of variation was 23%. LGL frequency is either given as the relative percentage among peripheral blood mononuclear cells after separation on Ficoll-Isopaque or as the absolute number per milliliter of peripheral blood. The latter counts were obtained by multiplication of the percent LGL with the absolute number per milliliter of peripheral blood. The latter values were calculated according to the formula:

\[
\text{Percent specific lysis} = \frac{\text{cpm (experimental release)} - \text{cpm (spontaneous release)}}{\text{cpm (maximum release)} - \text{cpm (spontaneous release)}} \times 100
\]

Maximum release was defined by lysis of K562 targets in 1% Triton X-100 (New England Nuclear, Boston, Mass). Spontaneous release represents isotope release from target cells incubated in the absence of effector cells and did not exceed 20% during a 12-hour incubation period. All results represent mean values of triplicate cultures. In previous experiments, it has been demonstrated that results obtained with the ³⁵S-methionine release are comparable to those obtained by means of the conventional ¹¹Cr assay. They are either expressed as percent specific lysis for a given target:effector ratio, or as specific lysis at a given target:effector ratio per milliliter of peripheral blood. The latter values were calculated according to the formula: specific lysis/mL of blood = (A x B)/C. A represents the number of mononuclear cells obtained from 1 mL of heparinized blood; B is the percentage of specific lysis of K562 targets at a target:effector ratio of 1:25; and C is the number of effector cells needed to achieve B lysis.

For comparison of the different disease groups, only data obtained at a target:effector ratio of 1:25 are demonstrated in the results section. This is because, at this ratio, the specific lysis values of all normal controls and of the vast majority of the patients were located at the linear part of the lytic curve.

Results from patients and controls were collected over a period of 24 months. During this time, standardization of both methods, evaluation of LGL and assessment of K562 lysis, was attempted. (A) First, freshly prepared mononuclear blood cells from 30 healthy laboratory workers were used as a reference. The values of the latter remained remarkably constant over this period of time: %LGL for this group was 21% ± 10% (mean ± 1 SD) and 23% ± 11% during the second year; %NK lysis was 28% ± 12% (mean ± 1 SD) during the first and 30% ± 12% during the second year. Although considerable fluctuations were observed in the follow-up of single individuals, controls exhibiting low or very high counts in either assay remained remarkably stable. (B) Interassay standardization was further carried out by distributing the collection of samples from homogenous groups of patients over the whole period of the study, and (C) by retesting 25 patients in steady states of their diseases several times. The coefficient of variation of this group was 27% for LGL and 36% for NK lysis.

**Target Cell Binding Assay**

We have previously described optimal conditions that enable preferential binding of enriched suspensions of LGL to K562 target cells. Briefly, K562 cells and effector cells were mixed at a ratio of 1:5 in round-bottomed plastic tubes (Becton Dickinson Co, Falcon, Oxnard, Calif). Cells were pelleted at room temperature for 5
minutes at 30 g and were then further incubated in a water bath at 37°C for 30 minutes. After vigorous resuspension by means of forced pipetting, an equal volume of 1% eosin solution was added. The numbers of viable peripheral blood mononuclear cells attached to 100 K562 blasts were evaluated in a Bürker hemocytometer. Results are expressed as the percentage of mononuclear cells bound to K562 targets at the target:effector ratio given above. Values represent the mean of the counts of two independent investigators.

Statistics

Statistical analysis was performed using the Kruskal-Wallis one-way analysis of variance by ranks and the Wilcoxon test. Correlations were estimated by the Spearman rank correlation coefficient.

RESULTS

Relative Frequency of LGL and their Relationship to NK Lysis Under Steady-state Conditions in Various Diseases

Analysis of a larger group of healthy controls revealed that 14% (5th-95th percentile: 6%-23%) of peripheral blood mononuclear cells separated by means of density fractionation on Ficoll-Isopaque exhibit the morphological characteristics of LGL. Examples of this morphology are demonstrated in Fig 1. Cytochemical staining performed in parallel revealed that these cells can be clearly distinguished from granulated myeloid precursor cells. As already detailed in Materials and Methods, morphological definition of LGL was reliable and reproducible. First evidence for the view that LGL are crucially involved in lysis of K562 targets was obtained by plotting their relative frequencies against the percent of specific lysis of K562 targets. When this analysis was performed for the normal controls, a weak but statistically significant correlation was obtained ($r = .3741, P < .05$, target:effector ratio 1:25).

<table>
<thead>
<tr>
<th>Diagnosis*</th>
<th>No. of Cases</th>
<th>Median Percent LGL (Range, 5th-95th Percentile)</th>
<th>$P$ Values vs Normal Controls</th>
<th>Median Percent NK Lysis$+$ (Range, 5th-95th Percentile)</th>
<th>$P$ Values vs Normal Controls</th>
<th>Ratio I/II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>42</td>
<td>14 (5-29;6-23)</td>
<td>.001</td>
<td>29 (9-57;11-45)</td>
<td>.001</td>
<td>1</td>
</tr>
<tr>
<td>Nonmalignant diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune states</td>
<td>34</td>
<td>6 (0-43;1-16)</td>
<td>&lt;.001</td>
<td>17 (0-41;2-34)</td>
<td>&lt;.001</td>
<td>0.7</td>
</tr>
<tr>
<td>SLE</td>
<td>6</td>
<td>4 (0-11)</td>
<td>8 (0-33)</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>8</td>
<td>7 (1-22)</td>
<td>21 (7-37)</td>
<td>0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>20</td>
<td>7 (1-43)</td>
<td>17 (2-41)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allograft recipients</td>
<td>32</td>
<td>5 (1-15;2-9)</td>
<td>&lt;.00001</td>
<td>17 (0-32.6-28)</td>
<td>&lt;.00001</td>
<td>0.6</td>
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<tr>
<td>SAA</td>
<td>4</td>
<td>11 (2-6)</td>
<td>NS</td>
<td>1.3</td>
<td></td>
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<tr>
<td>Myelodyplasias</td>
<td>5</td>
<td>5 (2-15)</td>
<td>NS</td>
<td>9 (0-24)</td>
<td>NS</td>
<td>1.2</td>
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<tr>
<td>Malignant diseases, untreated</td>
<td>52</td>
<td>7 (0-22;0-14)</td>
<td>&lt;.00001</td>
<td>8 (0-67;0-20)</td>
<td>&lt;.00001</td>
<td>1.8</td>
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<td>NHL</td>
<td>6</td>
<td>5 (0-15)</td>
<td>9 (3-18)</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>4</td>
<td>12 (8-13)</td>
<td>22 (4-38)</td>
<td>1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid tumors</td>
<td>20</td>
<td>8 (2-20)</td>
<td>11 (0-67)</td>
<td>1.5</td>
<td></td>
<td></td>
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<tr>
<td>AML</td>
<td>5</td>
<td>3 (0-6)</td>
<td>0 (0-4)</td>
<td>$\infty$</td>
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<td></td>
</tr>
<tr>
<td>CML</td>
<td>7</td>
<td>6 (0-22)</td>
<td>0 (0-16)</td>
<td>$\infty$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLL, B type</td>
<td>7</td>
<td>6 (0-14)</td>
<td>9 (1-18)</td>
<td>1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLL, T type</td>
<td>2</td>
<td>2 (0-3)</td>
<td>1 (0-2)</td>
<td>4.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLL, NK type</td>
<td>1</td>
<td>82</td>
<td>75</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Malignant diseases, treated</td>
<td>43</td>
<td>15 (0-41;2-33)</td>
<td>NS</td>
<td>24 (0-59;2-55)</td>
<td>&lt;.05</td>
<td>1.3</td>
</tr>
<tr>
<td>HD, CR$+$</td>
<td>11</td>
<td>16 (8-41)</td>
<td>32 (4-59)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid tumors</td>
<td>18</td>
<td>14 (2-36)</td>
<td>24 (2-38)</td>
<td>1.2</td>
<td></td>
<td></td>
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<tr>
<td>CLL</td>
<td>4</td>
<td>1 (0-11)</td>
<td>5 (1-12)</td>
<td>0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML, CR$+$</td>
<td>3</td>
<td>22 (15-29)</td>
<td>19 (0-43)</td>
<td>2.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple myelomas</td>
<td>7</td>
<td>16 (7-32)</td>
<td>27 (0-59)</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*SAA, severe aplastic anemia; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; NHL, non-Hodgkin's lymphomas; HD, Hodgkin's lymphomas; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia.

†K562 targets, E:T ratio = 25:1.

§I and II expressed as percent of the normal control values, according to the formula, by using the median values of %LGL and %NK lysis:

$$I/II = \frac{\%LGL \text{ test}}{\%LGL \text{ controls}} \times 100 \times \frac{\%NK \text{ lysis test}}{\%NK \text{ lysis controls}} \times 100$$

$\$CR, complete remission defined by complete disappearance of all disease manifestations lasting for a minimum of 12 months.
Comparison of the data from normal controls with those obtained from a variety of nonmalignant diseases revealed a statistically significant reduction of the relative numbers of LGL in the latter group \((P < .0001)\). A composition of these results and their statistical analysis is shown in Table I. Also reduced \((P < .001)\) was the capacity of peripheral blood mononuclear cells from these patients to lyse K562 targets (Table 1). The reduction of NK lysis corresponded to the extent of diminution of LGL demonstrated by a \%LGL/\%K562 lysis ratio similar to that obtained in healthy controls (range 0.6–1.3). Normal or reduced numbers of LGL were observed in the overwhelming majority of patients with untreated malignancies (findings are presented in Table 1). The only exception was a 70-year-old white female presenting with atypical lymphoid leukemia and marked splenomegaly.

Atypical lymphoid cells in this case exhibited the morphological features of LGL and were also highly efficient in mediating NK lysis and ADCC. Morphological examples of this patient’s cells are shown in Fig 2 (A,B). For the whole group of patients with malignant diseases, LGL counts were significantly reduced when compared with normal controls \((P < .0001)\). NK lysis in patients with untreated malignancies, except the above-mentioned atypical CLL, was also diminished, and this reduction was statistically significant for the whole group \((P < .0001)\). Diminution of NK lysis, however, was more pronounced than that of the numbers of LGL in nonmalignant states, indicated by a \% LGL/\% NK lysis ratio ranging from 1.1 to \(\infty \) \((P < .001)\).

Evaluation of LGL of mononuclear cell suspensions of patients with malignant diseases following treat-
ment revealed different results. The numbers of LGL in complete remission states of Hodgkin’s lymphomas or of acute myelogeneous leukemias, as well as of solid tumors and multiple myelomas under chemotherapy, were almost normal and did not differ statistically significantly from normal controls (Table 1). This was accompanied by an almost normal NK function (Table 1).

In conclusion, comparison of LGL numbers with NK function in various disease states indicated that reduction of LGL is invariably associated with impaired NK function. On the other hand, reduction of lytic capacity sometimes markedly exceeded the diminution of the relative numbers of LGL. The observation that normal lytic capacity in the presence of reduced percentages of LGL never occurs is of particular importance. These findings, together with those presented by others, support the view that LGL represent the effector cell for NK lysis of K562 tumor blasts, but additional factors are involved in regulating the functional efficacy of these cells.

**Absolute Numbers of LGL Among Circulating Peripheral Blood Mononuclear Cells in Various Disease States**

NK cells have been indicated as playing a crucial role in the elimination of certain virus-transformed or malignant cells. If so, their absolute, rather than their relative, numbers presumably determine the biologic efficiency of this cellular defense mechanism. Knowledge about the absolute numbers of NK cells might be of particular importance when diseases such as leukemias, which are frequently associated with markedly increased absolute numbers of mononuclear blood cells, are studied. We have addressed this question by calculating the absolute numbers of LGL per milliliter of venous blood. Data are presented in Table 2. As shown, in all nonmalignant states and in untreated states, such as solid tumors, the numbers of LGL/mL were significantly reduced ($P < .005$). In untreated myelogeneous leukemias (AML, CML) and Hodgkin’s lymphomas, however, the average number of LGL/mL did not significantly differ from normal controls. In contrast, a statistically significant increase of the absolute LGL numbers was observed in non-Hodgkin’s lymphomas and CLL cases ($P < .001$). In chemotherapy-induced remission states of acute leukemias, a tendency to increased numbers of LGL/mL compared to untreated states was detected ($P < .05$), whereas in solid tumors, chemotherapy resulted in a significant reduction of absolute numbers of LGL ($P < .02$).

**Frequency of LGL and Their Relationship to NK Lysis After Bone Marrow Transplantation or Treatment With Interferon.**

Further evidence for the existence of an intimate relationship between LGL morphology and the functional capacity to lyse K562 cells was obtained in follow-up studies of patients undergoing bone marrow transplantation or treatment with interferon for eradication of metastatic malignant diseases. LGL and NK lysis data of autologous bone marrow transplantation recipients after high-dose cyclophosphamide and total body irradiation are shown in Fig 3. A strikingly close correlation between the patterns of both LGL and NK lysis was observed. From day $-1$ to day $+9$, neither LGL nor NK function was demonstrable. After day

---

**Table 2. Absolute Numbers of LGL in Various Disease States**

<table>
<thead>
<tr>
<th>Diagnosis*</th>
<th>LGL x 10$^{-4}$/mL</th>
<th>No. of Cases</th>
<th>Median (Range; 5th-95th Percentile)</th>
<th>$P$ Values vs Normal Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal controls</td>
<td>42</td>
<td>17 (12-62;3-46)</td>
<td></td>
<td>&lt;=.00001</td>
</tr>
<tr>
<td>Nonmalignant diseases</td>
<td>39</td>
<td>2 (0-18;0-8)</td>
<td></td>
<td>.0001</td>
</tr>
<tr>
<td>SAA</td>
<td>1</td>
<td>5</td>
<td></td>
<td>.00001</td>
</tr>
<tr>
<td>Myelodysplasia</td>
<td>6</td>
<td>6 (2-18)</td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>Allograft recipients</td>
<td>29</td>
<td>2 (0-10)</td>
<td></td>
<td>.00001</td>
</tr>
<tr>
<td>Malignant diseases, untreated</td>
<td>63</td>
<td>13 (0-278;2-46)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>NHL + CLL (B and T type)</td>
<td>10</td>
<td>46 (20-90)</td>
<td></td>
<td>.002</td>
</tr>
<tr>
<td>CLL, NK type</td>
<td>1</td>
<td>278</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>HD</td>
<td>4</td>
<td>10 (5-15)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>AML</td>
<td>3</td>
<td>6 (2-14)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>CML</td>
<td>7</td>
<td>16 (0-22)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>29</td>
<td>10 (1-43)</td>
<td></td>
<td>.005</td>
</tr>
<tr>
<td>Malignant diseases, treated</td>
<td>31</td>
<td>17 (0-88;2-43)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>HD, CR</td>
<td>10</td>
<td>22 (2-88)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Acute leukemias, CR</td>
<td>6</td>
<td>25 (13-63)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>11</td>
<td>4 (0-13)</td>
<td></td>
<td>.0001</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>4</td>
<td>26 (19-50)</td>
<td></td>
<td>NS</td>
</tr>
</tbody>
</table>

*For abbreviations, see legend to Table 1.*

---

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+10, both parameters increased in parallel. Our interpretation of these data is that a bone marrow-derived cell is responsible for both LGL morphology and NK lysis.

In contrast to in vitro findings, the in vivo application of interferon is known to cause transitory depression of NK lysis. In a group of patients with metastatic malignant diseases, we have studied whether decreased NK lysis after interferon treatment is associated with reduced numbers of LGL. Each application of interferon was followed by a prompt fall in both parameters investigated (data not shown). The differences, however, were not statistically significant. In conclusion, we state that the close relationship between LGL and NK function is not only seen under steady-state conditions, but is also apparent in conditions affecting production or the intravascular lifespan of LGL.

LGL and Their Relationship to Target Binding Cells in Various Disease States

Also investigated was the relationship between LGL and the numbers of target binding cells (TBC) in disease states. Results are shown in Fig 4. As demonstrated, no significant correlation between the percentages of TBC and LGL was observed. Moreover, morphological evaluation of cytocentrifuge smears suggested that LGL, under the conditions applied, represented only a minority population among TBCs (results not shown). Significant numbers of TBC were also seen in patients who were highly deficient in LGL and NK lysis. On the other hand, extremely high numbers of TBC, reaching levels of more than 40%, were found in the patient suffering from LGL leukemia. Based on these findings and those previously published by others, we conclude that the simple evaluation of TBC in suspension does not represent a reliable means of assessing the frequency of NK effector cells.

DISCUSSION

Growing evidence in experimental animal systems and man suggests that NK cells exhibiting LGL morphology represent a host defense mechanism directed against certain malignant or virus-transformed cells. Although the exact biologic role of this immune surveillance system has not yet been clearly determined, this newly discovered defense mechanism has attracted much interest. Clinical implications have been further suggested by the observation of impaired NK lysis associated with advanced malignant or autoimmune states, as well as with certain fatal virus infections. Although functional impairments of NK lysis have been demonstrated in a variety of different diseases, the exact mechanism of this alteration is still poorly understood. The aim of this study was to evaluate the numbers of LGL as the presumable NK effector cell in different clinical situations and to correlate these results with those obtained by in vitro testing of cytolytic NK function.
In this study, two independent sets of observations strongly suggested that LGL represent the effector cell mediating spontaneous lysis of K562 targets: (1) a statistically significant correlation was demonstrated between the relative numbers of LGL and the NK lysis for both normal controls ($r = .3741$, $N = 42$) and all patients studied ($r = .7912$, $N = 157$); (2) shifts in the numbers of LGL following total body irradiation and autologous bone marrow reconstitution, or subsequent to treatment with polychemotherapy or radiotherapy, were associated with a concomitant shift in the NK lysis. Although reduction of LGL was invariably associated with impaired NK lysis, normal LGL numbers were not always accompanied by normal function. All homogeneous groups of malignant disorders and, in particular, solid tumors and leukemias, exhibited a pattern with preferential reduction of NK lysis even in the presence of normal numbers of LGL. Thus, one must conclude, in agreement with recent reports, that defects other than the simple reduction of effector cells are involved in this malignancy-associated impairment of NK function.

From the hematologist’s point of view, it is most gratifying that a new cell type, which seems to mediate biologically meaningful functions, can be defined by simple morphological means. The clinical data on the frequency of these cells and their relationship to natural immune functions presented here suggest that LGL should be evaluated on a large scale clinical basis. Such studies are now in progress at our institution.

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Human large granular lymphocytes and their relationship to natural killer cell activity in various disease states

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