Cell Surface Markers in Acute Lymphoblastic Leukemia*

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ABSTRACT

During the last nine years, two important methodologies have been used to characterize the cell surfaces of normal lymphocytes and malignant lymphoblasts. Normal mature T-cells have a receptor for sheep erythrocytes (E+) while mature B-cells bear membrane-bound immunoglobulin molecules (sIg+). These two findings can be used to divide acute lymphoblastic leukemia of childhood into three major groups; B-cell leukemia (sIg+ E-), which is rare (approximately 2 percent) and has the poorest prognosis, T-cell leukemia (sIg-, E+) which is more common (10 percent) but also has a poor prognosis and null cell leukemia (sIg-, E-) which is the most common (85 percent) and has the best prognosis.

By the use of additional immunological methods, subgroups within T-cell leukemia and null cell leukemia have also been proposed. One of the most valuable of these additional methods is the detection of surface antigens. Three of the more commonly detected antigens currently being evaluated are (1) common leukemia antigen (cALL), (2) a normal B lymphocyte antigen the Ia antigen (Ia) which is not generally expressed on most T lymphocytes and (3) a normal T lymphocyte antigen (T) not expressed on B lymphocytes. Within null cell leukemia, the most commonly identified and probably the largest subgroup is Ia+, cALL+, T-, E-, sIg-. In another but smaller subgroup within null cell leukemia, the lymphoblasts contain cytoplasmic immunoglobulin but do not express surface immunoglobulins or E receptors. This subgroup is designated pre B-cell leukemia. Subgroups with T-cell leukemia have also been suggested. These include T+ E-, T+ E+, in which the rosettes are thermodlabile and T+ E+, in which the rosettes are thermostable. Whether or not there are any prognostic differences in these three subgroups remains to be determined.

Introduction

Acute lymphoblastic leukemia (ALL) in children is morphologically a relatively homogeneous entity. However, a wide range of clinical responses to therapy observed over the past two decades has suggested that ALL is a heterogeneous disease. Early extensive evaluation of clinical and laboratory data identified a number of prognostic factors such as age, initial white count, presence or absence of a mediastinal mass. While these prog-
nostic factors have been of value, the search for surface markers as correlates of major groups within ALL has dominated leukemia research for the past nine years and is the principle topic of this review.

In the early 1970's, several laboratories reported that normal human peripheral blood T-lymphocytes spontaneously formed rosettes with sheep erythrocytes. During the same period of time, the demonstration of surface immunoglobulin on peripheral B-cells became a common laboratory procedure. These two discoveries were applied to bone marrow lymphoblasts obtained from children with leukemia and have resulted in the identification of three major groups within this disease: T-cell leukemia, B-cell leukemia and null cell leukemia.

Other methodologies have also been applied to ALL cells to identify further subgroups based on cytogenetics, cell culture growth characteristics, etc. Subtle morphological differences based on light microscopy have been used to characterize blast cells. An international cooperative committee proposed the French-American-British (FAB) classification of ALL which subdivides ALL into three morphological types: L1, L2 and L3. These morphological groups have been related to surface marker studies and have been shown recently to be of prognostic significance.38

The application of human lymphocyte differentiation and subpopulations to the immunological diagnosis of other disorders has been the subject of recent reviews which are recommended for a more detailed background study of this important and rapidly developing area of clinical and laboratory research.20,46,50

Surface Markers

Cell surface markers have been used to identify functional subdivisions of lymphocytes. For example, B-lymphocytes are identified by the presence of surface immunoglobulin. A precursor cell of the mature B-cell has been demonstrated to have cytoplasmic immunoglobulin (cIg) but not surface immunoglobulins (sIg) and is designated a pre-B-cell. A mature lymphocyte has receptors for sheep erythrocytes (E). For human cells, receptor for complement and the Fc portion of IgG were initially thought to be limited to B-lymphocytes. Subsequent research has shown that these two receptors can also reside on subpopulations of some T-cells and are therefore not used independently to identify either T or B-cells.

The Major Groups Within ALL

For the purpose of discussion, ALL will be divided into three major groups. T-cell, null cell and B-cell leukemia. T-cell leukemia will be limited to those cases that are E-receptor positive. No distinction will be made in this section as to thermodatable and thermostable subgroups of E-receptor positive cases. B cell disease will be limited to those cases that are surface immunoglobulin positive. In some of the early literature, the presence of a Fc receptor or complement receptor was used to identify cases designated B-cell disease or B-cell leukemia. As both of these receptors can be found on both T-cells as well as B-cells, these markers will not be accepted as characterizing B-cell disease for this discussion.

Null cell disease will include those cases that do not express either the E-receptor or have detectable surface immunoglobulin (sIg). In many articles, null cell disease is diagnosed by exclusion and is referred to as non-T non-B cell disease.

B-CELL LEUKEMIA

B-cell leukemia is the rarest of the major or well established groups. This group has a very poor prognosis, as response to chemotherapy results in short remis-
sions. The patients tend to be older and a male predominance has been suggested. Although leukemic presentation of Burkitt's lymphoma is unusual, there are a number of characteristics which suggest that B-cell leukemia and Burkitt's lymphoma are closely related or are even the same disease. For example, a 14q+ chromosome has been reported in both B-cell leukemia and Burkitt's lymphoma. The morphology of both is of the L3 type and malignant B-cells have been described as "Burkitt cells."

**NULL CELL LEUKEMIA**

Approximately 85 percent of childhood ALL is classified as null cell leukemia. Null cell leukemia has the best prognosis of the major groups. The clinical characteristics of this group include those generally associated with good prognosis such as younger age, lack of tumor mass at presentation, and a lower initial white cell count. The bone marrow is thought to be the origin of null cell leukemia. These patients respond well to both induction and remission therapy. This is true for both median duration of remission and survival.

**T-CELL LEUKEMIA**

T-cell leukemia accounts for approximately 10 percent of childhood cases of ALL. T-cell leukemia has a poorer prognosis than null cell leukemia, but a better one than B-cell leukemia. T-cell leukemia occurs more frequently in males than females and in older children, the median age being 10 to 12 years in studies limited to children. There is a high frequency of leukemic masses (76 percent reported in one series) of which approximately 40 percent will be a mediastinal mass. Patients with T-cell leukemia also present with high initial leukocyte counts, mean values being reported in the neighborhood of 150,000 cells per μl. Many of these clinical characteristics, i.e. a high white cell count, mediastinal mass and older patient population, were known to be of poor prognostic significance prior to the application of markers to ALL.

The remission induction rate of T-cell leukemia is similar to that of null cell disease with both groups responding well to vincristine/prednisone therapy. On standard ALL therapies, such as 6-mercaptopurine and methotrexate, a short median duration of remission has been reported by a number of investigators. When alkylating agents such as cyclophosphamide or an anthracycline such as adriamycin is added to the maintenance regimen, longer median durations of remission are being reported.

**CYTOCHEMICAL METHODS AS RELATED TO MAJOR GROUPS**

Cytochemical methods have been used for a number of years to classify the leukemias. This has been especially true for the differential diagnosis of acute myeloblastic leukemia from acute lymphoblastic leukemia. Recently, there has been a number of papers published that have attempted to correlate surface markers with some enzyme systems in leukemic cells.

In table I are summarized some of the recent studies in which both immunological and enzyme markers in leukemia have been studied. Leukemia cells with T-cell surface markers have a markedly reduced 5-nucleotidase activity, while null lymphoblasts have normal levels of this enzyme. One of the most widely studied enzymes is TdT. Elevated levels of TdT have been found in children with both null cell and T-cell leukemia. In general, TdT levels are low in B-cell leukemia, but exceptions have been reported.

While increased levels of adenosine deaminase (AdA) activity have been reported in both T-cell and null cell leukemia, one report emphasized that AdA activities did not show any correlation with immunological markers of pa-
TABLE I

Enzyme Markers and the Major Group of ALL

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Null Cell</th>
<th>T-Cell</th>
<th>B-Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Nucleotidase</td>
<td>Normal</td>
<td>Low</td>
<td>---</td>
</tr>
<tr>
<td>Terminal deoxynucleotide</td>
<td>Increased</td>
<td>Increased</td>
<td>Low</td>
</tr>
<tr>
<td>transferase</td>
<td>Low</td>
<td>Increased</td>
<td>Low</td>
</tr>
<tr>
<td>Adenosine deaminase</td>
<td>Increased</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Hexosaminidase I</td>
<td>Increased</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Acid phosphatase</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Alkaline phosphodiesterase I</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Acid esterase</td>
<td>Low</td>
<td>Faint</td>
<td>localized activity</td>
</tr>
</tbody>
</table>

Patients with ALL, but in fact there was a wide range of AdA activity in both T-cell and null cell cases.33

Extracts of normal lymphocytes, thymocytes and granulocytes give different isoenzyme patterns of hexosaminidase. Increased levels of the hexosaminidase component I are found in most cases of acute lymphoblastic leukemia, suggesting that this may be of diagnostic value in an analysis of this type of leukemia.15 Twenty-three out of 27 null cell cases (defined by antigen studies) demonstrated a pattern of raised hexosaminidase I. Cases of T-cell and B-cell leukemia did not show the raised hexosaminidase I pattern.

The last four enzymes listed in table I have been used for at least a decade and are generally thought of as histochemical stains rather than enzyme markers. Acid phosphatase, alkaline phosphatase and alkaline phosphodiesterase I are probably of value in distinguishing T-cell disease from null cell disease, but are not reliable enough to replace immunological markers for the distinction of these two groups.2,31

Four different staining patterns have been recognized for the non-specific acid alphanaphthol acetate esterase or acid esterase activity. Normal peripheral T-lymphocytes show a localized, intense activity (T-like) while a subpopulation of thymocytes express a fine localized non-intense activity (thy-like). In four out of five cases of T-cell leukemia, the acid esterase was thy-like while in only one out of nine cases of null cell leukemia was thy-like reactivity expressed, the remaining cases being negative.32

It is our opinion that enzyme markers and histochemical stains will continue to be useful in the differentiation of acute myelocytic leukemia (AML) from ALL. However, at present, these enzyme markers cannot be substituted for immunological markers in the identification of T, B and null cell disease.

FAB CLASSIFICATION, PROGNOSIS AND MAJOR GROUPS WITHIN ALL

The FAB classification defines three classes of ALL based upon the amount of cytoplasm, predominance of nucleoli, the basophilia of the cytoplasm, and other characteristics.5 In an analysis of 566 children with ALL who were not classified by surface markers, 83 percent were L1, 15 percent were L2 and only 1 percent was L3. L2 morphology was associated with a significantly higher relapse rate.38 When FAB morphology is related to null cell leukemias, 75 percent of these cases were L1 and 25 percent were L2.19 T-cell leukemia can be either the L1 or L2 type. The L4 morphology is thought to identify a Burkitt's type of malignant cell that is surface immunoglobulin positive. Whether the FAB classification is an independent prognostic variable or whether it is more significant than some of the subgroups that are currently being defined within T-cell and null cell leukemia remains to be determined.

Surface Antigens on Lymphocytes and Lymphoblasts

The current direction of research in this field relates to the use of antisera to detect surface antigens which are expressed on normal T and B lymphocytes and on
human leukemia cells. While these antisera can be used alone to subclassify ALL, most laboratories use both antisera and rosetting techniques to identify surface markers. Before discussing the impact of both antigen detection and surface receptors on subdivision within null, B and T-cell leukemia, a review of surface antigens and corresponding antisera will be necessary.

Over the past several years, there have been numerous reports of the detection of antigens associated with human leukemia cells. The antigens detected may be truly leukemia specific or may represent differentiation antigens present on various precursors of the cells of the lymphoid series. Alternatively, the antigens may represent fetal antigens which could be present on fetal tissues other than lymphoid progenitors. In addition, antigens detected on mature T and B-lymphocytes have given valuable information which is beginning to allow subclassification of ALL.

An antigen found on the common form of acute lymphoblastic leukemias has been extensively studied. It is an antigen with a molecular weight of about 100,000 daltons and is found on cells of all patients with “common” ALL. Although the antigen was originally not detected on blasts cells of T-cell leukemia, more recent evidence has shown weak reactions in 10 percent of T-cell cases. Cells of Philadelphia chromosome positive CML in blast crisis express the antigen as do AUL and a few lymphomas. The antigen has not been found on the surface of normal, mature lymphocytes. The antigen was detected on normal fetal bone marrow cells and on the cells of regenerating juvenile bone marrow cells, but it was not detected on bone marrow cells of adults. The ALL antigen does not cross-react with any known oncogenic virus, and it is thought to represent a normal differentiation antigen of the cell type involved in malignant transformation.

In addition to antigens which may be present on precursors of mature T and B-lymphocytes, other antigens have been detected in the common form of ALL which are expressed on mature T and B-lymphocytes. The antigens expressed on leukemic blasts are apparently identical to those expressed by mature B-cells and by a certain T-cell subpopulation. Since the antigen can also be found on immature myeloid cells of bone marrow, as well as bone marrow cells of patients with megaloblastic anemia and myeloid hyperplasia, it has been suggested that Ia expression on leukemic blasts may reflect their hematopoietic stem cell origin. A recent study showed that the presence or absence of the Ia antigens on the surface of the blast cell could be useful in the subclassification of “null” ALL. Other investigators have reported that normal B-cell antigens can be detected on one subgroup of common ALL. It is not possible to determine from these reports if the antisera which they have produced is identical to anti-Ia antisera or if they have detected other B-cell differentiation antigens.

The B-lymphocyte antigen, BDA (B-cell differentiation antigen), is distinct from Ia and is present on B-lymphocytes in all stages of differentiation. BDA was

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* Chronically myelogenous leukemia.
† Acute undifferentiated leukemia.

† Acute myelogenous leukemia.
expressed on leukemic blasts of most (14/18) patients with lymphocytic leukemia but was not present on leukemias of myelogenous origin.

Just as B-cell antigens have been detected on ALL blasts, so have normal T-cell antigens. An antigen present on thymocytes and leukemia cells of mice has been called the TL antigen. Antiserum having similar reactivities to anti-TL have been produced by injection of rabbits or non-human primates with human thymus cells. One such antiserum detected antigens present on thymocytes and on E-rosette positive ALL blasts. The antigen was not found on peripheral T-cells or E-rosette negative blasts. Blasts from other types of leukemia were not tested for the presence of the "TL-like" antigen. The antigen described by Mohanakumar and Metzger, although TL-like, as determined by its presence on thymocytes and leukemic blasts, was present on ALL blasts as well as CLL blasts, a leukemic cell which is known to possess B-cell markers. It is not possible to determine if these two groups have described the same or different antigens.

Antigens characteristic of peripheral T-cells can also be found on the surface of leukemic blasts. Leukemic blasts, which are classified as T-cell leukemia on the basis of their ability to form rosettes with sheep erythrocytes, express these antigens as do some ALL cells which do not possess the sRBC receptor. Among the "null" cell ALL, those cells which express the T-lymphocyte associated antigen (TLAA) do not express Ia and vice versa.

A final possible source of leukemia associated antigens which may someday prove useful for classification of leukemic blasts is those antigens which are associated with C-type ribonucleic acid viruses. Although there is currently some information regarding the presence of such antigens on the surface of blasts cells in ALL, the data have not yet proven useful for subclassification. Certainly this area of investigation deserves to be monitored as researchers begin to sort out the complex specificities which are detected by their anti-viral reagents.

Subclassifications Within T-Cell Leukemia and Null Cell Leukemia

The preceding discussion of ALL as three major groups was based on only two surface markers, the E-receptor and slg, and represents a simple but well recognized or "well established" division of ALL. These three major groups are now being divided into subgroups by research laboratories that are analyzing bone marrow lymphoblasts for cytoplasmic immunoglobuln, additional surface receptors such as the complement and Fc receptor, surface antigens as well as the two standard tests (E and slg). At present, there is no uniform definition of these subgroups owing to the different techniques being employed, different sources of antisera and the lack of uniform application of all available surface markers to the cells being analyzed. Despite these problems, some very interesting subgroups have been identified.

A few examples of subgroups currently being identified are listed in table II. It is important to note that in table II the shorthand designation has been used as described in the original research article. This takes into account minor differences in technique or different sources of antisera. Using a strict definition of B-cell leukemia which requires the presence of surface immunoglobulins, no major subgroups have been identified within this major grouping. Since B-cell leukemia is rare and extensive evaluations for a complement receptor, Fc receptor, Ia antigen and of the different subclasses of immunoglobulins have not been widely applied to this disease category, it is not surprising that it remains a single group at this time.

§ Chronic lymphocytic leukemia.
Greaves and coworkers have identified two subgroups for both null cell and T-cell leukemia using antisera which detect common leukemia antigen (cALL), Ia, and a T-antigen (HUTL A). Within null cell leukemia, most cases were identified as common ALL by the presence of both cALL and Ia positivity. A smaller subgroup listed as unclassified expressed only the Ia antigen. For T-cell leukemia, four cases of THY ALL were identified by the presence of both an E-receptor and positivity for HUTL A. One case described as true T-cell leukemia also expressed the Ia antigen.

Sallen and coworkers have followed a large cohort of children for up to four years using an antiserum against a human T-leukemia antigen (HTL) and the Ia antigen. The two antisera were used to identify either null cell leukemia or T-cell leukemia. The disease free survival of the 76 patients identified as Ia positive was 80 percent at four years with a median followup of 28 months. However, for the HTL positive cases, disease free survival was only 15 months with all patients having relapsed by 24 months. While these two antisera have been used to define null cell leukemia or T-cell leukemia rather than subgroups, their observations are included in this portion of the review because of the length of followup.

Anderson and coworkers using antisera to detect human T-cell associated antigen (TLAA) and Ia antigens as well as the E-receptor have identified two subgroups within T-cell leukemia. Their group 1 (E positive T positive Ia negative E+ T+ Ia-) was more common (11 cases) than group 2 (E negative T positive Ia negative E- T+ Ia-) which included only four cases. There were 11 cases of null cell leukemia (their group 3) which were E negative T negative Ia positive (E- T- Ia+). These investigators believe that both E+ T+ Ia- and E- T+ Ia- cases respond poorly to therapy. This approach suggests that a

### Table II

Major Groups Within ALL

<table>
<thead>
<tr>
<th>Reference</th>
<th>B-Cell</th>
<th>Null Cell</th>
<th>T-Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greaves(^{20})</td>
<td>ALL(^{+}) Ia(^{+}) E(^{+}) HUTL A(^{+}) SMig(^{+}) (B-ALL)</td>
<td>ALL(^{+}) Ia(^{+}) E(^{+}) HUTL A(^{+}) SMig(^{+}) (common ALL)</td>
<td>ALL(^{+}) Ia(^{+}) E(^{+}) HUTL A(^{+}) SMig(^{+}) (Thy-ALL)</td>
</tr>
<tr>
<td>Sallen(^{47}) Anderson(^{1})</td>
<td>E(^{+}) TLLA(^{+}) Ia(^{+}) (III)</td>
<td>E(^{+}) TLLA(^{+}) Ia(^{+}) (I)</td>
<td>E(^{+}) TLLA(^{+}) Ia(^{+}) (II)</td>
</tr>
<tr>
<td>Kaplan(^{25}) (Humphrey)</td>
<td>E(^{-}) S1g(^{+}) Anti T(^{-}) Anti B(^{+})</td>
<td>E(^{-}) S1g(^{+}) Anti T(^{-}) Anti B(^{+})</td>
<td>E(^{-}) S1g(^{+}) Anti T(^{-}) Anti B(^{+})</td>
</tr>
<tr>
<td>SWOG(^{22})</td>
<td>E(^{+}) S1g(^{+}) Anti T(^{+}) Anti B(^{+})</td>
<td>E(^{+}) S1g(^{+}) Anti T(^{+}) Anti B(^{+})</td>
<td>E(^{+}) S1g(^{+}) Anti T(^{+}) Anti B(^{+})</td>
</tr>
<tr>
<td>Crist, Vogler (SWOG)(^{57})</td>
<td>E(^{-}) HTLA(^{-}) SMig(^{-}) E(^{-}) S1g(^{-}) Anti T(^{-}) Anti B(^{-})</td>
<td>E(^{-}) HTLA(^{-}) SMig(^{-}) E(^{-}) S1g(^{-}) Anti T(^{-}) Anti B(^{-})</td>
<td>E(^{+}) HTLA(^{+}) SMig(^{+})</td>
</tr>
<tr>
<td>Bowman(^{7})</td>
<td>E(^{-}) T(^{-}) S1g(^{-}) Ia CALL</td>
<td>E(^{-}) T(^{-}) S1g(^{-}) Ia CALL</td>
<td>E(^{-}) T(^{-}) S1g(^{-}) Ia CALL</td>
</tr>
<tr>
<td>Netzel(^{12})</td>
<td>Smig(^{+}) (group VI)</td>
<td>Anti CALL(^{+}) (group II)</td>
<td>Anti CALL(^{+}) Anti T(^{+})</td>
</tr>
<tr>
<td>Varbro(^{61}) (Pullen)(^{43})</td>
<td>E(^{-}) S1g(^{-}) Ia L/L CLL C(<em>{3}) Fc(</em>{3}) (peripheral blood E(_{37/4}) ≤ 10%; 10-40% &gt; 40%)</td>
<td>E(^{+}) MLC(^{-}) GCR(^{+})</td>
<td>E(^{+}) MLC(^{-}) GCR(^{+})</td>
</tr>
</tbody>
</table>
portion of null cell leukemia defined by E-receptor and sIg methods alone is actually T-cell leukemia, further suggesting that antisera may be of more value than E-receptor in detecting T-cell leukemia.

As mentioned in the section on surface antigens, Kaplan and coworkers have generated two antisera against a B-cell and T-cell line.29 Within cases of null cell leukemia, Kaplan identified two males, each of whom had high white counts and a mediastinal mass that were T-antigen positive but did not express the E-receptor. The remaining nine cases within the null cell group reacted with the B antiserum.

In 1974, the Pediatric Division of The Southwest Oncology Group (SWOG) initiated a group-wide protocol22 requiring bone marrow blasts to be evaluated for E rosettes at both 37° C and 4° C. A year later, the protocol was amended and evaluation of peripheral blood at both 37° C and 4° C was added. In contrast to the earlier report that all cases of T-cell leukemia would form stable rosettes at both 37°C and 4°C in approximately one-third of the cases, the T lymphoblasts were not thermostable (E_{RS}) but were thermodabile (E_{TL}) at the higher temperature.21 This observation has been confirmed by other investigators.55 There is some suggestion that this difference in thermal stability may have prognostic significance.

The median duration of remission for the E_{TL} subgroup was longer than the E_{RS} group; however, this difference has not yet reached statistical significance.21 Within the null cell group, the number of circulating peripheral blood normal T lymphocytes may have prognostic significance. The peripheral blood of children with less than 20 percent E positive cells in their bone marrow or having null cell leukemia was analyzed for E rosette formation at both 37°C and 4°C, resulting in the identification of three groups.

In group I, children had less than 10 percent E positive cells in their peripheral blood. There was a statistically significant proportion of children with bad clinical prognostic signs, such as a high white cell count or age greater than ten years. Conversely, for those children in group III with greater than 40 percent E positive cells in their peripheral blood, there were none who presented with both a high white cell count and an age greater than ten (p ≤ 0.001).25 The group with 10 to 40 percent E positive cells in their peripheral blood was intermediate between the first and third groups with regard to clinical prognostic features. Whether or not this observation is an independent prognostic variable remains to be determined.

Vogler and Crist, working independently and in collaboration with the Pediatric Division of SWOG, have identified the best characterized subgroup within the null cell leukemias.14,57 Their observation was preceded by extensive work with animal and human fetal tissue. Investigations into lymphocyte ontogeny have suggested the existence of a sIg^-cIg^+ B-cell precursor. These pre B-cells contain small amounts of intracytoplasmic IgM and are initially found in the fetal liver and later in the bone marrow.

Vogler first described four cases of pre B-cell leukemia out of a sample of 22 cases of ALL, suggesting that this subgroup might constitute a significant percentage of the null cell group.57 These leukemic pre B-cells also express the common leukemia antigen and a "B-cell" antigen. Of particular interest was the finding of two of the four cases that had Fc receptors and one case that had complement receptor. Complement receptor and Fc receptor are not found on normal pre B-cells, suggesting that leukemic transformation occurred beyond the pre B-cell stage or that the transformation induced the expression of these receptors. The existence of this subgroup has been confirmed by French investigators who reported six cases out of a sample of 50 children.9 In four of these cases, the disease had
tumoral presentation. These cells also expressed the Ia-like and common ALL antigens.

The clinical and laboratory characteristics of pre B-cell leukemia in childhood have recently been summarized by Crist, Vogler, et al. Thirty five out of 189 cases, or 18 percent, were pre B-cell leukemia. Tumoral presentation was not a common feature and the distribution of patients with regard to hepatosplenomegaly, lymphadenopathy, extramedullary disease and bone marrow involvement was similar to null cell and T-cell leukemia. Sex, age and race distribution, as well as the initial diagnostic white count, hemoglobin and platelet count values, were also the same for pre B-cell and null cell disease. The initial response to therapy was excellent. The median duration of remission for this group has not yet been reached; the prognostic significance of the pre B-cell subgroup is yet to be determined.

Esbar and coworkers have made a very interesting observation with the regard to the prognostic significance of complement and Fc receptors. Null cell cases that express neither of these two markers had a significantly longer median duration of remission than those cases that expressed either the complement or Fc receptor markers. This is of particular interest considering Crist and Vogler’s observation that T-cell, null cell and pre B-cell subgroups in each case express these receptors in some, but not all, cases.

Using antisera directed against B-cell antigen (Ia) and the common leukemia antigen (cALL), Bowman and coworkers have identified two groups within null cell leukemia. Fifty-five patients expressed both the Ia and the cALL antigen while 12 patients expressed either the Ia or the cALL antigen but not both (undifferentiated leukemia). For both these subgroups, all cases were E-receptor negative, T-antigen negative, and sIg negative.

While adverse clinical features such as high white count, central nervous system leukemia, or mediastinal mass were not common features of the undifferentiated leukemia, six of their 12 patients were early treatment failures whereas only eight out of 55 children expressing both the Ia and the cALL antigens were early treatment failures. From their experience, these authors concluded that a common leukemia typing pattern of IA+ cALL+ represented a favorable prognostic group.

Netzel and coworkers have divided ALL into six groups (I–VI) in a recent study of 67 patients. In attempting to fit their six groups into B, null and T-cell leukemia, group number VI clearly falls into B-cell leukemia, two groups within null cell leukemias (I and V), two within T-cell leukemia (III and IV) and one group (II) that was intermediate between T-cell and null cell leukemia. This classification was based on the use of two antisera, one directed against a common leukemia antigen (anti cALL+) and the second directed against a normal T-cell antigen (anti T).

The most common subgroup within null cell leukemia was group I (38 percent) expressing the common leukemia antigen (anti cALL†). The smaller group V (6 percent) expressed neither the common leukemia antigen nor the T-cell antigen. Group (II) which accounted for 32 percent of the patient sample was intermediate between T-cell and null cell leukemia because these cells expressed both the T-cell antigen (suggesting T-cell leukemia classification) and the cALL antigen (which could suggest null cell leukemia).

Within T-cell leukemia, group III (anti T+ E+) accounted for 14 percent of the cases and group IV (anti T+ E−) for only 9 percent. The T-antigen positive E-receptor negative cases (group IV) deserve special comment as Anderson has also reported the existence of this sub-
group. Thiel has recently summarized the clinical significance of the E\(^-\) T\(^+\) group and reported that it may be significant because five out of nine patients within this subgroup died soon after diagnosis.\(^{55}\)

Yarbro and coworkers have evaluated two unique properties of lymphoblasts and have related them to T-cell and null cell leukemia.\(^{61}\) The presence of glucocorticoid receptors (GCR) in the cytoplasm and the ability of bone marrow lymphoblasts to act as stimulators in a mixed lymphocyte culture (MLC) have been used to evaluate cases of ALL. The T-cell cases (E\(^+\)) failed to stimulate in the MLC and had low levels of GCR. Most of the null cell cases (18) stimulated in the MLC and contained high levels of GRC. There was a small group of patients (9) whose cells did not stimulate in the MLC and that had intermediate levels of GCR. These findings may have therapeutic significance based on other observations.\(^{48}\)

Currently the Pediatric Division of SWOG is evaluating all newly diagnosed cases using institutional laboratories for some of the less complicated methodologies such as E-receptor, complement receptor and Fc receptor. Specially prepared bone marrow samples are shipped to two research reference laboratories. The first laboratory, at Duke University, is measuring surface antigens such as the peripheral T lymphocyte antigen (TP), thymus antigen (T), B-cell antigen (Ia), leukemia lymphoma antigen (L-L), and common leukemia antigen (cALL). The second laboratory, at the University of Alabama, is measuring cytoplasmic immunoglobulin (cIg), surface immunoglobulin (sIg), and Fc receptors for IgM (Fc \(\mu\)). While this is a very ambitious undertaking, the feasibility for such an approach among institutions has already been proved and multiple subgroups are currently being identified.\(^{43}\)

One of these subgroups, pre B-cell leukemia, has already been discussed.\(^{14,57}\) Doctors Metzger, Falletta and others, working independently at Duke University Medical Center and in cooperation with the Pediatric Division of the Southwest Oncology Group, have recently analyzed 238 cases. Cells from 24 of these cases were E\(^+\) T\(^+\) and 11 cases were E\(^-\) T\(^+\).\(^{34}\) Thus, 15 percent of the total population were classified as T-cell leukemia.

One other current direction of research needs to be briefly discussed. Serial studies of surface characteristics are currently being evaluated in order to look for possible changes in membrane biology at relapse. In most cases, the same cell phenotypes have been found; however, exceptions have been reported.\(^{6,18}\) These changes may be due to selective effects of therapy or some other malignant advantage that allows a small previously undetected subgroup to become dominant or more easily recognizable.

Acknowledgment

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References


43. PULLEN, J.: Personal communication.


