The Detection of Iso-Antigens on Leukemic Cells Using the Cytotoxicity Test

By Ivan Peacocke, Bernard Amos and John Laszlo

With the development of information concerning the iso-antigenic content of human leukocytes and other tissues, detailed studies of antigenic alterations of human tumors have become practicable. Qualitative and quantitative iso-antigenic alterations have been found in tumor cells and leukemic cells derived from rodents. These alterations have been best described in mice, in which the antigenic composition of normal tissues was known in detail and in which a direct comparison with genetically identical animals was possible. Loss of ABO blood group antigens in certain human neoplasms, and alteration of these antigens in the red cells in human leukemic patients, have been reported. Other antigenic alterations have been described for human tumors, but lack of information concerning antigens of the normal tissue counterpart in many of the earlier studies has made interpretation difficult.

As a preliminary to our study of possible antigenic changes in human neoplasms, it appeared desirable to study the antigenic content of human leukemic cells, particularly chronic lymphocytic leukemia (CLL). These lymphocytes are readily available and offer a homogenous cell population for study. Previous investigators have studied normal lymphocyte antigens using leukoagglutination technics and several well-defined antigens have been described. We have preferred the use of a cytotoxicity technic for the study of lymphocytes because it is more quantitative and gives a direct comparison between normal and leukemic lymphocytes. In applying this technic to a systematic study of iso-antigens of human leukemic cells, it was necessary to determine the reproducibility of the test and to verify the specificity of reactivity by absorption studies. This paper details our experience with the use of this test in describing the antigenic content of cells derived from 10 patients having chronic lymphocytic leukemia and from 5 patients with acute granulocytic leukemia.

Materials and Methods

Ten patients with chronic lymphocytic leukemia (CLL) and five patients with acute granulocytic leukemia (AGL) were selected for admission to this study on the basis of

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standard hematologic criteria. The 10 patients with CLL were tested at frequent intervals, with up to 15 determinations being performed on cells from a single patient over a 25-week period. Seven patients of this group had at least two determinations performed prior to the onset of therapy; the other three had received treatment before admission to this study, but had shown no hematologic evidence of improvement. At least 3 determinations were performed on each of the five patients with AGL, while they were in the “blastic stage” of their disease. A control group of 50 normal subjects (hospital employees or students) was used for comparison. The control group was not adjusted for sex, age, nationality or race.

Iso-Antisera

Sixteen iso-antisera were used; 13 were from multiparous women and 3 from subjects who had been immunized with intradermal lymphocyte suspensions. These iso-antisera were selected for the following reasons:

1. They were known to give reproducible results when tested repeatedly against cells from a standard panel of normal subjects.
2. Large quantities of serum were available for repeated testing and for absorption studies.
3. The sera had been shown to detect antigens or antigenic groups found to be transmitted by simple Mendelian inheritance in family studies.
4. From concomitant studies on normal cells, these antibodies were thought to detect different antigens or groups of antigens.

In most instances serum was obtained by a single plasmaphoresis, but in instances in which two samples were required, the sera were first tested against a standard panel of normal cells to guard against any change in reactivity. Sera were distributed in small (0.5 ml.) amounts and stored at -80 C. Some samples were stored at -20 C. for approximately one week between experiments.

Cytotoxicity Test

The cytotoxicity test, described in detail elsewhere, was basically a modification of that described by Gorer and O’Gorman. Rabbit serum was used as a source of complement. Each new batch of complement* was titrated against normal lymphocytes to determine its optimal dilution. It was also tested for intrinsic cytotoxic effects in the absence of antibody. If the differential cell count revealed fewer than 90 per cent lymphocytes, the granulocytes were removed by passage through a nylon column. In studies of patients with AGL, the cell population was predominantly myeloblastic and further separation was unnecessary. As controls, each cell preparation was incubated in rabbit serum alone, and in group AB Rh-negative serum with complement. Cell damage was measured by estimation of trypan blue uptake. The following grading system was used:

1. When fewer than 20 per cent of the cells were stained with trypan blue, the result was scored negative (−).
2. When 21–30 per cent of the cells stained, it was scored +.
3. When 31–60 per cent of the cells stained, it was scored ++.
4. When 61–100 per cent of the cells stained, it was scored +++.

Both reactive and nonreactive CLL cells were used in the absorption studies. Seventy million leukemic cells were suspended in 1.0 ml. of antibody; the mixture was shaken at 10-minute intervals at room temperature for 30 minutes and then centrifuged at 16,000 g for 30 minutes. The supernatant was removed and stored in small aliquots at -20 C. A sample of the same serum with no added cells was handled in an identical fashion and used as a nonabsorbed control. The absorbed sera were then tested against a panel of cells from 32

*Obtained from Robbins Laboratories, Chapel Hill, North Carolina.
DETECTION OF ISO-ANTIGENS

normal individuals and against the patients own cells to test for completeness of absorption. Absorption studies were not performed on the AGL cells.

Results

The reactions of cells from the 10 patients with CLL are shown in Table 1. The reproducibility of the test was 97.4 per cent. A total of 534 tests were performed and 520 of these showed close agreement. In 7 of the remaining 14 tests the variability was slight (cells scoring plus on one test scoring negative in a repeat determination or vice versa). The discrepancies in the other 7 tests indicated greater variability, such as a change from negative to ++ or ++++, or vice versa. This variability never occurred more than once with any given cell-antibody combination and was thought to be attributable to occasional uncontrollable variations or technical error.

Eleven of the 16 sera showed essentially the same frequency of reactivity with CLL cells as with cells from 50 normal subjects. The remaining 5 iso-antisera all gave a higher incidence of reaction with cells from the CLL patients (Table 2).

In these tests discrimination between positive and negative was usually much clearer than with normal cells. The nonreactive cells gave a very low background in the tests. In positive reactions the proportion of cells killed at a given antibody dilution was frequently higher than the proportion of cells killed from a normal subject. For example, the average proportion of positively reacting leukemic cells killed by serum COL was 66 per cent, while the average for positive normal cells was 42 per cent; for the serum GS, the proportions were 83 per cent and 57 per cent, respectively, and the other sera behaved in a similar manner. This increased sensitivity was confined to the CLL cells. Cells from AGL donors reacted more like cells from normal positive subjects. One peculiarity noted with cells from some patients with AGL was an extreme sensitivity to rabbit serum. Cells from some subjects with AGL could not be included because of this high background.

The specificity of the reactions was tested by absorption. A representative excerpt from the data obtained with 25 cell-antibody combinations is given in Table 3 (the absorbed iso-antibody was actually tested against cells from 32 donors instead of the 15 donors shown in the table). On no occasion did negatively reacting cells affect the reactivity of the iso-antibody against normal cells. Cells which did react showed two distinct patterns of absorption. Sera believed to be monospecific lost cytotoxic effect for cells from the absorbing donor and for all normal cells tested. Sera known to be complex usually showed residual activity for certain cells of the panel after absorption, although no activity remained for the absorbing leukemic cell. Of particular interest is the absorption data of a complex serum shown in Table 3. In this instance, the serum was known to have at least four components, three of which have been identified in other sera. Each of these three sera reacted with cells from the absorbing donor. The reactivities of the sera were well-known, and it was postulated that the cell donor had the three corresponding antigens. These three components were specifically removed by the leukemic cells and the fourth component was left intact.
### Table 1.—Reactions of Patients with Chronic Lymphocytic Leukemia

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<td>25 weeks</td>
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<td>6 weeks</td>
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<td>#4</td>
<td>17 weeks</td>
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<td>17 weeks</td>
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- <20% of cells stained with trypan blue.
+ 21-30% of cells stained.
++ 31-60% of cells stained.
+++ 61-100% of cells stained.
Blank space indicates that testing was not done.

### Table 2.—Comparison of the Frequency of Reactivity of the Iso-Antibodies against the C.I.I. Cells and Lymphocytes from 50 Normal Adults

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<tr>
<td>Normal controls (%) reaction</td>
<td>40</td>
<td>20</td>
<td>20</td>
<td>47</td>
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<td>36</td>
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<td>62</td>
<td>75</td>
<td>58</td>
<td>74</td>
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<td>CLL (%) reaction</td>
<td>30</td>
<td>22</td>
<td>50</td>
<td>80</td>
<td>77</td>
<td>55</td>
<td>83</td>
<td>66</td>
<td>50</td>
<td>40</td>
<td>60</td>
<td>100</td>
<td>100</td>
<td>64</td>
<td>88</td>
<td>44</td>
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Table 3.—Examples of Absorption Data with CLL Cells

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<th>A</th>
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<tr>
<td></td>
<td>CLL Cell (1)</td>
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<tr>
<td></td>
<td>Normal Cells</td>
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<td>Normal Cells</td>
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<tr>
<td>Nonabsorbed serum</td>
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<tr>
<td>Absorbed serum</td>
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<td>Normal Cells</td>
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A: Control absorption with negative reacting leukemic cells.
B: Absorption of sera believed to be mono-specific.
C: Absorption of complex sera.
*Actually tested against lymphocytes from 32 normal individuals.
(1) CLL cell was the cell used for the absorption.
### Table 4.—Comparison of Reactions of Lymphocytes from 4 Patients with CLL before Rx and after Remission

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<tr>
<td>#4</td>
<td>Before Rx remission</td>
<td>-</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
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<tr>
<td>#5</td>
<td>Before Rx remission</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
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<td>#6</td>
<td>Before Rx remission</td>
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<td>#7</td>
<td>Before Rx remission</td>
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### Table 5.—Reactions of Patients with Acute Granulocytic Leukemia

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<tr>
<td>#1 16 weeks</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
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<td>#2 1 week</td>
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<td>#3 1 week</td>
<td>+++</td>
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<td>#4 1 week</td>
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<td>#5 1 week</td>
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Chemotherapy with streptonigrin, chlorambucil, 6-mercaptopurine or prednisone did not appear to affect the results of the tests.

Four of the patients have been studied from the time of diagnosis until they were in a hematologic remission. In all, a total of 36 iso-antibody cell combinations were used, and there were no changes in the reactions of 34 of the 36 combinations (Table 4). The two exceptions are worthy of further elaboration.

**Patient #6:** This patient was found to have a +++ reaction with isoantibody G.W. on two occasions before therapy was begun with chlorambucil. One month later, when the patient appeared to be in or very close to remission, the reaction was weaker and scored only +. Seventeen weeks after the onset of chemotherapy, when the patient was in complete remission, the reaction was negative. The antibody was known to be active against other cells, and cells from this patient reacted as expected with the other nine sera used. The patient had not received chemotherapy for two months prior to the last determination.

**Patient #4:** This patient was found to react strongly (+++), with iso-antibody Col, on each of three separate determinations before treatment with streptonigrin. One week after the onset of therapy, three separate determinations on the same antibody sample were negative. At this time, the patient had not shown any hematologic improvement. Five weeks later, one determination revealed a weak reaction. Nine weeks after the onset of therapy, the patient was thought to be in remission, and three determinations were negative.

Of a total of 210 cytotoxicity tests performed on five patients with acute granulocytic leukemia, only one minor example of variability was found. This was a change from a weak positive to a negative reaction. Highly reproducible reactions were found with cells from each patient (Table 5). Patients 1 and 3 reacted with several antisera and their reactions showed essentially the same pattern as would be expected with lymphocytes from a normal donor. Patients 4 and 5 reacted with fewer antisera but the reactions were quite strong. Cells from Patient 2 reacted weakly with one antibody and failed to react with 13 others. This probably represents a deficiency of reactivity. It is interesting that the cells of the myelogenous series did react with the iso-antibodies in the cytotoxicity test.

**DISCUSSION**

The purpose of these experiments was to evaluate the cytotoxicity test in a study of antigenic content of human leukemic cells. Earlier experiments using normal lymphocytes have shown the test to be reproducible and specific. Antigenic specificity has been determined by studies of large families and monozygous twins, and by absorption tests using reactive and nonreactive normal lymphocytes. The present report shows that the reproducibility of the test is at least as good with leukemic lymphocytes as with normal lymphocytes. Furthermore, absorption tests have demonstrated the reaction to be dependent upon antigenic specificity.

The data show that leukemic cells contain normal iso-antigens and that the distribution frequency of these antigens in CLL is normal or above normal. It was also found that CLL cells are more sensitive to cytotoxic iso-antibodies than are normal lymphocytes. There clearly was no indication of loss of normal lymphocyte antigens or of decreased cellular reactivity. These studies could
not exclude the possibility of loss of particular antigens having a low frequency of occurrence in the normal population, or of loss of antigens not detected by the cytotoxicity test with the sera which were used. Since the antisera employed herein were directed against normal leukocytes, possible antigens unique for leukemia could not be detected by this method.

The stability of CLL antigens was of particular interest. Some of these patients were tested before and after blood transfusions, infections, and chemotherapy (with chlorambucil, methotrexate, prednisone, streptonigrin, 6-mercaptopurine) and no significant antigenic changes were noted. Cellular antigens generally remained constant as the clinical course changed from active disease to remission. However, there were two significant instances of antigenic loss which appeared to be related to remission status. These observations are too limited to suggest a meaning for these isolated events.

Cells tested from patients having acute granulocytic leukemia were found to contain antigens in common with normal lymphocytes. There was considerable variability in the number of reacting antigens, but the reproducibility of the test was excellent. It is not possible to compare the antigenic frequency of AGL cells with normal myeloblasts since the latter are not available for comparison.

It can be predicted from these studies that the cytotoxicity test would be applicable to genetic studies in leukemia. Experiments are in progress to determine the pattern of inheritance of leukemic cell antigens and to decide if the increased frequency of reactivity of CLL cells is due to an increased cell fragility because of a nonimmunological property and, if not, whether it is due to inheritance or to mutation.

**Summary**

The cytotoxicity test has been shown to give reproducible information concerning specific iso-antigens of human leukemic lymphocytes. The distribution frequency of these antigens is at least as great in chronic lymphocytic leukemia antigens or of decreased cellular reactivity. The majority of patients were tested repeatedly and in most instances the cytotoxicity test remained constant, regardless of drug therapy and disease status. Cells from five patients having acute granulocytic leukemia were typed in a similar fashion and contained antigens in common with normal lymphocytes.

**Summario in Interlingua**

Le test pro cytotoxicitate se ha provate capace a render reporducibile information relative a specific iso-antigenos de leucemic lymphocytos human. Le datos indica que le frequentia de iste antigenos in chronic leukemia lymphocytic es normal o plus que normal. Esseva etiam trovate que cellulas in chronic leukemia lymphocytic es plus sensibile a iso-anticorpores cytotoxic que lymphocytos normal. Esseva trovate definitemente nulle indication de un perdita de normal antigenos lymphocytic o de un declino del reactivitate cellular. Le majoritate del patientes esseva testate repetitemente, e in le majoritate del casos le test de cytotoxicitate remaneva constante sin reguardo
a efectos chimeterapeutic o al stato del morbo. Cellulas ab cinque patientes con acute leucemia granulocytic esseva investigate in le mesme maniera, con le constatation que illos contineva antigenos in commun con lymphocytos normal.

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The Detection of Iso-Antigens on Leukemic Cells Using the Cytotoxicity Test

IVAN PEACOCKE, BERNARD AMOS and JOHN LASZLO

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