Antigenic Differences between Leukemia L1210 and a Subline Resistant to Methylglyoxal-bis(guanylhydrazone)¹

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SUMMARY

Cells from leukemia L1210 and a subline resistant to methylglyoxal-bis(guanylhydrazone) elicited a demonstrable humoral antibody response in DBA/2Ha-DD mice. Using paired-label γ-globulin mixtures containing ¹³¹I-labeled normal and ¹²⁵I-labeled immune γ-globulin, we showed that the specific uptake of antiresistant L1210 cell γ-globulin by resistant L1210 cells was consistently higher than that of anti-L1210 cell γ-globulin by L1210 cells. Moreover, above a certain level of cross-reactivity, the specific uptake of immune γ-globulin was 4 to 10 times higher with the cell type that was used to immunize the serum donors than with the other cell type. A greater uptake of γ-globulin by homologous cells was also found in vivo. The residual specific uptake of antiresistant L1210 cell γ-globulin by resistant L1210 cells was completely removed after 10 subsequent absorptions with resistant L1210 cells but not after 10 absorptions with L1210 cells. The data indicated that the resistant leukemic cells are more immunogenic than the L1210 cells in DBA/2Ha-DD mice, that the two cell lines share some common antigens, and that, in addition, the two cell types have different antigenic components.

INTRODUCTION

In the DBA/2Ha-DD mouse, leukemia L1210 grows progressively and eventually results in the death of all animals inoculated with 10 to 100 cells or less (7, 10). Indeed this leukemia is considered to be specific for the DBA/2 strain, because it does not grow at such low inocula in any of the other mouse strains tested. In spite of this apparent specificity, leukemia L1210 was slightly immunogenic in F₁ hybrids (2, 14), in backcrosses of the DBA/2 mouse (13), and also in 3 sublines of the DBA/2 mouse strain itself (9). In the backcrosses, which had been immunized with X-irradiated leukemia L1210 cells, the response was relatively inefficient, since it could be demonstrated only in mice challenged with 10 cells or less (13). In DBA/2 mice, an immunological response sufficient to cope with a challenge of 10³ leukemic cells became effective in animals previously inoculated with 10⁶ cells and cured with selective chemotherapeutic treatments (8, 9).

Initial investigations showed that low doses of arabinosylcytosine caused a higher incidence of 50-day cures in DBA/2 mice bearing a subline of leukemia L1210 resistant to methylglyoxal-bis(guanylhydrazone) than in those bearing the parent line (9). Later, these results were confirmed, and it was found that 4,4'-diacetyldiphenlurea-bis(guanylhydrazone), 2-chloro-4', 4'-di-2-imidazolin-2-ylterephthalanilide, and carzinostatin also were more effective against the resistant subline than against the parent leukemia (10). Since no difference in therapeutic effects was noted in preirradiated mice (9, 10), the greater therapeutic responses in nonirradiated animals were attributed to a greater effectiveness of host defenses against the resistant cells than against the parent cells. In the absence of chemotherapy, survival of mice from 3 DBA/2 lines was longer after the i.p. inoculation of resistant leukemic cells than after inoculation of sensitive cells in corresponding numbers, when 10⁶ cells or less were given (10). No significant survival difference was noted in preirradiated mice, however, regardless of the inoculum size. These findings suggested that the leukemia L1210 subline that is resistant to methylglyoxal-bis(guanylhydrazone) is more immunogenic than the parent leukemia in the mouse lines tested or is more sensitive than the latter to the immunological response of these mice.

The present study was carried out in an attempt to clarify whether the resistant subline is more immunogenic than the parent line or solely more sensitive than the latter to the host response and also to determine whether the possibly greater immunogenicity of the resistant subline is due to the presence on the resistant cells of more antigen or of different antigens. To this end, differences in DBA/2 antibody binding to antigenic sites actually present on the 2 cell types were investigated by means of a paired-label antibody technique which had been previously proven useful in measuring the binding of alloantibody to leukemia L1210 cells (18). Some of these results have been reported in a preliminary communication (4).

MATERIALS AND METHODS

Animals and Cells. The animals used were 2- to 3-month-old DBA/2Ha-DD female mice weighing 20 to 25 g. They were...
obtained from the breeding colony of this Institute. The DBA/2Ha-DD subline of DBA/2 was derived from intense-brown-coat mutants of dilute-brown DBA/2Ha-dd mice, commonly known as DBA/2Ha, and has been maintained by strict inbreeding since 1952. DBA/2Ha-DD and DBA/2Ha-dd mice share the same histocompatibility characteristics, as indicated by reciprocal skin graft acceptance (T. S. Hauschka, personal communication). The DBA/2Ha mice are DBA/2 mice originally obtained by Dr. T. S. Hauschka in 1943 at the Lankenau Hospital Research Institute, where the strain had been obtained directly from Dr. C. C. Little in 1929 (Cross 212 of DBA mice).

The leukemia L1210 used in this study was obtained in 1957 from Dr. A. Goldin, National Cancer Institute and thereafter was transferred every 6 to 7 days in female DBA/2Ha-DD mice by the i.p. inoculation of $10^6$ ascites cells. The subline resistant to methylglyoxal-bis(guanylhydrazone) (L1210/CH$_3$-G) was developed in this laboratory in 1966 (6) and was thereafter transferred in a manner similar to that used with L1210, except that the host mice were treated i.p. once daily for from 4 to 6 days with methylglyoxal-bis(guanylhydrazone), 50 mg/kg. Prospective donors of serum or target cells were not treated with this drug.

The target leukemic cells used in the *in vitro* antibody-binding reactions were obtained from the i.p. cavity of mice that had been inoculated with $10^6$ cells 3 days before sacrifice. The cells were washed once with RPMI* 1640 medium, separated from red blood cells, purified by ficoll gradient centrifugation (12), and finally washed 3 times with RPMI 1640 medium. Normal spleen cell suspensions were obtained by mechanical dissociation through a stainless steel wire mesh and were treated in the same way as were the leukemic cell suspensions. Suspensions of cells from spontaneous mammary tumors of the DBA/2Ha-DD mouse were obtained by gentle 30-min stirring of 1-cm$^3$ tumor pieces in ice-cold Earle's solution, without the addition of enzymes. At least 10 ml of solution were required for each g of tissue. After this stirring the suspension was filtered through 3 layers of 182

Preparation of Antiserum. One million L1210 or L1210/CH$_3$-G cells were inoculated i.p. into DBA/2Ha-DD mice. Arabinosylcytosine was injected i.p. at the dose of 10 mg/kg/day for 6 consecutive days, starting the day after that of leukemia inoculation. The drug was obtained through the courtesy of Dr. G. Fonken, The Upjohn Co., Kalamazoo, Mich. Animals surviving on Day 50 were challenged with $10^5$ live leukemic cells and were rechallenged at 2-week intervals with successively increasing numbers of cells ($10^5$, $10^6$, $10^7$, and $10^8$). Serum was obtained 2 weeks after the last challenge. The immune sera from individual mice were pooled according to antigen and were stored at $-70\degree$ until used. Pooled sera from nonimmunized mice were also stored at $-70\degree$. In each case, these pools contained serum from 30 to 45 mice. The experiments reported herein were carried out with 3 separate pools of each antiserum. For identification, they were called Pools A, B, and C (chart legends).

Preparation and Iodination of γ-Globulins. Two ml of serum were dialyzed overnight against 0.02 M phosphate buffer solution (pH 8.0) and then centrifuged for 15 min at 4 and 3000 rpm in an International Model PR2 refrigerated centrifuge. The γ-globulin was obtained from the supernatant by diethylaminoethyl cellulose column fractionation at pH 8, after suitable concentration, it was measured with a Zeiss spectrophotometer at 280 nm and expressed as mg of protein. The γ-globulin solutions were kept at $-20\degree$ and were used within 2 to 3 months after fractionation.

γ-Globulin from antiserum was labeled with $^{125}$I and γ-globulin from normal serum was labeled with $^{131}$I. $^{125}$I was purchased from Tracerlab, Inc., Waltham, Mass.; $^{131}$I was purchased from E. R. Squibb & Sons, New Brunswick, N. J. Iodination was carried out by the chloramine-T method (13). Unreacted iodine was eliminated by ammonium sulfate precipitation of the iodinated γ-globulin and by centrifugation for 20 min at 4 and 15,000 rpm in a Beckman ultracentrifuge. The pellet containing the iodinated γ-globulin was dissolved in borate buffer -0.9% NaCl solution, pH 7.4, to a final volume of 2 ml containing 10 to 15 mg of protein. The iodinated preparation contained 1 to 2 mCi of label per mg of protein and was kept frozen.

The $^{125}$I-labeled immune γ-globulin preparation was mixed with the $^{131}$I-labeled normal γ-globulin preparation at an appropriate ratio, usually 1:1 with respect to protein content. This paired-label reagent was used in the absorption tests (17). The day before the specific uptake test, the paired-label mixture was absorbed with 5 ml to 10 x $10^8$ normal spleen cells from female DBA/2Ha-DD mice at 37° for 1 hr. Immediately before use, the paired-label mixture was centrifuged for 60 min at 4 and 40,000 rpm in a Beckman Model L2 ultracentrifuge.

Absorption Tests. For the *in vitro* tests, 0.5 ml of the paired-label mixture was placed into an 8-ml tube, and 0.1 ml of the desired target cell suspension in RPMI 1640 medium (1 to 10 x $10^6$ cells) was added. After 60 min of incubation at 37° with gentle shaking, the cells were washed twice with the RPMI 1640 medium and transferred into new tubes. The radioactivities in pellets obtained by centrifugation at 3000 rpm for 20 min were measured in a 2-channel γ-ray spectrometer.

The specific antibody uptake by the target cells in the sample was calculated according to the following formula:

$$\text{Specific uptake} = \left(\frac{\text{cpm on leukemia cells}}{\text{cpm on normal cells}}\right) \cdot \frac{\text{cpm/ml antiserum globulin}}{\text{cpm/ml antiserum globulin}}$$

where $R_o = 1.25$ cpm on normal cells/$131$ cpm on normal cells.

Specific uptake was also measured in each case (17).

For the *in vivo* tests, 0.2 ml of the paired-label mixture was injected i.p. into mice that had been inoculated i.p. with 10 x $10^6$ leukemic cells 3 days previously. One hr after injection of the mixture, the mice were sacrificed by cervical dislocation, and the cells in the peritoneal cavity were harvested by washing with RPMI 1640 medium. The cell suspension was processed for counting as described above. An indication of the specific absorption *in vivo* was provided by
the ratio between $^{125}\text{I}$ and $^{131}\text{I}$ binding to cells, corrected as follows:

\[ \text{Ratio} = \frac{^{125}\text{I}}{^{131}\text{I}} \text{ cpm on tumor cells} \]

where $R_o = \frac{^{125}\text{I}}{^{131}\text{I}}$ cpm in original mixture.$^{125}\text{I}$ cpm in original mixture.

**RESULTS**

The results of typical *in vitro* uptake of anti-L1210 and anti-L1210/CH3-G γ-globulin by L1210 and L1210/CH3-G cells are shown in Chart 1. In this experiment, the undiluted paired-label reagents were incubated with 5 or 10 million cells. As is shown on the left part of the chart, the specific uptake of anti-L1210 γ-globulin on L1210 cells was about 4 times that on L1210/CH3-G cells, regardless of the number of cells incubated. Conversely, as is shown on the right part of the chart, the uptake of anti-L1210/CH3-G γ-globulin was higher on L1210/CH3-G than on L1210 cells. In this case, the difference was about 10-fold. The specific uptake of this antibody to cells from a spontaneous mammary tumor of the DBA/2Ha-DD mouse was nil. Although the specific uptake of each antibody on the cross-reacting mammary cells was of the same order of magnitude, the specific uptake of anti-L1210/CH3-G γ-globulin on L1210/CH3-G cells was about twice that of anti-L1210 γ-globulin on L1210 cells. Results consistent with those shown in this chart were obtained in 6 uptake tests carried out with 3 pools of serum.

The specific uptake of antibody by the leukemic cells was tested as a function of serial dilutions of the paired-label reagent. The results obtained in 1 experiment carried out with serum Pools B are summarized in Chart 2. Similar data were obtained in 2 additional experiments carried out with the same serum pool. Also in this set of tests, anti-L1210 γ-globulin was specifically taken up by L1210 more than by L1210/CH3-G cells; conversely, anti-L1210/CH3-G γ-globulin was taken up by L1210/CH3-G more than by L1210 cells. The ratio between specific uptakes by the 2 cell types was constant, regardless of the dilution of the paired-label mixture, and was smaller for anti-L1210 γ-globulin than for anti-L1210/CH3-G γ-globulin.

The results obtained in the tests carried out with serum Pools A and B, shown in Charts 1 and 2, respectively, are consistent in suggesting that γ-globulin anti-L1210/CH3-G contains more specific antibody than does γ-globulin anti-L1210, and that, above a relatively constant level of cross-reactivity, specificities are different for the 2 cell types.

The distinct specificities of γ-globulin anti-L1210/CH3-G were verified further by preabsorbing 10 to 50 μg of various types of unlabeled γ-globulin on 10 million target L1210/CH3-G cells for 60 min and then reacting the paired-label mixture containing 10 μg γ-globulin anti-L1210/CH3-G. Serum Pool A was used. The results of this "blocking" experiment, which are not shown, indicated that preabsorption with γ-globulin from untreated mice or from mice treated with DBA/2Ha-DD liver homogenates had no influence on the subsequent specific uptake of anti-L1210/CH3-G γ-globulin. In contrast, preabsorption with anti-L1210 γ-globulin reduced the subsequent specific uptake of anti-L1210/CH3-G γ-globulin by about 50%, whereas preabsorption with anti-L1210/CH3-G γ-globulin blocked the subsequent specific uptake of this γ-globulin by about 70%.

The absorption of paired-label mixtures onto leukemic cells *in vivo* was evaluated in 4 experiments performed with serum Pool A. The results of a typical test are shown in Table 1. By comparison of the ratios of the label uptake, it is evident that each immune γ-globulin was absorbed more to the cells used as the immunizing antigen than to the cross-reacting cells. Thus, these experiments provide an indication that, *in vivo* also, distinct specificities condition the binding of antibody to L1210 and L1210/CH3-G cells.

The possibility that L1210/CH3-G has antigenic specificities different from those of L1210 was substantiated further in 3 experiments which were carried out with serum Pools B and C. In these tests, the effects of repeated prior absorption of antibody with L1210 or L1210/CH3-G cells on the subsequent specific uptake of this antibody by homologous cells were measured. The results obtained with serum Pool C are shown in Chart 3, as an example.

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**Chart 1.** Specific uptake of immune γ-globulin by cells from leukemia L1210 (L1210) or a subline resistant to methylglyoxal-bis(guanylhydrzone) (L1210/CH3-G) as a function of the number of reacting cells. *SMT,* spontaneous mammary tumor cell suspension. *Left,* results obtained with the paired-label mixture containing $^{131}\text{I}$-labeled anti-L1210 γ-globulin; *right,* results obtained with the paired-label mixture containing $^{125}\text{I}$-labeled anti-L1210/CH3-G γ-globulin. The paired-label mixtures and the cell suspensions were prepared as described in "Materials and Methods." The serum pools used were identified as Pool A. Each incubation mixture contained 10 ng of immune γ-globulin and the number of cells indicated. The incubation was carried out at 37° for 60 min. The specific uptake was calculated as described in "Materials and Methods" and was expressed as ng antibody (AB) protein bound to the total number of cells in the incubation mixture. *Bars,* average value of 4 determinations; *vertical lines,* S.D.
As indicated in the legend of Chart 3, the specific uptake of the unabsorbed immune \( \gamma \)-globulins to L1210 and L1210/CH\(_3\)-G cells, respectively, was quite similar to that shown in Chart 1. This uptake is not shown in Chart 3, in which only the residual specific uptake to homologous cells after 1 to 10 serial absorptions onto either cell type is presented. After 1 absorption of anti-L1210 antibody with either L1210 or L1210/CH\(_3\)-G cells, the slight difference in residual specific uptake by L1210 cells was not significant; after 2 to 4 serial absorptions, no difference in residual specific uptake by L1210 cells was found. In contrast, as shown by the divergence of the corresponding curves after 3 subsequent absorptions, anti-L1210/CH\(_3\)-G antibody was absorbed more completely by L1210/CH\(_3\)-G than by L1210 cells, at least within the scope of the 10 repeated absorptions. The fact that no significant differences in residual specific uptake by L1210/CH\(_3\)-G cells was noted after 1 or 2 absorptions with either L1210 or L1210/CH\(_3\)-G cells is probably related to the fact that the anti-L1210/CH\(_3\)-G immune \( \gamma \)-globulin contains a relatively large amount of antibody (Charts 1 and 2). Therefore, it is conceivable that the 10 million cells used for each absorption were not sufficient to put in evidence differential absorption until most of the cross-reacting specificities were taken up. The results obtained with serum

Table 1

<table>
<thead>
<tr>
<th>Target cells</th>
<th>Immune ( \gamma )-globulin</th>
<th>( 131^I \times 10^3 )</th>
<th>( 131^I \times 10^3 )</th>
<th>Ratio (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1210, 1 x ( 10^5 )</td>
<td>Anti-L1210 (14 mg)</td>
<td>14.6</td>
<td>11.5</td>
<td>1.1</td>
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<td>L1210, 5 x ( 10^5 )</td>
<td>33.1</td>
<td>25.5</td>
<td>1.3</td>
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<tr>
<td>L1210, 1 x ( 10^6 )</td>
<td>63.0</td>
<td>42.6</td>
<td>1.5</td>
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<tr>
<td>L1210, 5 x ( 10^6 )</td>
<td>118.0</td>
<td>85.0</td>
<td>1.4</td>
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<tr>
<td>L1210/CH(_3)-G, 1 x ( 10^5 )</td>
<td>9.0</td>
<td>12.8</td>
<td>0.7</td>
<td></td>
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<tr>
<td>L1210/CH(_3)-G, 5 x ( 10^5 )</td>
<td>15.1</td>
<td>18.8</td>
<td>0.8</td>
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<tr>
<td>L1210/CH(_3)-G, 1 x ( 10^6 )</td>
<td>24.7</td>
<td>29.7</td>
<td>0.8</td>
<td></td>
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<tr>
<td>L1210/CH(_3)-G, 5 x ( 10^6 )</td>
<td>78.3</td>
<td>98.7</td>
<td>0.8</td>
<td></td>
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<tr>
<td>L1210, 1 x ( 10^5 )</td>
<td>Anti-L1210/CH(_3)-G (14 mg)</td>
<td>12.3</td>
<td>4.6</td>
<td>0.7</td>
</tr>
<tr>
<td>L1210, 5 x ( 10^5 )</td>
<td>19.5</td>
<td>6.8</td>
<td>0.7</td>
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<td>L1210, 1 x ( 10^6 )</td>
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<td>7.9</td>
<td>0.7</td>
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</tr>
<tr>
<td>L1210, 5 x ( 10^6 )</td>
<td>12.3</td>
<td>4.3</td>
<td>0.7</td>
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<tr>
<td>L1210/CH(_3)-G, 5 x ( 10^5 )</td>
<td>48.5</td>
<td>12.2</td>
<td>0.7</td>
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<tr>
<td>L1210/CH(_3)-G, 1 x ( 10^6 )</td>
<td>72.5</td>
<td>17.4</td>
<td>0.7</td>
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<tr>
<td>L1210/CH(_3)-G, 5 x ( 10^6 )</td>
<td>100.0</td>
<td>21.8</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>L1210/CH(_3)-G, 5 x ( 10^6 )</td>
<td>104.6</td>
<td>23.7</td>
<td>0.7</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) The paired-label mixture was injected i.p. (0.2 ml/mouse) 3 days after the i.p. inoculation of \( 10^6 \) leukemia cells. Cells were harvested 60 min after label injection and were processed as described in "Materials and Methods."

\(^b\) The ratio of uptake was calculated as described in "Materials and Methods."
The results of this investigation demonstrate that L1210 and L1210/CH3-G cells are immunogenic in the DBA/2Ha-DD mouse. In fact, both cell lines elicit in this mouse the production of humoral antibodies that can be shown to bind specifically to cells from the same leukemia line that was used for the immunization. Moreover, with 3 different pools of each antiserum, it was consistently found that the specific uptake of anti-L1210/CH3-G γ-globulin by L1210/CH3-G cells was at least 2 times as high as that of anti-L1210 γ-globulin by L1210 cells. This observation per se suggests that antiserum from mice immunized with L1210/CH3-G cells contains more specific antibody than does antiserum from mice immunized with L1210 cells and, as a corollary, that L1210/CH3-G cells are more immunogenic than L1210 cells in the DBA/2Ha-DD mouse. This greater specific uptake of γ-globulin anti-L1210/CH3-G by L1210/CH3-G cells cannot be ascribed solely to the presence of more antigen- or antibody-binding sites on the resistant cells, because the specific uptake of anti-L1210 γ-globulin was greater on L1210 cells than on L1210/CH3-G cells (Chart 1).

The specific uptake of anti-L1210/CH3-G γ-globulin was seen with cells from spontaneous mammary tumors of the DBA/2Ha-DD mouse further substantiates the specificity of this γ-globulin. The initial observation that low doses of arabinosylcytosine cause a higher incidence of 50-day cures among DBA/2Ha-DD mice bearing the resistant subline than among those bearing L1210 and the observation that this difference was not seen in preirradiated animals (9) have been confirmed and extended in more recent studies (10).

These investigations showed that, in the absence of chemotherapy, DBA/2Ha-DD mice survived longer after the i.p. inoculation of 105 or less L1210/CH3-G cells than after the inoculation of corresponding numbers of L1210 cells. Moreover, a significantly higher incidence of 50-day cures was obtained after selective treatments with 4 different drugs among mice bearing L1210/CH3-G than among those bearing L1210. In both experiments, no difference in survival was found if the animals had been given total-body X-irradiation the day prior to leukemia inoculation. The occurrence of an immunological reaction to L1210 in DBA/2Ha-DD mice had been indicated by the observation that resistance to L1210 challenge could be transferred by means of serum or spleen cells (8). The question arose, therefore, whether the mentioned differences between L1210 and L1210/CH3-G were related to a greater sensitivity of L1210/CH3-G cells to the host response or to a greater immunogenicity of these cells leading to a more effective host response. Although the results of the present study cannot exclude the possibility that L1210/CH3-G cells are more sensitive than L1210 cells to immunotoxicity, they clearly demonstrate that L1210/CH3-G cells are more immunogenic than L1210 cells in the mouse used. The data reported herein are related only to measurements of antibody binding sites and do not cast any light on possible differences in cytotoxic antibodies against the 2 cell types, but these data are quite consistent and in parallel with the survival data obtained in the animal.
The mechanisms by which L1210/CH₃-G cell populations acquire immunogenicity greater than and specificities different from those of L1210 cell populations are unknown at present. Both resistance and increased immunogenicity in DBA/2Ha-DD mice, as assessed on the basis of survival data only, are retained after 185 transplant generations in these mice without maintenance treatments with methylglyoxal-bis(guanilhydrazone) (10). This observation would suggest that these changes are genetically determined and that the greater immunogenicity of the resistant leukemia line is relatively stable, in spite of possible change by immunoselection. The recent findings that a subline of L1210 resistant to 4,4′-diacetyldiphenylurea(bis(guanilhydrazone)) also appears to be more immunogenic than is L1210 in DBA/2Ha-DD mice (10) and that other sublines of L1210 resistant to a variety of drugs behave in F₁ hybrids of the DBA/2 mouse as though they were more immunogenic than L1210 (1, 11, 15, 16) make it unlikely that the antigenic differences between L1210/CH₃-G and L1210 demonstrated in this study are specifically and exclusively related to the development of resistance to methylglyoxal-bis(guanilhydrazone). For the purpose of understanding the mechanism of this phenomenon, it would be important to know whether the antigenicity of other resistant L1210 sublines is cross-reactive with that of L1210/CH₃-G.

It is possible that cell populations with increased immunogenicity may arise during treatment with a drug with immunosuppressive effects leading to a decreased immunoselection. Consistent with this hypothesis is the fact that, in mice, methylglyoxal-bis(guanilhydrazone) inhibited host defenses (5). Other L1210 sublines with increased immunogenicity (1, 11) were indeed resistant to drugs with immunosuppressive action. Moreover, a cultured line of L1210 cells that was sheltered from immunoselection for several months appeared to be much more immunogenic in DBA/2 mouse than was the line of L1210 transferred in vivo (10). Obviously, further experimentation will be required before the validity of this idea can be assessed and before the basis for the development of more antigenic-resistant leukemia lines can be understood.

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