Collateral Sensitivity of Resistant Lines of Mouse Leukemias L1210 and L5178Y

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SUMMARY
Resistant sublines with pronounced patterns of collateral sensitivity of the mouse leukemias L1210 and L5178Y were studied. The sensitivity to cytoxan, carbazilquinone, methotrexate, 6-mercaptopurine, and cytosine arabinoside was greatly increased. Median survival times of all lines, except L1210, were shorter when mice were X-irradiated. The growth potential in homologous mice and in hamsters was inversely related to the sensitivity to the chemotherapeutic agents. No uniform pattern in the distribution of chromosome numbers was associated with change in oncogenic potential.

INTRODUCTION
The literature on drug resistance to chemotherapeutic agents in rodent leukemias is extensive. Past studies have been primarily concerned with induction of resistance and with the biochemical aspects of resistance and cross-resistance. Less attention has been paid to collateral sensitivity. This term was first used by Szybalski and Bryson (22) to describe the following: by acquiring resistance to one agent the cell becomes more sensitive to another. Originally, it was called “induced sensitivity” and no biochemical mechanisms were proposed (23).

Many instances of collateral sensitivity have been collected by Hutchison (13, 14). In our continuing studies on drug resistance with murine leukemias, occasionally the resistant sublines have shown a greater response to chemotherapeutic agents than the parent lines.

Presented herein are studies with the resistant variants of L1210 and L5178Y which have pronounced patterns of collateral sensitivity. The characteristics determined include: (a) response to several chemotherapeutic agents, (b) growth in X-irradiated mice, (c) oncogenic potential in homologous mice and in hamsters, and (d) karyotypes.

MATERIALS AND METHODS
The 6 lines of mouse leukemia studied were the parental line L1210 (V), L1210/MP (III) resistant to 6-MP,2 L1210/MP/Q (XXIX) resistant to 6-MP and N-[p-[(2,4-diamino-6-quinazolyl)-methyl amino] benzoyl]-L-aspartic acid (quinasper), leukemia L5178Y, sublines L5178Y/CA55 resistant to ara-C, and L5178Y/CA55/CTX resistant to ara-C and CTX.

The leukemias were maintained in BDF1 (C57BL/6 × DBA2) mice obtained from A. R. Schmidt Co., Madison, Wis. The treated and control groups consisted of 5 or 10 mice weighing 19 to 23 g.

Groups of 5 AKR/J and C57BL/6J female mice, 8 weeks old (Jackson Laboratories, Bar Harbor, Maine) were used in the homotransplantation experiments. The X-irradiated mice received 400 R total-body radiation 24 hr prior to s.c. injection of 10 million cells into the right axillary region. The factors were: 280 kVP; 20 ma; 0.4-mm copper filter; rate, 150 R/min.

Used for the heterotransplantation experiments were golden hamsters (Chick Line, Newfield, N. J.) weighing 80 to 120 g. They received total-body X-irradiation of 600 R 24 hr prior to s.c. injection of 20 million cells into the right axillary region. Twelve daily i.p. injections of streptomycin sulfate, 100 mg/kg, were given starting on the day of irradiation, because golden hamsters are susceptible to enteritis and a fatal diarrhea known as wet tail (10, 20). Neomycin is also effective against this disease (20). Streptomycin treatment has been found to increase the 50% lethal dose of a single total-body X-ray exposure from 700 to 800 R in adult golden hamsters (21).

CTX, ara-C, and streptomycin sulfate were dissolved in 0.9% NaCl solution and MTX was dissolved in 0.9% NaCl solution and sodium bicarbonate. Carbazilquinone [2,5-bis(1-aziridiny1)-3-(2-carbamoyloxy-1-methoxyethyl)-6-methyl-1,4-benzoquinone] (3) was dissolved in dimethyl sulfoxide and then diluted with 0.9% NaCl solution. 6-MP was suspended in 0.5% carboxymethyl cellulose. In general, the compounds were administered i.p. in a volume of 0.01 ml/g of body weight.

The sensitivity of the lines to the chemotherapeutic agents was studied in BDF1 mice. One million leukemia cells were implanted i.p. Treatment was started 24 hr later and administered i.p., either as a single injection or every other day, for 10 injections or until 50% of the mice in a group were dead. This study was intended mainly as an intercomparison of parent line and resistant sublines. Therefore, the therapeutic responses, measured by MST, of identically treated groups of the parent line and sublines were compared.

After 6 hr of treatment in vivo with 15 mg/kg of colchicine, cytosine arabinoside; CTX, cytoxan; MTX, methotrexate; MST, median survival time; DIC, 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide.

1 Supported in part by Grant CA 08748 from the National Cancer Institute, Grant T-107 from the American Cancer Society, and the Elsa U. Pardee Foundation. Part of the data was presented at the 62nd Annual Meeting of the American Association for Cancer Research at Chicago, Ill., April 8 to 10, 1971.

2 The abbreviations used are: 6-MP, 6-mercaptopurine; ara-C, cytosinearabinoside; CTX, cytoxan; MTX, methotrexate; MST, median survival time; DIC, 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide.
chromosomes were counted on aceto-orcein preparations pretreated with 1.12% sodium citrate.

RESULTS

The chemotherapeutic response of L1210 and 2 resistant sublines to 2 alkylating agents and 3 antimetabolites is shown in Table 1. The effects on L1210 of CTX and carbazilquinone were similar both after single and multiple injections; the MST's resulting from the higher doses were about twice those of the controls. The sensitivity of the 6-MP-resistant line to carbazilquinone was greatly increased; the MST's (following multiple injections) were 47 to more than 60 days, versus 9 to 16 days in the sensitive line. The sensitivity, however, to CTX

Table 1
Effect of CTX, carbazilquinone, and 3 antimetabolites on sensitive and resistant lines of the L1210 mouse leukemia

Treatment was started 1 day after i.p. injection of 1,000,000 cells. Every other day treatments were given for 10 injections or until 50% of the mice were dead. The doses (mg/kg) causing less than 50% mortality in nonleukemic mice were, for multiple injections: CTX, 75; carbazilquinone, 0.75; MTX, 9; 6-MP, 60; and ara-C, 200; for single injections: CTX, 200; and carbazilquinone 2. A doubling of the doses caused death in all animals.

<table>
<thead>
<tr>
<th>Drug</th>
<th>MST (days)</th>
<th>L1210</th>
<th>L1210/MP</th>
<th>L1210/MP/Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
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<td>8</td>
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</tr>
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<td>75</td>
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<td>&gt;60</td>
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<tr>
<td></td>
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<td>47</td>
<td>&gt;60</td>
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The chemotherapeutic response of the L5178Y lines is presented in Table 2. During the development of the ara-C-resistant line, the MST's increased from 11 to 19 days, (following multiple injections) was about the same as that of the original line. The L1210/MP/Q line which is resistant to 6-MP and to quinaspar changed in the process of developing resistance to the quinaspar to such a degree that an inoculum of 1 million cells no longer killed the host. The groups treated with the various doses of CTX and carbazilquinone had equal or greater MST's than the corresponding groups of the singly resistant L1210/MP line.

The 6-MP-resistant variant had greater sensitivity than the parent line to MTX; the MST's following all doses except the high toxic dose were greater than 30 days. It was completely resistant to 6-MP and had the same sensitivity as the parent line to ara-C. The untreated controls of the L1210/MP/Q line had MST's of more than 60 days, and usually all became free of leukemia. After treatment with various doses of MTX, the MST's were less than 20 days, as they were in the sensitive line. Except following 100 mg/kg of 6-MP, the 6-MP- and ara-C-treated groups had greater MST's than the corresponding groups of the parental L1210 line. However, compared with the untreated control mice (L1210/MP/Q), the groups treated with 60, 80, and 100 mg/kg of 6-MP and with 100, 150, and 200 mg/kg of ara-C had shorter survival times.

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Table 2
Effect of CTX, carbazilquinone, and 3 antimetabolites on sensitive and resistant lines of the L5178Y mouse leukemia

Treatment was started 1 day after i.p. injection of 1,000,000 cells. Every other day treatments were given for 10 injections or until 50% of the mice were dead.

<table>
<thead>
<tr>
<th>Drug</th>
<th>MST (days)</th>
<th>L5178Y</th>
<th>L5178Y/CA55</th>
<th>L5178Y/CA55/CTX</th>
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<tbody>
<tr>
<td>Control</td>
<td>11</td>
<td>19</td>
<td>&gt;60</td>
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</tr>
<tr>
<td>CTX</td>
<td>25</td>
<td>11</td>
<td>15</td>
<td>17</td>
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<td>75</td>
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<tr>
<td>Carbazilquinone</td>
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<tr>
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<td>0.75</td>
<td>25</td>
<td>25</td>
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</tr>
<tr>
<td>CTX</td>
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<td>11</td>
<td>15</td>
<td>23</td>
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<td></td>
<td>200</td>
<td>17</td>
<td>18</td>
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<tr>
<td>Carbazilquinone</td>
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<td>&gt;60</td>
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<td></td>
<td>200</td>
<td>22</td>
<td>14</td>
<td>16</td>
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</table>
during the further development to double resistance to ara-C and CTX, they increased to more than 60 days. Carbazilquinone had a slightly better effect in the singly resistant line than in the parent line, and in the doubly resistant line survivals were even longer. The MST's of both resistant sublines after treatment with CTX were only slightly greater than those of the sensitive line. They ranged from 11 to 17 days in L5178Y and 15 to 23 days in the 2 resistant sublines. The MST's of all CTX-treated groups of the L5178Y/CA55 subline were less than those of the untreated mice. In the L5178Y/CA55/CTX line, the MST of the control was greater than 60 days, but the MST's of all treated groups, except after the low carbazilquinone doses, were less than 60 days.

Table 2 also shows that, compared with the corresponding sensitive line, the MST's of the MTX- and 6-MP-treated groups of L5178Y/CA55 were greater than those of the parent lines and that the drugs had more effect on the resistant sublines than on the sensitive lines.

The effect of total-body X-irradiation of 400 R of the BDF<sub>1</sub> mice bearing these L1210 and L5178Y leukemia lines is shown in Table 3. The survival times of all irradiated groups, with the exception of L1210, were shortened. The MST's of nonirradiated mice given injections of only 1000 cells of L1210/MP/Q, L5178Y/CA55, and L5178Y/CA55/CTX were greater than 60 days. In the nonirradiated BDF<sub>1</sub> mouse, usually an i.p. inoculum of 100 cells of L5178Y is not lethal, but an inoculum of 1 to 10 LI 210 cells produces leukemia (F. A. Schmid and D. J. Hutchison, unpublished observation).

The oncogenic potential of the 6 mouse leukemia lines was first compared in homologous mouse strains. Ten million cells of the L1210 and L5178Y leukemia lines were injected into nonirradiated and irradiated AKR/J and C57BL/6J mice. None of the nonirradiated mice died of leukemia, and by Day 21 all tumors at the site of injection had fully regressed. L1210 and L1210/MP cells killed the irradiated mice by Day 7, but all mice bearing L1210/MP/Q survived longer than 30 days (Table 4). LSI78Y and LSI78Y/CA55 killed the irradiated mice within 12 days, but the L5178Y/CA55/CTX-bearing mice died after about 20 days. Autopsies were performed on all mice. Leukemia was diagnosed macroscopically as well as in most cases by bioassay of liver-cell suspensions.

Table 3

<table>
<thead>
<tr>
<th>Leukemia</th>
<th>MST (days)</th>
<th>30-day survivors</th>
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</thead>
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</tr>
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<td>L1210/MP</td>
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<td>0/5</td>
</tr>
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<td>12/15</td>
</tr>
<tr>
<td>L5178Y</td>
<td>11</td>
<td>0/10</td>
</tr>
<tr>
<td>L5178Y/CA55</td>
<td>19</td>
<td>0/10</td>
</tr>
<tr>
<td>L5178Y/CA55/CTX</td>
<td>&gt;60</td>
<td>4/5</td>
</tr>
</tbody>
</table>

Table 4

<table>
<thead>
<tr>
<th>Leukemia</th>
<th>MST (days)</th>
<th>30-day survivors</th>
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</tr>
<tr>
<td>L1210/MP</td>
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<td>0/5</td>
</tr>
<tr>
<td>L1210/MP/Q</td>
<td>30</td>
<td>5/5</td>
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<tr>
<td>L5178Y</td>
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<td>L5178Y/CA55/CTX</td>
<td>19</td>
<td>0/5</td>
</tr>
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</table>

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was 76, and for L5178Y/CA55/CTX the median number was
by 36 to 43 chromosomes with the modes at 39 or 40 (Table
infiltration. Enteritis caused the death of the untreated
6). The 2 sublines of LSI78Y were hypotetraploid. The
controls and the nonleukemic hamsters.
shorter in preirradiated mice. The differences in survival
that died of leukemia showed perivascular leukemic
mice and by histological evaluation. The livers of the hamsters
determined by bioassay of hamster liver suspension in BDFi
treated golden hamsters. Death due to leukemia was
20 million leukemia cells into X-irradiated and streptomycin-
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of CTX was due in part to its immunosuppressive activity. The
chemotherapeutic agents is in agreement with the results of
in the appearance of strong new transplantation antigens.
Bonmassar et al. (6) found that a subline of L1210 which
serially treated with DIC was considerably more sensitive to
1,3-bis(2-chloroethyl)-1-nitrosourea than the parent line. Many
more of the DIC-derived L1210 cells than of the parental line were necessary for successful growth. These
authors suggested that DIC treatment may have selected highly
antigenic variants or induced somatic mutations that resulted
in the appearance of strong new transplantation antigens.
The increased response of our resistant sublines to the
chemotherapeutic agents is in agreement with the results of
the described experiments (6, 16). The slight antitumor effect of
CTX was due in part to its immunosuppressive activity. The
immunosuppressive activity especially of the 3 antimeatabo-
lites, MTX, 6-MP, and ara-C, overpowered in some instances their antitumor effects, particularly in the doubly resistant
variants.
In all lines, with the exception of L1210, MST’s were
shorter in preirradiated mice. The differences in survival
between the irradiated and nonirradiated groups can be
attributed either to different immunogenicity of the leukemic
cells or to differences in the sensitivity of the leukemia cells to
the response of the host. Thus, changes in survival time of
tumor-bearing mice can be due to little or no changes in
antigenicity of the tumor cells combined with great changes in
oncogenic potential or vice versa. Oncogenic potential or
malignancy is defined as the association of characteristics of
the neoplastic cell, such as infiltrative growth, formation of
metastases, etc. One of the major parameters for measuring
oncogenic potential is the determination of the range of
transplantability.
Heterotransplantation is the method of choice for the study
of oncogenic potential, although homotransplantation has also
been used (2). L1210 and L5178Y originated in the DBA₂
mouse with the H²-histocompatibility locus d. AKR/J and
C57BL/6J have the H² alleles of k and b, respectively, and
differ, therefore, from the DBA₂ mouse. The MST’s of the
leukemia lines in the irradiated AKR/J and C57BL/6J mice
were similar and corresponded essentially to those of the
heterologous transplantation experiment with the golden
hamsters. The results of the transplantation experiments in
mice and hamsters reveal that L1210 had the greatest potential
and the 2 doubly resistant lines, L1210/MP/Q and
L5178Y/CA55/CTX, had the least oncogenic potential.
The cheek pouch of the hamsters is usually preferred for the
study of the growth potential of murine or human tumors (1,
7, 9) because the lymphatic drainage is deficient (4). The
tumors grow localized and usually do not metastasize. In the
present study, streptomycin treatment allowed greater
conditioning by X-irradiation. Thus death by leukemia was the
parameter of evaluation.
This question arises; is the increase in survival time of these
resistant variants due to antigenic changes of the tumor cells or
to changes in their sensitivity, i.e., changes in oncogenic
potential? The increase of the MST’s in the homologous and
especially heterologous transplantation systems indicates a
decrease in oncogenic potential.
Any system involving long-transplanted tumors is not well
suited for the study of changes in tumor-specific and isologous
antigens. Immugenetic drifts may occur during successive
transplantation of a tumor and within separate colonies of
inbred animals. Consequently, minor differences in
histocompatibility between tumor and host may exist in
varying degrees even when the same tumor is implanted in
presumably the same inbred strain of mice obtained from

Table 5 shows the results obtained after transplantation of
20 million leukemia cells into X-irradiated and streptomycin-
treated golden hamsters. Death due to leukemia was
determined by bioassay of hamster liver suspension in BDF₁
mice and by histological evaluation. The livers of the hamsters
that died of leukemia showed perivascular leukemic
infiltartion. Enteritis caused the death of the untreated
controls and the nonleukemic hamsters.

Cells of the 3 L1210 and L5178Y lines were characterized by
36 to 43 chromosomes with the modes at 39 or 40 (Table
6). The 2 sublines of L5178Y were hypotetraploid. The
median number of chromosomes per cell for L5178Y/CA55
was 76, and for L5178Y/CA55/CTX the median number was
74.

DISCUSSION

Many cases of collateral sensitivity have been cited in the
literature (13, 14). More recent reports (6, 15–17) are
especially relevant to these studies.

Mihich (16) reported that a subline of L1210 resistant to
methylglyoxal-bis(guanylhydrazone) (L1210/CH₃-G) was
much more sensitive than the parent line to low doses of ara-C.
In preirradiated animals, L1210 and L1210/CH₃-G had similar
responses to ara-C. This finding suggested that the apparent
greater sensitivity of L1210/CH₃-G to ara-C in nonirradiated
animals was related to the greater immunogenicity of the
resistant tumor line.

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the described experiments (6, 16). The slight antitumor effect of
CTX was due in part to its immunosuppressive activity. The
immunosuppressive activity especially of the 3 antimeatabo-
lites, MTX, 6-MP, and ara-C, overpowered in some instances their antitumor effects, particularly in the doubly resistant
variants.

In all lines, with the exception of L1210, MST’s were
shorter in preirradiated mice. The differences in survival

Table 6

<table>
<thead>
<tr>
<th>Leukemia</th>
<th>No. of cells scored</th>
<th>≤37</th>
<th>38</th>
<th>39</th>
<th>40</th>
<th>41</th>
<th>42</th>
<th>43</th>
<th>&gt;60b</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1210</td>
<td>50</td>
<td>6</td>
<td>22</td>
<td>60.8</td>
<td>8</td>
<td>2</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1210/MP</td>
<td>50</td>
<td>4</td>
<td>2</td>
<td>89</td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1210/MP/Q</td>
<td>50</td>
<td>9</td>
<td>40</td>
<td>30</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>L5178Y</td>
<td>50</td>
<td>12</td>
<td>48.6</td>
<td>30</td>
<td>6</td>
<td>2</td>
<td>1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L5178Y/CA55</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>L5178Y/CA55/CTX</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

* a Scored for individual chromosomes.
* b For polyploidy, 300 to 500 cells were observed.
Franz A. Schmid and Doms J. Hutchison

different sources. As mentioned, an inoculum of 1 to 10 cells of the L1210 strain used is usually lethal to 100% of the BDF1 mice (F. A. Schmid and D. J. Hutchison, unpublished observation). It has been observed, however, by D. J. Hutchison and M. Shimoyama (unpublished data) and by other investigators (8, 18, 19) that the so-called strain-specific mouse can be immunized relatively easily against the various L1210 strains. Thus, in the mouse strains used, the oncogenic potential of L1210 is sufficient to overcome the immunological reactions of the host. A loss in growth potential, however, would result in cells that are more sensitive to the immunological response of the host and consequently less capable of surmounting even weak immunological barriers. This observation may partially explain the results of the present experiments. The resistant lines, especially the doubly resistant lines, lost growth potential. The immunological host reactions are probably partly responsible for the marked increase in the antitumor effect of certain doses of the chemotherapeutic agents used. Although the results in general suggest changes in the oncogenic potential of the leukemia lines used, they do not exclude changes in the antigenicity of the tumor cells. Mihich (16) and Bonmassar et al. (6) considered that the greater drug sensitivity of their resistant lines was due to an increase in antigenicity. They did not, however, test for oncogenic potential.

The numbers of chromosomes per cell increase occasionally after treatment with chemicals and especially as cells become malignant (5, 11, 12). The results of the chromosomal analyses of the leukemia lines used were not uniform. The resistant sublines of L1210 remained diploid, whereas the chromosome numbers of the resistant LI5178Y variants increased.

Certain drug-directed modifications have been observed in the resistant sublines of the L1210 and LI5178Y mouse leukemias. Such modifications could become an important adjuvant to chemotherapy.

ACKNOWLEDGMENTS

The chromosomal analysis was done by Miss M. Gay Sargent.

REFERENCES

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