Cell Proliferation Kinetics and Drug Sensitivity of Exponential and Stationary Populations of Cultured L1210 Cells

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INTRODUCTION

In 1966, Bruce et al. (8) compared the drug sensitivity of rapidly proliferating lymphoma cells to that of the hematopoietic stem cells in the resting state. Chemotherapeutic agents were classified into: (a) cycle-specific agents such as FU,2 actinomycin D, or cyclophosphamide, which were much more cytotoxic to cells in the proliferative state than in the resting state; and (b) cycle-nonspecific agents such as \gamma\text{-}radiation, which killed both cycling and resting cells. Since then, many workers have compared the drug sensitivity of cultured mammalian cells in the exponential and plateau phases of growth (1, 2, 12, 13, 21, 25, 27-29). This interest is based on the similarities that exist between the kinetics of stationary-phase cultures and experimental tumors in animals (14). The drug sensitivity of certain cell types has been studied in detail: (a) cells in monolayer: Chinese hamster ovary, CHO (2); Chinese hamster lung, V79 (21); Chinese hamster ovary, HA1 (13); embryonic Chinese hamster (25); human cervical carcinoma, HeLa (21); and mouse mammary sarcoma, EMT 6 (27); and (b) cells in suspension: mouse leukemia, L1210 (4, 29); murine mastocytoma, P815 X2 (12). Among these cell lines, the EMT 6, the P815 X2 and the L1210 can be maintained both in vitro and in vivo.

We report here the cell cycle parameters and the drug sensitivity of cultured L1210 cells in exponential and stationary phases of growth. Parts of these results were reported previously (4). We chose the L1210 cells because of the existence of an animal model counterpart, because it seems to be an adequate model for human leukemia, and because of its widespread use in screening for cancer chemotherapeutic agents (18).

MATERIALS AND METHODS

L1210 Cell Culture. L1210 cells were maintained in culture in Roswell Park Memorial Institute Medium 1634 supplemented with fetal calf serum (5%), NaHCO₃ (0.75 mg/ml), penicillin (0.1 mg/ml), and streptomycin (0.05 mg/ml) as described previously (5). In this medium the cells grew exponentially with a generation time of about 12 hr. Exponential growth was maintained until a cell density of $4 \times 10^8$ cells/ml was reached; stationary I cultures had $6 \times 10^8$ cells/ml, and stationary II cultures had about $8 \times 10^8$ cells/ml (see Chart 2). These cell counts were obtained by planting cells at $5 \times 10^4$/ml and using them after 24 (exponential), 42 (stationary I), and 72 hr (stationary II) of growth. Cells were counted in a Coulter counter.

Drug Exposure and Cell Survival. Adriamycin (NSC 123127), daunomycin (NSC 82151), BCNU (NSC 409962), CCNU (NSC 79037), DCNU (NSC 178248), FU (NSC 32065), BCNU (NSC 19893), and VCR (NSC 67574) were obtained from the Division of Cancer Treatment, National Cancer Institute, Bethesda, Md. ara-C (NSC 63878) and streptozotocin (NSC 85988) were developed by The Upjohn Company. ara-C, HU, VCR, adriamycin, and daunomycin were dissolved in medium. Streptozotocin was dissolved in 0.1 M potassium phosphate, pH 4. Actinomycin D was dissolved in acetone. BCNU, CCNU, and DCNU were weighed into chilled bottles and were dissolved in dimethyl sulfoxide. Drugs were dissolved and then diluted in medium prior to addition to cells. At the end of drug exposure, cells were centrifuged and washed to remove drug and then suspended in medium to determine cloning efficiency. Cell survival was determined by cloning in soft agar (16) and has been described previously (5). In the calculation of percentage survivals, the

SUMMARY

Drug sensitivity and cell cycle parameters of L1210 cells in culture in exponential ($10^8$ to $4 \times 10^8$ cells/ml) and plateau phase ($>8 \times 10^8$ cells/ml) of growth were compared.

The percentage of cells in \(G_1\), \(S\), and \(G_2 + M\) for exponential and plateau-phase cultures was 24.1, 70.0, and 5.9, and 42.5, 45.6, and 11.9, respectively. These values correspond to those reported previously for early and late L1210 mouse leukemia cells. Cell survival (measured by cloning) after drug exposure showed that actinomycin D, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, chlorozotocin, and streptozotocin were all equally lethal to cells in both phases, and 1-\(\beta\)-d-arabinofuranosylcytosine, high-specific-activity (20 Ci/m mole) \[\text{[H]}\text{thymidine},\ vincristine, daunomycin, adriamycin, and 5-fluorouracil were more lethal to exponential cells than to plateau-phase cells. The percentage kill by \(S\)-phase-specific agents such as 1-\(\beta\)-d-arabinofuranosylcytosine and \[\text{[H]}\text{thymidine}\) corresponded well with the percentage of cells in \(S\). Finally, 1,3-bis(2-chloroethyl)-1-nitrosourea was more toxic to plateau cells than to exponential cells.

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control (no drug treatment) samples were normalized to 100% survival. The coefficient of variation in determining cell survival was about 15%, the coefficient of variation being the standard deviation expressed as a percentage of the mean.

**Glucose, Lactic Acid, and Amino Acid Analysis.** The cells were centrifuged prior to determining glucose, lactic acid, or amino acid content of the supernatant medium. The glucose content of the medium was determined by an enzymatic procedure using the Glucostat provided by Worthington Biochemical Corp., Freehold, N. J. (24). Lactic acid content was determined by an enzymatic procedure using the test pack supplied by Calbiochem, Los Angeles, Calif. (17). Amino acid content was determined (by Dr. A. J. Parcells, The Upjohn Co.) by ion-exchange chromatography on a Spinco Model MS amino acid analyzer (22).

**Determination of Macromolecule Synthesis.** The incorporation of [3H]thymidine, 5-[3H]uridine, and L-[3H]valine (generally labeled) into DNA, RNA, and protein, respectively, was determined as described previously (7).

**Autoradiography.** The cells were prepared for autoradiography as described previously (3).

**RESULTS**

**Growth Characteristics.** The population kinetics, glucose, and lactic acid concentration and the pH of the medium in a roller culture are shown in Chart 1. Although the glucose was metabolized rapidly, a 0.8-mg/ml concentration of glucose was remaining in the medium when exponential growth ceased. About a 0.9-mg/ml concentration of lactic acid was produced per 0.9-mg/ml concentration of glucose metabolized. The pH of the medium decreased from an initial value of 7.3 to about 6.2 to 6.3. The amino acid content of the medium was analyzed when the cell density was 2 x 10^6 cells/ml (81 hr) and at 0 hr. The results (Table 1) indicate that: (a) up to 40% of the original concentration of the amino acids aspartic acid, cystine, glutamic acid, glycine, histidine, isoleucine, lysine, proline, threonine and valine were used during cell growth; (b) 40 to 70% of phenylalanine and leucine were utilized; and (c) 70 to 100% of arginine, methionine, tyrosine, and serine-asparagine-glutamine were depleted from the medium.

The rate (cpm/10^5 cells/hr) of DNA, RNA, and protein synthesis in the stationary cells was about 20% (range 13 to 31%) of that in the exponential cells. In order to expose the cells to the same labeled precursor (thymidine, uridine, or valine) concentration, both exponential and stationary cells were centrifuged and resuspended at their original cell concentration in fresh medium or in medium (called exponential medium) that had supported growth of exponential cells or in medium (called stationary medium) that had supported growth of stationary cells. For example, the rate of incorporation of [3H]thymidine into DNA by stationary cells suspended in fresh, exponential, or stationary medium was 24, 30, and 21%, respectively, of that of exponential cells suspended in the same media.

The rate of DNA synthesis can also be expressed as cpm/10^6 S-phase cells. The exponential population had 78.8% cells in S as compared to 45% in the stationary II population.
were synthesizing DNA at 38% of the rate of exponential cells.

**Reasons for Onset of Stationary Phase.** We investigated 2 possible reasons for the cessation of exponential growth. The 1st possibility was depletion of essential nutrients. When medium containing stationary cells was adjusted to pH 7.2 and then enriched by adding amino acids, vitamins, glucose, or fetal calf serum, growth still ceased at about 2 × 10^6/ml. The 2nd possible reason was production of toxic metabolites (such as acid pH or high lactic acid concentration or toxic metabolites). Even if the pH was maintained at 7.2, growth ceased at 2 × 10^6 cells/ml. Lactate had minimal effect on cell growth, when added to give 400 to 800 μg/ml.

We found that partially depleted medium (which had already supported cell growth to 10^6 cells/ml) still allowed a fresh inoculum to grow to 8 × 10^6/ml with a doubling time of 18 hr. This indicates that the accumulation of toxic metabolites in the partially depleted medium slowed down but did not completely inhibit cell growth.

Our results do not clearly indicate the factor or factors that caused the onset of stationary phase.

**Viability of Cells in Exponential and Stationary Growth.** The viability, as determined by cloning efficiency, is shown in Chart 2. Viability decreased the longer the cells stayed in stationary phase. In this experiment the cells reached stationary at about 52 hr, and by 76 hr, cell viability had decreased to 40% of that of the exponential cells.

Stationary cells at 76 hr were diluted and replanted in fresh medium at 5 × 10^6/ml. There was an initial lag phase of 14 hr following which the cells grew with a doubling time of 12 hr. This lag could be explained by the fact that only 40% of the 76-hr cells were viable, indicating an initial viable inoculum of 2 × 10^4 cells/ml.

**Distribution of Cells in Different Phases of the Cell Cycle.** The distribution is shown in Table 2. The percentage of S-phase cells determined by flow-microfluorometry was similar to the values obtained by autoradiography after labeling with [3H]TdR.

In these experiments cell samples were taken at 2 × 10^6/ml (mid-log), at 6 × 10^6/ml (beginning stationary or stationary I) and at 7.5 × 10^6/ml (24 hr in stationary or stationary II). At these times the average percentage of viable cells was 75.6 ± 2.6 for exponential and stationary I and 51.5 ± 2.5 for stationary II cells. The percentage of G1 and G2 + M cells, respectively, increased from 24 and 5.9% in exponential cells to 42.5 and 11.9 in stationary II cells. This increase was evident even at stationary I when the cell number had just stopped increasing exponentially. The percentage of S-phase cells decreased from 70.1% in exponential cells to 45.6% in stationary II cells.

These values for L1210 cells in culture compare well with those reported by Hartman and Dombernowsky (15) for L1210 in vivo (Table 2). The distribution of cells in the exponential and stationary II cultures is similar to that seen in L1210 ascites cells obtained 5 and 8 days after injecting 10^8 cells.

**Survival of Exponential and Stationary Cells Exposed to Cytotoxic Agents.** The survival of cells exposed to various cytotoxic agents is shown in Table 3. The agents can be divided into 3 groups: (a) those that are more cytotoxic to exponential than to stationary cells, e.g., ara-C, HU, high-specific-activity [3H]TdR, FU, VCR, Adriamycin, and daunomycin; (b) those that are equally cytotoxic to both groups of cells, e.g., actinomycin D, streptozotocin, DCNU, and CCNU; and (c) BCNU, which was more cytotoxic to stationary cells than to exponential cells.

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**Table 2**

*Distribution of Cells in Different Phases of the Cell Cycle*

<table>
<thead>
<tr>
<th>Growth phase</th>
<th>Flow-microfluorometry</th>
<th>[3H]TdR-labeled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exponential culture</td>
<td>G1 (%)</td>
<td>G2 + M (%)</td>
</tr>
<tr>
<td>Day 5 ascites</td>
<td>24 ± 1.7</td>
<td>5.9 ± 0.7</td>
</tr>
<tr>
<td>Stationary I culture</td>
<td>29.5</td>
<td>7.6</td>
</tr>
<tr>
<td>Stationary II culture</td>
<td>34.1</td>
<td>7.1</td>
</tr>
<tr>
<td>Stationary III culture</td>
<td>42.5</td>
<td>11.9</td>
</tr>
<tr>
<td>Stationary IV culture</td>
<td>44.8</td>
<td>8.4</td>
</tr>
</tbody>
</table>

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*a* The flow-microfluorometric determinations were done by Dr. H. Crissman (Los Alamos Scientific Laboratories, Los Alamos, N. M.) according to methods published before (26).

*b* The percentage S-phase cells were also determined by pulse labeling (15 min) with [3H]TdR (2 Ci/mMole, 10 μCi/ml) followed by autoradiography.

*c* The exponential and stationary I and II cultures contained 2 × 10^6, 6 × 10^6, and 7.5 to 9 × 10^6 cells/ml, respectively.

*d* The values for the ascites cells were obtained from Table 1 of Hartman et al. (15).
The time course of survival of cells exposed to the S-phase-specific agents, ara-C, HU, and high-specific-activity $[\text{H}]$TdR is shown in Chart 3. The results show that the percentage of cells killed by these agents correlates well with the percentage of S-phase cells in the population (see Table 2). That would explain why a much higher percentage of the exponential cells were killed than stationary cells. For example, ara-C killed 70 and 53% of the exponential and stationary II cells, respectively. These populations had 70 and 46% cells in S phase. These results also show that the cells in S in the stationary population were metabolically active, and, although they had a diminished DNA synthesis capacity, they were still susceptible to these S-phase-specific agents. Second, the percentage of exponential cells killed increased with time of exposure, indicating the progression of non-S-phase cells into S during the exposure period. The lower cell kill seen at 6 hr with ara-C and HU as compared to $[\text{H}]$TdR is presumably due to the accumulation of cells by the former agents at the G1-S border (5). With the stationary population the percentage of cells killed did not increase significantly from 2 hr to 6 hr exposure. This suggests that very few non-S-phase cells progressed into S during this period.

The time course of survival of cells exposed to adriamycin and daunomycin is shown in Chart 4. The results clearly show that at all times adriamycin and daunomycin were much more toxic to exponential cells than to stationary cells. For example 0.1 and 50% of the exponential and stationary cells, respectively, survived a 6-hr exposure to adriamycin at 0.05 $\mu$g/ml.

The cytotoxicities of the nitrosourea compounds, BCNU, CCNU, DCNU, and streptozotocin are compared in Table 3.

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**Table 3**

Survival of exponential and stationary cell populations after exposure to cytotoxic agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>2-hr Exposure</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-hour</td>
<td>Exponential I</td>
<td>Stationary I</td>
<td>Stationary II</td>
<td>Exponential</td>
</tr>
<tr>
<td></td>
<td>Survival (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-specific-activity $[\text{H}]$TdR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ara-C</td>
<td>5</td>
<td>30.1</td>
<td>48.5</td>
<td>47</td>
<td>5.2</td>
</tr>
<tr>
<td>HU</td>
<td>300</td>
<td>23.8</td>
<td></td>
<td>56.2</td>
<td>4.3</td>
</tr>
<tr>
<td>FU</td>
<td>0.25</td>
<td></td>
<td>38.2</td>
<td></td>
<td>11.3</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td></td>
<td>61.3</td>
<td></td>
<td>11.3</td>
</tr>
<tr>
<td>VCR</td>
<td>0.025</td>
<td>44.6</td>
<td>80.2</td>
<td>85.7</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>14.5</td>
<td></td>
<td>87.7</td>
<td>0.09</td>
</tr>
<tr>
<td>Daunomycin</td>
<td>0.025</td>
<td>69.7</td>
<td>78.5</td>
<td>100</td>
<td>38.5</td>
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<tr>
<td></td>
<td>0.05</td>
<td>16.2</td>
<td>87.8</td>
<td>91.1</td>
<td>11.3</td>
</tr>
<tr>
<td>Streptozotocin</td>
<td>100</td>
<td>63</td>
<td>63</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>53</td>
<td>47</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>CCNU</td>
<td>0.5</td>
<td>32.3</td>
<td></td>
<td>49.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>6.5</td>
<td></td>
<td>15.1</td>
<td></td>
</tr>
<tr>
<td>DCNU</td>
<td>0.5</td>
<td>59.9</td>
<td></td>
<td>64.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>~ 1.0</td>
<td>20.6</td>
<td></td>
<td>25.3</td>
<td></td>
</tr>
<tr>
<td>BCNU</td>
<td>0.25</td>
<td>79.6</td>
<td></td>
<td>46.8</td>
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<tr>
<td></td>
<td>0.5</td>
<td>49.7</td>
<td></td>
<td>18.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>11.2</td>
<td></td>
<td>3.3</td>
<td></td>
</tr>
</tbody>
</table>

* Exponential, stationary I, and stationary II populations contained $2 \times 10^6$, $6 \times 10^6$, and $7.5$ to $9 \times 10^6$ cells/ml, respectively.
* High-specific-activity $[\text{H}]$TdR (20 Ci/mmol) was added to give 10 $\mu$Ci/ml.
* Cells were exposed to FU for 24 hr.
found (Table 4) that there was significantly greater toxicity of BCNU for stationary cells as compared to exponential cells at all concentrations of serum in the medium. In accordance with the finding of Hahn et al. (13), BCNU was more toxic in the absence than in the presence of serum. BCNU binds to serum proteins. Also, the utilization of serum components by cells can result in a different protein concentration in the media supporting exponential or stationary cells. In order to determine whether this effect could modulate BCNU toxicity, the experiment shown in Table 5 was done. It is clear that stationary cells were more sensitive than exponential cells irrespective of the medium they were suspended in.

**DISCUSSION**

**Cell Metabolism.** Our results on glucose utilization showed that glucose was utilized rapidly even after exponential growth had ceased. A glucose concentration of about 900 μg/ml was used per 2 × 10^6 cells (equivalent to 0.3 mg protein) produced. Practically all of the glucose utilized was converted to lactic acid. Eagle et al. (9), with human cell cultures, and Graff and McCarty (11) with L-cells, reported that about 50 to 80% of the glucose is converted to lactic acid. It is quite clear that the end of exponential growth was not due to depletion of glucose. Except for lysine (only 11% used up), all the amino acids that were used less than 20% (namely, aspartic acid, cysteine, glycine, glutamic acid, and proline) belong to “nonessential” amino acids as identified by Levintow and Eagle (19). These results were further corroborated (by S. L. Kuentzel of our laboratory) when it was shown that Roswell
Park Memorial Institute Medium 1634 without aspartic acid, cystine, glutamic acid, and proline could support rapid cell growth (12 hr doubling time), similar to that seen in medium containing these amino acids.

Our results did not clearly indicate the factors that caused the onset of stationary phase. There are other possible causes that we have not investigated. For example, Glinos et al. (10) clearly showed that PO2 in medium was one of the factors governing the growth of cells in suspension. Thus, the PO2 in medium of a high-density culture was less than 10 mm Hg compared to >100 mm Hg in a low-density culture of L929 cells in suspension.

Cell Viability. The viability of L1210 cells decreased rapidly when the cells were kept in stationary phase. Different cell lines respond differently to being maintained in stationary phase. For example, CHO (2), P815 (12), and EMT 6 (27) cells retained close to 100% viability for several days in the stationary phase. On the contrary, the viability of HeLa (21), V79 (21), and HA-1 cells (14) decreased in the stationary phase.

Cell Cycle Parameters. As the cells progressed from exponential to stationary phase, the following changes took place. The cell number remained constant although there was decreased cell viability. The mitotic index decreased. The percentage of S-phase cells decreased while the percentage of cells in G1 and G2 increased. The cell size decreased.

We do not know whether the constant cell number was due to a balance between cell loss and cell proliferation or whether dead cells remained, without being lysed, in the culture. Microscopic examination showed many small cells with marked nuclear derangement in the stationary population.

The percentage of S-phase cells determined by autoradiography correlated well with that determined by flow-microfluorometry. This shows that all the cells with DNA content corresponding to S phase, both in the exponential and stationary populations, were synthesizing DNA. However, the rate of DNA synthesis of the S-phase cells in stationary culture was 38% of that in exponential culture.

We found that, while 100% of the exponential cells were labeled by continuous exposure to $[^3H]$Tdr for 7 hr, only 80% of stationary II cells were labeled after 24 hr. Therefore 20% of the cells in stationary culture can be operationally defined as noncycling and may be either truly stationary (G0) cells, or progressing through the cell cycle at very slow rate, or dead cells.

The distribution of cultured L1210 cells in G1, S, and G2 + M in the exponential and stationary phases compared well with those reported by Hartman and Dombenerowsky (15) for 5- and 8-day-old L1210 ascites (see Table 3). Hartman and Dombenerowsky (15) reported that, according to their model, 96% of the G1 population and 11% of the G2 population in the 8-day ascites were resting (Q1 and Q2) cells. Similar data are not yet available for the L1210 cells in culture.

Cytotoxicity of Drugs. ara-C and HU kill only S-phase cells. HSA-[3H]Tdr kills cells by being incorporated into the DNA and therefore also kills only S-phase cells. The percentage of cells killed by these S-phase-specific agents correlated well with the percentage of S-phase cells determined by microfluorometry or autoradiography. These results served to check the validity of our experimental techniques.

The greater sensitivity of exponentially growing L1210 cells as compared to stationary-phase cells for the drugs we tested has been confirmed by other workers: ara-C was studied by Bruce et al. (8), Wilkoff et al. (29), and Barranco et al. (1). HU was studied by Mauro et al. (21). However, their experiments also showed that after 6 hr exposure, more plateau-phase V79 cells were killed as compared to exponentially growing cells. Our results do not corroborate this finding. Results similar to ours were also obtained by Wilkoff et al. (29) and Barranco and Novak (1). Adriamycin was studied by Twentyman and Bleehen (27) and Barranco et al. (1). FU was studied by Madoc-Jones and Bruce (20) and Bhuyan et al. (6).

For actinomycin D, VCR, and BCNU, different results have been reported by different workers using different systems. Twentyman and Bleehen (27) and Bruce et al. (8) found that actinomycin D was much more toxic to cycling than to noncycling cells. Thatcher and Walker (25) found that confluent (i.e., stationary) hamster embryo cells were more sensitive to the drug than cycling cells. In our experiments, actinomycin D was almost equally toxic to both exponentially growing and stationary cells. VCR was reported by Rossner et al. (23) to be more cytotoxic to stationary human lymphoid cells in culture than cycling cells. However, vinblastine (an analog of VCR) was found by Bruce et al. (8) to be much more cytotoxic to rapidly cycling lymphoma cells than to normal hemopoietic cells. In our experiment, VCR was clearly more active against exponentially growing cells than against stationary cells.

The variety of results obtained for BCNU in different systems has been outlined in detail by Hahn et al. (13). Barranco et al. (2) found that stationary CHO cells were 1000 times more sensitive than exponentially growing cells. Although we did not see such a great difference in sensitivity, stationary-phase cells were consistently more sensitive than were exponential cells. However, we must realize that the cell distribution in the stationary phase of L1210 is significantly different from that of CHO. Thus in stationary II culture of L1210, the cells are distributed throughout the cell cycle (Table 2), whereas most of the cells reside in a G1-like compartment in stationary CHO culture (2). Results similar to ours were reported by Hageman et al. (12) and Hahn et al. (13). Twentyman and Bleehen (27) and Thatcher and Walker (25) found that BCNU was equally cytotoxic to cells in exponential and stationary phases. Our results showed that the greater sensitivity of the stationary cells depended on the cell type and not on other medium constituents.

The greater toxicity of BCNU for stationary cells was not seen with other nitrosoureas such as CCNU and streptozotocin, the latter two being equally cytotoxic to both types of cells. We do not know the reason for this difference.

The reports published clearly show that different cell types will respond differently with regard to the drug sensitivity of the exponential and stationary-phase cells. This situation exists in spite of the fact that the change in age distribution from exponentially growing cells to stationary-phase cells is similar. Therefore, in order to use this
system as a model for noncycling cells, we need to understand changes in cell properties (such as membrane transport, etc.) other than just cell-age distribution.

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REFERENCES


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