EDITORIAL

Cell Cycle Kinetics in Leukemia

By Frederick Stohlman, Jr.

The chemotherapy of leukemia has been directed primarily toward agents that interfere with the generative cycle of the cell. Initially it was thought that leukemia was the result of rapidly proliferating cells, but with the advent of studies with tridiated thymidine it became evident that the disease was more appropriately considered a failure of differentiation. Further, it became clear that the kinetics of proliferation of leukemic cells is a complex one. In acute leukemia there appears to be not only an actively proliferating population of “blast” cells but also a substantial and variable proportion of resting cells. The proportion of resting cells varies not only from patient to patient but within the same patient at various stages of the disease.

Investigation of cell cycle kinetics of leukemia and the proliferative capacity of the resting blast cell is significant not only in an understanding of the disease process but also in the design of chemotherapy programs in which multiple drug therapy directed at different phases of the generative cycle is contemplated. The question of the proliferative potential of the resting cells has been approached by Stryckmans and his associates through study of the capacity of resting cells for DNA repair. In the current issue of Blood they report on studies in which they demonstrate that most, if not all, resting blast cells of the peripheral blood possess the capacity for DNA repair. One may consider, therefore, that the DNA-synthetic mechanism is intact. This is in contrast to the end-stage normal myeloid elements, the metamyelocyte and segmented granulocytes. These data, then, suggest that the entire resting blast cell population is capable of entering an active generative cycle and contributing to the expansion of the leukemic population.

One may further question what controls the entry of blast cells into a resting phase or causes reentry into active cycle. The studies of Gavosto and Gabutti et al. indicate that the resting blast cells enter cycle to maintain the leukemic population after perturbation. This suggests some measure of population control, as contrasted with unlimited cell growth. Understanding the nature of this limited control mechanism is clearly important in the therapeutic approach to leukemia. If one could cause more of the proliferating cells to enter a resting phase, growth of leukemia would be curtailed. Conversely, if resting cells could be induced to enter cycle, a therapeutic advantage might be gained because most of the cytotoxic agents are effective during a specific phase of the generative cycle. Entrance of resting cells into active cycle would then make them more susceptible to eradication by drug therapy. Mauer et al. have recently discussed synchronization of leukemic population as a promising approach to achieve more effective use of chemotherapeutic agents in acute leukemia, but they pointed out that more experimental data are needed.

Preliminary studies on synchronization of leukemic cell populations have
been reported by Gabutti et al.\textsuperscript{2} and Lampkin et al.\textsuperscript{4} It was clear from these studies that further information relative to the effects of drugs on the cell cycle is of importance in the evaluation of chemotherapy with multiple drugs. Such an approach has been utilized by Ernst and Killman in the present issue of \textit{Blood}. Using cell cycle techniques, these authors have extended the previous observations of Lampkin et al.\textsuperscript{4} on the effect of high doses of steroids on leukemic cells in patients with acute lymphoblastic leukemia. Both present evidence that steroids, in addition to the well-known lymphocytolytic effect, have a selective effect on lymphoblastic leukemic cells in $G_1$. This apparently results in a delayed entry into $S$. A similar effect is not seen in normal myeloid cells nor in acute myeloblastic leukemia. As discussed by the authors, these studies have important implications in the timing of subsequent drug therapy directed at the DNA-synthetic or mitotic phase of cycle.

We would not be presumptuous enough to suggest that clinically effective means of chemotherapy be altered in view of these early findings. However, the application of techniques of cell cycle kinetics to the clinical approach to chemotherapy of leukemia appears to have significant potential. Further studies of this type, using the known effective drugs and other agents yet to be developed, hold promise of leading to true synchronization of cell populations, more complete entry of the resting population into cycle and perhaps more effective therapy.

\textbf{REFERENCES}


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