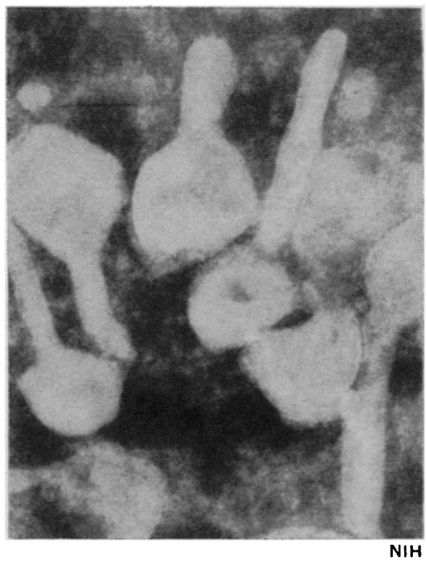
CANCER CHEMOTHERAPY

Cell cycles give clues

Timing is critical in using drugs to kill cancer cells, known to be susceptible at certain stages of their life cycle

by Barbara J. Culliton



NIH

Mouse leukemia virus, x150,000.

10^{12} is a lethal number.

When a trillion leukemia cells infest a child's body, death is at hand. But if physicians can kill 999,999,000,000 of those cells, leaving only one million behind, the child is cured—temporarily.

Four years ago, leukemia victims seldom lived more than 12 to 18 months. Today, half of them are well for three years; many even longer. Success depends on speed. Eventually those million remaining cells will multiply and outpace scientists' ability to kill them, and the patient will die.

But hope is seen in the fact that all human research is predicated on animal experiments. The next step, already charted in animal work, is a key one: Once, mouse leukemia, like human, was fatal. Now it can be cured.

"We tried half-blindly for 15 years to cure mouse leukemia with only flickers of success," says Dr. Howard E. Skipper of the Southern Research Institute, Birmingham, Ala. "We could treat the leukemic animals and increase their survival time, but during these 15 lean years we must have buried several million mice that died in spite of our best efforts to save them."

Today, with carefully programmed drug attacks, the population of leukemia cells in a mouse can be reduced to zero and the animal cured. In doing this, researchers have learned a lot about how cancer cells and anticancer drugs behave, and are armed with new concepts and approaches to cancer.

"How often have we cautioned ourselves that 'cancer is many diseases,' and that any attempt to extend what has been observed about one type of cancer to another type of cancer is fraught with danger," Dr. Skipper remarks. "This was good advice in a way because there certainly are behavioral differences and quantitative biochemical differences between different types of cancer." But he stresses that above all else "we seek efficiency in time and effort in achieving clinical progress."

Success in curing mouse leukemia and generalizations about the behavior and ways of killing other types of cancers, gleaned from years of study, have brought researchers to a new approach to treating cancer, or, more accurately, new understanding of how to use efficiently tools that are already available.

Cell kinetics—the study of cells in motion—moves into the forefront as scientists focus on coordinating what they know of drug therapy with what they are learning about the cyclic stages of cell division and multiplication. Fundamentally, they are using cell kinetics as a principle that in practice reduces cancer to one disease.

"During the last two years," says Dr. C. Gordon Zubrod, director of the cancer chemotherapy program of the National Institutes of Health, "we have been coordinating information gained by a number of individual researchers. Some of it has been around since 1960, but only now are the implications apparent." (Much of the cancer chemotherapy work in the United States is supported by the NIH program which, since 1955, has been operating on a budget of about $25 million a year.)

Specific drugs, it has been determined, kill cancer cells at specific stages in their reproductive cycle. Some are effective against cells that are dividing. Others act against cells in the S phase, during which DNA (deoxyribonucleic acid) is synthesized. Some work just prior to the S phase. The goal, therefore, is to perfect a combination regimen that will wipe out malignant cells in all their vulnerable phases. The ability to do this depends on the speed with which a given tumor grows.

Cancers fit into two broad categories: fast-growing and slow. Current advances apply only to the first class, which includes leukemia, Hodgkin's disease, choriocarcinoma and Burkitt's lymphoma. Presumably they will in time extend to slow-growing cancers such as lung, breast, prostate and kidney tumors. "Within five years we will know whether our theory of kinetics applies to slow-growing, solid tumors," Dr. Zubrod predicts.

Fast-growing cancer cells multiply to lethal numbers in a matter of days or weeks. Slow-growing tumors take months or years to proliferate to a lethal level—the fatal 10^{12}.

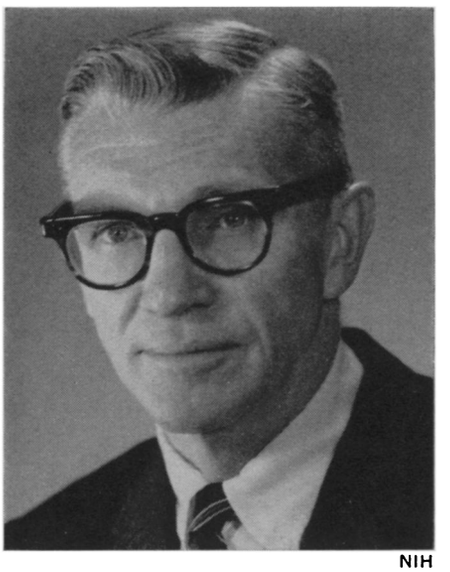
Dr. William R. Bruce of the University of Toronto, like Drs. Skipper and Zubrod, has been focusing on the life cycle of cells. Division, he explains, occurs in four phases, designated G1, S, G2, and M. Phase G1 is a pause during which the cell gets ready for the S phase and its DNA synthesis. Phase G2 is another pause in which the cell builds up energy to carry it through the M phase's mitosis or cell division. Cancer cells also exist in a temporarily non-dividing stage, during which they are not particularly susceptible to known drugs, and in a permanently non-dividing stage which is of little concern.

All cells within a tumor are not in the same phase at the same time. Some make DNA while others divide and others pause. The trick is to subject these cells to proper doses of various drugs to overwhelm them simultaneously, at whatever their cyclic phase.

- Alkylating agents, such as nitrogen mustard, act against cells during all four phases.
- Antimetabolites mimic cellular nutrients needed for DNA synthesis; they enter the cell, but cannot be used since they have no nutritive value. Metho-

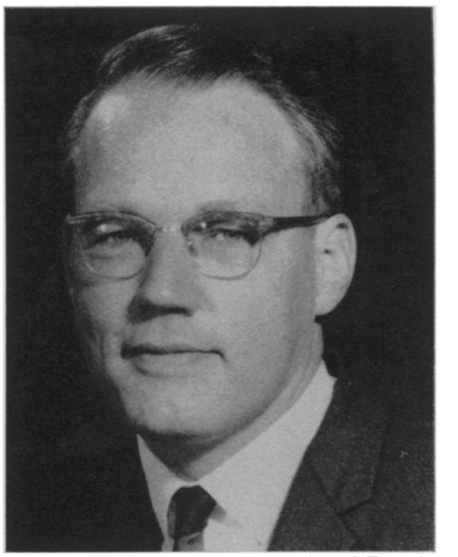
Southern Research Institute

Skipper: several million mice.



NIH

Zubrod: implications apparent.



University of Toronto

Bruce: focusing on cell cycles.

trexate is among those antimetabolites which work against a cell in its S phase.

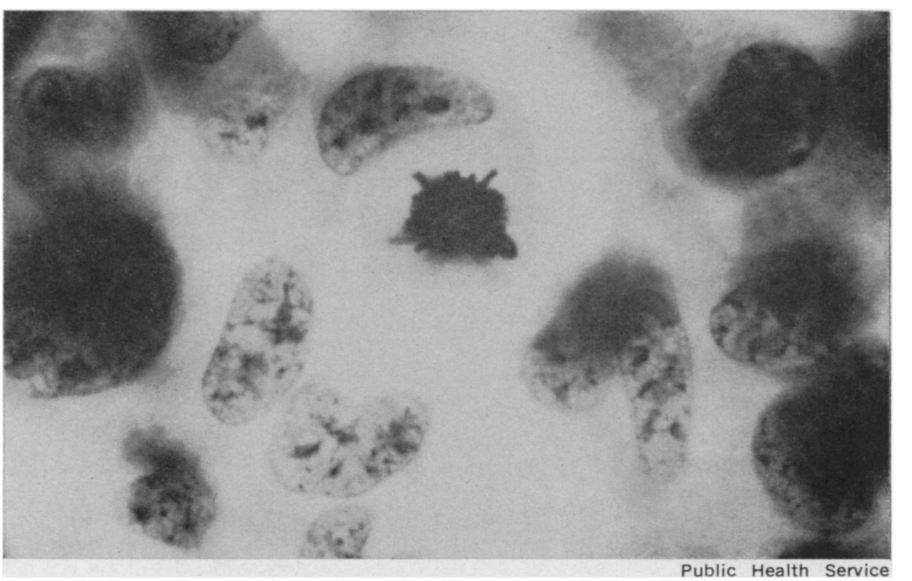
• Plant derivatives, such as vincristine and vinblastine, kill cells at or near mitosis.

Employing combinations of these and similar drugs, scientists have been able to induce complete remissions of disease for two years and longer in persons with such cancers as choriocarcinoma, lymphocytic leukemia and Hodgkin's disease. All of these cancers are fast-growing, which means that most of their cells are in one or another of the four division phases all the time. Some 50 percent to 80 percent of the cells of these tumors may be active at any time.

It is this unusual activity which makes fast-growing tumors vulnerable. If they are dividing, normal cells are killed just as readily as these cancer cells by the drug. But a given dose catches far more cancer cells in the open than healthy cells, and thus fewer healthy tissues are damaged.

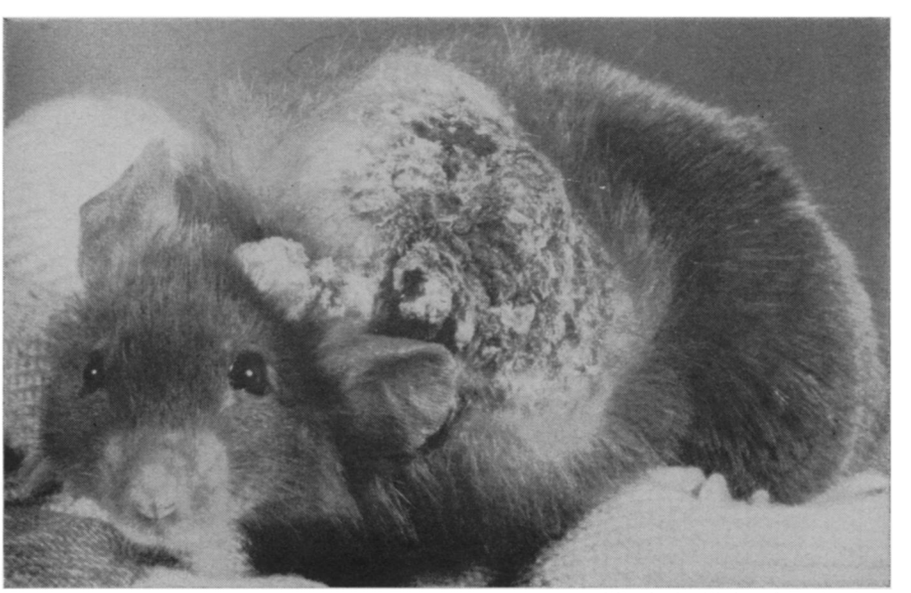
By contrast, in slow-growing tumors, a majority of cells exist for long periods in non-proliferating, drug resistant phases. Recent studies of slow-growing tumors in animals show that only about one percent of the cells are proliferating at any given time, which makes them almost impossible to treat with drugs at present. Before these can be cured by drugs, scientists will have to develop highly specific drug regimens with doses given close enough together to knock out cancer cell populations faster than they can replenish themselves, and yet far enough apart to allow normal cells, which may also be affected, to regenerate.

The challenge with slow-growing cancers is either to learn more about the nature of their cell cycles or to find ways to transform them into fast-growing tumors susceptible to drugs. ◇



Public Health Service

Cancerous liver tissue: dividing cells have irregular shapes and sizes.



Illinois Institute of Technology

Air-polluting gas exhaust extracts induced a malignant tumor on this mouse.