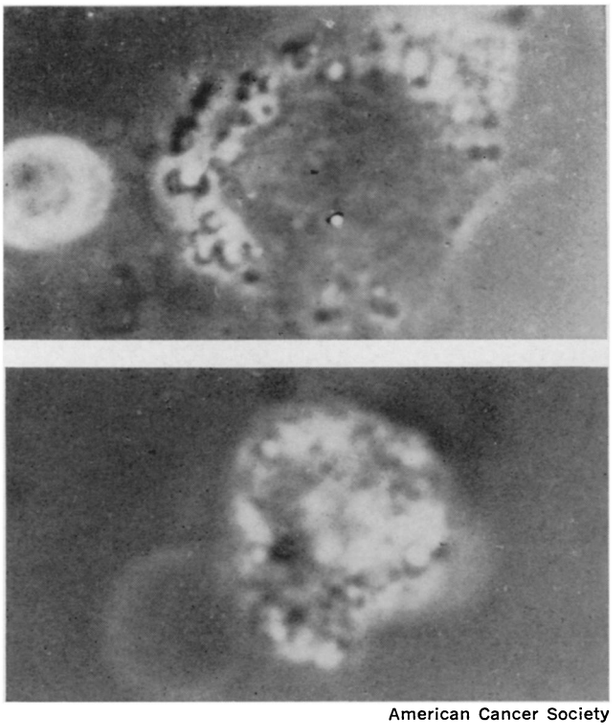
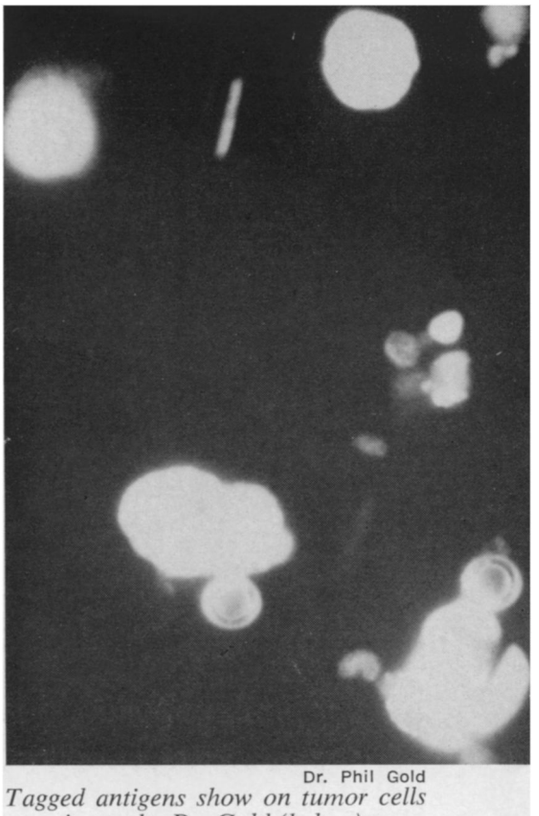


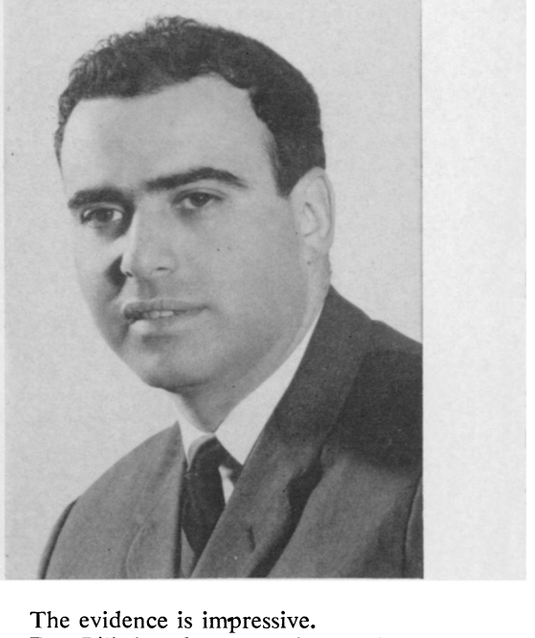
Antibody (left) attacks malignant cell and reduces it to a mass of protoplasm.

American Cancer Society



Dr. Phil Gold

Tagged antigens show on tumor cells in test by Dr. Gold (below).



CANCER

Antigens on the cell

The immune system appears to play an essential role in the growth and control of human cancers

by Barbara J. Culliton

Although the theory that the immune system plays a role in cancer has been on the books since the early 1900's, controlled experiments did not really begin until after 1953 when the era of inbred laboratory animals was ushered in. Firm evidence that there is a connection between immunity and cancer is as recent as two year to even a few weeks old.

In that time, the combined results of experiments from laboratories throughout the United States and Canada have clearly implicated the immune system in the course of cancer, pointed to new directions in therapy, and even suggested that some previous approaches may have led to more harm than good in treating patients.

"Every week we may get cancer, and every week we may reject it," says Dr. Robert Good of the University of Minnesota in Minneapolis.

But sometimes, cancer is not rejected. Sometimes a person's ability to fight cancer fails, allowing cancer cells to proliferate unchecked. This will happen to one of every four Americans at some time during his lifetime. Some 300,000 of the millions of cases will turn out to be fatal.

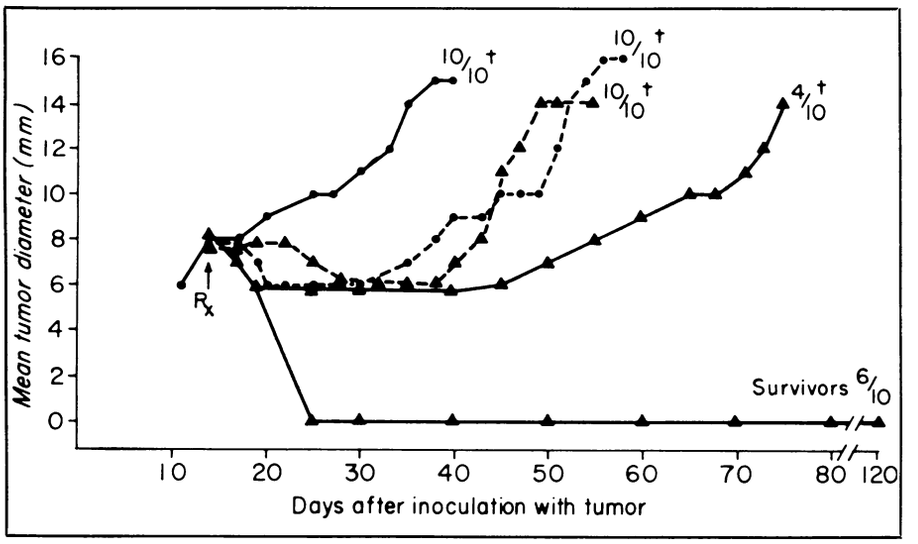
Among the most important of the new wave of discoveries is the realization that nearly all animal tumors and at least some human tumors have on their cell surfaces molecules called antigens—structures that are foreign to the body and which it could, or should, recognize and fight. These antigens are highly specific—one set of antigens for one type of tumor—and are not present on normal cells. By isolating them and developing antisera to them, it may be possible to use them in diagnosis and treatment.

"Tumor antigens," says Dr. Karl Hellstrom of the University of Washington Medical School in Seattle, "provide the greatest hope for prophylaxis and treatment." With his wife, Dr. Ingegerd Hellstrom, and with Dr. Alexander H. Bill, also of the University of Washington, Dr. Hellstrom reports that white blood cells or lymphocytes can recognize antigens and kill the tumors that carry them.

The evidence is impressive.

Dr. Bill has been treating patients with neuroblastoma, the third most common malignancy of childhood, and one that is unusual in that it goes away spontaneously in 10 percent of cases, suggesting that in those patients, a powerful army of lymphocytes is able to defeat a growing cancer. "A careful statistical analysis," he says, "shows a correlation between survival and the numbers of lymphocytes in the patient's blood during treatment." Children who have a high white blood count when treatment begins live longer than those whose count is low. Drugs that kill

. . . antigens



Dr. Alex Fefer

In mice, no treatment and drug treatments (●—●, ● - - - ●, ▲ - - - ▲) failed. Cytoxan in combination with immune lymphocytes (▲—▲) cured.

some cancer cells but also suppress the immune system, as most known drugs do, may actually be working against the patient, Dr. Bill believes, by destroying what natural, though inadequate, ability he has to fight. Knocking out the immune system for any reason is now known to be highly risky.

To gain laboratory support for his clinical findings, Dr. Bill and some physicians from other hospitals, supply the Hellstroms with cells from patients with neuroblastoma. These cells are then grown in a culture medium and exposed to lymphocytes from either the patient himself or other individuals. The lymphocytes recognized the foreign antigens on the tumor cells and killed the cells. Why this does not always happen in a living patient is still a question, but the laboratory result does demonstrate that lymphocytes are powerful anti-cancer agents.

Recent reports that immunosuppressive drugs given to transplant patients foster the rise of cancer (SN: 9/28, p. 319) are further evidence of the relationship between cancer and immunity and the need for moderation in drug therapy.

Still further evidence that lymphocytes are at work in combating tumors, and that if they are inadequate they may be strengthened, comes from Dr. Alexander Fefer of the University of Washington, who has developed an animal system in which further tests can be performed—tests that for genetic and moral reasons cannot be performed in human beings. He induces tumors in genetically like mice, using the Moloney sarcoma virus. Tumors in these animals treated with an anti-cancer, immunosuppressive drug called Cytoxan at first regress somewhat. The anti-cancer activity of Cytoxan affects the bulk of cancer cells, but it is not potent enough to kill them all, and because the immune system is partially repressed, any steps it might take to eliminate the remaining cells are blocked. Shortly, the remaining cells multiply and kill. But when Cytoxan treatment is followed by injection of lymphocytes from animals that have been made immune to the tumor, all tumor cells are wiped out and the mouse is cured.

It is unlikely, Dr. Fefer explains, that immunotherapy itself will be the total solution to eliminating cancer. Apparently, it is most effective when the size of the tumor, the number of malignant cells present in the body, is small, but it may be vital in killing off those cells which are not hit by X-rays or drugs or removed by surgery and which eventually replenish their population to lethal numbers. If specific tumor antigens can be identified, then preparations of lymphocytes, made specifically immune in the same way that a virus vaccine is active against a specific virus, may be vital to treatment.

Tumor antigens also figure strongly in work recently reported by Dr. Phil Gold of McGill University Medical School in Montreal. He and his colleagues have isolated from bowel tumors an antigen that appears in no healthy tissue. In fact, he finds, the only other place this bowel tumor antigen appears is in fetal gut tissue, isolated from fetuses that were spontaneously aborted. "Possibly," he says, "this antigen, present in the fetus before its immune system fully develops, disappears within the cell and only reappears when malignancy occurs."

Dr. Gold has developed a test to detect as little as one-billionth of a part of this antigen, called carcinoembryonic antigen, in blood. He hopes that if further experimentation confirms his highly encouraging but preliminary results, it will mean a diagnostic test for bowel cancers. These cancers are among the most difficult to find and, after lung cancer, kill more persons (46,000) annually than any other kind of cancer. The antigen-detecting test was recently applied to 150 persons in a double-blind study in which the technicians did not know which of the patients had previously confirmed bowel cancer and which did not. All of the 30 cases of bowel cancer were correctly identified, a success that Dr. Gold's colleagues call "fantastic."

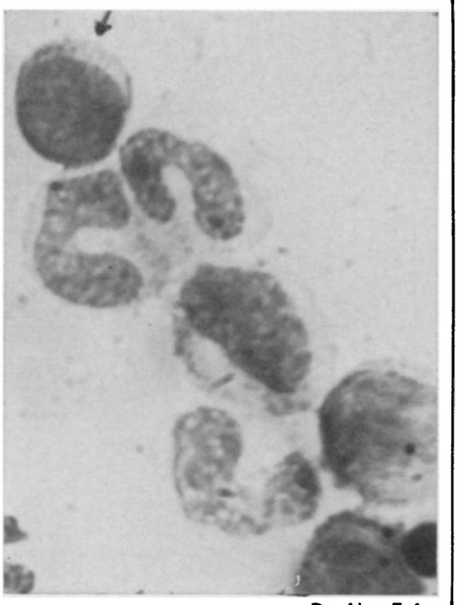
"Dr. Gold's findings are immense," says Dr. Fritz Bach, an immunologist at the University of Wisconsin. "If his theory proves to be true, the test could become as simple and routine as a pap smear to detect cancer of the cervix."

The phenomenal growth of information about the immune system, the development of immunosuppressive drugs that accompanied and fostered progress in organ transplantation, and work by Dr. Bach (SN: 9/28, p. 319) and by Dr. Paul I. Terasaki of the University of California at Los Angeles in typing tissues to tell whether or not different persons have immunologically compatible cells, have had another effect. They have led to a rebirth of bone marrow grafting as a treatment of patients with leukemia and with immune deficiencies.

"We are entering a second phase of marrow transplants in human beings which we hope will be more successful than attempts in the 1950's," says Dr. Robert Epstein of the University of Washington. He has performed successful marrow transplants in dogs and succeeded in storing marrow cells for a matter of months. "If the technique can be applied to human marrow, it could be banked like blood, typed for tissue compatibility and transplanted into suitable donors," he says.

The purpose of such a transplant is to supply patients with active lymphocytes, made by bone marrow cells, to fight cancer and other diseases. A mix of blood and marrow cells is drawn from the pelvis of the donor and injected into the recipient. In at least two cases this has been successful in human beings.

On Aug. 24, Dr. Bach transplanted marrow into a two-year-old boy who was unable to produce certain antibodies. On the same day, in Minneapolis, Dr. Good gave new marrow cells to a four-month-old boy with immune deficiency disease. Both boys received marrow taken from their sisters who had been typed previously for tissue compatibility (SN: 11/30, p. 550). To date, both are doing well, having accepted the transplant successfully, and have healthy marrow populations.



Dr. Alex Fefer

Marrow and lymphocyte (arrow).

Pursuing the relationship between the immune system and cancer, Dr. Good points to the fact that the majority of cancers develop in older persons and that the immune system loses vigor with age. In addition, he reports that all known cancer-causing agents also suppress the immune system. And, seeking other evidence to back his contention that there is an essential connection between the lymph system, immunity and malignancy, he, with his wife, Dr. Joanne Finstad, have traced the phylogenetic history of tumors.

The capacity to develop cancer, they contend, appeared hundreds of millions of years ago, close to the time the lymph system evolved in mammals. Scrutiny of fossils at the Smithsonian Institution, among other places, has revealed, for example, evidence of tumors among forms ancestral to the most primitive of fishes, including the lamprey. Malignancies, however, appear not to occur among invertebrates. Dr. Finstad recently uncovered preliminary evidence that vertebrates possess an enzyme not found in invertebrates and which may yield clues to differences between cancerous and noncancerous cells.

"Malignancy and immunity," Dr. Good hypothesizes, "can be considered to be antithetical adaptive processes." The immune system, in short, evolved to be a watchdog against cancer. Its occasional failure may be part of the process of natural selection. ◇