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COVER: If government and industry experts are correct, coal production and use will soon take a sharp upsurge. If so, more monsters like the strip mining shovel shown on the cover can be expected to open new coal fields in the western United States. See page 10. (Photo: National Coal Association)

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Virus enzymes: Weapons of destruction

A virus enzyme has been shown for the first time to inhibit the function of a host cell

Viruses are cores of genetic material —DNA or RNA—wrapped in coats of proteins. Viruses also make enzymes that they use to kill or to exploit host cells. But how these virus enzymes serve as weapons of destruction has been largely a mystery.

Now an enzyme produced by a noncancer virus, a smallpox virus, has been found to turn off the synthesis of DNA --the genetic material—of a host cell. This is the first time that any virus enzyme, whether from a noncancer virus or from a cancer virus, has been shown to inhibit a function of a host cell.

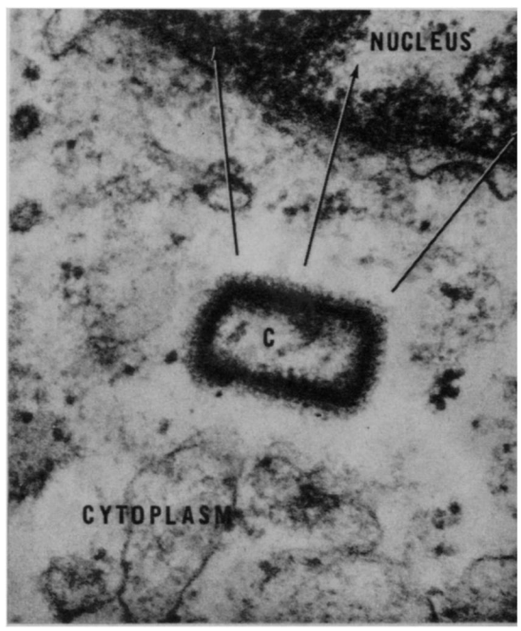
The finding, by Beatrix G. T. Pogo and Samuel Dales of the Public Health Research Institute of the City of New York, is reported in the June PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES. "We have even more evidence now," Beatrix Pogo told SCIENCE NEWS, "than when we submitted our paper to the PROCEEDINGS."

The smallpox virus is a member of the group of viruses known as poxviruses. Poxviruses have DNA for their genetic material. The smallpox virus is known to make several enzymes. Two of these enzymes are known as DNases. Their function has not been known. What the New York City cytobiologists have found is that one of these DNases is released after the smallpox virus enters a host cell. The DNase then switches off the synthesis of the host cell's DNA.

The smallpox virus has been known for a few years to turn off host cell DNA synthesis. What was not known is that a smallpox virus enzyme, specifically a DNase, serves as the virus's hatchetman.

Virologists will probably view this finding with enthusiasm. It is a significant advance in cytopathology, or in the understanding of how one kind of virus alters a host cell. But the advance also throws light on how all viruses, noncancer and cancer alike, affect host cells.

Poxviruses kill the cells they infect. So a smallpox virus might very well use one of its enzymes, a DNase, to stop DNA synthesis in the host cell and thereby kill the host cell. But viruses do not always kill the cells they infect. Evidence suggests that cancer viruses do one of two things when they enter a host cell. They turn off a cell's DNA and kill the cell, or they allow the cell to go on making DNA and to live. In other words, a cancer virus appears to have the choice of whether it is going to turn off host-cell DNA and kill the cell, or whether it is going to allow the cell to go on making DNA, survive and, by some mechanism yet unknown, become cancerous. Whether virus-enzyme



Poxvirus in host cell one hour after virus invasion. DNase presumably is released by virus core (C), then moves into cell nucleus (arrows), where it stops DNA synthesis.

Dales, PHRI

turnoff of host-cell DNA is used only by poxviruses, or also by other noncancer viruses or cancer viruses only time will tell. It may be pecular to viruses that kill cells.

The discovery may have less bearing on the action of cancer viruses in cells, and more bearing on cancer therapy. This is the view of Lawrence Loeb of the Institute of Cancer Research. "Most cancer drugs that work seem to do so by turning off DNA synthesis," the Philadelphia cancer virologist says. "Now we have a viral enzyme that can turn off DNA synthesis. It opens the possibility of using a viral enzyme to turn off DNA synthesis in cancer cells, and thereby perhaps arresting the cancer process." The challenge, of course, is to find a viral enzyme that acts specifically on DNA in cancer cells, and not on DNA in healthy cells. Such an achievement, Loeb anticipates, is some way off. Dales, however, is not particularly hopeful that his and Beatrix Pogo's work will prove to be relevant to cancer therapy. □

A major advance in preventing rejection of transplanted tissue

William T. Summerlin, chief of transplant immunology at the Sloan-Kettering Institute for Cancer Research, has been quietly conducting research during the past five years that may solve the problem of the body's rejection of skin grafts and organ transplants. Rejection has kept many skin grafts and organ transplants from succeeding and has discouraged physicians from undertaking more such procedures, particularly heart transplants.

If foreign skin or organs are not from twins or close relatives, the body usually rejects them. This holds true for both humans and animals. Summerlin has found that if foreign skin or foreign organs are grown in laboratory culture before they are grafted or transplanted, they are not rejected by the recipient. So far, he has used the technique on several hundred laboratory animals and on a handful of patients with almost complete success.

Summerlin described his work last week at a symposium at the Georgetown University School of Medicine. Physicians are enthusiastic about his achievement. Says Charles A. Hufnagel, chief of surgery at Georgetown and the first surgeon to conduct a kidney transplant: "Summerlin's work is an interesting development. No one has ever done it before satisfactorily. Obviously it has certain applications. But it is open to more work."

It all started, Summerlin says, when other scientists pronounced skin taken from people or animals as dead. Summerlin had doubts. He put skin samples in a laboratory dish and gave them nutrients. To his delight, the skin came to life and grew. Subsequently he cultured more skin and attempted to see whether it might be accepted by recipients.

He grafted cultured skin from black mice onto white mice, and vice versa. All the foreign skin took. White patches of fur grew on the black mice where they had received skin transplants from white mice. Black patches of fur grew on white mice where they had received skin grafts from black mice. He also grafted patches of skin from guinea pigs onto mice and vice versa. Again the skin took, and patches of fur grew on the grafted foreign skin.

Summerlin had some patients whose wounds would not heal. With their permission, he grafted some of their own skin, some fresh foreign skin and some cultured foreign skin onto their wounds. As he expected, they accepted their own skin but not the fresh foreign skin. And as he hoped, they accepted the cultured foreign skin.

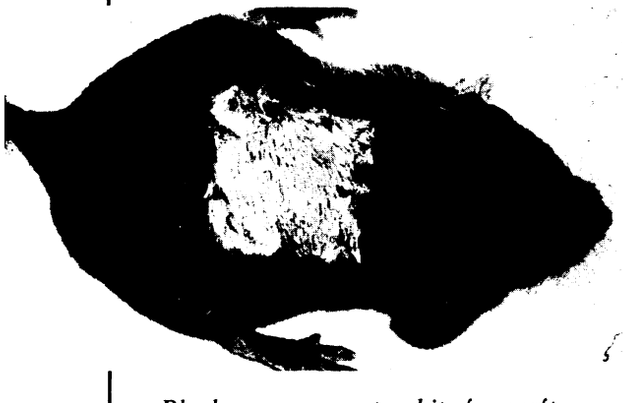
Summerlin turned to culturing human corneas and to transplanting them into the eyes of rabbits. The corneas were accepted. Opthalmologists examined the corneas and said they looked perfectly normal. "The longer we culture corneas," Summerlin says, "the better success we have in transplanting them." He then attempted to culture adrenal glands and found that too was possible. He transplanted cultured adrenal glands into 120 mice. All the glands took, and they made their usual hormones.

He is now trying to culture—with the aim of grafting and transplanting them—kidneys, gonads, thymuses, pancreases and large sheets of skin. The organs and skin are from both humans and animals. Although results are preliminary, they are "amazingly encouraging," Summerlin says. Essentially two challenges now face him: getting enough organs and skin to culture and getting those organs and skin to acquire the right properties in culture.

But what are the right properties? Summerlin is trying to find out. He devised a test to see why fresh foreign skin is rejected and cultured skin is not. He found, in more than 200 mice, that they made lymphocytes to fresh foreign skin, but not to cultured skin. Lymphocytes are cells, a major immune defense of the body, and a well-known factor in the rejection of foreign tissues. But why don't recipients make lymphocytes to cultured foreign cells?

Summerlin showed some of his cultured skin to scientists adept at working with the electron microscope. All but one said they had never seen skin like it before. The scientist who had was an anatomist. "The cultured skin cells," he said, "look like human embryonic ectoderm." In other words, the cultured skin cells look like the skin cells of an embryo. The cultured skin cells may be differentiating into a more primitive embryonic state and thereby losing some of their genetic information. As a result, the cultured cells, unlike fresh cells, are not able to make the proteins, sugars or other compounds that a recipient's lymphocytes consider foreign. The same phenomenon probably also takes place in cultured organs.

Summerlin likes this hypothesis and is anxious to confirm it.



Black mouse accepts white fur graft.

Photos: Summerlin

Cornea grown for transplant.