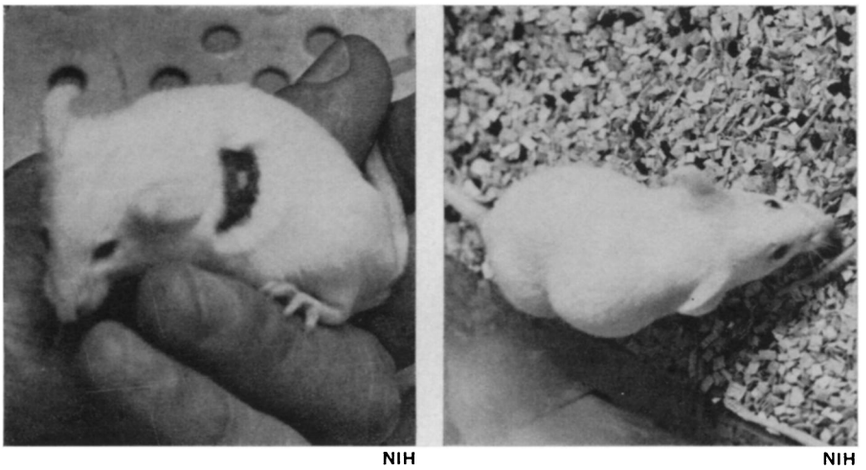
POLY I:C

Against cancer and viruses

An artificial inducer of interferon slows the growth of tumors



NIH NIH

Tumors caused by human adenovirus slough off mice treated with poly I:C.

The body's first line of defense against virus infection is an anti-viral protein, manufactured within hours of attack and sent out to protect healthy cells. Identified in 1957 by British researchers Drs. Alick Isaacs and Jean Lindenmann, it is called interferon because it inhibits viral replication by interfering with the ability of a virus to take over a cell's genetic machinery.

A broad-gauged fighter that works against virtually every known virus, interferon promises to be for viral infections what penicillin was to bacterial infections: a wonder drug. It would be effective against diseases from the common cold to encephalitis.

During the years since its discovery, scientists have found a number of compounds that induce the body artificially to produce interferon, though side effects and other problems stand in the way of their use as drugs. But in 1967 Dr. Maurice R. Hilleman of the Merck Institute for Therapeutic Research in West Point, Pa., reported development of a chemical that triggers interferon production by mimicking infectious viruses (SN: 8/19/67, p. 173). Dr. Hilleman's inducer, called poly I:C, for polysinosinic-polycytidylic acid, has been used by scientists at the National Institutes of Health in Bethesda, Md., to cure serious infections in rabbits.

And their work has produced a bonus: Poly I:C appears to act against slow-growing cancers, such as lung and breast tumors, which resist chemotherapy (SN: 12/21/68, p. 626).

Toxicity studies have yet to be completed on the highly potent chemical; in high doses it kills mice and dogs. But Drs. Hilton Levy, C. Gordon Zubrod and others hope to begin trials in terminal cancer patients within a few months. Safe doses in monkeys, they say, will guide the doses given to patients.

Most viruses consist simply of a protein coat covering a core of genetic material—double-stranded RNA. When a virus attacks a cell, only its infectious core invades the cell's interior, leaving the coat outside. The RNA core then triggers its own destruction by stimulating interferon production.

The need for an artificial interferon inducer arises because there are times when natural production is too slow or too limited to prevent viruses from taking hold. Artificial induction, on the other hand, opens the door to interferon production in advance of infection, or to production of significantly greater than normal amounts.

In designing poly I:C, Dr. Hilleman reasoned that an ideal inducer would mimic viral RNA. Hence, poly I:C is structurally like double-stranded RNA.

Tests since 1967 have shown poly I:C to be highly efficient at imitating viral RNA. Most recently Dr. Samuel Baron, of NIH, with Dr. John Park of New York Medical College, showed that this double-stranded chemical induces enough interferon to cure rabbits of possibly fatal eye disease. The viral infection, called herpes simplex keratoconjunctivitis, occurs in man with varying degrees of seriousness. "In a city the size of Washington, there may be a few thousand cases a year," says Dr. Baron, whose findings point the way to use of poly I:C, or a derivative, as an anti-viral drug in man.

Interferon is manufactured in a cell on protein factories called ribosomes, just as is any other protein. But its genetic blueprint is apparently locked within the gene in the cell under normal conditions. Viral RNA and poly I:C release this blueprint, inducing interferon. Once made it spreads to other cells where it attaches to their ribosomes, inhibiting their ability to accept and make new viruses while leaving their ability to make normal proteins intact.

In view of this behavior, researchers hypothesized that other modifications of genetic control might be taking place—modifications that could affect tumors. Dr. Hilton Levy and co-workers at NIH have inoculated mice with a variety of cancerous tissues, some virus-caused, some not. Twenty-four to 48 hours after inoculation, thrice-weekly injections of poly I:C were begun. In all studies, viral and nonviral, Dr. Levy reports, poly I:C slowed the rate of tumor growth. In one study of animals with reticulum cell sarcoma—cancer of the lymph system—all poly I:C treated animals were alive after 41 days and all untreated animals were dead. Some animals are still alive three months later.

"At this point," Dr. Levy says, "we can only speculate on the mechanism of poly I:C action, but it appears to stimulate the immune system quite independently of its interferon effect."

All tumors have foreign proteins on their surfaces, proteins that the immune system should recognize as foreign and reject. But some of these foreign proteins may not be strong enough to elicit this response. Conceivably, poly I:C somehow soups up the system, pushing it to recognition and rejection of tumors.