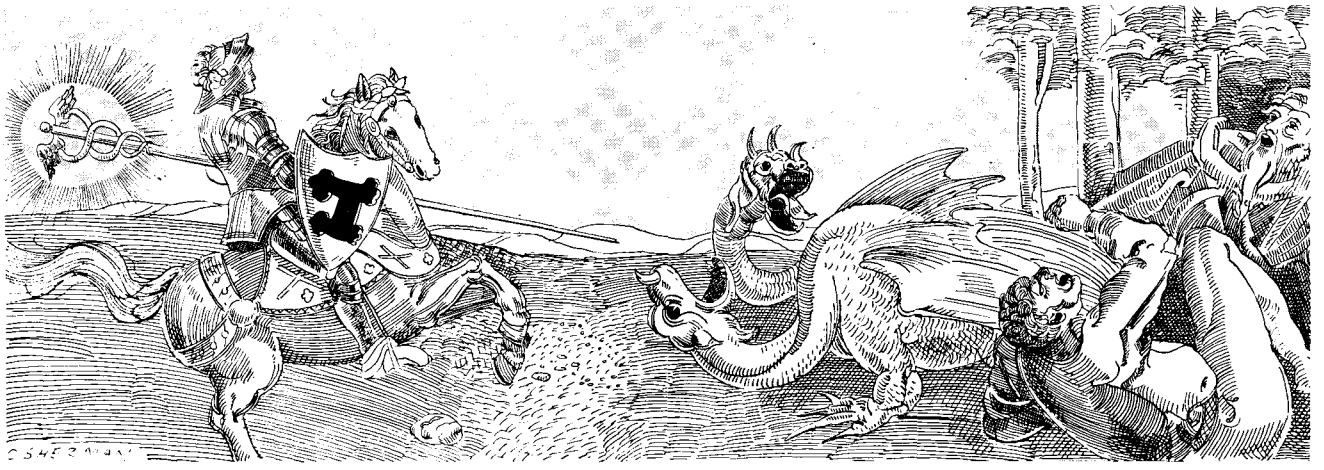
SCIENCE LETTER

Interferon: Medicine for Cancer and the Common Cold?

by Albert Rosenfeld



INTERFERON. A chemical that interferes. A mystery molecule made by the body itself to thwart the subversive intentions of invaders.

Because the American Cancer Society (ACS) has announced the launching of a $2 million program to test it clinically, interferon is already being referred to as a "cancer drug"—which it may well prove to be. But those who have been studying interferon for its multiple other potential uses fear that, should it perform disappointingly in its cancer trials—if it is only marginally useful, for instance, as has been the case with so many other promising anticancer agents—then, as one scientist puts it, "Interferon may become a dirty word, because 'It was tried and didn't work.'"

In fact, interferon gives early promise of becoming one of the most versatile medications of all time—even if it should fail against cancer. It is by far our best hope, for example, for conquering the common cold. Indeed, in preliminary trials carried out in England in human volunteers, interferon in the form of a nasal spray has already demonstrated a significant protective capacity against cold and influenza viruses.

For a while, the principal hope for long-term relief from the common cold was a multivirus vaccine; but researchers have now virtually given up the vaccine project because colds may be caused by more than a hundred different strains of viruses. (The polio vaccine, by contrast, had only three strains of polio virus to contend with.)

But viruses are precisely what interferon interferes with. And its prospects lie in its ability to combat not merely one specific virus but a whole spectrum of viruses. It could prove to be an antagonist to almost all viruses. Virtually every cell in the body—except red blood cells, which, in mammals, have no nuclei—can produce interferon when challenged by a virus. Animal experiments have offered strong suggestive evidence that interferon may well serve as prophylaxis against, or therapy for, viral diseases ranging from shingles to eye infections, from encephalitis to hepatitis. It looks so promising in the case of rabies that even cautious investigators are predicting that it should at least enhance the effectiveness of the rabies vaccine; those less cautious believe it will supplant the vaccine altogether.

The whole updated story is told in a book-length special issue of *Texas Reports on Biology and Medicine*, published by the University of Texas Medical Branch (UTMB) at Galveston. Called "The Interferon System: a Current Review to 1978," the volume contains 76 articles by interferon investigators the world over.

INTERFERON was discovered back in 1957 by the late Alick Isaacs, the brilliant British investigator, and his Swiss colleague at Oxford, Jean Lindenmann. What spurred their curiosity was the well-known but puzzling fact that a patient rarely contracts two viral diseases at the same time. One might guess, through common sense and logic, that a human body already weakened by a bout with one virus would fall prey all the more easily to the next viral invader. Yet, even in laboratory tissue cultures, it has proven difficult to infect cells with more than one virus at a time; and investigators have long since learned that two live-virus vaccines cannot be administered simultaneously at the same body-site without some degree of mutual interference.

Another puzzle for researchers and physicians alike was why, considering the way viruses work, so many viral diseases seem to be "self-limiting," carrying their depredations only so far and no further. The known facts about the body's normal immune defenses did not suffice to explain this viral containment. When a virus invades a cell, it usually takes over the cell's metabolic machinery, somehow shutting off the flow of genetic instruction from the cell's own DNA and instructing the cell to manufacture instead mainly viral proteins. Thus it may often effectively destroy itself and turn loose a host of new viruses ready to invade the surrounding cells. What no one knew, until recently, was what made the virus's takeover end of its own accord.

The careful studies of Isaacs and Lindenmann made history by providing answers to both these puzzles. They discovered that a cell, when first challenged by a virus—before that virus takes over completely—produces the protein they named interferon. Though interferon does not itself attack viruses, it triggers the production of another substance simply called antiviral pro-

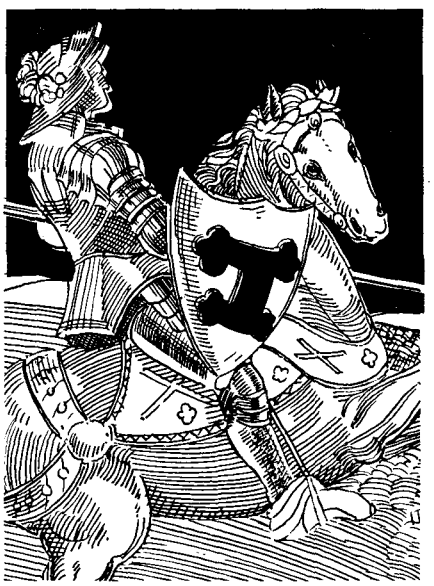
tein (AVP). It is AVP that interferes with the continuing production of viral proteins—not so much in the invaded cell, where considerable viral inroads have already been made, but in *adjacent* cells. Unlike the more familiar immune reaction, where invading microorganisms are attacked, while still circulating in the bloodstream, by antibodies and phagocytes, interferon clearly constitutes the cell's own first line of defense. Moreover, it springs into action within hours after a viral intrusion. One can see, then, that a cell actively making interferon and AVP is *not* a hospitable place for a new virus to come in and carry out its operations unmolested.

Well, then, if the body has its own built-in defense against viruses, should this molecule not make the ideal antiviral drug, exhibiting minimal—if any—adverse side effects? The challenge was taken up eagerly by a number of researchers around the world, supported especially by the National Institute of Allergy and Infectious Diseases in the United States and the Medical Research Council in England.

WITH ALL THIS INTENSIVE activity, why has so little been accomplished in the way of progress toward interferon therapy over the 21 years since the Isaacs-Lindenmann discovery? One difficulty has been that interferon, unlike many other therapeutic substances (insulin, for one), is species-specific—which is to say that, with rare exceptions, interferon from one species will not work in another species. And human interferon has turned out to be devilishly difficult—and expensive—to isolate and produce. This being the case, an obvious alternative was to develop a substance that could induce a cell to increase its own production of interferon, thereby giving itself added antiviral protection. Several such inducers have been found, but so far none has demonstrated enough activity without producing unacceptable toxic side effects. In the face of these dilemmas, it did not take long for the initial excitement over interferon to subside—first to caution, then to resignation, finally almost to despair—before techniques were developed to make enough interferon to carry out meaningful experiments.

Even today, the Western world's entire supply of interferon remains severely limited. It takes hundreds of gallons of white cells to get minuscule quantities of usable interferon. Most of it has been produced in Finland from the white blood cells of human donors; hence it is called human leukocyte interferon. This is the kind the American Cancer Society's grantees will use in their clinical trials; they have enough to test no more than about 150 patients who have advanced cancer. A $2 million investment may seem to represent a fairly huge project until one considers that human leukocyte interferon may cost as much as $50 million a *gram*—or more than $22 *billion* a pound! Fortunately, only minute doses are required; interferon units are measured in picograms—trillionths of a gram (the average dose will be in the millions of units). Even at that, each patient's supply for a few months' trial will cost many thousands of dollars.

Nonetheless, it is important to remember that the first antibiotics had the same handicaps. They too were very scarce and very expensive until



production breakthroughs made them both plentiful and affordable. The same should be true of interferon and, perhaps, of interferon inducers as well. There already exists at least one alternative to leukocyte interferon. It is produced by fibroblasts—connective-tissue cells that grow readily in laboratory cultures. In a pilot project at New York University supported by NIAID, for example, fibroblasts from human foreskins were used. Stimulated by chemical inducers and harmless viruses, they began to produce interferon in the culture. Over a four-year period, the research team found ways to increase interferon production 100-fold. A new breakthrough at MIT has boosted production another 10-fold. This method, used elsewhere as well, is now being scaled up for larger production in Europe. Since the fibroblasts grow for generations in the same culture media, the resultant interferon supply does not depend on continued massive donations of blood; nor is it as subject to contamination, since it does not have to be extracted, imperfectly purified, from the blood of ever-changing donors. Fibroblast interferon may turn out to be more useful in the long run. In the even longer run, genetic-engineering techniques may also provide a more efficient answer. If the gene for interferon can be isolated and inserted into the genome (genetic instructions) of a bacterium—as was recently done with the gene for insulin—then one could hope for cheap mass production.

Though there is no official "interferon race," some claim nevertheless that the Russians are in the lead. This is based on the fact that vials of interferon have been on sale without prescription in Moscow pharmacies for a few years now. American scientists visiting the U.S.S.R. were able to buy vials of it for only 75 cents apiece! They were able to extract from a vial containing about an ounce of material a bare thousand units of unpurified interferon. At least a thousandfold greater concentration—and probably more—would be required for a minimally effective dose. Even so, they are cautious about deprecating the Soviet effort. The Soviets have clearly pursued interferon production aggressively, holding large blood-donation drives and making much of their interferon in a manner similar to that of the Finns. And the fact that interferon is already in Moscow drugstores gives us hope that a more effective variety will one day be in our own drugstores.

But even if a pure and abundant supply of interferon were suddenly to be made available to the United States right now, the FDA would certainly not permit it to be marketed without previous thorough testing in animal (with their own interferon) as well as human subjects. Which is as it should be—especially since interferon has already shown itself to be not as entirely free of side effects as was originally hoped. For example, there turns out to be a second type of interferon that is produced not by viral challenge but by certain of the body's immune cells, the T-lymphocytes. This "immune" interferon, which seems to have a natural role in regulating the body's immune functions, *suppresses* immunity when it is used therapeutically. The same is true, to a lesser extent, of the viral interferon. Hence people with diminished liver function or lowered blood-marrow reserves would have to be careful about taking it. (The effects do seem, so far, to be reversible.) This disadvantage, however, carries with it a

concomitant potential benefit: If interferon can suppress immunity, it might be employed to prevent the rejection of transplanted organs or to combat autoimmune diseases. In fact, it is being seriously considered for both these uses.

What does all this have to do with cancer?

Research so far has not yet turned up the pure interferon molecule with its coded sequence of amino acids, knowledge that would allow us perhaps to produce it synthetically. But we have learned a great deal about interferon. We know that, except for the "immune" variety, the cell produces it only when a virus or a chemical inducer is present. The arrival of the virus somehow triggers the turn-on of the interferon gene (we know its chromosomal location) that tells the cell to make interferon. In turn, the interferon's presence, operating on the *membranes* of adjacent cells, induces those cells to turn on the gene for antiviral protein (we know its chromosome location, too). More than that, the AVP—which protects *its* host cell even though that cell contains no interferon whatever—somehow lets still other adjacent cells know *they* are in danger. No one knows how AVP does this—presumably by inducing the release of yet a third "messenger" substance. Once a cell has acquired interferon protection against viruses, it responds even more rapidly to any new viral challenge.

In any case, since interferon and its by-products do act on the cell at both the membrane and nuclear levels, they can interfere with cell division (liver regeneration, for instance). So it was natural that someone would try it as a cancer remedy.

After the demonstration of strong antitumor activity in animals, interferon was first used on human cancer patients at Stockholm's Karolinska Institute. In patients with bone cancer of the leg, treated with interferon after amputation, the cancer did not spread as readily to other parts of the body as it customarily would. Interferon has since been used on other types of cancer by a handful of other patients, with encouraging results.

The results are admittedly sparse. Yet they do seem to justify the Cancer Society's large new effort. Some critics argue, nevertheless, that it would be better to wait until interferon is more plentifully available before launching large-scale tests; but if these first trials are convincing they might very well ignite an intensified effort to speed interferon production.

One of the important questions surrounding the use of interferon for prevention or treatment on a large scale is: Since interferon (via AVP) disrupts the production of viral proteins, how can we be sure that added quantities of interferon—especially if administered when no virus is present—will not disrupt production on the cell's own protein-assembly lines? Fortunately, painstaking research has provided a fairly convincing and reassuring answer: The so-called ribosomal RNA—the molecule that strings together proteins out of amino acids—is *not* disturbed, nor any of its information content destroyed, by the presence of interferon. What interferon does is add to the ribosomal RNA molecule *new* information that tells it how to inhibit the making of the viral protein. But this new information is not used; it is held in abeyance as a just-in-case precaution. If no viruses appear, it simply remains dormant, and normal protein manufacture proceeds as usual. In any event, the effects of interferon are only temporary.

The cancer trials are about to begin, with high hopes tempered by caution hard-won through past experience. We certainly do not yet know the whole interferon story. We know it is only one aspect of the body's immune defenses (though a vitally important aspect). Even so, the hopes seem warranted—not only for cancer but for potential use against graft rejection and auto-immune disease. And they seem most warranted against a whole catalog of infectious diseases, as already mentioned, from shingles to rabies to acute hemorrhagic conjunctivitis. *And* respiratory diseases, including the common cold. Imagine a world with no colds! More recently interferon—though virus-induced—has also been showing some promise against bacterial, rickettsial, protozoal, and parasitic infections as well.

In interferon do we have at last the long-sought panacea, the universal remedy? Alas, no. Thus far, at least, it does not look as if interferon will be effective against headache, frostbite, fractures, or infertility. ◉

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Fighting Back With White Man's Weapons

by Mark Kellogg

The Bettmann Archive

On the plains of Montana—"Their tribal heritage is now seriously threatened."

IN THE FALL OF 1621, the Wampanoag sachem, Massasoit, brought 90 of his people, loaded with venison and other game, to visit his English guests at a place they called "Plimouth." For three days the sachem displayed his largesse while the English fired off salvos of gratitude. But in the three and a half centuries that have intervened since that celebration, the salvos have been turned against the original natives of our land; to them, Thanksgiving commemorates only duplicity and exploitation.

The shameful history of our treatment of Native Americans is well known. What is not so well publicized, however, is that new and serious threats are being made to the Indians' tribal heritage. Today those threats stem, ironically enough, from newfound resources on Indian lands: the minerals and gases that lie beneath reservation soil, the water that flows through that earth, and the fertile land itself. In their battle to retain power over these vast resources, Indians face not only a formidable array of interested parties, but the peculiarly modern, and insidious, problem of striking a balance between developing these resources for themselves and maintaining their ancient traditions.

The value of the natural resources on Indian-controlled lands cannot be overestimated. Indians now occupy areas that hold huge deposits of oil and gas. Sixty percent of the known uranium supply in the country lies under Indian lands. They also claim large timber stands.

The biggest holdings are in the coalfields of New Mexico and especially Montana, where possibly as much as 14 billion tons of low-sulphur coal lie, much of it under the reservations of the Crow and the Northern Cheyenne. When these reservations were created late in the 19th century no one suspected that minable coal existed in Fort Union; now it is the target of intense speculation by dozens of power companies.

In addition, tribes from the Northeast to the Great Plains and the West live in areas ripe for development by real-estate speculators, resort and recreation entrepreneurs, motel and food chains. And in the Southwest, where water is in chronically short supply, the Indians are also being challenged by developers whose plans are dependent on water sources to which the tribes have rights.

If the developers, their political bedfellows, and the power companies have their way, all of these regions will be mined for their natural resources and converted into centers of industry and recreation. The Indians will probably be given cash settlements for their lands, resources, and water rights, but will not otherwise be a part of the plans. Apparently, the developers assume that once the Indians have been paid off they will be assimilated into the general population.

The tribes' current crisis is vividly illustrated by the case of the Northern Cheyenne, whose desire to preserve their heritage is under the greatest pressure from public-utility groups, private industry, and the federal government. The Northern Cheyenne know that the way out of their poverty is to give up their past, and to permit the exploitation of their share of the Fort Union deposits. But they also are aware that those deposits lie under a portion of their ancestral grounds.

The tribe has toughened its position on sovereignty and control of its resources because it was misguided in 1966 by several coal companies and the Bureau of Indian Affairs (BIA) into granting the companies mining leases and permits at rates egregiously low in proportion to the profits the companies would realize. So much land was to be mined, according to these agreements, that there would have been nothing left of the reservation. The coal companies knew that the tribe could not accurately estimate the value of its assets, and the BIA failed in its trust responsibility to advise the tribe of that value and to inform it that the amount of land involved was over the legal amount. But both the Crow and the Northern Cheyenne have learned something about survival under pressure. The Cheyenne hired a crack West Coast law firm to represent their suit to renegotiate the leases, and in the resulting litigation, so many violations were uncovered that Secretary of the Interior Rogers C.B. Morton suspended the Cheyenne leases and permits in 1974, and Secretary of the Interior Thomas Kleppe suspended the Crow leases in 1977.

"As far as I'm concerned," said tribal president Allen Rowland, "the coal can stay just where it is until they find a way to get it out without wrecking everything else. They're saying we're against progress," he said, leaning across the desk in his small office. "Hell, we're not against progress. We need progress; you can see that for yourself. But we're against the kind of progress that comes in and takes everything you have and leaves you with big holes in the ground. People don't understand that this is all we have," Rowland continued, waving toward the land beyond the window. "There's no-

Paul Fusco/Magnum

Right: Protest in the Sixties—"Indians speak up when their rights are in jeopardy."