Drugs That Fight

Biological response modifiers appear to be an attractive alternative to other cancer therapies. But recent research shows they may be just as toxic.

By DAWN D. BENNETT

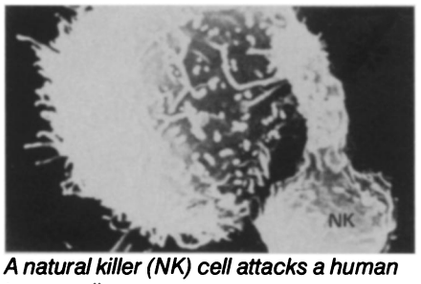
They sound like a sophisticated biomedical technology with a down-home touch: drugs that fight cancer not by invading the body with damaging radiation or chemotherapy but by enhancing the body's built-in immune response. In theory, it's the perfect setup, but clinical trials have proved less than heartening.

The National Cancer Institute (NCI) defines biological response modifiers as "agents or approaches that modify the relationship between tumor and host by modifying the host's biological response to tumor cells with resultant therapeutic effects." The drugs have been the subject of research at NCI and elsewhere for the past 10 years. Attitudes and expectations about their value in treating cancer have fluctuated from a high degree of optimism to widespread doubts about their value or even potential in cancer therapy.

At a recent NCI-sponsored conference, researchers from the United States and France gathered in Bethesda, Md., to discuss the current status and future applications of polyribonucleotides, one class of biological response modifiers. These, as their name implies, are many (poly) RNA subunits (ribonucleotides) joined together. The polyribonucleotides can be made of inosinic acid (poly I), cytidilic acid (poly C), adenylic acid (poly A) or uridylic acid (poly U).

If two polyribonucleotide strands are combined, they may bind to each other to form Watson and Crick's well-known double helix, in this case, double-stranded RNA. And it's the double-stranded RNA, in various combinations (poly I poly C, poly A poly U and others), that is the key to the immune system-enhancing effects of these biological response modifiers.

The double-stranded nucleic acids apparently masquerade in the human body as "artificial viruses," says William Carter of the Division of Clinical Research at Hahnemann University in Philadelphia. Carter is working on a biological response modifier called Ampligen (poly I • poly $C_{12}U$), so named because it amplifies the body's immune system response. Like natural viruses (which can be made of single- or double-stranded DNA or RNA), double-stranded RNAs can induce antibody formation, interferon production and activation of macrophages and natural killer (NK) cells, two types of immune system cells that fight off viral infections and tumors.



Carter

A natural killer (NK) cell attacks a human tumor cell.

Research thus far has concentrated on the drugs' enhancement of interferon and natural killer cell activity, which Carter calls the "fighting couple" of the immune system. A viral infection triggers interferon production, which stimulates natural killer cell activity; together, the two fight off foreign substances.

So why not mimic natural viral infections to stimulate a person's immune response? That is what researchers in the field have tried to do in both animal and clinical studies. In many cases, they have achieved the desired immune enhancement, measured by increased interferon production and NK activity. However, they have also observed toxic side effects typical of natural viral infections — fever, convulsions and low blood pressure.

Because of such side effects, researchers working with biological response modifiers are cautious not to be overly optimistic about the drugs. "With interferon, we learned a lesson," says Hilton Levy, head of the molecular virology section of the National Institute of Allergy and Infectious Disease (NIAID) at the Frederick (Md.) Cancer Research Facility. "We thought it would be the wonder drug and were shocked when it wasn't. These drugs have potential, but we can't push it beyond that."

Part of the problem with interferon injections, Levy says, is that mixtures of alpha, beta and gamma interferons are probably necessary for the substance to have any effect in a given disease or tumor state. "There are 16 different types of alpha interferon alone," he says, "each of which can be made by recombinant techniques and each of which has different biological activity." The tricky part is knowing which particular interferons are needed for which diseases. Double-stranded RNAs, like natural viruses, induce the entire mixture, so that matching laboratory-produced interferons to different diseases is not necessary.

A problem with injecting interferon, he says, is that the drug must travel through a person's bloodstream before it reaches a target cancer cell, dissipating its effect. Biological response modifiers, on the other hand, are thought to cause the tumor cells themselves to produce gamma interferon, concentrating it around the cells where its action is needed.

Yet another problem with interferon is its pronounced toxicity. Although biological response modifiers are toxic in many cases, researchers are not sure whether those toxic side effects are due to some property of the drugs themselves or to the interferon production they induce.

The concept of using double-stranded RNA as biological response modifiers started several years ago when Merck Sharp and Dohme of West Point, Pa., introduced a promising new drug, poly I poly C, that could induce interferon production but, they hoped, bypass interferon's toxicity and other disadvantages. Since then, several such double-stranded RNA biological response modifiers have been introduced, including poly ICLC, poly A poly U and Ampligen.

Researchers soon found that poly I poly C successfully treated tumors in mice but had little effect in humans. It induced little interferon production, Levy says, because human blood serum has large amounts of an enzyme that breaks it down.

So Levy and his colleagues at the NIAID stabilized poly I poly C against enzymatic breakdown by adding polylysine and carboxymethylcellulose to the compound.

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Cancer...Naturally

Polylysine wraps around the double-stranded helix, Levy says, and carboxymethylcellulose caps the compound. This makes the compound, called poly ICLC, more resistant to enzymatic attack in the bloodstream, he says, but because it stays around longer, it is more likely to cause toxic side effects.

Poly ICLC's toxicity dominated discussion of the compound at the recent NCI-sponsored conference. Brigid Leventhal of Johns Hopkins University in Baltimore discussed her study of poly ICLC's effectiveness in treating laryngeal papillomatosis, a viral disease in which benign tumors beneath the vocal cords cause respiratory blocking and ultimately death. Papilloma growth slowed in four of the 10 patients treated in the clinical trial, but four other patients had to have their courses of treatment interrupted or stopped altogether because of the drug's toxic side effects. One patient who received poly ICLC died, Leventhal says, "but we're not implicating the drug in her death."

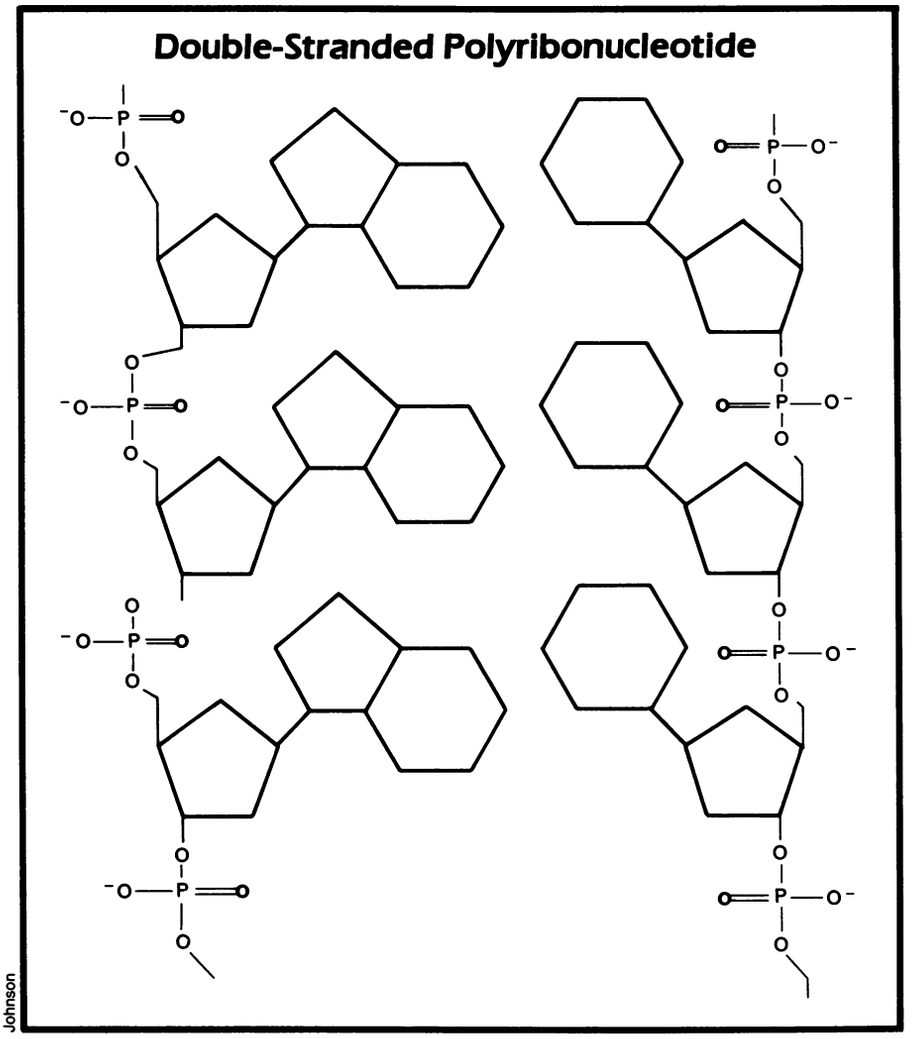
Other researchers' studies of poly ICLC's effectiveness in treating various cancers have mirrored Leventhal's results. NCI's Michael Hawkins, who studied poly ICLC's effectiveness in treating malignant melanoma, a type of skin tumor, concluded that "poly ICLC's side effects were more serious than those of interferon."

Dale McFarlin, of the National Institute of Neurological and Communicative Disorders and Stroke, did a study of poly ICLC's role in treating multiple sclerosis. He concluded that poly ICLC has significant side effects in most patients and that "this drug should not be given anywhere to multiple sclerosis patients except in an experimental setting."

Results of experiments with poly A poly U by Jean and Fanny LeCour of the Institut Gustav-Roussy in Paris have been more heartening. From 1972 to 1979, the LeCours studied 300 patients with breast cancer and found that patients given poly A poly U survived significantly longer than control patients not given the drug. They are now doing a clinical trial on breast cancer patients receiving chemotherapy alone or chemotherapy alternating with poly A poly U. "Clinical trials confirm the adjuvant value of poly A poly U in breast cancer," they say, "but longer trials are needed to determine the respective values of chemotherapy and poly A poly U."

The patients selected for the LeCours' clinical trials differed in an important way from those in the U.S. clinical trials: Their tumor burden, or the amount of cancer cells spread throughout the body, was much less. The LeCours treated mainly solid tumors with few metastases (secondary growths), the latter having been eradicated by previous surgery or chemotherapy.

Such a strategy may be vital if biological response modifiers are ever to be used routinely in clinical settings, Levy says. "I think their maximum use will be in reaching small or residual parts of tumors not reached by surgery or chemotherapy," he says. "Biological response modifiers probably can't handle large tumors. But they can augment host responses to de-



The double-stranded polyribonucleotide, composed of a polymerized purine and a polymerized pyrimidine, forms the basis of biological response modifiers.

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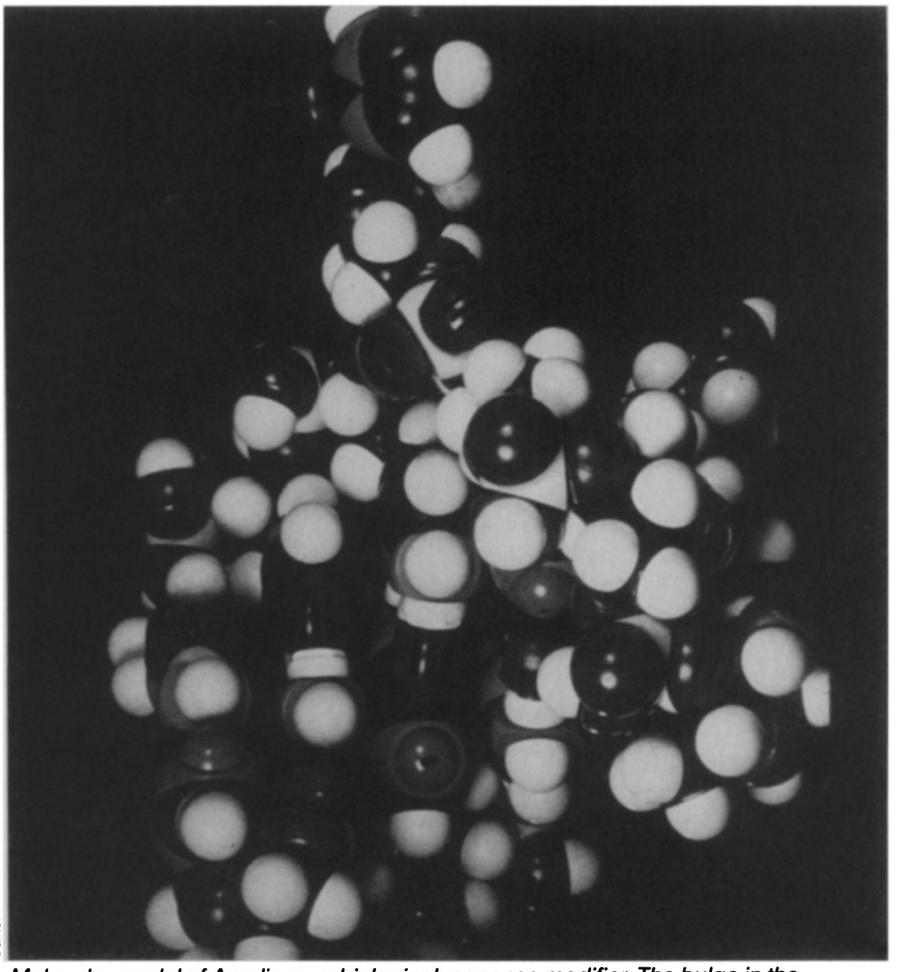
stroy the last bits of a tumor."

Biological response modifiers may also play a role in knocking out tumors before they get too large. "If the tumor burden is small to begin with," Levy says, "biological response modifiers may work in the first stages of the disease."

Arthur Johnson of the University of Minnesota School of Medicine in Duluth has worked with poly A poly U in female mice. He has found that the sex life of female mice is important to whether or not their immune systems respond to biological response modifiers. A young virgin mouse given poly A poly U has a strong immune response, he says, but an old virgin mouse has only one-third that response. And an old breeder mouse has the best immune response of all to poly A poly U. He and his colleagues are now trying to determine why the discrepancy exists. "We believe it may be due to a hormone elaborated by breeders as they go through breeding and birth — maybe prolactin," Johnson says. Similar experiments have not yet been conducted on humans.

Ampligen received the most kudos at the conference. The drug was developed by Carter and by Paul O.P. Ts'o, both at Johns Hopkins University in Baltimore at the time. It differs from the other double-stranded RNA biological response modifiers in that when the drug is made, it is treated so that it's not perfectly helical throughout its entire length. These interruptions in the double helix are caused by unpaired bases (uridine) in the molecule. The chemical formula, poly I • poly $C_{12}U$, indicates that for every 12 cytosines in the helix, there is one uridine. The unpaired bases, Carter says, cause outpouchings of the molecule that are unusually exposed to the blood. Blood enzymes quickly attack these points, making Ampligen "self-destruct" much faster than poly I poly C or poly ICLC. Thus this compound is less toxic than other double-stranded RNAs, Carter says.

Another advantage of Ampligen, Carter says, is that it doesn't cause antibody formation. "The other drugs [prompt the body to] develop antibodies against them, probably because they stick around in the blood so long," he says. "After this happens, they are no longer candidates for biological modifiers; they're no longer biologically active." Ampligen, however, has not yet caused antibody production in animals or humans, Carter says, "probably because it's biodegraded in the blood so fast."



Carter

Molecular model of Ampligen, a biological response modifier. The bulge in the molecule to the right represents a mispaired base in the double helix.

Biological response modifiers, then, definitely deserve mixed reviews. Ronald Herberman, chief of the NCI Biological Therapeutics Branch at the Frederick Cancer Research Facility, gave them just that in an article in the May ANNALS OF ALLERGY: "In addition to agreeing that the initial attitudes about [biological response modifiers] were overly optimistic," he says, "I think the present skepticism is an overreaction." He recommends changing the protocol of clinical trials, including giving lower dosages of the drugs to decrease their toxicity.

Perhaps the words of Carl Pinsky of Sloan-Kettering Cancer Center in New York best sum up the current status of research in double-stranded RNA biological response modifiers: "[Even] if there's no way to change the biological responses of people with cancer, ... at least you've tested the hypothesis." □