Bound to Provoke a Reaction

Injection of polymer-bound and free drugs directly into tumors not only kills the tumor but also provokes an immune reaction

Anticancer drugs bound to polymers are much less toxic than the free drugs and can be used in much higher concentrations, says Eugene P. Goldberg of the University of Florida. If the polymer-bound drugs are injected directly into solid tumors in animals, he reported at the recent Fourth International Symposium on Affinity Chromatography in the Netherlands, the drugs not only kill the tumor but also provoke an immune reaction that destroys tumor cells that have spread to other sites in the animals' bodies. Intratumor injections may eventually provide an important way to attack solid tumors, those in which the malignant cells exist in a discrete mass—such as cancers of the breast, lung, or colon.

Conventional chemotherapy is widely used to treat malignant tumors, but most chemotherapeutic agents produce serious side effects at the required doses and they often hinder the body's ability to fight off malignant cells by suppressing immune reactions. It is possible that these problems could be overcome if the agent were localized in the tumor. Many investigators are thus studying anticancer drugs that have been attached to antibodies to tumors, embedded in fat emulsions, or treated in some other fashion so that they are preferentially taken up by the tumor. Alternatively, the drug might be injected directly into a solid tumor.

Among the first to use this approach were Jeanne Bateman of George Washington University, A. Pillat of West Germany, and Edmund Klein of the Roswell Park Memorial Institute. In the early 1960's, they found that topical application of certain drugs directly onto or into certain types of skin tumors would cause them to regress rapidly. This is now a clinically useful method for squamous cell carcinomas and other cancers of the skin.

The current interest arose about 1974 when Herbert Rapp and Burton Zbar of the National Cancer Institute treated cultured transplantable guinea pig hepatoma (liver tumor) cells with BCG before injecting them into guinea pigs. BCG (bacillus Calmette-Guérin) is an attenuated strain of the bacterium that causes bovine tuberculosis, and has been used experimentally to induce an immune response to tumors. They observed that the tumor cells grew for a week, then regressed. These animals also became resistant to further challenge with the same strain of tumor cells.

This work was followed up by Sarkis H. Ohanian and his colleagues at NCI, who injected chemotherapeutic agents, including adriamycin, BCNU, melphalan, and actinomycin D, into the tumors after they had established themselves in the guinea pigs. Ohanian reported recently that a single injection of a drug is most effective when given about 7 days after the tumor cells are transplanted—a time when metastasis has already occurred. Both the primary tumor and the metastases are killed, and the cured animals are resistant to a subsequent challenge with tumor cells from the same line, indicating that an immune response is indeed stimulated. If too high a concentration of drugs is used, however, immunity does not develop, presumably because the drug interferes with proliferation of lymphocytes.

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About the same time, Goldberg and Charles McLaughlin, John Cantrell, and Edgar Ribi of the National Institutes of Health's Rocky Mountain Laboratory independently began injecting the hepatomas with a combination of anticancer drugs and BCG cell wall preparations. They hoped that the drugs would destroy the primary tumors and that BCG would provoke an immune reaction that would destroy metastasized cells. That appeared to be what they observed, but, surprisingly, they observed the same phenomenon in animals treated only with mitomycin C or adriamycin, confirming Ohanian's results. Goldberg speculates that dying tumor cells release or expose antigens that are normally shielded from the host's immune system, and that intratumor injection is actually a specialized form of immunotherapy.

Both investigators observe that the concentration of drug that will cause a tumor to regress when injected into the lesion is not effective—and is often lethal—when given systemically. Timing is also crucial. Ohanian finds that the treatment is not effective when given 14 days after transplantation when the tumor has grown considerably; Goldberg and his co-workers find it is effective at 14 days only when both BCG and drug are injected.

Because tumors are highly vascularized, the drugs enter the bloodstream rapidly and the concentration in the tumor quickly decreases. Goldberg speculates that intratumor injection could be even more effective if the drug remained in the tumor longer. He and Cantrell have, in fact, obtained a higher success rate when the one large dose of drug is divided into three or four equal doses given at hourly intervals. They are thus investigating preparations in which adriamycin and mitomycin C are bound to soluble polymers such as polyglutaraldehyde or dextran-aldehyde, to natural cell-binding proteins such as lectins, or to solid supports such as albumin, dextran, or agarose beads. These preparations, Goldberg reported at the symposium, either chemically link themselves to tumor cells or are physically immobilized within the tumor and prolong the drug activity within the tumor. The polymer-bound drugs show preliminary evi-

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dence of efficacy against the guinea pig hepatomas, but have been less successful against mouse mammary tumors. Goldberg argues, though, that the mouse is not a good model for assessing immune responses and he is looking for other animal models. Meanwhile, he and Cantrell are refining their results with polymer-bound drugs, and Ohanian is working with Jurgen Bier of Frei Universitat in Berlin, West Germany, to obtain a better understanding of how intratumor therapy works in both guinea pigs and mice.

Despite these preliminary successes, it may be quite some time before the technique is used to any significant extent in humans. Both surgery and radiation are effective therapies for solid tumors, and the use of a new therapy would provide an ethical dilemma for physicians. Goldberg suggests that one way to avoid this problem would be to inject the tumor with drug prior to surgery to provoke an immune reaction, and then to remove the tumor perhaps a week or two later. Goldberg and Cantrell have recently shown that this is one of the most effective treatments in guinea pigs. Even this approach, however, might present difficulties when applied to humans since most surgeons prefer to remove a tumor as soon as it is diagnosed and are reluctant to manipulate it in any way for fear of dislodging cells that might produce metastasis. To meet this situation, Goldberg suggests, the surgeon might coat the interior of the cavity with a chemotherapeutic agent after the tumor is removed to attempt to kill any residual cells. Such "intracavity" therapy may only be feasible with the polymer-bound drugs, since Ohanian has already shown in animals that it is not successful when the free drug is used.—THOMAS H. MAUGH II

Magnetic Fusion in Flux

Technical maturity and a federal law mandate a new emphasis on fusion engineering; industry ponders its role

There is a growing consensus within the magnetic fusion research community that advances in plasma physics are no longer enough, that it is time to get to work on the practical engineering problems of designing a working fusion power plant. This perception has been solidified into law as the Magnetic Fusion Engineering Act of 1980, and it was the inspiration for a recent conference on industry's involvement in fusion, sponsored by the Atomic Industrial Forum (AIF).*

"Scientific feasibility is at hand," declared one session chairman, Sidney H. Law, director of research at the Northeast Utilities Service Co. and chairman of the AIF committee on fusion. Major research programs are under way in the United States, the Soviet Union, Europe, and—a recent strong contender—Japan. Each nation is constructing an advanced, toroidal tokamak device; within the next few years one of these machines should achieve scientific breakeven, generating as much fusion energy as was required to start the reaction. Meanwhile other devices, such as the linear magnetic mirror machines, are emerging as attractive alternatives to the tokamak.

Industry's involvement in all this stems from the ever-increasing size and complexity of the experimental reactors, said Frank Graham, special projects manager for the AIF and an organizer of the conference. Contractors and consultants from the private sector will become more and more important because of their experience in managing large-scale engineering projects.

Not surprisingly, a glance at the nametags of the 130 conference participants showed affiliations such as Exxon, General Atomic, Battelle, and Electric Power Research Institute, organizations that are already leaders in the fission power industry. If fusion research continues to go well, many of these companies will be selling fusion power equipment in a few decades. And the lessons to be learned from the fission experience were much on everyone's mind.

Make sure that the research results in a power plant that utilities will want to buy, said Howard R. Drew of Texas Utilities Services, Inc. That means a plant that is affordable, maintainable, and reliable.

Be sure to give plenty of thought to such issues as plant safety, radioactive waste disposal, materials availability and public acceptance, warned serveral more speakers. Do it now, while fusion power plants are still in the conceptual stage.

And don't overpromise, said AIF public information head Carl Goldstein. "Erase from your lexicons the words 'breakthrough,' 'threshold,' 'unlimited,' and 'nonpolluting.' "

The immediate incentive for greater industry interest in fusion is the federal largess promised by the Magnetic Fusion Engineering Act of 1980, the legacy of former Representative Mike McCormack of Washington State (*Science*, 24 October 1980, p. 415). The bill calls for construction of a fusion engineering device (FED) by 1990. Although all fusion reactors have their engineering aspects, FED would be the first in which the study of engineering problems would predominate over plasma physics. It would serve as a test-bed for reactor systems in a more or less realistic reactor environment, providing engineering data for constructing a demonstration power reactor by the turn of the century. A Center for Fusion Engineering would be created to manage the program, possibly from outside the Department of Energy (DOE).

According to Allan Mense, the congressional staffer who worked for McCormack on the bill, the billion-dollar fusion engineering program enjoys wide support in the DOE, in Congress, and even in David Stockman's Office of Management and Budget (OMB). The Reagan Administration's recently revised budget gives it essentially no money, however. For once this had little to do with Reaganomic frugality: OMB actually offered more money for fusion energy than the DOE was willing to accept—at least not while its other energy programs were being cut back drastically.

Thus, the fusion engineering schedule has been delayed at least a year. The DOE's director of fusion energy research, Edwin E. Kintner, without ever quite saying so, appealed to industry for lobbying support as planning starts on

*Industry's Role in the Development of Fusion Power, 3 to 6 May, New York.

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