CANCER THERAPY

Hope for a Magic Bullet That Moves at the Speed of Light

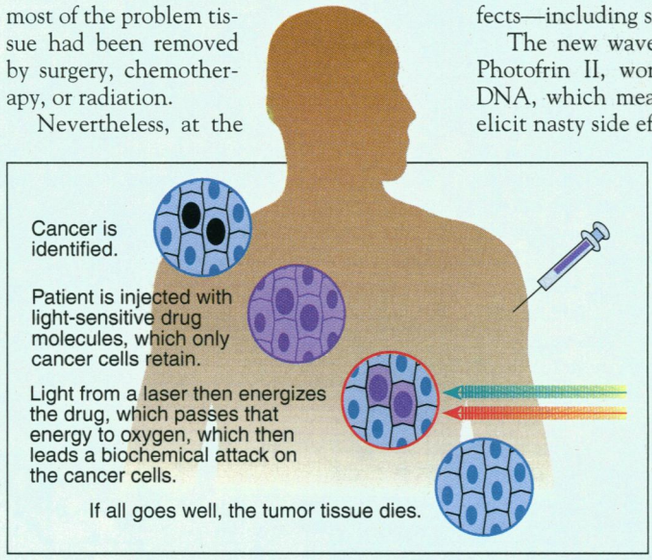
One of the coveted goals of Western medicine is to come up with therapeutic agents that work like smart bombs—zeroing in on diseased tissue but leaving healthy cells unscathed. The reason this strategy is so appealing is that most known medications are not so discriminating: They afflict healthy and diseased tissue alike, which is the reason anticancer treatments such as radiation and chemotherapy have such devastating side effects. Clever molecular tools such as monoclonal antibodies offer hope for more precisely targeted cancer therapies with fewer side effects, but for the most part biomedical researchers have had to accept these unwelcome consequences of cancer treatment.

Now, for some cancers and a few other conditions, chemists have figured out a way to throw some light on the problem—literally. Researchers have long known that certain compounds are inactive until they're hit by light. If these inactive compounds could be selectively concentrated in cancerous tissues, then activated by light, the researchers reasoned, they would eradicate only the tumor cells. That approach—known as photodynamic therapy (PDT)—has been tried with a mixed record of success since the 1970s, partly because the drugs being used all had serious drawbacks. Now, however, researchers are working on a new generation of PDT compounds that may promise greater success.

As a result of these new drugs, PDT "is a red hot area," says Leonard Grossweiner, a biophysicist and laser specialist at the Illinois Institute of Technology who works on PDT clinical trials at the Ravenswood Hospital Medical Center in Chicago. The PDT compound that's furthest along, Photofrin II, was approved this April in Canada for treatment of recurrent bladder cancer; it's the first PDT substance approved for cancer treatment in any country. But that could be only the first in a long line. "I expect a number of new PDT drugs to come out within the next 1 to 5 years," says dermatologist Rox Anderson of the Wellman Laboratories of Photomedicine at Massachusetts General Hospital, where he is administering clinical trials of PDT treatments for skin ailments.

Hot as the field may be, it faces some difficult problems that could cool it down. In most PDT schemes, the light needed to activate the drug is delivered to the tumor by a laser. In the Food and Drug Administration (FDA), different groups are responsible for vetting drugs and devices such as lasers, and both groups must work together to evaluate PDT, which complicates matters. That's one reason why no PDT method has yet been approved by the FDA. In addition, none of the PDT treatments so far has proved to be dramatically successful, and some cancer researchers believe PDT will never be much more than an adjunct to cancer therapy, used, for example, to clean up residual cancer cells after most of the problem tissue had been removed by surgery, chemotherapy, or radiation.

Nevertheless, at the moment hopes among those in the field are high. And those hopes are rooted in a remarkably long medical tradition. The earliest light-based treatment recorded made use of psoralens, a class of compounds found in a Nile River weed and used by Egyptian physicians thousands of years ago to treat skin disorders. When taken internally, psoralens concentrate in unhealthy skin cells (or in areas of increased vascularization). In the 1970s, researchers found that psoralens, when activated with ultraviolet radiation, chemically cinch the two strands of DNA in their host cells. Like a stuck zipper, the DNA molecules no longer operated properly and, in turn, neither did the cells, which ceased dividing. This turned into a progenitor of PDT called psoralen-UVA, or PUVA, which was approved by the FDA for use on psoriasis. During the same time period, researchers also found that psoralen compounds could serve in a dialysis-like therapy for treating patients with malignancies of their white blood cells.



ABCs of PTD. Photodynamic therapy, a combination of light-activated drugs and lasers, is making its way into the anticancer armamentarium.

But psoralen-based drugs have considerable drawbacks, argues David Dolphin, a chemist at the University of British Columbia who also works for Quadra Logic Technologies Inc. (QLT), the pharmaceutical company that developed Photofrin II in collaboration with American Cyanamid's Lederle Laboratory. One problem is that only UV light of wavelengths between 200 and 400 nanometers activate psoralens, and light with wavelengths this short doesn't penetrate very deeply into living tissue. "The longer the wavelength, the greater the depth," Dolphin says. The other problem with PUVA is considerably more serious. Since its mode of action is to chemically modify cells' DNA, its use over time brings with it increased risks of serious side effects—including skin cancer.

The new wave of PDT agents, such as Photofrin II, work without fiddling with DNA, which means they are less likely to elicit nasty side effects, particularly cancer. Photofrin II traces its molecular origin to an oxygen-shuttling chemical in the blood known as hematoporphyrin (Hp). Chemist Thomas Dougherty at the Roswell Park Cancer Institute in Buffalo, following leads from researchers at the Mayo Clinic in Minneapolis, worked on modifying Hp throughout the 1970s and developed it into Photofrin II. Unlike the psoralens, Photofrin II and the new generation of PDT agents it represents are activated with longer wavelengths of light and therefore can be used to treat tissue farther from a light source.

After the drugs absorb energy from a light source, they transfer it to oxygen molecules dissolved in the tissue. In PDT, the energized form of oxygen, known as singlet oxygen, reaps biochemical havoc by oxidizing and damaging virtually every biomolecule within reach. But only until the light is removed. "As soon as you turn the light off, the toxic effect disappears," Dolphin says.

Like the psoralens, these new agents are benign until activated by light and they concentrate in diseased tissue. The segregation occurs, researchers think, because these chemicals link to the blood's lipoprotein molecules, which are busy carrying cholesterol to dividing cells. The lipoprotein molecules bail out of the blood, along with their stowaway, when they encounter lipoprotein receptors, which happen to be especially plentiful in blood vessels servicing abnormally active tissues such as cancerous tumors. So

more PDT agent goes to where doctors want it.

Photofrin II does have limitations of its own. It takes up to 2 months to leave the body, meaning patients must avoid direct sunlight during that period. But data from clinical trials of a potential new PDT agent called benzoporphyrin derivative (BDT) indicate that BDT clears from the body much faster. The trials, by researchers from QLT, Massachusetts General Hospital, and the British Columbia Cancer Agency, which were presented in June at a meeting of the American Society for Photobiology, showed BDT builds to proper levels within hours of being injected and clears from patients within a week. "The patients can be treated with both drug and light on the same day," says Anderson, an author on the report.

That may make for an elegant scenario of selective site-specific drug action, but the real question is whether BDT, or other PDT compounds, will help sick people in new and better ways. "I'm a skeptical optimist," says Anderson. He expects the Canadian approval of Photofrin II to spur studies that ought to provide the quality data needed to see just how good or limited PDT will be. Photofrin II is now under evaluation in Canada, the United States, Europe, and Japan for cancers of the lung, stomach, cervix, and esophagus.

Some of the most provocative data comes from Japanese researchers who, since the 1980s, have been testing PDT for the early detection and treatment of lung cancer. If cancer cells are present in a patient's lung, the PDT agent concentrates in the cancerous tissue and sends out a beacon of fluorescence to doctors. Not only does this signal a cancerous presence, but doctors can then begin treatment by activating the agent with light. "They showed that you could eradicate early stage lung cancers this way," says Dougherty, whose early work in purifying hematoporphyrin-based compounds made the new era of PDT possible.

But most of the PDT trials done to date, which have involved an estimated 5000 patients over a period of 15 years, have been either too small or have lacked enough controls for researchers to determine how well PDT compounds work in comparison to existing or competing treatments. In the United States, Anderson adds, the trials often have involved desperately ill patients who have not responded to conventional therapies, and so their value in early cancer treatment remains difficult to ascertain.

Eli Glatstein, head of radiation oncology at the University of Texas Southwestern Medical Center at Dallas, notes that the trials need to produce more reliable data before therapeutic value can be assessed. "What the field has lacked on the whole is a compulsive and meticulous attention to the physics and dosimetry of this sort of therapy," he says. Still, he is confident that PDT therapy will find its place in the armamentarium of anticancer therapies. Says Glatstein: "Its ideal use will be for cancers close to the surface of an organ and probably in conjunction with surgery." Bruce A. Chabner, director of the division of cancer treatment at the National Cancer Institute, also cautions that PDT "may not have far-reaching potential." But he seconds Glatstein's assessment that it could serve at least as an adjunct therapy for cancers at or near tissue surfaces.

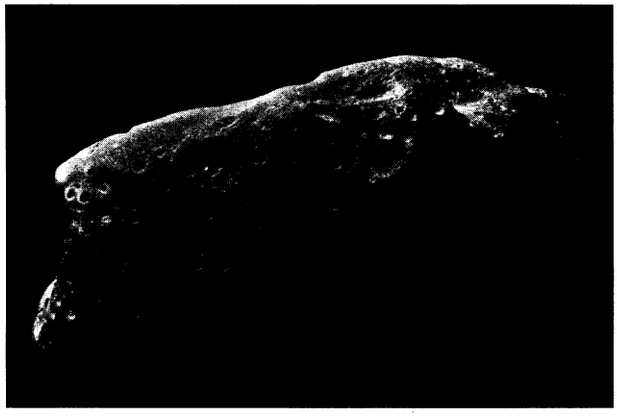
Before PDT even gets to that stage, however, it will have to overcome another obstacle having to do with the lasers used for activating the drug molecules. At the moment the only lasers available require special power supplies, are complicated to operate, and are bulky. But at least one company, PDT Inc. in Santa Barbara, is already bench testing a new solid-state diode laser designed specifically for PDT. Their experimental laser plugs into a wall and fits into a box the size of a large briefcase. As a result of new techniques like that, the light at the end of the PDT tunnel seems to be getting brighter and bigger.

–Ivan Amato

SPACE SCIENCE

Galileo Reveals a Badly Battered Ida

To some, it looks like the lower jaw of a cosmic serpent (try turning this image upside down). But to planetary scientists, the second closeup ever of an asteroid, taken by the Galileo spacecraft on 28 August as it was passing through the asteroid belt beyond Mars on its way to Jupiter, is more than a cosmic Rorschach test—it's a scientific goldmine. "It's a beautiful picture," says Clark Chapman of the Planetary Science Institute in Tucson, a member of the Galileo scientific team. Because of its abundant detail, says Chapman, "There's an order of magnitude more information here for geologists" than in the first ever asteroid closeup: the image Galileo returned after flying by the 19-kilometer-long asteroid Gaspra in 1991 (*Science*, 1 January, p. 28).



NASA JPL

A hard life. Asteroid Ida has taken more hits than expected.

The glacial rate of data transmission through Galileo's crippled communications system delayed the release of the image (a mosaic of five frames) until last week, and scientists are still in the midst of deciphering the asteroid's history from signs of surface wear. But already the battered visage of the 52-kilometer-long asteroid has researchers suspecting that it has been kicking around the asteroid belt for several hundred million years, a good deal longer than some had expected.

Galileo's bonanza of detail comes courtesy of a combination of serendipity and gutsy planning. Ida's large size provided more surface to look at, and a fortuitous lighting angle highlighted many details. But in addition, the space probe's handlers, emboldened by their success at getting Gaspra in the cross hairs, held their fire until the probe was just 3500 kilometers from Ida and then hit it with six overlapping shots. At that range, the camera achieved a resolution of 35 meters, almost twice as good as the sharpest image of Gaspra.

The advanced age suggested by that pockmarked surface is surprising to many researchers because of Ida's history. Ida belongs to a small flock of asteroids in similar orbits, the debris from the breakup of a large parent asteroid. Some researchers saw signs in these asteroids' spin rates and other properties indicating that the breakup was recent. Ida, they expected, would be considerably younger than Gaspra, which has been estimated to have been broken off a larger asteroid about 200 million years ago. Instead, says Peter Thomas of Cornell University, Ida "looks at least as old as Gaspra," if not older.

Revealing as the first glances at this image are, there's much more to come. For now, color and infrared images and other data are stored aboard the spacecraft; they will be transmitted next spring when Earth's motion brings Galileo closer, speeding transmission of the stored data. Then planetary scientists can start getting even more familiar with Ida.

–Richard A. Kerr