Radical-Scavenger Hunt

The search intensifies for a chemical that can protect the body from dangerous free radicals — molecules that form in numerous situations, including exposure to radiation

By LINDA GARMON

The patient has cervical cancer — the second most common cancer in women. As part of her treatment, she undergoes radiation therapy. Over a 6-week period, she receives a dose of about 4,000 rads — at least 40,000 times the amount of radiation a person is exposed to during a typical diagnostic chest X-ray.

While such a large dose of radiation sometimes can successfully destroy or at least shrink certain cancerous growths, it has a major undesirable side-effect: It can damage the healthy tissue in the patient's body. Specifically, the ionizing radiation enters normal cells and forms potentially dangerous free radicals — atoms or molecules with odd (unpaired) electrons. These highly reactive, unstable radicals in turn can injure biologically important molecules such as DNA.

For decades, researchers have screened thousands of chemicals in search of a drug that could selectively "rid" healthy tissue of the dangerous radicals and thereby permit the use of larger radiation doses in the treatment of cancer. The most promising "free radical scavenger" that turned up in that search now is being tested in several clinical trials in the United States. The preliminary results of two of these trials, along with findings from related free radical research, were reported at the recent "First Conference on Radioprotectors [radiation protectors] and Anticarcinogens,"* held at the National Bureau of Standards in Gaithersburg, Md.

Free radical chemistry in biological systems is not sufficiently understood, says NBS researcher Michael G. Simic, who served as the conference chairman. "We need to stimulate more research on free radical mechanisms," he says, "and that's what the [NBS conference] was all about."

Such work would have several long-range applications in addition to developing a free radical scavenger to protect cancer patients undergoing radiation therapy. It could, for example, have implications for protecting astronauts who are exposed to high radiation levels in space. Also, certain drugs, including two commonly used in cancer chemotherapy, "have [undesirable] side-effects, which are believed to be a consequence of free radical reactions," Simic says. Finally, free radicals are thought to be at least partly responsible for some diseases, including certain cancers and possibly even arthritis.

Free radicals can cause such harm because they are "energized" due to the loss of electrons, explains John M. Yuhas of the University of Pennsylvania in Philadelphia. Certain drugs and other foreign substances can lose electrons — and thereby form free radicals — when they are being broken down in the human body. In the case of radiation-induced radical formation, high-energy light pulses "blow electrons away" from the (mostly water) molecules in cells, Yuhas says.

Not all free radicals are villains; some play key roles in the body's vital enzymatic reactions. "Obviously, though, if you put too many of them in a system — which is what occurs, for example, with ionizing radiation — you're in trouble, because they go haywire," Yuhas says. The free radicals can actually cut DNA strands or alter their configuration in some other way. "The same free radicals can out-and-out kill [healthy tissue]," Yuhas says.

One way to prevent this havoc that free radicals can wreak is to "scavenge" them — to "neutralize" them by replacing their missing electrons. One of the most extensive searches for a chemical that could scavenge in humans was actually a U.S. Army program, established in 1959, whose purpose was to find a drug that could protect troops from radiation damage after a nuclear attack. Eventually, the Army program caught the eyes of National Cancer Institute officials, who then began reviewing the data on the scavengers already synthesized by the Army.

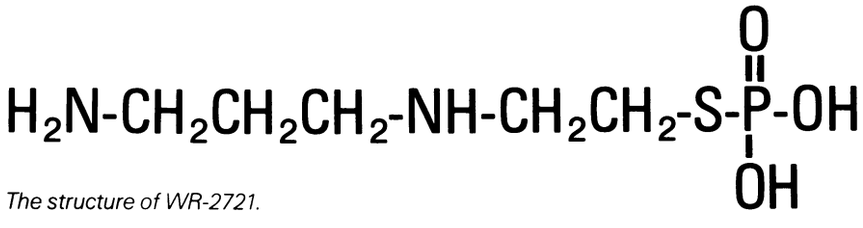
The chemical S-2-(3-aminopropylamino) ethyl dihydrogen phosphorothioate was deemed most promising in the NCI review (SN: 4/3/82, p. 233). This chemical, labeled Walter Reed (WR)-2721 by the Army, was first synthesized by Thomas P. Johnston and J. Robert Piper of Southern Research Institute in Birmingham, Ala.

WR-2721 de-energizes a free radical by donating an electron-containing hydrogen atom (H) from its SH (sulfhydryl) group. Researchers long have known that SH groups are too toxic to circulate freely in the body, Yuhas says. "One of the beauties of WR-2721," he explains, "is that it includes a phosphate group (H_3PO_3) that shields the SH until the drug enters the body tissue"; there, a common enzymatic reaction removes the shield and exposes the radical-scavenging SH group.

But does WR-2721 selectively protect normal body tissues and avoid cancerous tissues — a necessary criterion for a successful radioprotector? Researchers believe that this scavenger generally concentrates more in normal than in cancerous tissues, because tumor cells are fed by fewer blood vessels, and because certain chemical constraints prohibit tumor cells from actively pumping in the phosphate-shielded drug. Nonetheless, studies that measure degrees of protection in animal tissue show that WR-2721 is far from an ideal radiation-protector scavenger.

In various animal studies, researchers have found that bone marrow treated with WR-2721 can tolerate up to three times as much radiation before it is injured as it can without the scavenger. In addition, WR-2721-treated skin, small intestine, colon and testes all can tolerate about twice as much radiation. However, the drug appears to afford little or no protection to lung, kidney and oral mucosa tissues, says Morton M. Kligerman of the University of Pennsylvania. Moreover, the drug unfortunately protects liver tumors.

Despite its several shortcomings, WR-2721 remains the "championed prototype," the highest-ranking among the radioprotectors that have thus far been tested in animals, Yuhas says. The Food and Drug Administration has approved the drug for use in clinical investigations, and about a half-dozen of these now are being conducted in the United States. It is hoped



The structure of WR-2721.

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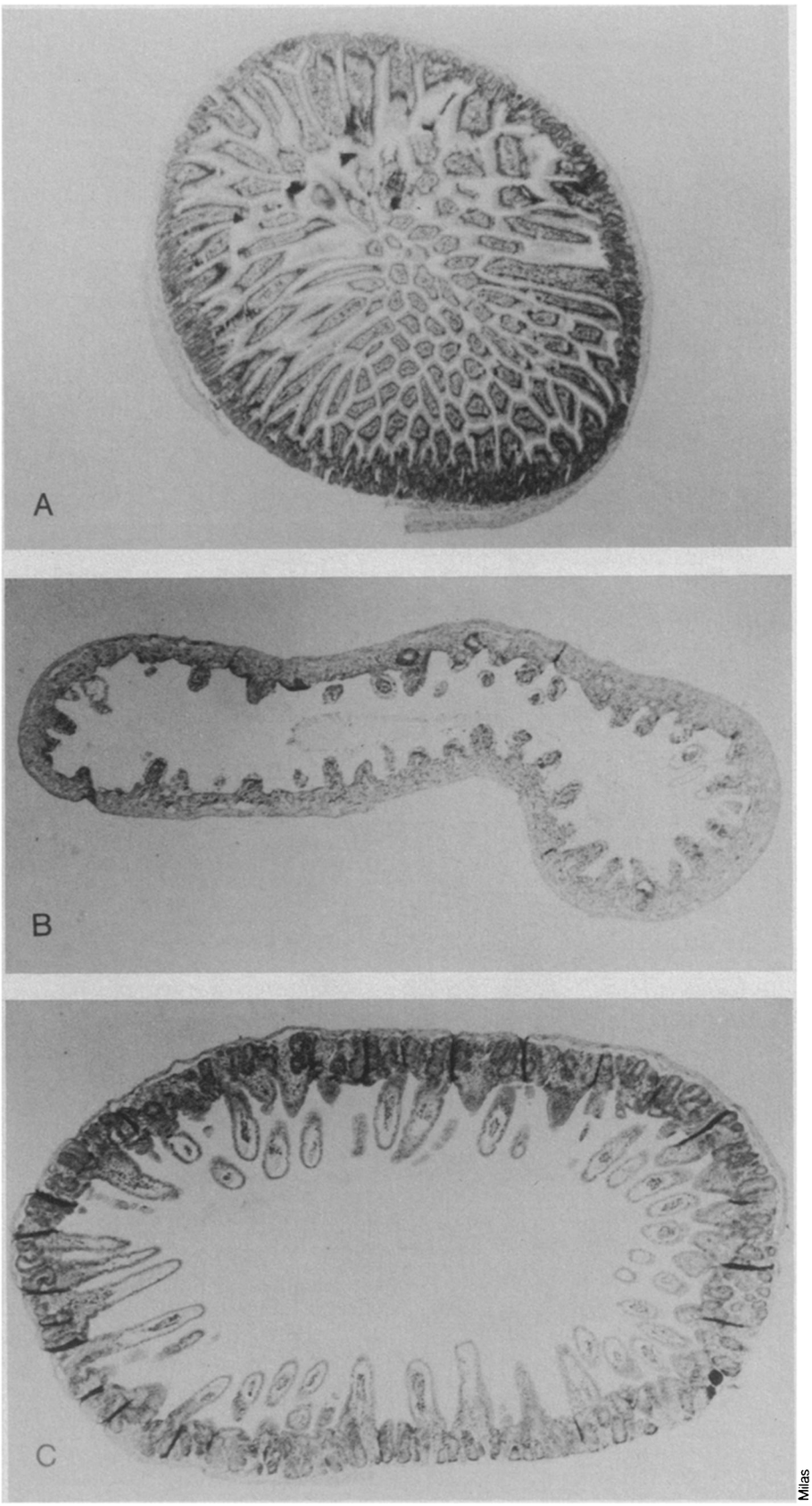
that information collected in the trials eventually can be used to develop a new radioprotector that will eclipse its prototype. But this goal lies much further down the road: Trials of the prototype still are in their initial stages.

Preliminary results of such trials at the University of Pennsylvania were presented at the NBS conference. At the university hospital, 74 patients undergoing radiation therapy and 46 patients undergoing chemotherapy are receiving WR-2721, reported Kligerman, who was the first researcher to give the drug to patients in the United States. (Yoshimasa Tanaka, now of the Kansai Medical University in Moriguchi, Japan, began his clinical trials before Kligerman's.)

The chemotherapy patients—under the direction of John H. Glick — receive, via intravenous infusion, doses of WR-2721 ranging from 450 milligrams per square meter of patient body surface to 910 mg/m^2. The radiation therapy patients receive similar doses. In both groups, nausea, vomiting and lowered blood levels of calcium are among the toxic side effects. "But the major life-threatening toxicity observed," Kligerman reported, "is hypotension" — abnormally low blood pressure, which is defined in the study as "a decrease in systolic blood pressure of 20 torr or greater lasting for 5 minutes."

In neither the radiation therapy nor chemotherapy groups are the trials "really at the point where we can say whether there is a protective effect [of WR-2721]," Kligerman says. However, Glick mentions that in one of his trials, the white blood counts of WR-2721-treated patients were not as low as is commonly observed in unprotected cancer victims undergoing certain forms of chemotherapy. Such a result suggests — and Glick emphasizes "suggests" — that WR-2721 may be protecting the white-blood-cell-producing bone marrow that usually falls prey to chemotherapy drugs. "But these data are so preliminary," Glick stresses; "we will need another six to nine months before this trial phase is completed."

Meanwhile, Glick, Kligerman and colleagues anticipate enticing other researchers to help them develop an analytical tool that will permit them to look at the pharmacokinetics (human pharmacological traits) of WR-2721. The pharmacological traits they are especially interested in elucidating are the drug's differential distribution — including subcellular localization—and its precise chemical state throughout the body. "We've been making assumptions — such as, 'The drug is optimally absorbed in 30 minutes'—based on our translation from mice to man," Kligerman says. "But we have no idea what the drug is really doing in man," he says. It's not understanding the pharmacokinetics of WR-2721, says Kligerman, that "is really holding us back" in the search for an effective radioprotector. □



Milas

The microscopic sections of small intestine, pictured above, were taken from a normal mouse (A), a mouse irradiated with 1,600 rads of gamma rays (B) and a mouse treated with WR-2721 30 minutes before irradiation (C). "Significant protection of [small intestine] mucosa can be appreciated in C," says Luka Milas, who conducted these experiments at M.D. Anderson Hospital and Tumor Institute in Houston, Tex., "and this protection was caused by WR-2721." Milas's research was published in the May CANCER RESEARCH.