Tumor-Associated Antigens:

Experimental techniques are extending the lives of patients with one of the leading cancer killers—lung cancer—and one of the techniques eventually may safeguard us all from lung cancer

BY JOAN AREHART-TREICHEL

Hollinshead with test-tube containing lung cancer cell membrane antigens.

The long and winding road that research often takes sometimes leads you where you want to go. Ariel Hollinshead has been on such a road for 15 years, and now she can almost see the end. As a young pharmacologist at George Washington University in Washington she began separating cancer viruses into bits and pieces. She then injected the various tidbits into hamsters to see whether they might stimulate the animals' immune systems against implanted tumors. To provide some kind of control substance in her study, she also injected membranes of virus-induced tumor cells into other animals with implanted tumors. None of the virus tidbits produced the hoped-for effects, but one of the cell membrane fractions did. Hollinshead was both surprised and interested. "There must be something in cancer cell membranes which, when injected, prompts a cancer victim's immune system to fight off cancer," she concluded. And she appears to have been correct. Her discovery has led to a highly promising technique for treating, and perhaps even preventing, lung cancer. The approach consists of injecting lung cancer cell membrane chemicals into lung cancer patients or into persons at high risk for lung cancer — the leading cancer killer of men and the second leading cancer killer of women in the United States.

To find out how Hollinshead and her colleagues have arrived at this technique, which is currently being tested in U.S., Canadian and European medical institutions, let's backtrack to Hollinshead's first major discovery....

The promising cell membrane substance that came to light in Hollinshead's hamster experiments was probably chemical markers (antigens) induced by the cancer process, which a cancer victim's immune system recognizes as foreign and hence rejects. A heightened immune reaction against cancer antigens then presumably kills off a tumor in the victim's body. One thing bothered Hollinshead, though: Because animals in her experiment had been outbred, it was possible that they had not shared the same cell membrane antigens, and if this was so, the animals' immune systems may have reacted against antigens from healthy cells that they considered foreign, rather than against antigens from cancer cells. The only way to make sure that the tumor rejection had really been due to cancer cell membrane antigens was to test cancer cell membrane material against implanted tumors in inbred hamsters, since the inbred hamsters would have the same healthy cell membrane antigens.

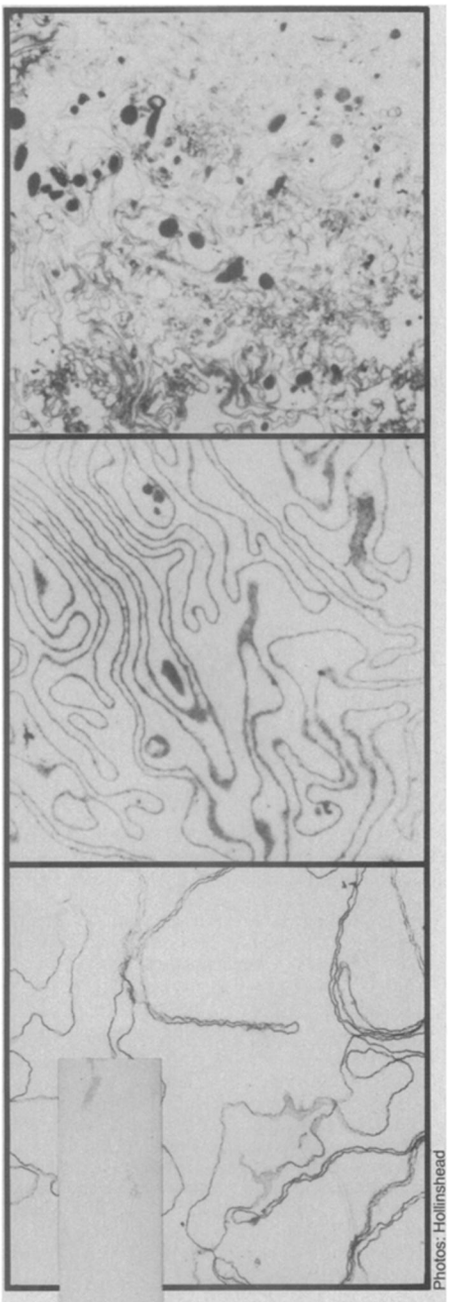
Here the road took an unfortunate turn. The scientist who had funded her initial experiment had not had his expectations borne out and wasn't interested in funding studies to pursue her lead. Cancer viruses were all the rage in those days, and Hollinshead couldn't get research money unless she ran with the crowd. She refused. "I'm not the world's bravest person," she admits, "but sometimes you have to stand on your flat feet!" The result: She went for eight months without research money or salary.

Her determination, however, eventually paid off. She was chatting with David Yohn of the Ohio State University School of Veterinary Medicine in Columbus about her exciting lead, when he told her that the school had a building chock full of inbred animals, and even a Ph.D. candidate eager to do experiments. So Hollinshead, Yohn and the Ph.D. candidate repeated the initial test on inbred hamsters. The cancer cell membranes protected all hamsters tested against implanted tumors, and 90 percent of the hamsters not getting cancer cell membrane injections could not fight off their implanted tumors. Hollinshead was sure that injected cancer cell membranes had an anticancer effect, presumably through antigens on the membranes' surfaces.

She then found, with the help of Morton Prager of the University of Texas Southwestern Medical School in Dallas, that cancer cell membrane materials were specific in their effects — that is, cancer cell membrane antigens could counter tumors only if they were specific for such tumors. But even more challenging tasks faced Hollinshead: isolating cancer antigens from cancer cell membranes and testing them in their isolated state for antitumor effects and isolating antigens from healthy cell membranes and comparing them with the cancerous ones. Medical scientists had little interest in cell membranes in those days, so Hollinshead was venturing into virgin territory. "One of the tricks," she recalls, "was not to be just a good chemist but also a good virologist or immunologist, because I wanted to maintain structural integrity of my antigens so that they would be immunogenic." She started exploring different ways of teasing antigens out of membranes so that the antigens would keep their structures. But because chemical precipitation techniques didn't work, she had to find another method — low-frequency sonication. Cell membranes were exposed to low-frequency sound waves, which gently separated out the antigens.

Around this time, in the late 1960s, a physician at the University of Ottawa was busy testing crude lung tumor cell membranes and healthy lung cell membranes on lung cancer patients. The physician, Thomas Stewart, found that the lung cancer patients responded immunologically to the cancer membranes, but not to the healthy membranes. He concluded that there was something on lung cancer cell membranes that stimulated the patients' immune systems — probably tumor-associated antigens — and that such antigens might well hold promise as a kind of immunotherapy for lung cancer. But Stewart was a clinician, not a research scientist, and thus not able to separate out membrane antigens for testing, as Hollinshead was doing. So when each investigator read about the other's work, a mutual admiration society blossomed.

Hollinshead recalls: "At this time there were only two other groups in the world



Photos: Hollinshead

Crude, semi-clean and clean cell membrane preparations prior to use of low-frequency sonication, which solubilizes tumor-associated antigens. And lung cancer antigens as seen in a test-tube.

Attacking Lung Cancer

working on cancer cell membrane materials besides myself. One was in Australia, and the other was Tom Stewart and his co-workers in Ottawa. He was doing beautiful things with membrane components. He wasn't separating them but using them in skin tests. He understood the import of these studies for eventual therapy." And Stewart recollects: "It was clear to me that I had gone as far as I could myself. As soon as I heard of Hollinshead's work, I thought, this is marvelous! She is doing what I would love to be able to do, and at the clinical level I was able to do what she wasn't, namely, take the next step, which was an immunotherapy trial." Then, by accident, Hollinshead and Stewart met at a 1968 cancer meeting in Montreal. That very night they decided to collaborate: Hollinshead would separate out lung cancer-associated antigens, and Stewart would test the antigens in lung cancer patients.

During the next several years, a pathologist at Ottawa General Hospital shipped cancerous lung tissues down to Hollinshead. But in isolating and purifying antigens from the tissues, she ran a real obstacle course. She had to separate lung cancer cell antigens from cancer cell membrane blocking factors. She had to characterize the cancer cell membrane antigens as hormones, enzymes or other kinds of proteins. She had to test the purported cancer antigens in test-tubes to make sure they reacted only with lung cancer cells, not with other kinds of cancer cells. The job took a while, but she finally managed to harvest large batches of the antigens. By March 1973 she and Stewart were ready to inject lung cancer-associated antigens culled from all four major kinds of lung cancers — squamous, large cell, adenocarcinoma and small cell — into patients who had had surgery for lung cancers (mainly of the first three kinds) but who were still at high risk for cancer recurrence, especially during the first two years following surgery. (Eighty percent of lung cancer patients die within two years after diagnosis, and long-term survivors have been few.) The reason that patients with small cell lung cancer were mostly excluded from the trial is that small cell is the deadliest of all four kinds of lung cancers — too quick to catch with surgery (a prerequisite for this first trial) and usually lethal within months.

From March 1973 to September 1976, 50 patients who had had squamous, large cell or adenocarcinoma lung tumors removed by surgery and two patients with early-stage small cell lung cancer were enrolled in the trial. Twenty-eight received injections of lung cancer-associated antigens once a month for three months. Twenty-four patients served as controls. Results five years later — as of February 1979 — showed an 80 percent survival among the patients getting the antigens and only a 49 percent survival among the control patients — a highly significant difference. In other words, there was only one possibility out of 10,000 that these results had occurred by chance.

Although the results were greeted with skepticism by some scientists, they brought praise from others. In May 1979 Frank Rauscher, former National Cancer Institute chief and now head of research for the American Cancer Society, declared: "In the past, people have been inoculated with BCG, for example, which is a pantropic kind of approach to enhance the body's general resistance and immunologic mechanism, but as far as I know there's never before been any notable successful trial of a specific antigen for a specific tumor. This would be the first." According to Gerald Vosika, a cancer specialist at the University of Minnesota Medical School who has had some modest success in extending the lives of large cell lung cancer patients with drugs, Hollinshead and Stewart's research "is an exciting area." And as Ben Papermaster of the University of Missouri Medical Center has written Hollinshead, "Your brilliant work in the field of human cancer antigens is among the most advanced and exciting in the world."

The proof of the pudding in science, however, isn't praise but confirmation of results in numerous studies by various investigators. And to date Hollinshead and Stewart's results have been partially replicated by Hiroshi Takita and his colleagues at Roswell Park Memorial Institute in Buffalo. But the real proof that lung cancer antigens can dramatically extend lives can come only from a study of a large sample of patients followed over a long period of time. Such a trial got underway in June 1978 at more than a dozen medical centers in the United States, Canada, England and France, with Hollinshead providing the antigens. By then she knew which cancer antigens to collect and could routinely identify them by their molecular weights, characterization with antisera and reactions with lung cancer cells in the test-tube. Some 100 patients who had had their lung tumors removed early got three injections of their specific kind of lung cancer antigens during a three-month period. Another 200 patients with similar conditions did not get injections and are serving as controls. If the antigens do extend survival time it should be apparent in the early 1980s.

Meanwhile, Hollinshead and Stewart are forging ahead with an even more ambitious plan — testing whether lung cancer antigens might prevent lung cancer in a

high-risk population. Heavy smokers who work around asbestos, uranium or other chemicals that cause cancer are at an especially high risk of getting lung cancer. So Hollinshead and Stewart now want to inject lung cancer antigens into 1,000 members of this population to see whether the antigens reduce their susceptibility to lung cancer. They held a workshop in early 1979 to discuss the idea with members of industry and labor; participants expressed both enthusiasm and reluctance. Hollinshead and Stewart decided to go ahead, provided they receive approval from the Canadian Medical Research Council. They expect approval to come through some time in 1980. Once the trial gets underway, it will take seven or eight years to get a good idea of whether the antigens can prevent cancer.

Even if antigens pan out as a cure and a preventive treatment for three out of four kinds of lung cancer, there is still the fourth major kind of lung cancer that the antigens probably cannot halt because it moves too swiftly even for surgery to catch.

There is hope, however, for victims of deadly small cell lung cancer—thanks to a research approach being used by John Minna and his colleagues. Minna works in an intramural branch of the National Cancer Institute located in the Washington (D.C.) Veterans Administration Hospital. He and his co-workers have treated more than 100 small cell lung cancer patients with a combination of different anticancer drugs, and some of these patients have had impressive survival rates — two to seven years rather than the usual few months. Several other physicians using the same combination of drugs have come up with comparable results.

Minna and co-workers are now attempting to see whether combining their drug regimen with radiation treatments is more effective than the drugs alone. They are also exploring an even more radical treatment — removing bone marrow from a patient, giving the patient such high doses of drugs and radiation that it would kill the bone marrow if it hadn't been removed, then reinjecting the bone marrow back into the body. This ploy, Minna and his team hope, will kill lethal small cell lung cancer but spare patients their bone marrow.

So it looks as if one of the most common and incurable cancers — lung cancer — may soon be successfully treated and perhaps even cured, just as other kinds of cancers are now being successfully treated or cured with a combination of regimens. In fact, lung cancer may eventually even be preventable with a lung antigen vaccine. Whether these dreams come true, of course, depends not on the greatest scientific hopes but on hard scientific evidence that the techniques really work — evidence that can only be culled from present and projected clinical trials. □

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THE CONQUEST OF PAIN—Peter Fairley. In the United States the cost of treating pain is estimated to exceed 60 billion dollars a year. This book tells the history of pain and man's attempt to eradicate it. Scribner, 1980, 272 p., illus., $12.95.

CREATURE COMFORTS—Joan Ward-Harris. A charming story of the wild creatures—raccoons, squirrels, Canada geese, hummingbirds and many other animals with which the author shares her home and her love, tending those animals who need her help and then releasing them once again to the wild. St Martin, 1980, 204 p., illus., $9.95.

DESIGN & MEMORY: Computer Programming in the 20th Century — Peter H. Huyck and Nellie W. Kremenak. According to the preface, "this book is an attempt — albeit slightly irreverent — to look at where the programming phenomenon came from, what it is, and where it is going." The authors suggest some new ways of looking at digital computing. McGraw, 1980, 152 p., $11.95.

ENERGY IN TRANSITION 1985-2010: Final Report of the Committee on Nuclear and Alternative Energy Systems, National Research Council— National Academy of Sciences. Five years in preparation, this report attempts to detail all aspects of the nation's energy situation likely to affect policy decisions from 1985 to 2010 (SN: 1/19/80, p. 36). W H Freeman, 1980, 677 p., charts and graphs, $24.95, paper, $11.95.

INLAND FISHES OF WASHINGTON — Richard S. Wydoski and Richard R. Whitney. Designed to be used to identify Washington state's inland fish and provide information on their life histories and habits. Includes color photographs of each species. U of Wash Pr, 1980, 274 p., color and b&w illus., $17.50, paper, $8.95.

LANGUAGE AND LEARNING: The Debate between Jean Piaget and Noam Chomsky — Massimo Piattelli-Palmarini, Ed. The originators of two of the most influential schools of contemporary cognitive studies met, along with other distinguished scientists, for a three-day symposium in 1975. This book includes the edited transcripts of the debate as well as afterthoughts and comments on the debate. Harvard U Pr, 1980, 409 p., $20.

MALIGNANT NEGLECT — Joseph H. Highland, Marcia E. Fine and Robert H. Boyle. Written by Boyle and staff members of the Environmental Defense Fund to show which chemicals are cancer-causing agents, how serious they are, what carelessness and neglect have done and are doing to increase cancer rates. Suggestions are made as to what individuals can do to protect themselves and generations to come. Originally published in hardback in 1979. Vintage Bks(Random), 1980, 275 p., paper, $3.95.

MEXICAN MASKS — Donald Cordry. The author's quest was to preserve and record Mexican masks, their significance and their links to their Pre-Columbian ancestors. Beautifully illustrated. U of Texas Pr, 1980, 280 p., color and b&w illus., $39.95.

A NATURALIST ON A TROPICAL FARM—Alexander F. Skutch. For nearly 40 years the author has lived on a farm in Costa Rica where he has attempted to preserve as much of the natural environment as possible. He tells of the birds, horses, trees, flowers and insects of his surroundings. One chapter follows the changing seasons of a tropical year and describes their influence on the vegetation and animal life. Charming drawings by Dana Gardner. U of Cal Pr, 1980, 397 p., illus., $16.95.

THE PINE TREE BOOK: Based on the Arthur Ross Pinetum in Central Park — Russell Peterson. Pines grow worldwide in the Northern Hemisphere and many species have been introduced to North America from their native habitats. This book is primarily an identification guide to pine trees with beautiful color illustrations. Pine trees are discussed in general terms in the introduction. Brandywine(Dutton), 1980, 144 p., color and b&w illus., $14.95, paper, $7.95.

SCIENCE IN EVERYDAY LIFE — William C. Vergara. Arranged in question-and-answer format, this book touches on all areas of science using nontechnical language to explain scientific concepts. Questions range from "Do insects engage in farming?" to "What is gravity?" Har-Row, 1980, 306 p., illus., $12.95.

TECHNOLOGICAL TERRORISM — Richard Charles Clark. A study of the extreme vulnerability of our modern nuclear power plants, computers, water systems, liquefied natural gas and other energy systems to terrorist attack. The ready availability of chemical and biological agents that can be used to wipe out whole populations is examined. Devin, 1980, 220 p., $10.

THERMAL SHUTTERS AND SHADES: Over 100 Schemes for Reducing Heat-Loss Through Windows — William A. Shurcliff. According to the introduction the heat-loss through windows of U.S. houses corresponds to about 300 million barrels of oil per year or about 3 percent of our total annual use of purchased energy of all kinds. Many different kinds of thermal shutters and shades are described in detail. Brick Hse Pub, 1980, 238 p., illus., $24.50, paper, $12.95.

UNKNOWN EARTH: A Handbook of Geological Enigmas— William R. Corliss, Compiler. Describes unusual geological phenomena as recorded in geological journals and other journals such as SCIENCE and NATURE. In most cases these anomalies contradict current geological theories. Sourcebook, 1980, 833 p., illus., $19.95.

THE VIKING WORLD — James Graham-Campbell, foreword by David M. Wilson. The Viking Age began in the last decades of the eighth century and lasted until 1100. Although the time was short, the influence of the Vikings was far-reaching and their impact on Western culture was tremendous. This magnificently illustrated book tells the story of the Vikings, their way of life, their culture and artifacts and their influence on the world. Ticknor & Field(HM), 1980, 220 p., color and b&w illus., $25.

THE WASTE WATCHERS: A Citizen's Handbook for Conserving Energy and Resources—Arthur H. Purcell. We have to look upon waste as the serious national problem that it is, says the author — a problem that, if left unsolved, will reduce our standard of living and make our lives less enjoyable. Dr. Purcell goes on to describe practical waste-trimming strategies. Anchor Pr/Doubleday, 1980, 286 p., illus., paper, $4.50.