Effects of ozone depletion not limited to skin cancer

Ultraviolet radiation suppresses immune system, laboratory studies show

A thin layer of ozone in the stratosphere protects us from 90% of the sun’s ultraviolet (UV) B radiation, the biologically active portion of the UV spectrum. This layer has been the subject of much debate since 1974, when researchers first proposed that it could be diminishing.

“A lot of effort has been spent trying to verify ozone depletion,” said Margaret L. Kripke, Ph.D., chairman of the Department of Immunology at The University of Texas M. D. Anderson Cancer Center. “But now we’re fairly confident that changes are occurring in the ozone layer.” As a result, research on the effects of these changes is becoming more important.

“Life on earth has evolved to cope with a very small amount of UV light,” Kripke said. “If there is a sudden, substantial increase in the amount of UV light in sunlight, then people, plants, and animals won’t have an opportunity to evolve protective mechanisms.” Changes in growth and photosynthesis could have significant effects on crops, ecosystems (and thus biological diversity), and phytoplankton (the base of the whole marine food chain), a variety of studies have suggested. Increased UV radiation is also expected to result in increased incidence of skin cancer, melanoma, and cataracts, Kripke said.

However, immune suppression as a result of UV radiation could have the broadest implications of all. Kripke, a pioneer of the field of photoimmunology, has shown that the UV radiation in sunlight not only can induce skin cancer, but also can weaken our immune systems, making us more vulnerable to the carcinogenic process and, perhaps, to infectious diseases.

“The world’s two major health problems—starvation and infectious disease—kill more people than cancer, war, or anything else,” Kripke commented. “Ozone depletion could aggravate both problems: one by affecting the food chain and the other by affecting the immune system.”

Texans could be particularly affected, for three reasons. First, we get large doses of UV radiation because of our geographical location. Second, many Texans have outdoor occupations, such as jobs in oil fields, on ranches, and in the shipping industry. Finally, a lot of immigrants from Wales, England, and Germany settled in Texas, and many of these families have very poor protective mechanisms against sun damage, Kripke said. Although the darker skin of blacks and Hispanics protects them somewhat from the carcinogenic effects of UV radiation, a study by University of Miami researcher Dr. Martin Vermeer and colleagues has suggested that pigment does not protect against immunological effects.

Predicting the impact on local and world health of increased UVB radiation will require a substantial research effort. Kripke is working to answer two fundamental questions: (1) what are the molecular and cellular events involved in UV-induced immune suppression and (2) do these events make an organism more susceptible to infection?

How does UV radiation lead to immune suppression?

Kripke is studying the first question from three different angles: the activation of the suppressive immune pathway, the molecular target of UV radiation, and the role of chemical mediators released from the irradiated cells.

“The immune system has an active pathway and a suppressive pathway,” Kripke said. When the active pathway is triggered, an immune response occurs. When the suppressive pathway is triggered, however, suppressor T lymphocytes are produced, which turn off the immune response. Kripke has shown that UV irradiation causes the immune

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Changing public behavior will be very important in lessening the eventual clinical impact of ozone depletion.

System to shift from the active to the suppressive pathway. For example, if the immune system is working correctly, then when a chemical like 2,4-dinitrofluorobenzene (DNFB) is painted on mouse skin, the skin becomes inflamed as phagocytic and lytic cells move to the vicinity. However, this contact hypersensitivity (CHS) response does not occur if the mice are first UV irradiated; that is, the normal immune response is suppressed. Kripke is working on several projects to determine how this shift from the active to the suppressive pathway occurs. Recent studies in her laboratory have focused on Langerhans cells, which carry antigen molecules to the lymph nodes and bind with T lymphocytes to induce the CHS response. Results suggest that the Langerhans cells, which are altered by UV radiation, are involved in the shift to a suppressive pathway.

A second area that Kripke is focusing on is the initial molecular target of UV radiation. She hypothesized that DNA damage induced by UV radiation triggers the immunosuppressive process. To test this hypothesis, she irradiated mice with UVB light, then treated them with liposomes designed to degrade when taken up by skin cells, releasing a DNA repair enzyme. She then immunized the mice with the chemical DNFB. Kripke found that they displayed a normal inflammatory response to DNFB even though they had been irradiated. In other words, CHS suppression was avoided because UV-induced DNA damage was repaired by the enzyme. It is possible that this liposome approach could one day be used therapeutically to repair DNA damage in humans.

A third aspect of Kripke’s studies of the cellular events of UV-induced immune suppression regards the role of cytokines, immunologically active mediators. Jorge M. Rivas and Stephen E. Ullrich, Ph.D., her coworkers in the Department of Immunology, recently discovered that interleukin-10 is one of the immunosuppressive cytokines released in UV-irradiated murine skin cell cultures. Although such mediators have immunosuppressive effects at certain concentrations, many have beneficial biological effects at other concentrations, Kripke said. Such beneficial effects may be the reason that a connection between UV radiation and immune suppression was selected during the course of evolution. “It doesn’t sound very logical that when you go out into the sun, your immune system is suppressed,” Kripke said. “But there must be a benefit at some UV dose.”

Why Texans Should Be Concerned about UV Radiation

- **Geography.** Southern regions receive higher doses of UV radiation
- **Outdoor occupations.** Many Texans work outdoors in oil fields, ships, ranches, and farms
- **Ethnic background.** Texas descendants of fair-skinned immigrants from Wales, England, and Germany are particularly vulnerable to UV radiation

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The physician as scientist

Emil J. Freireich, M.D., has led a distinguished career as a physician conducting basic clinical research. From 1955 to 1965, at the newly formed Clinical Center of the National Institutes of Health (NIH), he and his colleagues made several advances in childhood leukemia research. In 1965, he came to the University of Texas M. D. Anderson Cancer Center, where he turned to the study of adult leukemia. Freireich's work, a blend of clinical care and science, has always been guided by rigorous scientific principles. He terms this approach basic clinical research, and the person who conducts such research is a clinical investigator. Today, Freireich sees fewer and fewer young physicians choosing this type of research as a vocation, so few that he considers it a crisis. He has participated in an NIH workshop examining this issue (Cancer Res 51:753, 1991), and he has conducted his own study of it (J Natl Cancer Inst 83[12]:829, 1991).

In an interview with Oncolo's managing editor, Kevin Flynn, Freireich describes the crisis and proposes solutions.

Q

Distinguish basic clinical research from research in general. What's unique about it?

A

Basic clinical research links the laboratory with the bedside, and the clinical investigator is the interface between the clinic and the laboratory. He or she is a doctor who not only treats a cancer patient but also does research while treating a cancer patient. When I go to the clinic and see a leukemia patient, I'm doing research. I'm looking at that person and saying, "Here's a treatment that works in 75% of the people; why isn't it working in you?" One of my patients was a 19-year-old woman with leukemia who received three of the best treatments we've discovered over the past 40 years. None worked. The job of the clinical investigator is to find out why, by first developing a hypothesis and then devising a study according to rigorous scientific principles. To do so, clinical investigators need to be trained in the methods of science.

When I speak of the need for scientifically trained clinical investigators, I don't mean to minimize what basic scientists contribute to biology. I believe strongly that the fundamental knowledge that comes out of the laboratory is vital to progress in medical research, but we also need a special type of investigator who can commute successfully between the lab and the bedside. Without this kind of investigator, the valuable insights that basic scientists provide cannot be optimally translated into practice. Biomedical research is growing faster than we can apply it, and part of the problem is that the clinical investigator is a species that is dying.

Q

Why?

A

There are two reasons: First, it is very lucrative for physicians to work in other fields of medicine. A young physician who goes into emergency medicine or diagnostic radiology can make a six-figure income in the first year. Second, the grant application process is highly competitive. Only 15% of all grants are funded. It takes a lot of work to apply for grants and succeed. Combined, these two factors provide a powerful disincentive against choosing basic clinical research as a discipline.

I've traveled to the 20 leading cancer centers to see what was coming up from below, to see whether young, bright people were interested in being clinical investigators. When Dr. Tom Frei and I came to M. D. Anderson in 1965, we were probably 38 or 39 years old. [Dr. Frei left M. D. Anderson in 1972 to go to the Dana-Farber Cancer Institute, where he was physician in chief until 1992.—Ed.] Where are the 40 year olds coming into this field? There are very few. Frei has seen continued on page 4
"The crisis, today, is that there are insufficient funds to support the full-time clinical investigator"

the same thing. Our generation of clinical investigators is not being replaced. I believe we are at a crisis point. We need a major paradigm shift, a new way of thinking about the place of basic clinical research in medicine. Dr. Frei and I recently submitted an editorial on this topic.

Q
Talk about the first generation of clinical investigators. Why did you enter this field?

A
In 1955, I was a young scientist in training at Boston University. Dr. Chester Scott Keefer, dean of the Boston University School of Medicine, called me into his office. Keefer was the first assistant undersecretary for health affairs, in the Eisenhower administration. Apparently, he had heard of open positions at NIH and thought I would qualify. Keefer said, “Freireich, have you ever heard of the National Institutes of Health?” I said, “No sir.” He said, “Well, there’s this new place in Bethesda. I want you to go look at it.” I said, “Yes sir.” If he told me to jump out the window, I would have done it. So I got in my car, went to Bethesda, and got the job.

The place was about 20% occupied, so I got an entire floor. Those were times of great affluence. What happened at that time, in 1955, was the beginning of this discipline called clinical research. The NIH was a revolution in research. It was designed to allow investigators to study medicine scientifically. This idea is commonplace today, but when I was in medical school we debated whether medicine was a science or an art. In 1955, the NIH was just a bunch of young lab scientists and physicians learning science. They were given unlimited resources, and in a decade American medicine was changed forever. From this one little building in Bethesda poured revolutionary advances in cancer and heart disease treatment, among others.

Q
It seems that this approach was successful. If such was the case, what led the scientific community away from it?

A
All paradigms have a natural history. You choose a paradigm, or method of operation, because it’s successful, and its success encourages you to continue using the same paradigm. This is precisely what happened with our national research funding system. We were getting tremendous progress out of basic science, so we diverted an increasing proportion of money into basic science research. That was perfectly logical, but this approach becomes rate-limiting if no clinical investigators are available to bring the lab work to the bedside. The crisis, today, is that there are insufficient funds to support the full-time clinical investigator. The crisis, though, was not caused by a lack of vision on anybody’s part. The current system has led to enormous breakthroughs, but we need to find a way to let all this basic science knowledge flow through, from the laboratory to the clinic. The old paradigm is depleting itself.

Q
What’s the solution?

A
Dr. Frei and I propose three things. The first is to create a professional society, to ensure that basic clinical research is recognized as a unique discipline and to build an esprit de corps.

Second, all medical schools should create a three-track tenure system for physicians. Most schools have a two-track system, one track for physicians who stay in the clinic and don’t do research, and one for full-time laboratory people. Well, why not have a clinical research track for clinical investigators? The secret to having a clinical research track is to have a tenure and promotions committee run by clinical investigators and to provide full academic privileges. This would restore the clinical investigator’s credibility in the academic community by creating a peer review system for them (for tenure).

And third, we just have to face it: there has to be a study section at NIH run by clinical investigators, people who recognize the realities of clinical

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The goal ... is to establish a network for collaborative research between M. D. Anderson ... and community investigators

...Physician Network continued from page 8

a request for proposals to hospital-based oncology programs and oncologists and hematologists throughout the state. The respondents within each community were encouraged to form consortia of their institutions so that they could meet the minimum requirement of 800 to 1000 cancer cases per year. The applicants also had to demonstrate that they were capable of organizing and maintaining a consortium and that they had successfully participated in clinical trials and community-based research.

Of the 11 consortia that applied, six were accepted, and the network officially began in July 1992. The six consortia, which comprise 16 institutions, are located in Dallas, Fort Worth, Houston, Lubbock, Temple, and Tyler. The consortia in Dallas and Houston include only certain private hospitals, whereas those in the other cities represent all of the major facilities in the area, both public and private, that provide oncology services. The Texas Outreach Program funds a research nurse/data manager, a health services coordinator, and a research assistant at each of the six lead sites. Most of the data management and analysis is centralized in the Section of Community Oncology at M. D. Anderson, taking advantage of a system that was already in place as part of the Community Clinical Oncology Program (CCOP), a nationwide cooperative of 35 consortia funded by the National Cancer Institute (NCI). Winn is also the director of the M. D. Anderson CCOP research data base.

Philip A. Salem, M.D., is director of the Cancer Research Program at St. Luke’s Episcopal Hospital in Houston and leader of the Houston TCON consortium. To him, “TCON is the ideal model of cooperation between the comprehensive cancer center and the community hospitals because it is complementary and mutually beneficial. Patients can participate in beneficial research protocols while remaining in familiar surroundings, and M. D. Anderson is able to accrue larger numbers of patients into its protocols.”

Seventeen protocols are available to network participants

The cancer patients seen by network physicians represent from 10% to 17% of the estimated number of cases in Texas; the most prevalent cancers, such as those of the breast, lung, colon, and prostate, are well represented. After the participating institutions were selected, the first task was getting their institutional review boards (IRBs) to approve their participation in the clinical trials. These approvals have now been obtained, said Winn, and physicians from these institutions have begun recruiting their patients for the TCON clinical trials, which will eventually include many of the protocols active at M. D. Anderson. Right now about 15 protocols have been approved and are available to TCON patients, and many more will soon become available. Said Winn, “We have obtained permission from the NCI to use some of its protocols for TCON, and we are working with several pharmaceutical companies to provide experimental drugs for TCON protocols.”

Network makes study of rare diseases easier

TCON is particularly suited to the study of rare diseases. Even though M. D. Anderson has a large patient population, said Winn, “There are a lot of rare diseases that even M. D. Anderson physicians don’t see enough of to conduct proper clinical trials. These TCON patients will allow us to enlarge these trials, enhancing the validity of the results. Participation in the TCON trials also benefits the patients. Many patients suitable for protocols (that is, patients having received no prior therapy) stay in their communities and don’t get entered into protocols. By the time they come to M. D. Anderson, they are getting their second or third line of treatment and can’t be put on most protocols. With TCON, these patients can be placed on protocols right away, giving both us and the patient a great advantage.”

TCON patients, if eligible, may also participate in chemoprevention trials, in which mild, relatively nontoxic agents, such as vitamin A and E derivatives, are administered regularly in an attempt to prevent certain cancers in those at high risk of

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Patients can participate in beneficial research protocols while remaining in familiar surroundings.

The TCON network has also begun its first health services research project. The overall objective is to characterize the factors affecting the use of medical resources by women who died of metastatic breast cancer. The researchers are examining data on their diseases and treatments, the characteristics of their physicians and the centers where they received care, and the availability of support services in their counties of residence. They are gathering these data in an attempt to discern patterns and variations in the care these women received. From this study they hope to develop hypotheses about patient, physician, and hospital characteristics that determine the choice of therapy; these hypotheses will then be tested in a follow-up study of a group of living women with breast cancer. The follow-up study will attempt to document the sequence of decision-making events in the treatment process and will allow a better understanding of the variations in care and of the impact that these have on costs and outcomes.

Said Salem, “This program promotes communication and cooperation between research institutions and many community hospitals, and TCON is helping to break down that wall. Any physician in any practice setting can participate in research. Many of the physicians who’ve made important contributions to cancer research were not full-timers at a major research institution.” Winn concurred, “We know the community oncologists can do research; they all train in universities, where they are involved in research, before they go out into the community. What we have built for them is the structure they need to perform research. By participating in these clinical trials, they are able to give their patients new experimental therapies in their home towns without ever coming to M. D. Anderson.”

—KATHRYN L. HALE

Physicians who desire additional information may write Dr. Winn, Section of Community Oncology, Box 501, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas 77030, or call (713) 792-8515.
to clear the bacteria from their lymphoid tissues, so the course of the disease is prolonged. UV radiation can actually accelerate death from chronic mycobacterial infection.

Kripke’s group is also looking at how UV radiation affects Lyme disease, schistosomiasis, and infections caused by the opportunistic fungus *Candida albicans*. They have found that UV-irradiated mice have a reduced immune response to *C. albicans* compared with both unirradiated mice and irradiated mice treated with liposomes containing a DNA repair enzyme.

### Education will lessen clinical impact of ozone depletion

In all of these studies, the doses of UV light given mice are comparable to the amount of natural UV light many humans are exposed to. “We are not using megadoses,” Kripke said. One or two UV treatments causing minimal redness induce systemic immune suppression. In fact, in a recent study of sunscreen effectiveness, Peter Wolf, M.D., Cherrie K. Donawho, Ph.D., and Kripke found that it took more UV light to give a mouse a sunburn than it did to induce immune system alterations. Their findings raised the concern that sunscreens may not protect against the immunological effects of UV radiation. “Sunscreens may give us a false sense of security,” Kripke said. People who stay outside longer with the help of sunscreens may actually be getting more immunosuppressive UV light than they would otherwise.

Issues like these highlight the need to clarify the immunosuppressive effects of UV radiation. “We also need to educate people to protect themselves from excessive exposure,” Kripke said. In particular, patients who are taking immunosuppressive drugs or have had an organ transplant should avoid sunlight, she noted. “And it’s very important to increase the awareness of protecting children. Most UV exposure received in a lifetime occurs in childhood, because children spend so much time outdoors.” There is some epidemiological evidence that sunburns in childhood are predisposing factors for development of melanoma later, Kripke said. “Whether increased UV light in our environment will affect the incidence of melanoma is fairly controversial,” Kripke said, “but we have found that exposing mouse skin to UV light promotes the growth of implanted melanoma cells.”

Attitudes toward exposure to sunlight are changing in at least a segment of the population, Kripke notes. Tanning is not as fashionable as it once was. “But I’m not sure that people who work outdoors have changed their lifestyles at all,” she said. “Changing public behavior will be very important in lessening the eventual clinical impact of ozone depletion.”

—SUNITA PATTERSON

Physicians who desire additional information may write Dr. Kripke at Box 178, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas 77030, or call (713) 792-8578.

### Physician Scientists

research. Funding agencies have to recognize that a clinical investigator cannot spend all his or her time in the laboratory, and he or she shouldn’t have to compete with those that do. First of all, if you’re going to do clinical research, it doesn’t exempt you from taking care of sick people. If you want to treat four leukemia patients, you’re going to be up all night, the family is going to call you four times a day, and the patient is not going to agree to every treatment you want to do. It’s complicated. It takes a lot of time, skill, knowledge, and experience.

**Q**

If you wanted to convince medical students to be clinical investigators, what would you tell them?

**A**

I would tell them that the only deficiency in medicine is clinical research, and if I were young, I would look for an area where there was very little competition and lots of opportunity for the future. The thing to remember, though, is that you have to learn science but think like a physician. Some questions only a clinical investigator can ask.

Physicians who desire additional information may write Dr. Freireich, Department of Hematology, Box 55, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, or call (713) 792-2660.
New physician network brings M. D. Anderson to local communities

Many cancer patients in Texas who want aggressive, experimental care travel to The University of Texas M. D. Anderson Cancer Center in Houston. These travellers leave behind families, friends, jobs, and communities in search of the treatment that might make them well. The journey often creates financial as well as emotional hardships for the families, but they are willing to take on those hardships, certain that the newest and most effective therapies can be had only at a large clinical research center like M. D. Anderson Cancer Center.

A new program coordinated at M. D. Anderson, however, is making it much easier for residents in and near six communities in the state to get this investigational treatment much closer to home. The program, called the Texas Community Oncology Network (TCON), has created a cooperative of oncologists in these communities whose overall mission is improving the care of cancer patients.

TCON is one of the 10 projects funded through the Texas Outreach Program, an initiative that began last year to expand and improve cancer screening and prevention services to all Texas residents. The program is funded by up to $15 million in fees earned by M. D. Anderson physicians.

Involvement of local physicians is the goal

“The goal of TCON,” said Rodger J. Winn, M.D., director of the program and head of the Section of Community Oncology of the Division of Medicine, “is to establish a network for collaborative research between M. D. Anderson investigators and community investigators. We have four specific aims: to do clinical trials of new therapies, to launch large chemoprevention trials, to do what is now generally called health services research, and to use modern communication technologies to share information among network participants.” The network was created when Winn’s group sent