from a research trip to the Former Soviet Union (FSU), told his audience that a happy consequence of the breakdown of central environmental management has been the elevation of environmental activists from strident protesters to powerful voices in the new republics. Some even serve as surrogate enforcers of environmental laws. Indeed, Nancy Lubin, a Soviet affairs specialist at Carnegie-Mellon University, says that "any real change is going to happen from below."

The key environmental organization in the FSU these days is the Moscow-based Socio-Ecological Union (SEU), a 4-year-old umbrella organization for about 150 "green" groups scattered throughout Russia and 12 of the 14 other republics. The union grew dramatically in stature in April 1991, when the Soviet Ministry of Justice granted it the right to monitor natural resources and to sue polluters. Two steps forward and one back may be the rule because this March Russian President Boris Yeltsin signed a new law that limits nongovernmental organizations to suing over damage to health and property; no longer could they sue to protect public land or wild animals. Nevertheless, the SEU has made the most of its quasi-official status.

During its brief tenure, SEU has launched dozens of projects, including mopping up oil spills in western Siberia, monitoring dioxin pollution in Arkhangelsk, and saving endangered species such as the Moldavian sterlet, a small sturgeon prized for its caviar. "More often than not, the SEU is more organized than the government is," says Randy Kritkausky, who heads up Ecologia, a Harford, Pennsylvania-based green group that has been collaborating with SEU in monitoring heavy metals, nitrates, and organic pollutants such as benzene and toluene.

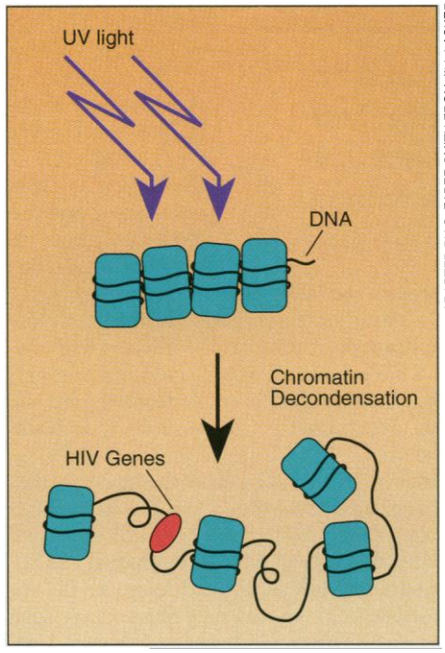
Ecologia is only one of the Western environmental organizations with which SEU has been forging ties; others range from the U.S. Environmental Protection Agency to green groups such as the National Audubon Society and Greenpeace. Such links with the West have brought funding, but also dangers: Some U.S. environmentalists warn that such ties might endanger SEU's position of strength in the FSU. They cite the potential for jealousy in the Russian Ministry of Ecology and Natural Resources, a body to be reorganized next month only a year after it was formed as a replacement for the State Committee for Environmental Protection, the Soviet version of the EPA. Says Kristen Suokko, the FSU project coordinator at the Natural Resources Defense Council: "The government is starting to see the NGO [nongovernment organization] community as a threat, especially when they see all the clout they're getting from the West." All of which may mean tougher times for the former Soviet Union's already beleaguered environment.

–Richard Stone

MOLECULAR BIOLOGY

Awakenings...UV Light and HIV Gene Activation

Like the "mole" in a John LeCarré spy novel, the AIDS virus has a disturbing ability. After entering a susceptible cell, it can go underground, hiding in latent form, often for many years, before flaring up and either destroying the host cell or transforming it into a virus-producing factory. Exactly what reawakens the sleeping virus remains a mystery, but recent work in several labs suggests that one culprit may be ultraviolet (UV) radiation, a worrisome finding given that people are routinely exposed to UV radiation.



ADAPTED BY C. FABER SMITH FROM JILL LASKER

A repair side effect? Chromatin unwinding during UV damage repair may allow the activation of integrated HIV genes.

While most UV exposures come from the sun's rays, millions of people are also exposed through sun lamps and tanning salons, and between 25,000 and 50,000 per year in the United States receive PUVA therapy, which is used for treating psoriasis and certain other skin diseases. And the evidence implicating UV radiation in HIV activation includes a finding by molecular virologist John Morrey of Utah State University in Logan that PUVA therapy, which combines UV with a light-sensitive drug, turns on HIV genes in an animal model, indicating that it might also activate the dormant viral "mole" in humans.

Does all this mean that HIV-infected people should avoid excessive exposures to sunlight and PUVA therapy? The jury is still out, but Janusz Beer of the Food and Drug Administration's Radiation Biology branch in Rockville, Maryland, says that researchers investigating UV's effects on HIV feel that further studies are certainly warranted. Indeed, the FDA itself is sufficiently impressed by the findings that the agency has studies under way aimed at assessing the risks of UV exposures for HIV-infected people. And should those studies show that the exposures contribute to AIDS virus activation, the current work may pay off in another way. Researchers are also beginning to uncover the molecular mechanisms by which UV light activates latent HIV, information likely to aid in the eventual design of drugs that prevent or slow the viral re-awakening.

Awareness that UV light can activate the AIDS virus dates back to work done in 1988 by molecular biologist Martin Rosenberg's group at SmithKline & French Laboratories in King of Prussia, Pennsylvania. Rosenberg and postdoc Kristoffer Valerie embarked on these experiments at a time when there was a strong focus in the AIDS research community on identifying the potential reactivating agents of latent HIV. Rosenberg's group chose to look at UV radiation, which is known to have DNA-damaging effects, since anything that could tweak the DNA might have the potential to trigger HIV activation.

First the researchers needed a good system for assaying the activity of the HIV genome. So they constructed a hybrid gene by fusing an HIV gene sequence called the "LTR" (which contains the "on/off" switch for the viral genes) to a reporter gene known as CAT (for chloramphenicol acetyltransferase) that makes a readily detectable protein. They then put the hybrid gene into human cells growing in culture and exposed them to UVC, the most energetic form of UV radiation having wavelengths ranging from 200 to 280 nanometers. The idea was that any increase in gene expression in response to the radiation would be reflected in increased CAT activity in the cells. And indeed, CAT activity went up 50- to 150-fold in the UVC-exposed cells, comparable to the levels achieved with other factors that had previously been shown to activate HIV gene expression. The Rosenberg team showed in further experiments that direct sunlight also activates HIV gene expression, although only about 12-fold.

Other groups have subsequently confirmed these findings, and Anthony Fauci's laboratory at the National Institute of Allergy and Infectious Diseases in Bethesda went a step further in 1989 by showing that UVB light

(wavelengths between 280 and 315 nanometers) activates latent HIV itself—not just an HIV LTR construct—in chronically infected cultured monocytes.

All these experiments were performed with cultured cells, but more recent work, described by Utah State's Morrey at this year's meeting of the American Society for Photobiology,* shows that UV radiation also induces HIV gene activation in a living animal—a much more clinically relevant situation. For these experiments, Morrey and his colleagues used genetically altered mice they had created by introducing into the animals a gene construct made by linking the HIV LTR to a reporter gene encoding either beta-galactosidase or firefly luciferease. Exposure of these transgenic mice, to either UVB radiation alone or to UVA light combined with a light-sensitive, DNA-binding psoralen compound—the PUVA therapy—produced a marked increase in reporter gene activity in the animals' skin cells, according to Morrey.

PUVA therapy turns on HIV genes in mice, indicating that it might activate the virus in humans.

UVA is the UV radiation with the longest wavelengths (315 to 400 nanometers) and therefore the least energy, and by itself it had no activating effect on gene expression. However, sunlight, which contains both UVA and UVB radiation, did work by itself, although it took 7 hours compared to only 2 hours when the mice had been pretreated with psoralen. Catherine Cavard and Cavard's group at the Cochin Institute in Paris and Gilbert Jay's team at the American Red Cross laboratory in Rockville have also found that UV light can activate HIV genes in transgenic mice.

Morrey cautions that while transgenic mice are convenient models for studying UV's effects on latent HIV in skin, even the mice do not completely reflect what happens in a natural HIV infection in humans. Nevertheless, he says, "of course, our results are worrisome." Morrey points out that the scientific literature contains several reports documenting the presence of HIV DNA in cells of the epidermis. Of particular concern is the isolation of HIV from Langerhans cells in the skin of HIV-infected people. Some AIDS researchers, including molecular biologist William Haseltine of Harvard University's Dana-Farber Cancer Institute and his Harvard colleague Erik Langhoff, think that Langerhans cells may even be the most significant target of HIV, partially because they can be infected more efficiently than the better known targets, the CD4 T cells and macrophages of the immune system.

*The meeting was held from 20 to 24 June on Marco Island, Florida.

Haseltine himself concedes that not everyone buys that idea. But even if he's wrong, the presence of HIV in Langerhans cells and the possibility that the virus might be activated by UV radiation are disturbing, given what's known about the function of the cells. Langerhans cells apparently detect and pick up foreign invaders or antigens in the skin. They then migrate into the circulation, where they mature into dendritic cells, which have the job of presenting the foreign antigens to the immune cells responsible for initiating a specific immune attack. These include the CD4 T cells —the very cells whose destruction results in the immune system collapse of AIDS patients. Work conducted in several laboratories in the past year, including Ralph Steinman's at Rockefeller University (*Science*, 17 July, p. 383), suggests that dendritic cells harboring HIV are capable of infecting CD4 T cells during antigen presentation, and this could contribute to the CD4 T cell decline seen in the later stages of AIDS.

Another reason for concern is that a significant proportion of HIV-infected individuals have dermatological conditions that may be candidates for PUVA therapy, which could do more harm than good if it really activates latent HIV in Langerhans cells of the skin. Indeed, in another talk at the meeting, Barbara Zmudzka of the FDA's Radiation Biology branch said that epidemiological and clinical data will have to be studied and patients carefully monitored to see if HIV-infected people should take precautions, such as protecting themselves from UV exposures.

But while those answers aren't yet in, researchers are moving ahead on another front: tackling the question of how UV radiation activates HIV gene expression in hopes of uncovering a mechanism that might allow them to prevent the effect. And their efforts appear to be yielding some answers, according to presentations at the meeting.

Although several possibilities are still under consideration, most researchers in the field see HIV activation by UV light as a side effect of the DNA damage that UV causes. The idea is that the cell, in an attempt to repair such damage, somehow turns on the viral genes integrated in the cellular DNA. Early evidence for this hypothesis came from work done in 1989 by Peter Herrlich and colleagues at the Nuclear Energy Research Center in Karlsruhe, Germany. They showed that the HIV gene expression induced by UV radiation is preceded by absorption of UV light by DNA, which is known to result in DNA damage. But the crux of the puzzle was—and still is—what happens during cell repair to turn on HIV genes.

At the photobiology meeting, Kristoffer Valerie, who's now at the Medical College of Virginia in Richmond, presented an intriguing hypothesis that may explain how the activation gets under way. In order for a cell to repair the DNA damage caused by UV, the DNA molecule has to unwind from its highly coiled state in the chromosome. This uncoiling exposes stretches of DNA and makes them accessible to the repair enzymes that correct the UV-induced lesions. What Valerie is suggesting is that the uncoiling also exposes HIV genes, thereby rendering them susceptible to transcription factors that might turn on the previously inaccessible viral genes. Evidence presented by Herrlich suggests that one of those factors might be NF-κB, a normal cellular transcription factor previously implicated in HIV gene activation by numerous research teams. He has found, for example, that UV irradiation increases NF-κB concentrations in cells carrying the HIV LTR.

Although Valerie has also found that NF-κB levels increase after UV irradiation, he says the increase was not big enough to account for the magnitude of increase in LTR activity. Valerie suggests, however, that his cell culture system more closely mimics the actual environment in human cells than Herrlich's. But Valerie adds that his findings don't mean that NF-κB isn't involved, but they do indicate that additional factors also contribute to HIV activation in response to UV irradiation.

Many more experiments need to be carried out before the question of how UV radiation trips HIV's transcriptional machinery is completely answered. But whatever the nature of the molecular mechanisms, researchers hope that laying them bare will lead to the design of agents that inhibit UV-induced activation of latent HIV. As Morrey's experiments with transgenic mice suggest, there is a certain urgency to finding the answers. Right now, the moles are winning out, and there's no George Smiley in sight.

–Brigid M. Wallace and Jill S. Lasker

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Additional Reading

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