Killer Cells, MHC: Factors in AIDS?

Squads of "killer" cells produced by the body are capable of destroying other cells infected with AIDS-causing viruses, two research groups reported this week. The findings may mean a better understanding of both AIDS vaccine development and why some infected persons develop full-blown AIDS while others do not.

However, the specialized cells may or may not be good news in terms of preventing the fatal disease. In those patients who develop AIDS, the complicated killing process — which involves genes that also govern the body's compatibility with transplanted tissues — may be a case of "too little, too late," or even of the body's own defense system doing more harm than good, suggest the scientists.

Using radioactive assays to measure the number of cells killed, scientists in France and the United States discovered that some of the blood cells called T lymphocytes turn into killers when confronted with other cells infected with the AIDS virus (HIV). The surfaces of those infected cells carry HIV material, which is recognized by the soon-to-be killer lymphocytes, whose presence had been noted in other viral diseases.

Mere one-on-one recognition, however, isn't enough for these killer cells, which require a "third party," called major histocompatibility complex (MHC), to handle the introductions. Scientists have known for several years that the target cell's surface also must hold materials coded for by a group of MHC genes. Unique to each individual, the MHC is responsible for the body's response to "foreign" tissue transplants and is related to some autoimmune diseases.

Both groups conclude in the July 23 NATURE that HIV-infected cells attract killer cells in a process controlled by an MHC component, the first time the mechanism has been described in AIDS. The French scientists did experiments more closely related to AIDS patients, while the U.S. team used a system that is part of the current push for an AIDS vaccine.

Researchers at Massachusetts General Hospital in Boston and the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Md., made target cells by collecting non-T lymphocytes from eight men who tested positive for the antibody to HIV and from five controls who tested negative. After being infected with recombinant vaccinia viruses containing different HIV genes, target cells from each donor were mixed with T cells either from that same donor (autologous) or from others (heterologous). None of the cells from negative subjects showed any killer-T activity, report the authors.

But in samples from positive individuals, there was a 2- to 14-fold increase in cell killing, with greater levels seen when the envelope-coding HIV gene was inserted into the vaccinia virus. Scientists developing AIDS vaccines are particularly interested in the HIV envelope as a noninfectious component that might induce immunity (SN: 5/9/87, p.297). The U.S. group reports that killing also was greatest when autologous killer cells were used, and responses using heterologous cells apparently occurred only when the two sets of cells shared MHC regions.

The French scientists, from the Institut Pasteur and two hospitals in Paris, took their studies a step closer to the clinic by using cells that had been washed from the lungs of positive patients with an AIDS-related respiratory disease. They found that killer T cells also interact with another white blood cell type called macrophages — which ingest HIV and, like lymphocytes, play a role in cell-mediated immunity. Although the antibody response to HIV has been fairly well described, the cellular response to the virus thus far remains largely a mystery.

Massachusetts General's Bruce D. Walker told SCIENCE NEWS that, while killer cells are important in recovery from certain viral infections such as influenza, their effect in AIDS is unclear. "We would think that their presence may be protective to some extent," he says. "But clearly [the killer response] doesn't seem sufficient [for the estimated 10 percent to over 50 percent of patients who go on to develop AIDS]."

The French scientists say that "the question remains as to the beneficial or deleterious effect of HIV-specific [killer-cell] activities in positive patients." They suggest that the interaction between the infected macrophages and the killer lymphocytes may exacerbate a patient's condition by causing inflammation that exposes the lungs, brain and other organs to further infection by bacteria or fungi associated with AIDS fatalities.

In addition, the Paris researchers say that when heterologous killing occurred, the cells from the two different AIDS patients shared specific MHC components called HLA-A2. Although a person's MHC is an inherited trait, NIAID's Thomas J. Kindt — who did not participate in the reported research — says it is far too early to say whether HLA-A2 individuals may be more susceptible to AIDS. He adds that, although there are examples of increased susceptibility to disease with certain HLA profiles, "unfortunately, there is no sweeping statement to be made about the genetic component of AIDS." — *D. D. Edwards*

Autoimmunity may cause infertility

The miracle of biological conception has long baffled geneticists, developmental biologists and just about everyone else who has taken a moment to think about it. But pity the immunologists who are stuck with the task of explaining how it is that a fertilized egg — which includes, after all, a fair share of father-furnished foreign material — manages to keep from being immunologically rejected by the mother.

That ultimate immunological question has yet to be answered (SN: 10/11/86, p.234), but scientists are making progress in understanding the many links between the fields of immunology and reproductive biology. Laboratory studies have already shown, for example, that anti-sperm antibodies in women can interfere with sperm function and fertilization — although little is known about where these antibodies come from or why some women appear to be more immunologically reactive than others.

Now researchers at Mount Sinai Medical Center in Chicago are using immunoreproductive studies to better understand the causes of infertility, and to provide clues about the body's business of self-recognition. Norbert Gleicher and his colleagues found that *in vitro*- ("test-tube-") fertilized women with abnormally high levels of autoantibodies (antibodies that erroneously attack normal tissue) got pregnant at only one-fifth the rate of women with normal autoantibody levels. Their research is to be published in the August OBSTETRICS AND GYNECOLOGY.

The study is the first to compare autoantibody levels in the blood with those in the follicular fluid — the fluid that bathes the fertilized egg near the ovaries — and hints at the possibility that the ovaries may be responsible for local production of autoantibodies.

"We found that women with abnormal autoantibodies in blood also have abnormal autoantibodies in follicular fluid," Gleicher told SCIENCE NEWS. "But what is even more important is that one group of autoantibodies, the phospholipids, appears to be concentrated in the follicular fluid in autoantibody-positive patients."

Gleicher kept track of *in vitro* fertilization successes in patients with and without these abnormal autoantibodies, and found that although the antibodies had no effect on an egg's capacity for fertilization, they *were* associated with a decreased chance of pregnancy. "The study therefore suggests that abnormal phospholipid autoantibodies may be associated with implantation failure," he says. Moreover, taking into account previous studies that have implicated the same class of antibodies with autoimmune diseases such as rheumatoid arthritis and lupus erythematosis, the new research suggests that unrecognized autoimmune diseases may be to blame for many cases of infertility.

"Infertility is a huge and ever-increasing problem," Gleicher says. "The data suggest today that approximately 15 percent of all couples in the United States who are trying to conceive do have an infertility problem." (Infertility is defined as one year of unprotected regular intercourse without conception.) "I think that autoantibodies will become a major issue in reproduction, from the earliest part of the reproductive process throughout pregnancy and up to delivery," he says, noting that certain antibodies have already been associated with fetal distress and fetal death in patients with autoimmune disease.

As for the bigger questions, such as how the body actually distinguishes between "self" and "nonself" and why certain people develop autoimmunity, Gleicher says, "If I knew that I'd win the Nobel Prize in medicine." However, he notes, autoantibody levels are normally regulated by specialized suppressor cells, and "suppressor activity in the female is set at a higher thermostat level than in the male," leaving even healthy women with relatively high levels of autoantibodies. It's possible, he speculates, that women have had to evolve a certain tolerance to high levels of autoantibodies in order to accommodate the partially foreign fetus. "Normally, of course, these levels are not a problem, but sometimes there's a glitch in the system," he says. Some cases of immune-mediated infertility or autoimmune disease "may be the price that women have to pay for being generally capable of tolerating higher autoantibody levels in pregnancy." *– R. Weiss*

The electric life of plants gives fungal spores a charge

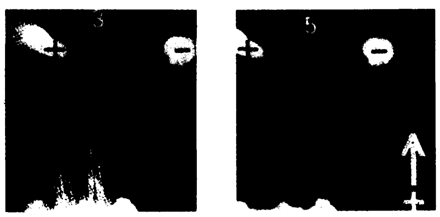
If the relative humidity in your area is falling this morning, you may find that plant-attacking fungi are energetically spewing out spores, spreading plant diseases throughout your garden. Scientists have known for some time that weather conditions can affect the release of fungal spores, but the exact mechanism for this has remained cloudy.

One theory cultivated for the last several years by Charles M. Leach, a plant pathologist at Oregon State University in Corvallis, is that plants possess electrostatic fields that can be influenced by weather changes. Spores, according to the theory, are jettisoned by an electrostatic repulsion that builds up between the similarly charged fungal spores and the underlying leaves suffering a fungal invasion. Leach is publishing his most recent evidence in support of this idea in an upcoming issue of ENVIRONMENTAL AND EXPERIMENTAL BOTANY. If his theory is correct, he says, it could suggest strategies for controlling fungal diseases that have ravaged forests of American elms, white pines and American chestnuts and have caused billions of dollars worth of damage to crops.

A traditional theory of spore release holds that fungi throw out spores when changes in humidity make the fungi twist. Leach notes, however, that if this were the case, spores would be ejected in all directions relative to the surface of the leaf being invaded by fungi. Instead, Leach has observed in laboratory experiments that ejected spores move at a right angle to the infected leaf. He also has found that the spores of some species, such as the downy mildew fungus (which causes disease in onions), are propelled in these parallel trajectories even though they are borne in grape-like clusters. The only explanation for this behavior, he says, is that the spores are moving under the influence of an electric field associated with the leaf surface.

Leach has demonstrated in laboratory studies with detached leaves that ejected spores are charged (since they are attracted to an electrode). He has also been able to stop spore release by electrically neutralizing the underlying leaf with an antistatic gun and, by changing the intensity of the leaf's electric field, he has altered the velocities of the ejected spores.

Most recently, Leach has extended his studies to whole plants in the natural environment. He discovered that there is



Leach/PHYTOPATHOLOGY

Paths of spores ejected from fungi (left) show that the spores are electrically charged, since they move toward an electrode. Spore release halts when the underlying leaf is neutralized (right).

an electrical potential of up to 120 volts between the ground and the surfaces of bean, cucumber and cherry leaves. Moreover, he found that the potential follows a diurnal cycle, peaking (usually with a positive polarity) in midafternoon and dropping to low values at night. Most notably, says Leach, this cycle is quite similar to the daily pattern of spore release.

What causes plants to become electrically charged "is the ultimate question," says Leach, "but I have not resolved it." It's possible that some process within the plant itself is responsible, he says, because the diurnal voltage changes under stable weather conditions resemble daily patterns of photosynthesis and transpiration. But it's also conceivable, he adds, that the plant is acting as an antenna and passively picking up changes in the ambient electric field.

Whatever the cause, says Leach, the finding of a diurnal voltage pattern has a number of ramifications. He suggests that farmers could more judiciously apply pesticides that have been electrically charged by noting the weather conditions, time of day and electrical polarity of the plants they are trying to protect. A better understanding of the electrostatics of plants, spores and pollen, he adds, might also provide greater insights for people trying to predict when allergy sufferers will be at their worst or what kinds of plant-damaging air pollutants might most easily settle on vegetation.

In addition to his work with plants and spores, Leach says he has measured the electrostatic fields of bees as they pass in and out of their hive. He found that bees can have fields of up to 9 kilovolts per meter, which is much higher than those found in previous studies. Depending on the weather, the bees' electric fields, much like those of plants, vary during the day, typically peaking in midafternoon. Leach's co-worker Sarah Corbet, at Cambridge University in England, has shown in the laboratory that charged pollen can jump between bees and flowers, but the researchers do not know for certain whether electrostatics is important to pollination in natural environments.

After measuring the high voltages at the surface of leaves, Leach says, he decided to look for currents in the plants. Scientists have postulated that there is some sort of electrophysiological movement of organic materials through plants, he says, but they have measured voltages within plants that have been thought to be too small to drive such currents. He now reports that "there is indeed a current in the microampere range that is consistently running through the plant day and night." To see how important this current may be to the development of plants, he is now raising a crop of sunflowers, some of which have been electrically grounded. *– S. Weisburd*