effect of orbital variations. Recently, Bernard Stauffer and his colleagues at the University of Bern reported that core samples from Greenland and Antarctica contained only 350 parts per billion of methane during the last glaciation compared to 650 parts per billion a few hundred years ago. D. Raynaud of the Laboratory of Glaciology and his colleagues have just reported a similar increase in the Vostok core at the end of the penultimate ice age. Methane too is a greenhouse gas. Raynaud estimates that methane's warming effect during interglacials was perhaps 25% that of carbon dioxide.

Another gas, dimethylsulfide (DMS), may indirectly intensify the cold of an ice age. Robert Charlson of the University of Washington and his colleagues have suggested that DMS produced by marine phytoplankton might brighten clouds, which would increase the amount of sunlight reflected back into space and thus cool the surface. Michel Legrand and Robert Delmas of the Laboratory of Glaciology have reportedly found a DMS proxy in an Antarctic ice core that indicates above-average production during the most recent ice age, which, like the decreases in methane and carbon dioxide, would tend to cool the climate (*Science*, 22 April, p. 393).

There is also increasing evidence that the atmosphere was dustier during glacial periods, especially at their maxima, than during interglacials. Legrand, Lorius, and Soviet colleagues found up to 5 times the sea-salt aerosol and up to 30 times the terrestrial aerosol during glacial maxima than during interglacials. According to some interpretations, the enhanced aerosols, like the brighter clouds, would reflect more sunlight back to space.

The number of known players is increasing, but sorting out their relative roles will take some time. First, there is the chicken-and-egg problem. For example, are changes in carbon dioxide an immediate cause of climate change or a result of climate change that simply reinforces that change? At the moment, marine sedimentary and ice core records disagree. The sequence of events in the Vostok core even seems to differ between the terminations of the last two ice ages. A first step will be resolving conflicts between the dating of marine and ice core records. ■ **RICHARD A. KERR**

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Another Glitch for AIDS Vaccines?

While some antibodies against the AIDS virus apparently block infection of blood cells, recent data suggest that others may enhance infection

WITHIN THE PAST FEW MONTHS, several groups of researchers have reported that certain antibodies against human immunodeficiency virus (HIV) may increase viral infection. Some researchers say the new data have potentially negative implications for candidate AIDS vaccines; others say the findings are too "shaky" to be a cause for concern. Regardless of its final resolution, the concern about enhanced infection is provoking widespread interest and investigation.

Researchers are probing three key issues. One is whether antibodies against HIV or other components of blood serum really do enhance infection of blood cells—monocytes and macrophages, in particular. To date, the phenomenon has only been documented in vitro and the ability to demonstrate it varies considerably from one laboratory to another. A second question concerns the mechanism of antibody-dependent enhancement of infection. Among the few laboratory groups that have shown the enhancement, researchers have differing ideas about how it occurs and what cell types it occurs in. The third issue is whether the enhancement, if it is real, is important clinically. Would it mean, for instance, that a person who develops low levels of antibodies against HIV after receiving a candidate AIDS vaccine might have an increased chance of becoming infected upon exposure to the virus? Or might it mean that an already infected person is more likely to progress to disease when certain kinds of antibodies are present or when antibody concentrations reach a threshold level?

Opinions about the danger of increased infection vary. "It's a theoretical possibility based on some interesting in vitro observations that at least must be taken into consideration in the monitoring of clinical vaccine trials," says Anthony Fauci of the National Institute of Allergy and Infectious Diseases (NIAID). "In theory it might pose a problem and could change our approach to vaccine development," says Thomas Folks, also of NIAID. "It is an important concern, but it is not something we hadn't thought of before," says Gerald Quinnan of the Food and Drug Administration. "It is an interesting area for investigation but I have seen no data so far to indicate that this is an important clinical problem," says Martin Hirsch of Massachusetts General Hospital in Boston.

A major reason for concern about the possibility of enhanced infection of monocytes and macrophages stems from growing evidence that monocytes and macrophages are infected early in the course of HIV disease and become virus-producing factories in the body. "The degree to which macrophage infection is important to the maintenance and spread of HIV infection is critical to any predictions about the importance of antibody-dependent enhancement of infection," says Scott Halstead of the Rockefeller Foundation in New York.

The debate about the significance of antibody-dependent enhancement of HIV infection in blood cells was stimulated, in part, by two observations reported by W. Edward Robinson, Jr., David Montefiori, and William Mitchell of the Vanderbilt University School of Medicine in Nashville. The first observation is that a person infected with HIV may make different categories of antibodies. One kind is referred to as "neutralizing" because it blocks replication of HIV in vitro. But another kind appears to do just the opposite; it increases the ability of HIV to infect lines of transformed lymphocytes growing in tissue culture. The researchers are not certain what kind of antibody molecule enhances infection, but according to Montefiori it may be "some portion of the gp160 envelope protein of HIV that elicits enhancing antibody." (The envelope protein, in either its gp160 or gp120 form, is the primary immunogen in at least three experimental vaccines.)

The second finding from the Vanderbilt group is that a different factor, probably the complex of blood proteins and enzymes known as complement, can block the neutralizing ability of the first category of antibodies. "Complement not only reduces neutralizing activity, but it is required for enhancing activity as well," says Robinson. "We see complement-dependent enhancement of HIV infection in at least 75% of the

sera that we test," says Montefiori. "It's not an all-or-nothing phenomenon but it's very dramatic."

Halstead, in contrast, does not think that the antibody-enhanced infection with HIV reported to date is dramatic. He cites dengue virus, an RNA virus carried by mosquitoes that causes fever and rash in most infected people, as a contrast. "With dengue, the effect of antibody is to increase infection of macrophages up to 10,000-fold," he says. "And in the dengue system the enhancement is clearly not complement-dependent."

Several other groups of researchers also report that antibodies against HIV can enhance infection of blood cells. "We first noticed the phenomenon in guinea pigs immunized with inactivated whole HIV particles," says Jacques Homsy, who collaborates with Jay Levy at the University of California in San Francisco. Levy, Homsy, and Masatoshi Tateno, also of UCSF, report that sera from chimpanzees, guinea pigs, and people infected with HIV, can enhance virus infection of blood cells in vitro. "There are three main differences between our data and Mitchell's," says Homsy. "We don't need complement to see the effect; we find it in animal sera as well as human sera; and we see the enhanced infection on freshly isolated lymphocytes and macrophages." Moreover, it occurs in immunized animals that are not infected with live virus.

The University of California researchers also find that the same human serum can have drastically different effects on viral growth in vitro. "Some human sera only neutralize the virus, others only enhance infection, and some do both," says Levy. "It depends on the viral isolate." For example, serum from a Haitian patient enhanced the ability of three different isolates of HIV to infect cells, whereas serum from an American patient neutralized two of the isolates and enhanced infection with the third.

Still other groups have tried to demonstrate the enhanced infection with human sera and not seen the effect. "We used human sera that was not heat-inactivated and saw only neutralizing activity," says Dani Bolognesi of Duke University Medical School in North Carolina. To increase the likelihood that antibody-dependent enhancement could occur, Thomas Matthews of Duke tested the sera on an isolate of HIV that preferentially infects cells of the monocyte-macrophage lineage and another isolate that infects T lymphocytes. He did not see enhancement of infection with either viral isolate.

Taken together, the in vitro results raise more questions than they answer. First, they do not identify clearly what laboratory conditions will allow researchers to observe antibody-dependent enhancement of HIV infection. Second, they do not identify a mechanism for the enhancement. Is it caused by an antibody and, if so, what type? Does it depend on the presence of the CD4 antigen, a surface protein on T4 lymphocytes and other blood cells that acts as a receptor for HIV? Alternatively, does enhanced infection occur through a pathway that involves complement and the complement receptor on macrophages? Or does it depend on the F_c receptors of macrophages that bind the tails of antibody molecules? (Some reason that antibodies against HIV may surround a virus particle and enhance its binding to macrophage F_c receptors, thus increasing the amount of virus engulfed by these cells. The phenomenon can occur with dengue virus and it is linked to more severe disease.)

The issue that is of ultimate concern, however, is not so much what happens in a tissue culture dish, but what happens in a person who has antibodies against HIV. Experiments by Ronald Derosiers of the New England Regional Primate Center in Southborough, Massachusetts, indicate that if the enhancement occurs, it does not appear to have much of an impact in vivo. In the course of his vaccine research, Derosiers injected killed whole simian immunodeficiency virus (SIV)—a virus that causes an AIDS-like disease—into rhesus monkeys. Immunization did not protect the animals from infection, but it does not appear to make them more susceptible to infection.

Another clinical issue is whether certain antibodies or low levels of antibodies, particularly those against the HIV envelope protein, can worsen disease in a person already infected with the AIDS virus.

"When I noticed that antibodies to the envelope persist throughout the life of an individual infected with HIV, I said 'maybe these antibodies are good for the virus but not for the patient,' " says Jonas Salk of the Salk Institute in La Jolla, California. No one has yet done experiments that specifically address this issue.

For Levy, the argument about the clinical relevance of antibody-dependent enhancement of HIV infection is unresolvable given current data and it misses the point. "The important issue is to look at it in clinical trials with candidate AIDS vaccines," he says.

He joins other researchers in suggesting that volunteers who are currently receiving experimental vaccines should be tested to see if their blood sera increases the rate or extent of blood cell infection in vitro. Bolognesi concurs. "We've got to nail this thing down, one way or the other," he says.

Wayne Koff of NIAID, who heads the institute's extramural AIDS vaccine evaluation effort, says that these studies are now in progress. But it is still too early to tell if any of the volunteers who are receiving a vaccine developed jointly by NIAID and MicroGeneSys in West Haven, Connecticut, show signs of antibody-dependent enhancement of HIV infection.

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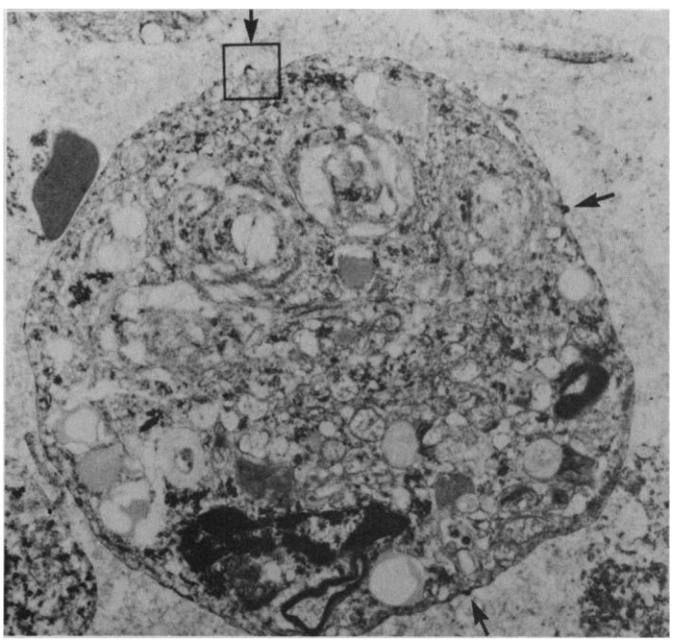

Virus-infected monocyte *from an AIDS patient. Will certain antibodies enhance infection? (Arrows show virus particles.)* [*S. Koenig* et al., Science, **233**, *1089 (1986)*].

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