The Cortisol Connection

Does a stress hormone play a role in AIDS?

By KATHLEEN FACKELMANN

Alfred T. Sapse believes that a stress hormone plays a role in the development of AIDS, cancer, multiple sclerosis, and other devastating diseases.

For years, immunologist Sapse promoted this theory on his own. Now, he's being joined by other researchers. If they're right, drugs that block the stress hormone cortisol could transform the treatment of millions of people.

In the 1970s, Sapse left his job as a researcher at the University of California, Los Angeles to work on developing such a drug. Eventually, he founded a company called Steroidogenesis Inhibitors, which is based in Las Vegas. That firm and other research groups are racing to test a variety of compounds to counter this stress hormone.

That tack has drawn fire from critics, some of whom claim there's no proof that cortisol is elevated above healthy concentrations in people infected with the AIDS virus or in people with the other diseases. Other critics say that although high concentrations of cortisol do occur in AIDS patients, they are the result—not the cause—of the disease.

Sapse contends that HIV, the AIDS virus, forces the adrenal glands to churn out lots of cortisol, which damages the immune system. "Cortisol is probably one of the most violent immunodepressants there is." Sapse detailed his theory on cortisol and disease in the September PSYCHONEUROENDOCRINOLOGY.

A second group has data that support an alternative theory of cortisol and AIDS. Its research hints that one of HIV's proteins masquerades as a glucocorticoid, the class of stress hormones that includes cortisol. That wily HIV protein then subverts the body's immune system.

Sapse and other researchers presented new findings on cortisol at the Second International Conference on Cortisol and Anti-Cortisols, held in Las Vegas this month. At that meeting, the International Association of Researchers in Cortisol and Anti-Cortisols was formally established to foster research on the hormone—a move sure to focus attention on cortisol's immunosuppressive effects.

Cortisol is part of the body's fight-or-flight response. Following a stressful event or an injury, the adrenal glands boost the production of cortisol. The hormone increases the amount of blood sugar available for fuel, temporarily slows down some essential bodily functions, and helps boost the heart rate so a person can fight off or run away from a threat.

Cortisol also assists the body in routing a viral infection or healing damaged tissue. Such reactions are usually beneficial, but when too much cortisol dampens the immune response, it shuts down the very process that fights a deadly microbe or keeps a malignant cell from exploding into an invasive tumor.

Sapse and others point to several European studies which have shown that concentrations of cortisol in the blood of AIDS patients can reach immune-punishing values. Laboratories in the United States measure cortisol in blood samples collected only in the morning and in the evening. The European studies, which rely on a different testing system, suggest that cortisol can surge at any time of the day or night. Those dangerously high amounts go undetected in the U.S. research, Sapse says.

At the international meeting, Sapse unveiled a new way of measuring cortisol, one that lets clinicians look at the hormone's values at various points throughout a 24-hour period. He predicts that the new method will reveal health-damaging amounts of cortisol in many people, not just those with AIDS.

Sapse predicts that the drug he's developed—procaine HCl, or ANTICORT—will reverse the immune decline caused by cortisol, and he is testing the drug on AIDS patients.

The evidence suggesting that procaine may benefit people with AIDS includes a pilot study presented by Sapse at the international AIDS conference held in Marrakech, Morocco, in 1993. The study showed dramatically elevated concentrations of cortisol in the blood of eight people with advanced AIDS. After treating patients with procaine for 9 months, researchers observed that one indicator of immune function had returned to normal, Sapse says. That treatment reversed the symptoms of HIV infection in all of the patients, he adds.

In another unpublished study, Sapse and his colleagues explored the drug's benefits in 20 people with either HIV infection or AIDS. After being treated with the anticortisol drug, those patients experienced an improvement in their immune function. The concentration of CD4 T lymphocytes, the infection-fighting white cells that decline dramatically during the course of AIDS, went from an initial average of 140 cells per cubic millimeter of blood on a slide to a healthier value of 360 cells per cubic millimeter. Sapse says the patients became asymptomatic after the treatment.

The team also presented evidence on procaine at the international AIDS conference held in Vancouver in 1996. That pilot study was carried out in São Paulo, Brazil, on 40 people showing symptoms of HIV infection. The researchers say that procaine again demonstrated some benefits. For example, 25 people taking only the experimental drug had an average increase of nearly 18 CD4 T lymphocytes per month. Study participants who were taking the experimental compound plus an established antiviral drug also showed a rise, although not as large, in their lymphocyte count.

Furthermore, treatment with procaine, either alone or in combination with other drugs, seemed to lower the death rate of patients in the study.

Those findings fit with Sapse's theory that although a person must be infected with HIV in order to develop AIDS, "cortisol is the killer, not HIV."

Another team has found a different line of evidence linking cortisol to AIDS.

David B. Weiner of the University of Pennsylvania Medical Center in Philadelphia and his colleagues have shown that an HIV protein mimics the actions of the glucocorticoids, including cortisol.

Weiner's team has focused on *vpr*, one of nine genes that make up HIV's genome. Until recently, *vpr* was considered an ancillary player in the saga of AIDS, says virologist Roger H. Miller of the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Md. Weiner's results suggest that *vpr* and the protein it encodes may have a pivotal role in the immune destruction that characterizes AIDS.

Researchers already had findings suggesting that HIV uses the vpr protein to pierce the membrane of macrophages, white cells that are among the first immune cells to host HIV infection. That initial breach may give HIV a foothold in the body.

Now, Weiner's group has results suggesting that this HIV protein dupes the body into suppressing its immune system.

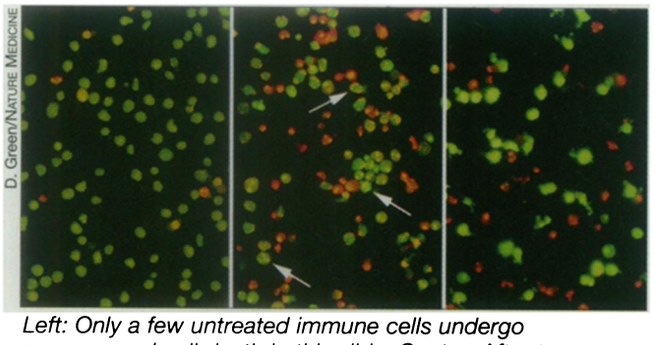
The researchers added a solution of the vpr protein to immune cells growing in

the lab. They found that the protein inhibited cell proliferation. If such an effect takes place in the body, it might block the immune system's attempt to fight an invader like HIV, notes Velpandi Ayyavoo, a researcher on Weiner's team. Ayyavoo presented the group's findings at the Las Vegas meeting and is a coauthor of a report in the October NATURE MEDICINE.

The group has also looked at immune cell production of cytokines—chemicals that call for an immune response to a virus or other microbe—and found that the vpr protein blocks the production of two types of cytokines.

In addition, the researchers discovered how HIV helps sabotage the cell's self-destruct mechanism. In test-tube experiments, they found that the vpr protein spurs healthy T lymphocytes to initiate programmed cell death. In the body of an AIDS patient, such T lymphocytes are free of HIV.

If the vpr protein causes uninfected cells to self-destruct, the immune system can't effectively attack HIV, Weiner speculates. Without a full roster of healthy T lymphocytes, the immune system will also lose the battle against microbes such as *Pneumocystis carinii*. Such organisms can cause lethal infections in people with damaged immune systems.



Left: Only a few untreated immune cells undergo programmed cell death in this slide. Center: After treatment with an HIV protein, half the cells commit suicide (arrows). Right: The drug RU-486 comes to the rescue of some immune cells treated with HIV protein.

In Weiner's research, the vpr protein protected T lymphocytes that had been designed in the laboratory to resemble HIV-infected T lymphocytes. Rather than die, such cells remained alive in culture. If the vpr protein has the same effect in the body of an AIDS patient, it might allow HIV-infected cells to escape death. Such cells could become virtual virus factories, Weiner says.

When the researchers treated lab-grown immune cells with glucocorticoids rather than the HIV protein, they got the same immune-dampening effects. This made them wonder if an antiglucocorticoid drug would block the vpr protein's actions.

They used RU-486, a drug that has already garnered quite a reputation as an abortion pill. The drug inhibits a hormone called progesterone. Weiner and other researchers know that RU-486 also counters cortisol and other glucocorticoids.

When the researchers added RU-486 to cells growing in culture, they found that it reversed the vpr protein's destructive effects on immunity. For example, T lymphocytes treated with the vpr protein and RU-486 continued to proliferate and to secrete immune-boosting cytokines. In addition, the drug prevented T cell death.

These findings fit with a growing body of research on stress, hormones, and disease.

Researchers know that people make cortisol and other hormones in times of stress. "If you're sitting there watching the stock market crash, your cortisol from the psychological stress is going to be up," says Esther Sternberg of the National Institute of Mental Health in Bethesda, Md. Then, if someone coughs in your face, "you're going to be susceptible to getting the flu," she says.

A stock market crash isn't the only stressor most people face. Aggressive rush-hour drivers, job pressures, financial problems, and other issues can add up to chronic stress. That ongoing stress increases the risk of developing a variety of diseases, from the common cold to heart disease.

For HIV, the link between stress and disease remains controversial, although it is clear that people infected with the virus face a raft of stressors. They must contend with the emotional stress of knowing they are likely to develop a lethal disease. In addition, their immune system faces the daily physical stress of fending off the virus.

There's no doubt that such stress sends a signal to the adrenal glands to pump out cortisol, says Roger M. Loria of Virginia Commonwealth University's Medical College of Virginia in Richmond. Indeed, in the right amounts this hormone will help the body fend off a viral invader like HIV. But does cortisol production become excessive, damaging the immune system of people with HIV? Sapse, Loria, and other researchers contend that it does.

Not everyone agrees. George Chrousos of the National Institute of Child Health and Human Development says people with early HIV infection may have mildly elevated cortisol concentrations. Such cortisol values are not likely to inflict a mortal wound on the immune system, he adds.

Weiner's data suggest another way that HIV may destroy the immune system. His findings indicate that the vpr protein acts as the functional equivalent of too much cortisol.

Indeed, Chrousos has independent evidence supporting that view. His team found that the vpr protein binds to the glucocorticoid receptors on cells, including immune cells. When the HIV protein docks with such a receptor, it has the same effect as an "army of cortisol," Chrousos says. The HIV protein tricks immune cells into thinking that cortisol concentrations are much higher than normal, he adds. His team presented that finding at the Endocrine Society's meeting in Minneapolis this June.

Scientists continue to seek drugs that counter cortisol and thus fight AIDS.

Loria's team is collecting evidence suggesting that a naturally produced hormone called androstenetriol reverses the immune suppression caused by cortisol. His team has yet to conduct tests of this hormone in people infected with HIV.

Meanwhile, Sapse's company has asked the Food and Drug Administration for permission to begin studying the effects of procaine on HIV-infected people who have not responded to standard antiviral therapy. If FDA agrees, that extensive study will start early next year, Sapse says.

The abortion pill RU-486 may itself prove a promising treatment for AIDS, Weiner adds. So far, no group has stepped forward to test this drug on AIDS patients, he says.

Sapse predicts that such drugs will provide an immune boost to people infected with HIV.

Harnessing the cortisol system may prove no easy task, however. Chrousos points out that glucocorticoid receptors are found on cells throughout the body, including heart cells. Some anticortisol drugs injected into the bloodstream would affect the heart as well as the immune system. "You may save patients from immune dysfunction and kill them with heart failure," he says.

The small band of cortisol researchers must also contend with scientists who remain deeply skeptical of the link between cortisol and AIDS. Carl Dieffenbach of NIAID points out that there's not much data on Sapse's drug and that Weiner's findings remain unconfirmed.

Sternberg, on the other hand, says that Weiner's findings are "spectacular." Moreover, she adds, Sapse's studies have a sound theoretical underpinning.

The wager on anticortisol drugs may pay off, Dieffenbach says, but he would place his bet on a more traditional approach to AIDS treatment. "My training teaches me that what matters is killing the virus."

Cortisol researchers counter that not everyone with AIDS, cancer, and multiple sclerosis benefits from standard therapies. For such people, anticortisol drugs may be worth a gamble.