been considered a trigger of a T_H1-type response. Some researchers believe that viruses are not the immediate trigger, but contribute to asthma susceptibility by attacking the lining of the lungs, leaving the inner layers more exposed to environmental allergens or other traditional asthma triggers—which would then activate T_H2 cells and the other responses they orchestrate. Others believe the viruses may have an inside role, activating certain genes in the nucleus that exacerbate or trigger the inflammatory cascade.

Those unanswered questions might explain why new treatments such as the leukotriene inhibitors will not work for everyone. But the fact that the drugs don't help some patients may be as important as the help they do give some people: "That is where it gets really interesting," Drazen says. "Up until now, we have graded asthma as mild, moderate or severe," which is only of limited help to physicians trying to determine the best course of treatment.

Patients' different responses to the various drugs may help doctors sort out what many suspect is the case: Asthma is not a single disease. Like pneumonia or anemia, Brigham and Women's Drazen says, asthma is a set of symptoms that has varied causes. The new treatments, by getting closer to those causes, may help doctors divide patients into subgroups based on how they respond to treatments, he adds. That, in turn, will help researchers determine how to treat each patient most effectively—a development, certainly, that will help millions breathe easier.

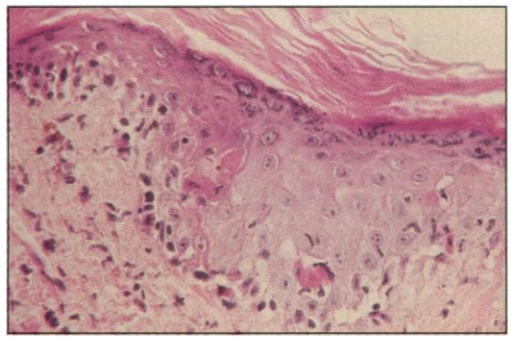
–Gretchen Vogel

IMMUNOLOGY

New Lead to Safer Marrow Transplants

Bone-marrow transplants have become a mainstay of medicine's battle against blood-cell cancers, such as leukemias and lymphomas, as well as against certain noncancerous blood diseases. But in at least half of all patients, the donor immune cells turn against the recipient's own tissues, triggering a deadly ailment called graft-versus-host disease (GVHD). Now a team of doctors led by hematologist Claudio Bordignon at the San Raffaele Scientific Institute in Milan, Italy, may have found a solution to this problem.

On page 1719, the group reports the first successful human test of a gene therapy designed to halt the attack of the donated cells on the recipient's tissues. The researchers genetically engineered the transplanted cells with a self-destruct button that enables doctors to kill them selectively with a drug if they turn mutinous. This allowed the team to wipe out GVHD in two of the three patients who developed it, and partially eliminate it in the third—without using immunosuppressive drugs.



Under attack. Multiple lymphocytes are invading the epidermis of human skin with graft-versus-host disease.

GEORGE SALE/FRED HUTCHINSON CANCER RESEARCH CENTER

That success is a boost for the struggling field of genetic therapy, says immunologist Drew Pardoll of the Johns Hopkins University School of Medicine in Baltimore, who calls the work "one of a very small cohort of examples in which gene therapy has been shown to have clinical utility." Indeed, if further studies bear out the early promise of the technique, it could make bone-marrow transplants much safer and more effective. Doctors might even start using such transplants more broadly, in patients with less advanced disease. The technique is "very exciting," says immunologist Philip Greenberg of the Fred Hutchinson Cancer Research Center in Seattle. "It has the potential to improve substantially the outcome of [bone-marrow] transplantation."

The strategy's seeds were planted in 1990, when Bordignon first heard about the problems with GVHD that were cropping up in the top bone-marrow transplant centers, particularly in patients who relapsed and required infusions of donor lymphocytes. Marrow transplants are needed because the high doses of chemotherapeutic drugs and radiation given to leukemia and lymphoma patients in an effort to rid them of all cancer cells also destroy the patients' bone marrow, the vital source of both the red cells and the infection-fighting white cells of the blood.

But unless the donor is an identical twin, the transplant may turn on a patient, causing GVHD, as the foreign white blood cells attack essential organs such as the liver, gut, and skin. Clinicians have sought to avoid this attack by sifting out all of the mature T lymphocytes from the foreign marrow before infusing it. Those are the cells that trigger GVHD, but their removal leaves the patient more vulnerable to infections or cancer relapse. If infection or cancer does develop, the patient can be infused with the donor T cells—again running the risk of GVHD.

Bordignon, a doctor trained in gene therapy, recalls that he asked himself, "How might one take advantage of gene-transfer technology to control this problem?" He set out in early 1992 to test whether he could introduce a "suicide gene" into these cells, then use the gene to kill the cells if they triggered GVHD. Results with cultured cells looked promising: Lymphocytes engineered with the gene for the enzyme thymidine kinase died when he doused them with the antiviral drug ganciclovir, which the enzyme converts to a deadly poison.

After showing that ganciclovir also kills the suicide gene–bearing lymphocytes in mice, Bordignon and colleagues began their pilot study in humans. In 1993, they infused donor lymphocytes bearing the thymidine kinase or suicide gene into 12 patients who, after receiving bone-marrow transplants, had suffered complications such as cancer relapse or virus-induced lymphomas. The lymphocytes survived in the patients for up to a year, battling the tumors to achieve complete or partial remissions in five of the eight patients for whom results are available.

Of the three patients who developed GVHD, ganciclovir totally shut down the immune attack in two; in the third, the disease was attenuated. The success may have been limited in the third patient, Greenberg speculates, because some of the infused lymphocytes may not have borne the suicide gene.

Still, if the new gene-therapy procedure helps two out of every three patients, it will be an improvement. Researchers caution, however, that tests in many more patients will be needed to determine just how effective the therapy is. Toward this end, Bordignon is organizing a multicenter European trial that he hopes will start by the end of 1997. But even that may not settle the question, says Pardoll, because transporting the Italian group's technique to other centers may be difficult: "I can count on one hand, with a couple of fingers missing, the number of groups that could do this [gene-transfer procedure] with high efficiency." He adds, however, that developing simple, reproducible protocols for the procedure could boost that number.

One thing is certain. The therapy has already shown sufficient promise, says Richard O'Reilly, a marrow-transplant pioneer at New York City's Memorial Sloan-Kettering Cancer Center, to ensure that it "will be looked at by many people."

–Ingrid Wickelgren