New transplant findings fit like a glove

This year, more than 10,000 kidney transplants will be performed in the United States, according to the National Kidney Foundation. But despite recent advances in immunosuppressive therapy (SN: 6/28/86, p.407), approximately 20 percent of these transplants will result in rejection – most of them in patients who at some time in their past have tested positive for human lymphocytic, or HLA, antibodies.

Physicians have known for years that a patient with HLA antibodies specific to a donor's HLA antigens is much more likely to reject that donor's transplanted organ. Indeed, with donated kidneys in short supply, anyone who has *ever* tested positive for these antibodies is considered a poor candidate for the lifesaving surgery – even if, as often happens, their antibodies inexplicably disappear at some point. Surgeons willing to perform transplants on such "historically positive" but currently HLA-negative patients have been frustrated by their inability to understand why some of these grafts are in fact very successful, while others are almost immediately rejected.

Recently, however, researchers have found evidence of a multi-tiered anti-antibody system that not only explains why HLA antibodies sometimes disappear, but also identifies HLA-converted patients for whom transplants will probably succeed. Like a series of bigger and bigger gloves fitting over an original hand, the anti-antibodies and anti-anti-antibodies – both known as anti-idiotypic antibodies – apparently will either block or potentiate a patient's original HLA antibodies. Their discovery, reported in the June 4 NEW ENGLAND JOURNAL OF MEDICINE, may lead to changes in the way patients are tested for organ compatibility and could lessen the uncertainty inherent in the transplant business, scientists say.

The research team, led by Elaine Reed at Columbia University's College of Physicians and Surgeons in New York City, performed retroactive blood tests on 20 kidney recipients with histories of antibody sensitization to their donor's HLA antigens. Half the patients rejected their transplants within 30 days, but the remaining 10 patients' grafts survived at least one year, despite no apparent significant differences between the two groups' immunological compatibility. With further testing, however, the researchers found that nine of 10 patients whose grafts were successful showed evidence of anti-antibodies capable of blocking their original HLA antibodies. Moreover, nine out of 10 of the patients who rejected their grafts showed evidence of anti-anti-antibodies, which seem to overwhelm the anti-antibodies, thereby reinstituting the original immune reaction.

"This is the most important finding I can think of to explain the loss of antibody in some sensitized [kidney transplant] patients, and to explain why some patients do well and others do not," Reed says. The test will be of particular benefit, she suggests, to the approximately 30 percent of would-be transplant recipients with a history of being highly sensitized to HLA antigens. Anti-idiotypic antibody testing, she says, will show that many of these patients who have until now been considered poor transplant candidates may in fact be ideal recipients. Similarly, would-be recipients who at first appear to be donor-compatible but who harbor undetected anti-anti-antibodies can be identified and spared the medical and economic expense of a transplant that is almost certainly doomed.

Thomas Fuller, a blood transfer specialist who is doing related research at Massachusetts General Hospital in Boston, says Reed's findings are significant not only because they open the door to better compatibility testing, but also because they may lead to sophisticated ways to induce antibody-specific immunosuppression in transplant recipients. "We all hope that someday we'll know enough about the immune system apparatus to allow us to manipulate it," he says. "If we could design or stimulate production of anti-idiotypic antibodies, it would probably allow transplants for many of the patients who have antibodies that now preclude them from getting organs." Such capabilities, he says, are still years away.

Meanwhile, Reed says of the two-hour test, "to have a tool that tests for an antibody associated with rejection is very important. Our goal is to implement these tests as routine clinical procedures on all our kidney transplants." – *R. Weiss*

Does fetal zinc affect later immunity?

Even a mild zinc deficiency in a fetus might lead to lasting, adverse effects on the immune system, according to new animal research. The study could have implications for humans, especially pregnant young teenagers who are socially disadvantaged and malnourished, says Pamela Fraker, who directed the study at Michigan State University in East Lansing. She worries that the demand for zinc by a pregnant 13- to 15-year-old's still-growing body could limit how much zinc the developing fetus gets.

Zinc is an essential trace metal. Because it is not stored in the body, it must be obtained daily from dietary sources – such as meat, seafood and vegetables. In Fraker's study, pregnant mice were fed a diet that was nutritionally balanced except for its zinc. Mice on the diet developed blood-zinc levels that were about 30 percent below normal. Fraker says this "marginal deficiency" produced no immediately observable symptoms other than a 10 to 15 percent smaller weight gain than in mice fed a fully balanced diet. At first glance, even litters of the marginally deficient animals appeared normal.

However, the Michigan State researchers found, these mice produced pups whose blood-zinc levels at birth were only 60 percent of that in pups whose mothers had eaten a zinc-sufficient diet. And immune function in these "deficient" pups – as measured by the numbers of antibody-producing cells – "starts out at about 50 to 60 percent of normal and remains that way through puberty," even when the pups are raised on a fully zinc-sufficient diet, Fraker says.

This finding contrasts with what happens in mice that become zinc deficient only after birth, in which case compromised immunity returns to normal as soon as the source of zinc deficiency is corrected. There are other signs, too, that *in utero* zinc deficiency may initiate unique immune-system changes. For example, Fraker notes, normally a zinc-deficient animal makes fewer lymphocytes and macrophages – cells important to immune function. However, her studies show, in animals deprived of zinc *in utero*, the normal numbers of lymphocytes and macrophages are present. "They just don't perform as well," she says.

These data linking zinc and immune function are consistent with other studies of zinc deficiencies in animals, according to James C. Smith, chief of the Vitamin and Mineral Nutrition Laboratory at the Agriculture Department's Beltsville (Md.) Human Nutrition Research Center. However, Smith adds, to date there has been little research investigating whether a similar link exists in humans. "There are little tidbits" of data suggesting such a link, he told SCIENCE NEWS, "but nothing conclusive."

Complicating the study of this link is the fact that "we don't know how to measure zinc nutrition in humans," explains William Beisel of the Johns Hopkins School of Public Health in Baltimore. Blood-zinc levels not only fluctuate rapidly, giving no measure of long-term zinc status, he says, but "even the slightest infection pulls zinc from the blood and dumps it in the liver." In such cases, zinc is not lost to the body, just largely unavailable for measurement. – *J. Raloff*