

Corneal Meltdown

A natural protein triggers an immune assault on the eye

By KATHLEEN FACKELMANN

Six-year-old Megan was blind in one eye. Then something went wrong with the cornea of her other eye. Without medical intervention, Megan (not her real name) would go completely blind. Ophthalmologist John D. Gottsch was determined to prevent that from happening, so he and his colleagues scheduled an operation to replace the girl's diseased cornea, the eye's transparent front section, which is critical to vision.

The corneal transplant was a success.

Within a year, however, Gottsch realized that Megan's new cornea had started to "literally melt away."

"Because she was young and had only one eye, it became a very desperate situation," recalls Gottsch, an eye researcher at the Johns Hopkins Medical Institutions in Baltimore.

So Gottsch scheduled another transplant operation. The same thing happened: The operation was a success, but the healthy cornea started to liquefy.

The Hopkins team did six corneal transplants in all. "Every month we had to take this little girl to the operating room and put her to sleep," says Gottsch. Finally, "I said, we can't keep doing this."

Gottsch suspected that his small patient had Mooren's ulcer. Described over a century ago, this condition is an extraordinarily painful ulceration of the dime-sized cornea. While ophthalmologists knew that in many instances the rare disease followed eye surgery or trauma, they didn't understand its cause.

Previous research had suggested that Mooren's ulcer was generated by an autoimmune response, in which immune cells attack the body's own tissue—in this case, the cornea. The disease may be similar to rheumatoid arthritis, in which the immune system attacks the body's joint tissue. In both cases, patients face excruciating pain.

Against that backdrop, Gottsch and his colleague Sammy H. Liu, an immunologist at Hopkins, decided to look for the underlying basis of

Mooren's ulcer. First, they took a blood sample from their patient. Then they ground up bits of cornea taken from cows. They used bovine corneas because human corneas are generally reserved for transplantation.

In Megan's blood they found antibodies, which normally fight off microbial invaders, directed specifically against something in her corneal tissue. Moreover, when added to the pulverized bovine cornea, those antibodies reacted hotly to one group of corneal components. The researchers focused their attention on that fraction and identified the bovine version of the protein responsible for revving up the antibodies in Megan's blood. They refer to both human and bovine versions as cornea-associated antigen, or CO-Ag.

Would other people suffering from Mooren's ulcer demonstrate an immune reaction to this protein? Gottsch, Liu, and their colleagues took blood samples from 15 people with Mooren's ulcer. They found that, compared to 14 people who did not have Mooren's ulcer, the blood from all 15 showed a heightened antibody response to bovine CO-Ag.

The researchers described their results in the July 1995 *INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE*. Those findings add to the evidence that Mooren's ulcer is an autoimmune disease, they say.

To find out more about the basis of Mooren's ulcer, the researchers set out to determine the exact sequence of amino acids—the building blocks of proteins—in CO-Ag. They found that the bovine version of the protein comprises 70 amino acids in a single chain. Moreover, CO-Ag is found only in the cornea. Gottsch and Liu report their findings in the April *INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE*. The team now wants to purify and analyze the human version of the protein.

Why does the body launch a frenzied attack on CO-Ag, which, after all, is a naturally produced substance? Gottsch

believes the answer may be a similarity between it and a true invader. When the researchers compared the amino acid sequence of CO-Ag to other known protein sequences, they found that a part of this corneal protein resembles a portion of a protein made by hepatitis C, a virus that can cause severe liver disease.

Even if the white blood cells can mistake CO-Ag for a threatening foreigner, they normally have no contact with it. A native, healthy cornea is not connected to the bloodstream. After eye surgery or trauma, however, blood vessels can invade the new cornea, Gottsch explains. Those vessels give immune cells a road into the cornea, where they encounter CO-Ag for the first time. The immune cells view CO-Ag as a foreign protein, and they attack the cornea.

While that sequence of events may underlie Mooren's ulcer in patients who have had eye surgery, other cases of the disorder also seem to have a link to hepatitis C.

Steven E. Wilson, a researcher now at the Cleveland Clinic Foundation, was the first to identify a clinical link between Mooren's ulcer and hepatitis C. In 1994, while at the University of Texas Southwestern Medical Center at Dallas, he and his colleagues described two Mooren's ulcer patients who were infected with hepatitis C.

In their report in the April 1994 *OPHTHALMOLOGY*, the researchers speculated that hepatitis C somehow initiates an autoimmune attack on the cornea. This idea foreshadowed the molecular data of Gottsch and Liu.

Wilson's team went on to study 15 more people with Mooren's ulcer. Half of the group had hepatitis C infection, he notes.

In people with hepatitis C infection, the immune system is already revved up to fight the virus in the liver. But how do immune cells, which normally do not enter the cornea, happen to encounter CO-Ag? There's no reason to think that hepatitis C patients have blood vessels

growing into their corneas. Instead, Gottsch speculates, juiced-up immune cells passing the surface of the cornea may somehow react to CO-Ag as they would the villainous hepatitis C.

That case of mistaken identity may explain the immune system's attempt to liquefy the cornea.

Wilson suspects that many people with Mooren's ulcer who test negative for hepatitis C have some other viral connection to the corneal disease. He points out that the newly discovered hepatitis G viruses closely resemble hepatitis C (SN: 4/13/96, p. 238). The G viruses commonly afflict people in West Africa, and so does Mooren's ulcer. He speculates that infection with one of the G viruses may lead to an immune attack on the cornea.

Wilson has sent blood samples from African Mooren's ulcer patients to the Chicago team that characterized the G viruses. If those samples test positive for a hepatitis G virus, researchers will have a whole new set of experiments ahead of them.

To preserve the sight of people afflicted with Mooren's ulcer, researchers are focusing on CO-Ag. Gottsch and Liu have data showing

that CO-Ag is a member of the calcium-binding family of proteins. Such molecules are involved in cell-to-cell communication, Liu says. The researchers speculate that CO-Ag is embedded in the outer membrane of corneal cells.

CO-Ag may play a role in keeping the cornea crystal clear, a prerequisite for good vision, Gottsch adds.

The Hopkins researchers are searching the 46 human chromosomes for the gene that codes for CO-Ag. Once they isolate it, they'll be able to study this elusive protein more effectively in an animal model of Mooren's ulcer, Gottsch adds.

For now, ophthalmologists give Mooren's ulcer patients immunosuppressive drugs to keep the immune system at bay, but those drugs often have serious side effects, such as liver damage. This is especially worrisome because patients with hepatitis C infection already have a damaged liver, Wilson points out.

His own research suggests that treatment with interferon alpha, a naturally produced antiviral substance, is a better bet for people with both disorders. He finds that this drug reduces the amount of virus in the bloodstream while quieting the immune blitz against the cornea.

Wilson suggests a round of interferon

treatment even for Mooren's ulcer patients who do not test positive for hepatitis C. His theory is that at least some of those patients are infected with hepatitis G—or another poorly understood virus—and may therefore benefit from the antiviral therapy.

Research has already paid off for a few people afflicted with Mooren's ulcer. The first patient Wilson treated with interferon alpha suffered a relapse a year later and was given the antiviral drug again. That was 5 years ago. Her hepatitis C infection remains quiescent, and her eyesight remains clear, Wilson notes.

For Megan, the end of the story has yet to play out. Her parents ruled out immunosuppressive drug therapy as being too harsh. Gottsch has responded by fashioning a cornea replacement from tissue in the girl's leg. Although not as transparent as corneal tissue, it gives Megan limited vision.

Gottsch hopes that the ongoing research will reveal a way to block the immune attack on the corneal protein without harmful side effects. If it does, Megan will have a shot at a new cornea and full-fledged sight, he says. □

Letters continued from p. 115

from wood pulp) may require more or less water, depending on the source of the wood pulp (whether discarded by-product or plantation-grown pulp). Thus, a "natural" fiber may demand more or less irrigation water, and impose greater or smaller economic and environmental costs, than a synthetic fiber.

This change of interpretation shows the dangers of cryptic compression and suggests that there are at least two sides to the choice of fibers, as there are to most choices.

Joel E. Cohen
New York, N.Y.

Good-enough examples of rationality

Gigerenzer's "fast and frugal" natural mental routines to extract decisions from incomplete data by choosing the first good-enough alternative ("Rational Mind Designs," SN: 7/13/96, p. 24) are strongly suggested in two ancient human narrative forms: rhetoric and jokes.

Key rhetorical methods are to mention the items that you want to influence people first, so they will sink in thoroughly, or last, so they will be the most recently encountered data, and to limit the total amount of information imparted at one time. This has become a fine political art. For example, those who read that children of divorce are "more than twice as likely" to suffer faulty social development as children from intact marriages seldom grasp the fact that over 75 percent of both classes of kids turn out OK.

Much humor arises from abrupt divergences from expectations. "A passenger fell from an airplane. Fortunately, with a parachute. Unfortunately, it didn't open. Fortunately, there was a haystack below. Unfortunately, it contained a pitchfork. Fortunately, the passenger missed the pitchfork. Unfortu-

nately, missing the haystack." The humor of this grim recitation arises from the repeated dashing of conclusions developed on the basis of each ensemble of facts that was good enough at any given moment.

David R. Burwasser
Oberlin, Ohio

Aren't democratic elections examples of the large-scale take the best approach?

The news media and special interest groups, acting "for the people," try to uncover as much information as they can about the candidates and their positions on issues. People "take the best" based on the information they have.

No one I know actually sits down and calculates the various characteristics and policy positions of each candidate, weights those positions according to some personal priority list, and then determines an ideal against which to compare each policy. It's too much effort. We all just "take the best." Are we all irrational?

Michael J. O'Donnell
McLean, Va.

If "take the best" applies to democratic elections, it may guide voters' choices first on the basis of recognizing one candidate more easily than his or her opponents. In that case, it would be rational, though cynical, for candidates to boost the familiarity of their names with voters, through ads and carefully managed media exposure, rather than dwelling on matters of substance.

—B. Bower

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Using state capitals may not be a valid recognition factor, particularly relating to size. There are frequently larger cities in the same states that are more recognizable. I seem to recall tests where high school graduates couldn't name the capitals of most states. Maybe the recognition factor hinged on something else for U.S. cities and that skewed the result.

James F. Longley
Bolingbrook, Ill.

If recognition of state capitals were near zero, students would have answered correctly at chance levels. However, they performed considerably better than that, indicating that recognition aided their decisions. —B. Bower

Frequency and percentage are the same thing. The difference is, it takes a mathematician and a complete set of data to use Bayes' theorem, whereas a "satisficing" algorithm would give as good or better results for the purpose of guessing which of the two events in ordinary experience is more likely.

Bayes' theorem tells you exactly how likely some event is. This is useful in its own right, since actual likelihood is often counterintuitive. A "take the best" algorithm could never tell you, for example, that Earth moves around the sun.

Kyle McDaniel Jr.
Knoxville, Tenn.

Frequency and percentage format the same information in different ways. Gigerenzer argues that humans have evolved to favor the frequency format. "Take the best" ranks types of information in a way that enables people to make decisions relevant to human experience, so it's not surprising that it doesn't apply to the physical movement of Earth in space.

—B. Bower