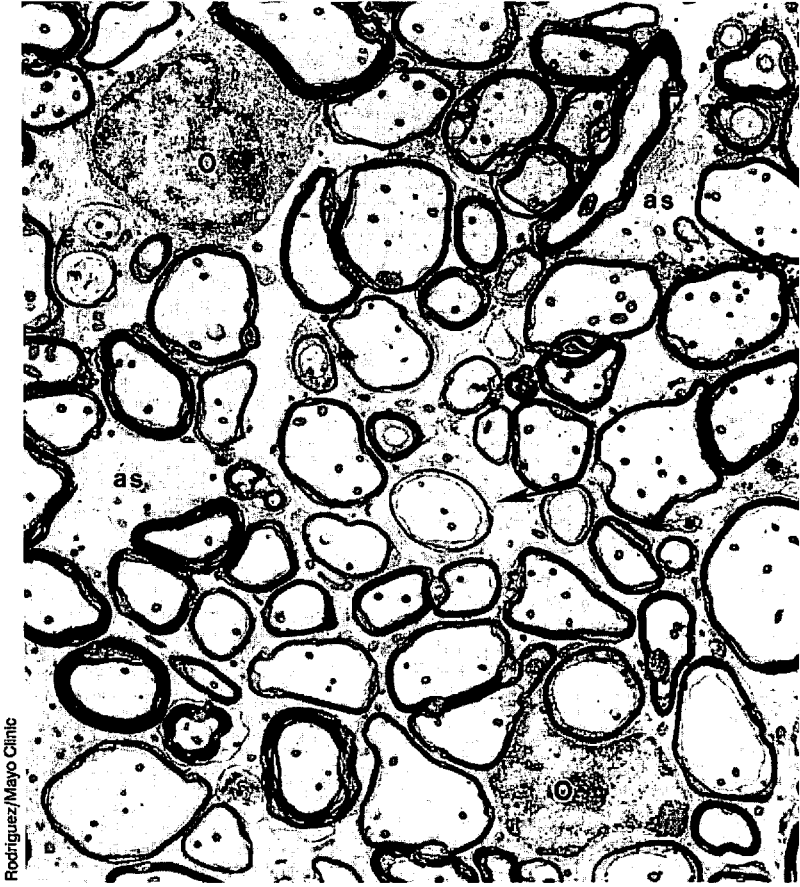
Myelin on the Mend

Can antibodies reverse the ravages of multiple sclerosis?



Rodriguez/Mayo Clinic

Mouse with a chronic, MS-like disease shows thinly myelinated nerve fibers (arrow) after treatment with a type of IgG. Myelin-producing oligodendrocytes (O) and cells called astrocytes (AS) are near areas of myelin repair in this electron micrograph.

By KATHY A. FACKELMANN

The immune system may play both villainous and heroic roles in the molecular drama of multiple sclerosis (MS).

MS researchers have long worked from a partial script of the disease, in which the patient's white blood cells turn traitor, marshaling an attack on the myelin sheaths that cover nerve fibers in the brain and spinal cord. The destruction of these protective fatty sheaths short-circuits electrical impulses traveling along the nerve fibers, resulting in the weakness, numbness, tingling, vision disturbances and loss of muscle control that are the hallmarks of MS. Scientists have assumed the myelin damage was irreversible, but their script left a puzzling observation unresolved: In many MS patients, the disease takes an up-and-down course, with long periods of remission following acute attacks.

These remissions have led some investigators to suspect that the body was spurring repair of damaged myelin. Their expanded script now suggests that certain antibodies make valiant attempts to rebuild lost myelin but can't keep up with the ongoing ruin wrought by the white cells. In essence, they propose, one component of the immune system struggles to right the wrongs of another.

That scenario springs from a mouse study conducted at the Mayo Clinic in Rochester, Minn., prompted by earlier experiments with guinea pigs at Albert Einstein College of Medicine in New York City. In the January ANNALS OF NEUROLOGY, the Mayo team reports "unprecedented" experiments in which they gave specific antibodies to mice afflicted with a progressive, MS-like disease, prodding them to rebuild lost myelin. Although the rebuilt myelin appears thinner than the sheaths normally wrapping nerve fibers, it does seem to improve the transmission of neural impulses in the diseased animals, the researchers say.

These and other investigators caution that the new findings apply only to the animals tested, but the rodent results do hold out hope that researchers may someday develop similar treatments for human MS, which currently affects 500,000 people in the United States.

"It's not a cure," stresses Patricia A. O'Looney of the National Multiple Sclerosis Society in New York City. "But it is a promising first step."

Scientists have yet to unravel the underlying cause of MS. The leading theory depicts the disease as an autoimmune disorder in which T-lymphocytes and macrophages, important white-cell components of the immune system, mistakenly "chew up" the body's own tissue, in this case myelin. Some researchers believe exposure to a virus triggers the out-of-kilter immune response in people genetically predisposed to MS.

Whatever the cause, scientists do know that lost myelin gets replaced by scar-like ("sclerotic") tissue, which disrupts messages sent from the central nervous system to the rest of the body. The new studies demonstrate, however, that the myelin damage can be reversed in rodents. Some animals on the experimental treatments regained at least partial ability to walk, the researchers report.

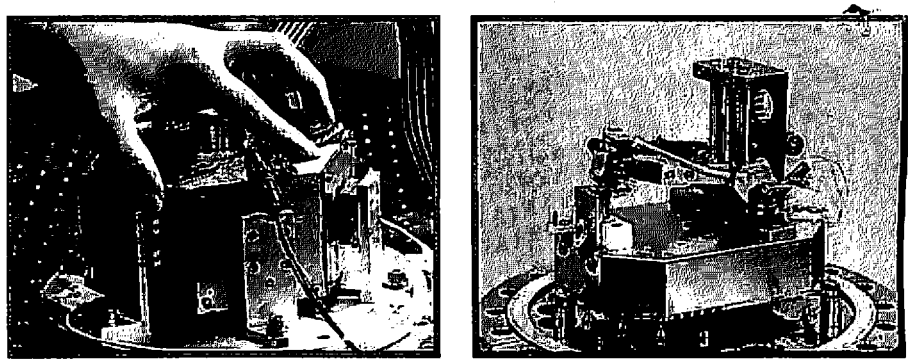
"It would be asking for a miracle for all the mice to be up and running," says immunologist Vanda A. Lennon, a co-author of the Mayo study. While no one is claiming miracles, Lennon and neurologist Moses Rodriguez say some severely crippled mice improved "dramatically" after treatment with antibodies belonging to a class called immunoglobulin G (IgG), produced by white blood cells called B-lymphocytes.

In their experiments, Rodriguez and Lennon used mice infected with a microorganism called Theiler's murine encephalomyelitis virus, which induced progressive myelin destruction and MS-like symptoms.

The team randomly assigned severely diseased mice to treatment or control

"corralled" molecules by encircling them with a computer-controlled STM tip. Such manipulations could become even more precise with the help of a magic wrist, Hollis says.

And the possibilities aren't limited to steering STMs. Hollis notes, for instance, that an eye surgeon in Memphis, Tenn., is considering using a magic wrist to manipulate minuscule scissors for delicately removing retinal scar tissue from diabetic patients and vision-obscuring tissue from the eyes of some infants.



Hollis et al.

By carefully moving the hexagonal magic wrist (left) within its frictionless magnetic cushion, a researcher can precisely steer the STM tip over a sample's surface (right). A computer immediately translates the tip's subtle vertical movements into humanly perceptible vertical movements of the magic wrist.

The magic wrist started out as an experiment in robotics. From the beginning, the IBM researchers saw their device as a way to refine a process called teleoperation, or the ability to control specific actions from a distance—the same principle underlying the use of tongs to retrieve an ear of corn from boiling water. To accomplish tasks in the inhospitable conditions of radioactive environments, the deep sea and outer space, human workers often must remain far away, relying on robots to do the manual labor through teleoperation.

But tasks that are simple for human hands can be daunting for a robot. When a person grabs an egg from a carton, for instance, tactile information from the hands feeds back to motor-control centers in the brain, which orchestrate the finger muscles to hold the egg without breaking it. Most industrial robots lack such precise feedback and control.

"The motivation of our work was to provide robots with a soft touch," says Hollis.

The magic wrist consists of a hexagonal box called a flotor, which hovers within a stationary frame (the stator) on a magnetic "cushion" formed between the stator's six permanent magnets and the flotor's electromagnetic coils. A set of light-emitting diodes and light sensors keeps track of the flotor's position and feeds this information to a powerful computer designed specifically for the magic wrist.

In robots, the stator attaches to an arm and the magnetically imprisoned flotor carries a gripper or some other tool. Lacking a direct mechanical connection to the arm, the flotor endows the robotic assembly with a delicate, cushiony touch, Hollis explains. A robotic arm positions the tool-equipped wrist near an object to be worked. Then the computer-guided magic wrist fine-tunes the placement and moves the tool. By distributing the magnetic forces according to mathematical algorithms formulated for different tasks, Hollis says he can control the wrist's position the way a pilot controls an airplane, specifying the roll, pitch, yaw and spatial location with a precision of one-millionth of a meter along any line and one-thousandth of a degree in rotation.

The researchers expect the wrist to expand the versatility of many standard industrial robots. "We have, in a sense, a universal mechanism," Hollis says. "We can change the mechanical properties [of the magic wrist] at will." To transform the wrist action from gripping to plunging, for instance, an operator would simply press a key on the computer keyboard.

By connecting the magic wrist to an STM, Hollis and his co-workers have converted their device into what they call a "tele-nanorobotic manipulation system." Using an algorithm that transforms human-controlled horizontal motions of the magic wrist into the horizontal positions of the STM's platinum tip, millimeter movements of the magic wrist downscale into nanometer-scale movements of the tip over an atomic landscape. A nanometer is one-billionth of a meter, and a typical atom spans several tenths of a nanometer.

But without some immediate feedback from the physical features of the landscape, a scientist operating the magic wrist would have a hard time guiding the STM tip to specific locations on a sample. To remedy this, the researchers formulated another algorithm, which magnifies the tiny vertical motions of the STM tip as it scans over the sample surface into a humanly perceivable vertical motion of the magic wrist.

"With this system, it is possible to manually probe surfaces at atomic scale, while feeling the atomic-scale topography back in the operator's hand," the researchers write in their proceedings paper. "It [the magic wrist] feels like it's floating on a very slippery block of ice," Hollis told SCIENCE NEWS.

To help scientists correlate the feel of atomic landscapes with the visual appearance of STM images, the IBM team plans to program an auxiliary computer to display images of sample surfaces that also show the path of the tip as it was steered by the teleoperator. Other possible extensions of the system include controlling the tip's vertical position by moving the wrist vertically, and using an atomic force microscope (an STM cousin) to "feel" atomic forces such as van der Waals forces. And by making the system responsive to sideways (as opposed to vertical) forces on the tip, researchers might get a feel for the tip as it automatically "slides off" a hillside, Hollis suggests. This feature could give an operator the sensation of gravity within the atomscape. In the present system, wrist operators feel no resistance or falling sensation as the STM tip ascends and descends over sample surfaces.

The IBM researchers are not alone in their pursuit to "manhandle" minute objects formerly off-limits

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Visualizing atomic terrain

When an STM performs its usual image-producing role, its tip sweeps back and forth over the atomic-scale hills and valleys of a sample's surface. A computer monitors the so-called tunneling current—a tiny flow of electrons that jumps the minuscule gap between the tip and the sample according to quantum mechanical rules. The tunneling current changes in proportion to the gap distance. As the tip scans, a computer controls micropositioners that slightly raise or lower the tip over the sample to maintain a constant level of tunneling current. A computer plots the tip's varying vertical positions, yielding a three-dimensional image of the surface. *—I. Amato*

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even to remote-controlled probing. Ian W. Hunter of McGill University in Montreal, working with colleagues from MIT and the University of Aukland in New Zealand, reports using a tele-microrobot system to grip and manipulate individual muscle cells while viewing the microscopic operation with a three-dimensional vision system. As with Hollis' system, an operator may literally get the feel of an object, Hunter and his collaborators suggested at last year's Institute of Electrical and Electronics Engineers conference on robotics and automation, held in Scottsdale, Ariz.

And at the February meeting in Napa, mechanical engineers Yotaro Hatamura and Hiroshi Morishita of the University of Tokyo described a prototype "nanomanipulator" for ultraprecise manufacturing tasks of the future. Although they say the ideal nanomanufacturing environment would enable a human teleoperator to experience even the sounds and smells of the ultra-Lilliputian operations, the Japanese researchers have set their sights for now on a "nanorobot system," which would enable workers to see and feel what the nanorobot is doing on submicron scales.

So far they have built and used a prototype robot to make millionth-of-a-meter scratches in aluminum with a fine tungsten needle. A stereoscopic scanning electron microscope helps the operator watch the actual process. A strain sensor monitors the tiny forces between the aluminum and the needle and provides feedback so the operator can better control the depth of the scratch. Hatamura and Morishita envision using improved versions of the technology for such applications as microsurgery, storing data as etched surface features, and modifying and testing tiny regions of microelectronic circuits, thin films and other materials.

Though nanomanipulation promises a wealth of practical uses, touch has its limits as a purely exploratory sense — as anyone who has groped and stumbled through a dark, unfamiliar room will agree. Hollis and his co-workers concede that the more conventional way of surveying microscopic terrains — converting them into a visual display — may be more reliable and revealing than tactile sensing alone. Nevertheless, they conclude in their proceedings paper, "we may learn something by trying to 'connect our own neurons' with atomic-scale phenomena using real-time teleoperation."

The direct experience of touch, Hollis adds, could give scientists a kinesthetic sense of atomic surfaces — and an exhilarating new realm of control — the way children get a whole-body feel for riding a bike. □

groups. One treatment group of nine mice got twice-weekly shots of blood serum for four weeks. The scientists had obtained the serum by injecting healthy mice with normal spinal-cord tissue and then collecting blood from these mice, isolating the clear, cell-free fluid portion.

Rodriguez and Lennon knew from their previous work that injections of this "crude serum" prompt myelin repair in mice crippled by the MS-like disease. They also knew that antibodies can sometimes stimulate various cell types to produce certain substances. So they looked for an antibody manufactured by healthy mice in response to spinal-tissue injections, and found a special type of IgG. They then gave a second treatment group of 10 diseased mice twice-weekly shots of the IgG antibody for four weeks.

In the sixth week, the team killed the mice and sectioned spinal-cord tissue for analysis. They discovered that the mice treated with either crude serum or purified IgG showed six times more new myelin than did diseased control mice receiving placebo shots. In addition, the total area of remyelination was greater in the treated mice. On average, 22 percent of the myelin-stripped areas in the central nervous system showed new myelin among IgG-treated mice, compared with about 4.2 percent in control mice.

Rodriguez used an electron microscope to study nerve fibers taken from the treated mice, finding that nearly all of the large-diameter fibers showed new myelin formation. Although the rebuilt sheaths were spare compared with the thick myelin sheaths of healthy mice, he says computer simulations by other research teams suggest that even thinly myelinated nerve fibers can conduct electrical impulses almost normally.

It's difficult to gauge improvement in animals that can't describe their symptoms. The researchers did observe, however, that most treated mice improved their ability to walk, Rodriguez told SCIENCE NEWS. The control mice remained severely disabled, he says, with tremors and muscle weakness making walking difficult and in some cases impossible.

The finding that IgG promotes myelin regrowth will infuse "new thinking into the MS story," Lennon predicts. Researchers already knew that spinal-cord fluid removed from human MS patients contains high levels of IgG, but they believed IgG antibodies took part in the attack on myelin rather than its repair, Rodriguez adds. That assumption stemmed from knowledge about other autoimmune disorders such as myasthenia gravis, in which antibodies help destroy specific receptors on nerve and muscle cells, leading to extreme muscle weakness.

Lennon and Rodriguez admit they are far from unlocking the mechanism of IgG's myelin-restoring effect, but they speculate that the antibody they isolated may directly or indirectly stimulate cells called oligodendrocytes, which manufacture myelin. Another type of IgG, found in the bloodstream of people with Graves' disease, prods thyroid cells to continuously churn out excessive amounts of a hormone called thyroxine, which controls the rate at which chemical reactions occur in the body.

Alternatively, Rodriguez says the IgG identified in the Mayo study may work by blocking T-lymphocytes — the white cells suspected of orchestrating the battle against myelin. In that scenario, IgG's blocking ability could allow oligodendrocytes to catch up with the steady fraying of myelin, ultimately outpacing the disease process.

The Mayo work builds on guinea pig studies reported in the October 1988 LABORATORY INVESTIGATION by Cedric S. Raine and his colleagues at the Albert Einstein College of Medicine. Whereas the Mayo team used a viral infection to mimic MS, Raine's team induced an autoimmune neurological disease by injecting animals with spinal-cord tissue containing myelin. Scientists say the differences in these two animal models of MS mirror the current uncertainty about what causes the disease in humans.

Raine and his co-workers knew that healthy guinea pigs injected with spinal-cord tissue develop a progressive, myelin-demolishing central nervous system disorder called experimental autoimmune encephalomyelitis. Apparently the animals' white blood cells go after the injected myelin, but the cells also begin to view the body's own myelin as foreign tissue — a process that seems to approximate the course of human MS.

The Einstein group theorized that injecting a preparation containing two components of myelin — myelin basic protein and galactocerebroside — might elicit a myelin-restoring immune response in guinea pigs with already established disease. To test that hypothesis, they gave 44 guinea pigs with the chronic, MS-like disease 10 injections of myelin basic protein and galactocerebroside during a 30-day period. They observed the animals for about 18 months, then obtained spinal-cord tissue from selected individuals.

Tissue from treated guinea pigs showed "widespread proliferation" of oligodendrocytes and "extensive" new myelin on nerve fibers previously stripped of their protective sheaths, the researchers report. After 15 months under observation, a control group of 18 untreated animals still had many stripped nerve fibers, showing scant evidence of remyelination.

Prior to treatment, the diseased guinea pigs appeared floppy, spastic and incontinent. In most cases, muscle control improved greatly after treatment, Raine reports. For example, one guinea pig with spastic hind legs regained most of its muscle control and walked normally after treatment, he says.

"The fact of the matter is we can reverse this disease [in animals]," Raine told SCIENCE NEWS.

Raine says he can't explain the recovery mechanism, but he speculates that injections of these two myelin components may trigger the production of a specific kind of antibody, perhaps the IgG identified by the Mayo researchers. He and his co-workers are now developing a serum similar to that used in the guinea pig experiments, which they hope to use in safety trials with six human MS patients. Raine says he can't speculate on when the human trials might begin.

The Mayo researchers are also seeking treatments to spur myelin repair in humans, in this case by trying to mass produce the special IgG antibodies that helped the crippled mice. Rodriquez cautions that no one can say yet whether antibodies from mice would work against human MS. And, like Raine, he has no idea when human trials of such a treatment might begin.

"Obviously, patients would like to have some answer to hang their hopes on," says Byron Waksman, former vice president for research and medical programs at the National Multiple Sclerosis Society in New York City. Nonetheless, he says, "for a scientist to commit to an actual number [of years] is both rash and meaningless." While basic animal studies can look promising for MS, they often fail the crucial test of clinical trials, he notes.

The rodent research does seem to suggest a partial explanation for the spontaneous, if temporary, improvement seen in some MS patients. "Some people do remit and stay healthy for 10, 20, 30 years, and you can speculate that it is due to remyelination," Raine says. Adds Rodriguez: "We see [a few] patients improve dramatically."

Indeed, a number of scientists have reported finding "shadow plaques," or thinly remyelinated nerve fibers, in spinal-cord tissue removed from MS patients during autopsy studies. Those shadow plaques suggest MS "is not a totally irreversible problem," says Dale E. McFarlin of the National Institute of Neurological Disorders and Stroke in Bethesda, Md.

Scientists need to figure out why the ongoing myelin breakdown eventually outpaces the human body's repair process, Rodriguez says. Whether they can give the repair process the winning edge by injecting patients with antibodies remains an open question — but one that hints at the possibility of a less frustrating future for people with MS. □