ceptor has deprived the animals of their normal defense against some as-yet-unidentified endogenous toxin. The lymphocyte problems are more difficult to explain, considering that the mouse thymus, where the cells begin to develop, appears to be healthy and to be producing adequate numbers of lymphocyte stem cells. "We don't know why the peripheral immune system is so depressed," says Fernandez-Salguero.

Still, says molecular biologist Chris Bradfield, who cloned the Ah receptor gene in 1992, the knockout mice appear "to favor a physiological role" for the Ah receptor in addition to its function in detoxification. Recent speculation along these lines has rested on circumstantial evidence. Researchers have found, for example, that the receptor is present in high levels in the fetal neural tube, which gives rise to the central nervous system, but is found in these tissues at much lower levels after birth. This suggests that it is needed for brain development, a hypothesis that may now be tested more directly in the knockouts.

But even though the Ah receptor may have several benefits, many researchers also think that the harmful effects of dioxin are triggered by its binding to the Ah receptor. Indeed, estimates of dioxin's health risk to humans are based on that assumption.

But just how risky dioxin is—and how it exerts its effects—is a matter of considerable debate. Not all researchers accept the current view that all of dioxin's harmful effects depend on it binding to the Ah receptor. The knockouts will enable researchers to determine whether some of dioxin's effects do in fact occur independently of the receptor. That information, in turn, might help pin down dioxin's risk to humans.

Much of the current concern about dioxin is based on developmental and reproductive effects seen in rodents. Extrapolating those results to humans would be reasonable if all the effects depend on the pollutant's binding to the Ah receptor, because the receptor is very similar in both humans and rodents. But if some of the effects in rodents occur independently of the receptor, then toxicologists would want to see if those alternate damage pathways are also present in humans. If they are absent, then it might be possible to downgrade dioxin's human risks.

Despite the potential of the knockout mice for such studies, Gonzalez cautions that experiments on the animals might be "very difficult" because of their sickly nature. But he is optimistic that this problem can be solved, perhaps by giving the animals an Ah gene attached to regulatory sequences that turn it on only in the liver. "If we can restore liver function," Gonzalez says, "we should be able to do long-term toxicity and carcinogenicity studies on these mice."

–Richard Stone

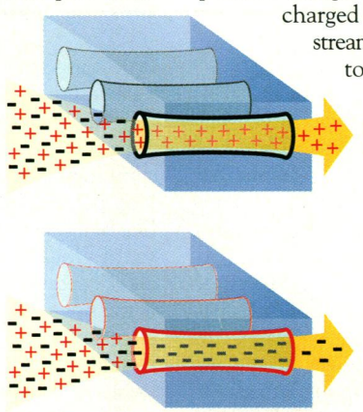
ILLUSTRATION: K. SUTLIFF

ELECTROCHEMISTRY

Throwing a Switch on a Nanoscale Sieve

Making things small is a big deal today. Scientists have built motors and gears no wider than a human hair, formed wires only a few atoms across, and carried out chemical reactions one molecule at a time. Now researchers at Colorado State University have created molecular sieves with pores as small as 1.6 nanometers (billionths of a meter) across that will let positive ions pass while blocking negative ions. Or vice versa. For, as electrochemist Charles Martin and his colleagues report on page 700, they've made the first artificial membrane whose selectivity can be changed as easily as flicking a switch.

The membrane can be adjusted to pass ions of either charge simply by changing its electric potential; the pore size can be modified as well. And these two attributes have other researchers eager to put the device to work. "It's a wonderful model for how ion-selective membranes work," says Henry White, a University of Utah electrochemist who studies ion transport through skin. Many biological membranes filter ions according to their electric charge, White notes, and "people want to know how ion transport is affected by the size and charge [of the pores in the membranes]." With the new membrane, they have the basis for an experimental model. And with further refinement, Martin suggests, the membrane could have industrial applications, separating molecules by size and charge.



Filter flip. With a negative electric potential *(shown as black)*, a gold-plated membrane lets through only positive ions. With a positive potential *(red)*, the situation is reversed.

Martin did not set out to invent a molecular sieve. His original plan, in 1990, was to make an array of nanoscopic electrodes that could, for example, detect trace levels of chemicals in solution. Martin and graduate student Vinod Menon began the construction project with commercially available filtration membranes: thin pieces of plastic riddled with tiny pores. By plating gold over the entire membrane, covering the two sides, and filling the pores, Menon created a structure of two gold layers connected by millions of tiny gold strands embedded in the membrane. Stripping off one of the gold layers left millions of gold disks scattered across the face of the membrane, each disk a viable nanoelectrode.

While building these nanoelectrodes, however, Martin realized that the same process might be used to produce a much more interesting device. By leaving both layers on and laying down less gold, he thought, it should be possible to create gold tubes through the pores instead of wires. The tubes maintained the membrane function, but the gold plating meant it would be possible to put an electrical charge on the tubes and control the types of ions they would let through. A positive charge would repel any positively charged ions but would allow a stream of negatively charged ions to pass through. A negative charge would reverse the effect and allow only positive ions to cross. The result: a switchable ion sieve.

There were membranes on the market that would pass either positive or negative ions, but none that could be switched back and forth without a complicated procedure to modify their chemical structure. Unfortunately, Martin recalls, "I didn't have enough person-power in the laboratory to start another new project, so I put it on the back burner."

The project moved to the front burner in 1994 when Matsuhiko Nishizawa, a postdoc from Japan, arrived in Martin's lab. It took Nishizawa a year of experimenting with temperature, pH, and other conditions of the gold-plating process, but when he was finished, he could not only create gold membranes but also control the tube width, ranging from an inner diameter of about 20 nanometers down to 1.6 nanometers.

The ability to switch ion selectivity is nice, Martin says, but the ability to make minuscule pores may prove more important. "These tubes have diameters approaching the size of molecules," he notes, "so maybe we can start thinking about filtering molecules on the basis of size." An industrial chemical process might, for example, require isolating a small, positively charged molecule from a solution containing both larger molecules and molecules with negative charges. A membrane with the correct pore size and charge would be able to physically filter larger molecules, and the membrane's charge would block those with negative charges. This could give the chemical industry a cheaper, one-step alternative to some of its multistep separation techniques. Martin says he has already started an experiment to test the nanoscheme. If it works, it would be no small achievement.

–Robert Pool