Somatogen, Inc. in Boulder, Colorado, reported that they had made normal human hemoglobin as well as a mutant with reduced oxygen-binding ability in yeast. In addition, says Stetler, who is vice president for research and development at Somatogen, the company has more recently made a double mutant that not only has the reduced oxygen affinity but is also stabilized to prevent the four chains of the molecule from coming apart. They've produced this mutant hemoglobin in both yeast and in the bacterium *Escherichia coli*.

The Somatogen groups prefers producing the customized hemoglobins in yeast or bacteria, Stetler explains, because the proteins are easier to purify. They don't have to be separated from pig hemoglobin. And besides that, there is little hazard of microbially produced hemoglobins carrying potentially dangerous animal pathogens, whereas hemoglobins produced in pigs might.

DNX's Logan counters that his company has devised an efficient method of separating human and porcine hemoglobins. He also notes that while both red blood cells and microorganisms contain endotoxins that can cause fever and other side effects in humans, it should be more economical to remove any contaminating red blood cell endotoxins. Lastly, pigs should make admirable production factories for proteins such as hemoglobin. They breed fast, have big litters, and produce large volumes of blood that can be removed without causing ill effects.

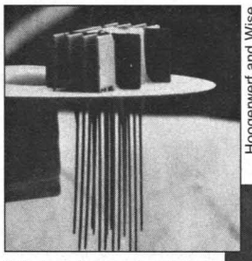
But even if genetically engineered hemoglobins can be made that are sufficiently stable and capable of releasing oxygen to be used as blood substitutes, a troubling question remains about the toxicity that has cropped up in the human studies of the chemically modified hemoglobins. "The central issue is whether the toxicity is caused by hemoglobin itself or a contaminant," says Robert Winslow, a pioneer of blood substitute research, who is currently moving his laboratory from the U.S. Army's Letterman Institute of Research in San Francisco to the University of California, San Diego.

Winslow and most other blood substitute researchers think that the toxicity has been caused by contaminants. "Red blood cells have all sorts of things that must be gotten rid of," says hemoglobin expert Sam Charache of Johns Hopkins University School of Medicine. "It is a tough problem." Tough, but Winslow suggests, ultimately solvable. Still, the difficult history of artificial blood research suggests that the solution may not come readily—or soon. ■ ANNE SIMON MOFFAT

Engineers Open a Dialogue With Neurons

"WE WANT A DEVICE WE CAN USE TO TALK TO nerves," says Gregory T. A. Kovacs, an electrical engineer in the Center for Integrated Systems at Stanford University. He was describing his own work on a tiny, perforated electrode meant to be implanted in regenerating nerves. But he might just as well have been speaking for a wider group of engineers who are looking for a way to put silicon microengineering in touch with nerves and muscles.

Kovacs and other engineers who spoke in San Francisco last week at Transducers '91, the Sixth International Conference on Solid-state Sensors and Actuators, are sculpting minute electrodes that can eavesdrop on the electronic chatter of small clusters of nerve cells or even join in the conversation. The work will equip neuroscientists with new research tools; eventually, it may open the way to a technological endrun around paralysis.



Hoogerwerf and Wise

Listening device. *Arno Hoogerwerf's 16-probe neural-recording array shown from the side and from above.*

Microelectrodes that can record or stimulate single neurons are nothing new, but the deft workmanship of these micromachinists is yielding sensors in entirely new forms. For example, University of Michigan graduate student Arno C. Hoogerwerf, who works with microengineering specialist Kensall D. Wise, described how he microfabricated a cage-like, 16-probe neural recording array. Hoogerwerf hopes the half-millimeter-wide array will be able to listen in on the activity of ensembles of tens or hundreds of neurons. Such ensembles are neglected by existing microelectrodes, which monitor several cells at most, and by global brain monitors such as positron emission tomography, which monitor millions or billions of cells.

Tayfun Akin of the University of Michigan's Center for Integrated Sensors and Circuits described another kind of silicon probe—one meant to have more intimate interactions with its target cells. Akin, Khalil Najafi, and workers in the University of Michigan's dental school have built electrodes shaped like tiny, flat sieves. When such an electrode is slipped between the severed ends of a peripheral nerve, regenerating axons find their way through the holes in the sieve, making it possible to monitor the electrical activity of several axons at once. Such a tool could prove useful for neuroscientists trying to understand how the nervous system transduces environmental stimuli into neural signals.

In a first test of the sieves, Akin says, the cut ends of taste fibers in rats' glossopharyngeal nerve successfully regenerated through the holes. Future studies will include recording from such regrown axons and stimulating the axons electrically—a step toward micromachined devices that might someday restore movement to paralyzed limbs. Kovacs has designed a similar perforated electrode, with which he has recorded and stimulated axons in a leg nerve of a rat.

Still other devices described at the meeting would take the place of nerves altogether. University of Michigan engineer Babak Ziaie envisions remotely controlled silicon prostheses that would stimulate paralyzed muscles directly. Ziaie, working with Yogesh Gianchandani and Najafi, is trying to build silicon strips small enough to slide through a hypodermic needle into strategic sites in the muscle. Each strip would host microelectrode arrays for jolting muscle cells into action, electronic circuitry for controlling the electrodes, and a tiny coil for receiving power and instructions from the outside world.

Ziaie and his colleagues are well on their way to completing several elements of their "implantable microstimulator." One is an array of electrodes, 450 strong, crowded together in a strip measuring 1.2 mm by .3 mm at one end of a thin silicon slab. The workers have tested the remote-control concept as well: Last year, Ziaie and Najafi, working with Akin, sent power and data to a different device using radio-frequency telemetry. Even so, Najafi thinks a full-fledged, implantable microstimulator will take a few more years of work. ■ IVAN AMATO