ARE YOU READY FOR A NEW SENSATION?

As biology meets engineering, scientists are designing the sensory experiences of a new tomorrow. **By Kathryn S. Brown**

THE FLIMSY STRIP of golden film lying on John Wyatt's desk looks more like a candy wrapper than something you'd willingly put in your eye. Blow on it, and the 10-centimeter foil curls like cellophane. Rub it, and the shiny film squeaks faintly between your fingers. In fact, you have to peer rather closely to spot an unusual patchwork of squiggles: 100 electrodes, carefully arranged to jump-start cells in a damaged retina and, Wyatt hopes, allow the blind to see.

The film is part of a prototype retinal implant. For the past decade, Wyatt—an engineer at the Massachusetts Institute of Technology—and his colleagues have devoted a fifth-floor laboratory and countless hours to this tiny device. At first, even Wyatt doubted the project could succeed. The retina, he says, is more fragile than a wet Kleenex: it's a quarter of a millimeter thin and prone to tearing. In about 10 million Americans—those with disorders called retinitis pigmentosa and macular degeneration—the delicate rod and cone cells lining the retina's farthest edges die, although ganglion cells closer to the lens in the center survive. In 1988 Harvard Medical School neuro-ophthalmologist Joseph Rizzo asked Wyatt two key questions: Could scientists use electricity to jolt these leftover ganglion cells and force them to perceive images? Could they, in effect, engineer an electronic retina?

Try as he might, Wyatt couldn't think of a reason why the approach wouldn't work. Today Wyatt and Rizzo have tested their retinal implant on three patients. The most recent, a woman who participated in studies this spring, reported seeing a four-dot design that perfectly matched the electrode stimulation to her retina. "Those were our best results yet," Wyatt remarks.

Despite these early returns, however, a practical working implant is still years away. Wyatt likes to call the project a "classic case of science: 10 seconds of brilliance followed by 10 years of dogged work."

When it comes to improving our senses, researchers have some truly brilliant ideas. In the coming years, if lab bench dreams become reality, we will see even when our eyes are damaged, hear even when our ears grow old, smell a whole new repertoire of scents and taste a much sweeter world. True, the goals are high and the technical hurdles steep. But the basic science is coming together today, as the worlds of engineering and biology blend. "Really, we are limited [only] by our imagination," claims Richard J. H. Smith, a molecular geneticist at the University of Iowa.

Smith's imagination travels to the recesses of the inner ear and the pea-size cochlea that holds some 16,000 noise-detecting cells, each of which is equipped with several hairlike projections that have earned them the name "hair cells." This precious stock of cells is a gift at birth: they never multiply, but they do die. Loud noise, disease and just plain aging damage hair cells, muffling one's ability to hear sounds that once seemed crystal clear.

SENSING THE FUTURE

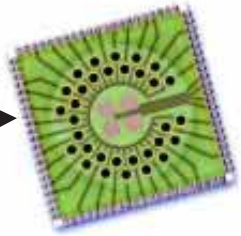
Today people with poor hearing have two choices: a cochlear implant or an old-fashioned hearing aid. A cochlear implant is a surgically implanted set of electrodes that stimulates inner-ear cells, whereas a hearing aid is essentially a removable microphone and receiver. But researchers say these technologies—which basically turn up life's volume—are like using a sledgehammer to set a watch. In the future, scientists hope to coax the inner ear gently into repairing itself—or, better yet, to protect hair cells from damage in the first place.

Regenerating damaged or destroyed hair cells has gone from a science-fiction dream to a realistic hope. "Fifteen years ago if I'd applied for a grant to study hair cell regeneration, I'd have been laughed out of town," says Edwin W Rubel of the University of Washington. "Now there are labs all over the world working on it."

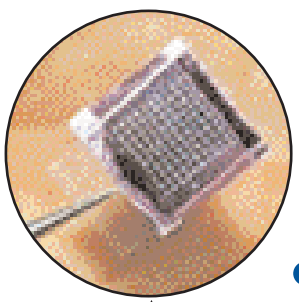
One of the most promising approaches is to find genes that make hair cells grow and then pump them, via gene therapy, into a patient's ear. This may not be as hard as it sounds. Smith and other investigators have already discovered more than 25 specific gene sequences that are involved in hearing loss or deafness, and the search has just begun. By starting with easy-to-spot genetic mutations that cause extreme, inherited troubles, such as the pro-

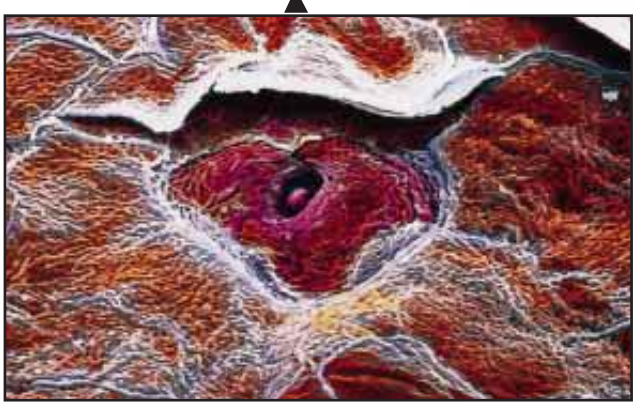
NICOLE ROSENTHAL

The buzz of a bee, the stripes of a butterfly, the perfume of a rose, the taste of a berry. It's all in the senses, and scientists are now on to how they work.



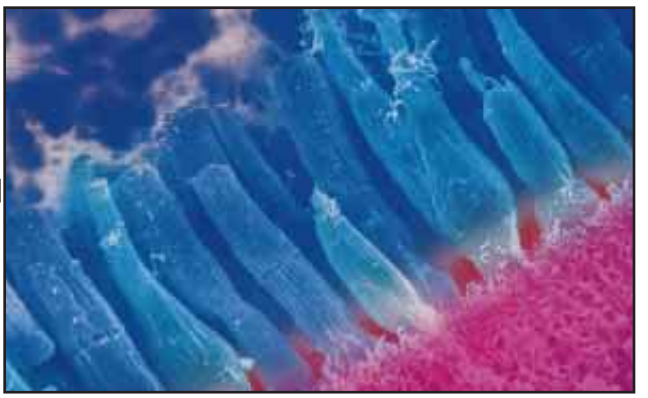
If someone tells you to wake up and smell the coffee, he or she might want you to use one of these. This orange blob is one of the thousands of olfactory receptors that make up the olfactory epithelium, a patch of mucous membrane way up in the nose that helps you sniff whether your milk has turned (among other things). Although the human nose isn't the best in the animal kingdom, researchers have mimicked it with a "nose on a chip" (*right*) that can be used by companies to monitor food quality. One day researchers might adapt the technology to develop an implant for people who have lost their sense of smell.





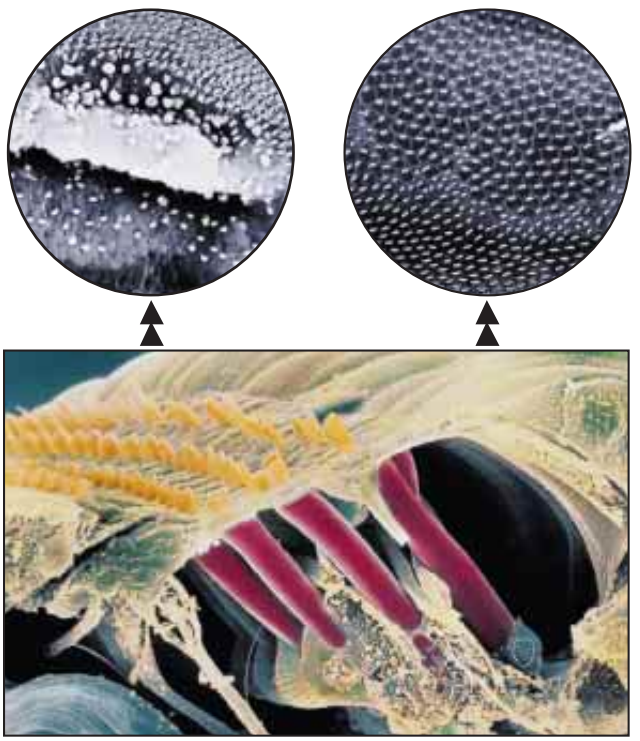
No, this isn't a close-up of one of those nubbly things on the surface of your tongue. Those are papillae; this is the opening of a taste bud. Hundreds of these barrel-shaped structures (*seen here from above*) are embedded in some types of papillae. When flavors enter the tiny pore in the center, they bind to and react with molecules called receptors on the surface of each of the taste cells, which make up the staves of the barrel. Scientists aren't producing an implantable artificial tongue just yet, but they have designed an electronic tongue, or e-tongue (*top*), that could be used to "taste" the quality of wine or the purity of water.

P. MOTTA *SPL/Photo Researchers, Inc.* (*top and bottom micrographs*); COURTESY OF CYRANO SCIENCES (*e-nose chip*); JOHN T. McDEVITT *University of Texas at Austin* (*e-tongue chip*)



ZACH GOLD (*woman*); PHOTO RESEARCHERS, INC. (*top micrograph*); BETH PHILLIPS (*retinal implant*); SPL/PHOTO RESEARCHERS, INC. (*bottom micrograph*); JEFFREY T. CORWIN AND DOUGLAS A. COTANCHE *University of Virginia (hair cell micrographs)*

The rods and cones that make up the retina—the inside lining of the back of the eye—got their names for a reason that's obvious from this photograph. The rods are most important for black-and-white vision in dim light; the cones provide color vision and high visual acuity in bright light. But in people with diseases such as retinitis pigmentosa and macular degeneration, these sight cells start to die off, robbing the individuals of their vision. Bioengineers have now designed a retinal implant (*above left*) that could restore vision by allowing so-called ganglion cells, which are usually left intact in such diseases, to send electrical signals to the brain to register visual stimuli. The device is now being tested in people.



This detail from the cochlea, a tiny snail-shaped structure in the inner ear, reveals rows of sensory cells called hair cells. Each cell's minuscule projections register sounds and pass the information on to nerves that notify the brain. Exposure to loud noises and some drugs can destroy hair cells, causing hearing loss. Biologists are now trying to get damaged hair cells to regenerate. They've had some success with chicks: the electron micrographs above show hair cells disrupted by loud sounds (*left*) that have grown back 10 days later (*right*).

We will **see** when our eyes are damaged, **hear** when our ears grow old, **taste** a much **sweeter world**.

gressive hearing loss that sometimes strikes college-age adults, researchers hope to find genes that might also cause more widespread, age-related hearing loss.

Other scientists are hunting for genes that are basic to hair cell development. In June geneticists at the Howard Hughes Medical Institute at Baylor College of Medicine, led by Huda Zoghbi, reported identifying a gene, named *Math1,* that is considered critical for the growth of hair cells in the inner ear. (*Math1* stands for m*ouse* at*onal* h*omolog-1*.) In their experiments, embryonic mice lacking *Math1* failed to develop hair cells at all. Adding extra copies of the human equivalent of *Math1* might trigger human hair cells to start growing again.

Once scientists know the correct genes to add, therapy becomes a matter of technique. Fortunately, Smith points out, the inner ear has two openings—the so-called round and oval windows—that doctors can use to shuttle genes into cells there. As with all gene therapy, scientists would have to find the right vectors—usually viruses engineered to carry an extra genetic payload—to get genes into specific cells. In some cases, physicians might bypass the faulty gene and instead simply repair the damage by, say, altering the chemical makeup of the fluid in the inner ear. "Depending on what we learn about hearing and genetics, we can come up with all kinds of creative ways to limit hearing loss or prevent it altogether," Smith predicts.

Some solutions might come from other animals. In 1974, during his first year of graduate school, Jeffrey T. Corwin, now a neuroscientist at the University of Virginia, discovered that sharks produce hundreds of thousands of hair cells throughout their lives. Corwin asked how—and whether human ears could be stimulated to do it, too. These questions still drive his research today.

Scientists now know that animals as diverse as zebrafish and chickens experience hair cell regeneration when their ears are damaged. By studying this faculty, investigators plan to pinpoint the key molecules involved, such as growth factors, and then design drugs based on the compounds. Even the runaway cell growth of cancer offers lessons in launching cell proliferation. If scientists learn how cancer nudges resting cells to suddenly start growing, they might also learn how to prompt hair cells to divide.

One day researchers could prevent hair cells from dying at all. With the right drug, predicts University of Virginia biomedical engineer Jonathan H. Spindel, it could be as simple as putting a few drops into someone's ear. Some studies suggest that nerve cells in the cochlea will grow toward certain growth factors. If that is true, a modified cochlear implant might slowly release growth factors into the ear, luring nerve cells to multiply toward stimulating electrodes that would keep them growing and healthy.

Peering into the future, in fact, investigators toy with the idea of dispensing with hair cells altogether and instead implanting an array of electrodes directly into the brain's crevices or onto its surface, where the electrodes would spark the perception of hearing. This approach, Corwin notes, is rife with questions—among them, exactly where to put the electrodes and how to avoid damaging the brain. But biocompatible materials and compact computers keep improving. At this rate, he forecasts, "areas of opportunity that once were the exclusive domain of science-fiction authors may come into areas of medical practice."

NICOLE ROSENTHAL

AN ARTIFICIAL NOSE?

For scientists who study smell, the world of nonfiction still holds many questions. Why can the scent of the family attic—or a stranger's perfume—prompt intense memories? How does your brain recognize a scent even before you can name it? And here's one that John S. Kauer really wants to answer: Why can't his wife smell the scent of the freesia flower?

Kauer, a neuroscientist at Tufts University, has been studying the olfactory system for 20 years, and he's still intrigued by anosmia, an absent or impaired sense of smell. Some people, like Kauer's wife, can't detect particular scents; others can barely smell anything at all. In fact, Kauer suggests, all human snouts could be missing out. "There is a world of [scent] molecules out there," he observes. "Just as there are animals that can see into the ultraviolet light or the infrared spectrum, there's likely a lot of odors we cannot smell."

Over the past few years Kauer and other scientists have been building "electronic noses": devices designed to sniff things we can't or might not want to, like land mines or spoiled food. Hewlett-Packard and Cyrano Sciences, a company based in Pasadena, Calif., for example, have designed an e-nose to help other companies monitor the quality of food and consumer products.

So far the e-noses only mimic human olfaction—and crudely at that, because each has just a few dozen sensors, compared with the millions of olfactory receptors in the human nose. But some scientists think that in the years to come, all this tinkering just might work in the other direction. "In a *Star Trek* kind of vision, you could imagine an artificial device that would allow you to recognize new scents in your environment," Kauer speculates. And just maybe, he posits, the device might live in a logical place: the lining of your own nose.

No matter how you engineer it, a stronger sniffer could improve life. Older adults whose sense of smell has gradually faded over the years often eat poorly, a reflection of the fact that most of food's flavor is really smell. According to the National Institute on Deafness and Other Communication Disorders in Bethesda, Md., more than 200,000 people in the U.S. visit a doctor for a smell or taste problem each year. And some of us might just want to enjoy the roses a bit more.

If Paul A. Grayson has his way, we'll soon get the chance. Grayson is president of an eclectic company called Ambryx in San Diego. Ambryx's goal is to turn today's molecular biology into a whole new field of products that pack a sensory punch. "What's

missing from the 21st-century sensory experience?" Grayson asks. "The ability to enhance the sensory environment."

Run by a team of neuroscientists, corporate directors and even a cookbook author, Ambryx plans to bring sensory biochemistry to drug development and agricultural biotechnology, among other fields. One example might be perfume that's concocted according to a person's genetic profile. For example, a woman who can't smell musk—a common substance in perfumes—might prefer an undiluted jasmine scent. With DNA chip technology, companies could design a range of perfumes based on someone's unique olfactory receptor genes, says Peter Mombaerts, a neuroscientist at the Rockefeller University. This summer Ambryx announced a deal to use olfactory receptor genes discovered by Mombaerts's lab to look into such products.

YUMMY SCIENCE

It seems only natural, perhaps, that Ambryx also wants to dabble in taste. In February a team led by Nicholas J. P. Ryba of the National Institute of Dental and Craniofacial Research in Bethesda, Md., and Charles Zuker of the University of California at San Diego reported a molecular coup: the discovery of two sentinel-like molecules on the surface of the tongue's taste cells that sense sweet and bitter flavors. Within two months of the announcement, Ambryx had licensed rights to conduct studies of the receptors.

Researchers currently know little about the molecules, which were dubbed TR1 and TR2, but they could hold the key to a new wave of medications that lack a bitter taste or of foods with a special sweetness. Ryba and his colleagues are now inactivating the genes that encode the two receptors in mice that will then be tempted with a smorgasbord of sweet and bitter treats to help confirm the receptors' flavorful roles. He says his lab will next begin hunting for receptors that sense salty and sour flavors.

Our sense of taste endures lifelong, Ryba says, so high-tech tongue implants aren't likely in the near future. But at least one research group has engineered a new spin on taste: the electronic tongue. Like the e-nose, the e-tongue takes a cue from human biology, using chemical sensors as artificial taste buds to sample less than appealing—or downright dangerous—fluids, such as blood or urine.

Ever since chemist John T. McDevitt and his colleagues at the University of Texas at Austin created the e-tongue last year, they have been peppered with ideas for using the device as diverse as wine tasting and virus assays. A Japanese travel agency even called to ask whether McDevitt could design an e-tongue to test the water in a foreign country to determine if it is safe for travelers to drink.

Could all this lead full circle to offer new ways to manipulate human taste? "That's an important direction for the science that we'd like to explore in the future," McDevitt comments. "But at this point, I just don't know."

One thing is certain. No matter what the goal, every lab that is blending electronics and biology—whether it's in the ear, on the brain, inside the nose or lining the eye—must figure out how to make human and machine communicate. M.I.T.'s Wyatt quips that the retina, which is sensitive to even the slightest pressure, doesn't welcome a brick of a microchip any more than you'd like being caressed by a bulldozer. The challenge is to stimulate sensory areas such as the retina *gently*.

Wyatt and Rizzo's retinal implant would do just that. The film, which slips inside a tiny incision made in the retina during a surgical procedure, has three thin layers: a 12-photodiode array to perceive light changes; a gold-colored strip with 100 electrodes to fire up retinal cells; and a stimulator chip that helps to direct current to the electrodes.

In the future, a patient who has received an implant will wear special glasses equipped with a miniature camera that captures images. The glasses will sport a small laser that receives the camera's pictures and converts the visual information into electrical signals that travel to the implant. The implant, in turn, will activate the retina's ganglion cells to pick up the sensation of the image coming in and convey it to the brain, where it will be perceived as vision.

If it sounds complicated, Wyatt comments dryly, that's because it is. Nevertheless, he and his colleagues have been slowly perfecting the technique over a series of experiments—lengthening the duration of the current pulses and fine-tuning the microelectrode arrays. One looming question is how the retinal implant will work over time. So far the researchers have performed only afternoon-long experiments, after which the microelectric array is removed.

Since Wyatt and Rizzo's work began, two other groups in the U.S. have taken up the cause. One is Optobionics, a start-up company headed by Wheaton, Ill., ophthalmologist Alan Y. Chow. Optobionics is now testing its implant, which is named the artificial silicon retina, in rabbits. The Optobionics device is a subretinal implant, meaning it's surgically implanted beneath the retina. It is different from the M.I.T. group's retinal implant in that it connects to the back side—the photoreceptor side—of the retina rather than to ganglion cells. The second team, a group of scientists at Johns Hopkins University and at North Carolina State University, is pursuing a retinal implant similar to Wyatt and Rizzo's. The device is promising, although researchers must still demonstrate its long-term biocompatibility with the tissues of the eye, says Wentai Liu of N.C.S.U.

Although it is unusual today, an artificial retina could fit quite comfortably into the bionic body of tomorrow. Eventually, Liu predicts, investigators might create miniature computer chips that can be integrated fully into the body, allowing someone to recover from any injury with the help of internal electronic signals. "That's the next century," he says. "Right now we'll be very excited if we can just help people recover their sight."

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ABOUT THE AUTHOR

KATHRYN S. BROWN is a science writer based in Columbia, Mo. She would use an e-nose to stop and smell the roses (or lavender) and an e-tongue to savor even more dark chocolate.