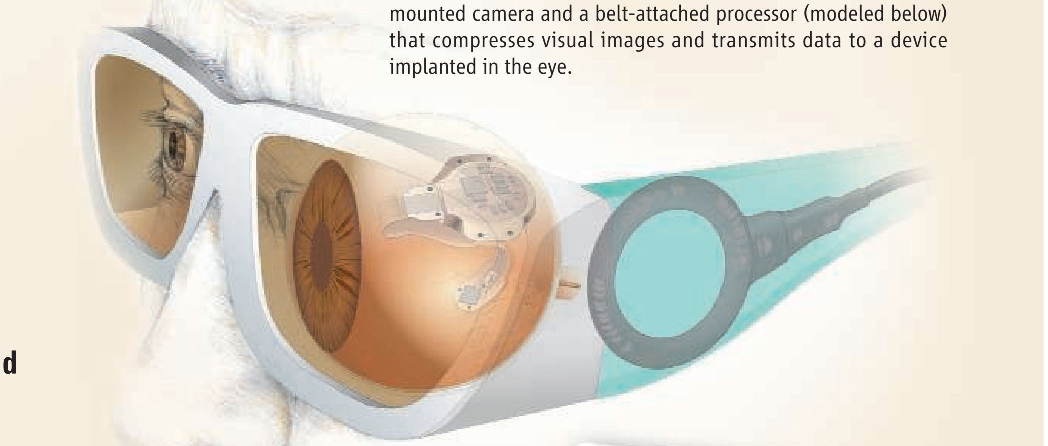


New views. A visual prosthesis (artist's illustration) developed by Intelligent Medical Implants in Germany employs a goggles-mounted camera and a belt-attached processor (modeled below) that compresses visual images and transmits data to a device implanted in the eye.

Early-stage artificial "eyes" are competing in the clinic, giving blind volunteers a glimpse of the future

A Vision for The Blind

WHEN STEFFAN SUCHERT, A LAWYER IN Nuremberg, Germany, learned that his two sons, who had been born deaf, were also going blind from a degenerative eye disorder, friends told him to pray and wait. Instead, he quit his law practice in 1998 and has spent nearly €3 million ($4.2 million) to found a company to develop a device that might return limited eyesight to his sons.

Researchers at that company, Intelligent Medical Implants (IMI) Group in Bonn, have since designed a gold implant containing a chip about the size of a small coin that sends signals to a pupil-sized patch of 49 electrodes, exciting cells in the retina at the back of the eye. Since November, ophthalmic surgeon Gisbert Richard of the University Clinic of Hamburg has implanted these chips on the eyeballs of four totally blind patients and tacked the electrodes onto their paper-thin retinas. The chips, which will ultimately be connected via an infrared receiver to a video camera, are now being tested with simulated visual input. When a computer sent each patient's chip infrared signals encoding simple patterns such as lines and spots, three of the patients saw the lines and identified the locations of the spots. In addition, one patient could see horizontal movement in either direction simulated by the computer, IMI's Chief Medical Officer Thomas Zehnder reported 2 May at the meeting of the Association for Research in Vision and Ophthalmology (ARVO) in Fort Lauderdale, Florida.

IMI is racing a growing cadre of companies and research groups to develop the first artificial "eye" that can supply useful vision to a subset of blind people. Just a few years ago, some artificial-vision investigators were lamenting that hype had outpaced clinical data in their field (*Science*, 8 February 2002, p. 1022). But now at least five teams have implanted experimental devices into people, and a sixth plans human tests within the next year or two. The pipeline of preclinical systems is also growing. At least 23 different devices are under development, a doubling in the past 4 years. "A critical mass" of research teams using innovative approaches has developed, says Joseph Rizzo, a Harvard Medical School neuroophthalmologist at the Massachusetts Eye and Ear Infirmary in Boston: "That kind of momentum makes it more likely that something will emerge that can really help blind people."

So far, even the most advanced of the experimental devices has provided blind people with only the crudest of black-and-white images, inadequate for navigating unfamiliar surroundings. Most of the artificial eyes currently under development would benefit just the minority of blind people who suffer from diseases such as retinitis pigmentosa (RP) and macular degeneration that degrade retinal cells but leave some of the retina intact. Much farther out are brain-implanted artificial-vision systems that can help people who have lost their eyes in accidents; none of today's devices will work for people who were born blind and whose visual system as a whole remains underdeveloped.

Chip in the eye. IMI's implant sends visual data via gold wires to a tiny electrode array tacked onto the human retina.

Lucian Del Priore, a retinal surgeon at Columbia Presbyterian Medical Center in New York City, warns that the field of visual prosthetics is still in its infancy. It is not realistic, he says, "to expect that a retina chip will restore vision to anything close to 20/20 in the near future."

Nevertheless, a combination of improved surgical techniques, miniaturization of electronics, advances in electrode design, and knowledge about how to safely encapsulate electronics in the body are inching the dream of artificial vision closer to reality. "It's very exciting for all of us to see the progress," says neuroophthalmologist Eberhart Zrenner of the University of Tübingen in Germany.

Entering the eye

Researchers have investigated the use of electricity to stimulate vision for nearly half a century. In the 1960s, physiologist Giles Brindley of the Medical Research Council in London and his colleagues implanted 80 electrodes on the surface of a blind person's visual cortex, a region at the back of the brain that is the first stop for

CREDITS: G. RICHARD/UNIVERSITY EYE CLINICAL CENTER, HAMBURG

visual signals coming from the eye. Wireless stimulation of the electrodes made the patient, an adult who had recently become blind from glaucoma and a retinal detachment in the right eye, see spots of light known as phosphenes. "That was the first bold demonstration of what one might be able to do," says Philip Troyk, a biomedical electrical engineer at the Illinois Institute of Technology (IIT) in Chicago.

By the 1980s, a crop of ophthalmologists began considering a narrower and seemingly easier-to-solve problem: making prostheses for the eye. Many of these physicians wanted a way to help patients with incurable degenerative retinal diseases such as RP and macular degeneration. Research suggested that such disorders, which degrade photoreceptor cells called rods and cones, still leave large portions of the retina intact even after a patient has become totally blind. On this assumption, researchers aimed to stimulate the remaining functional cells.

In the mid-1990s, ophthalmologist Mark Humayun, along with biomedical engineer James Weiland, then at Johns Hopkins Hospital in Baltimore, Maryland, and their colleagues, showed that this was feasible. When they stimulated the retinas of five blind people using handheld electrodes, the people saw spots of light in locations that matched the site of the stimulation.

Humayun, Weiland, and their colleagues then developed a more permanent prosthesis in conjunction with Second Sight Medical Products in Sylmar, California. The device consists of a small video camera perched on the bridge of a pair of glasses, a belt-worn video processing unit, and an electronic box implanted behind the patient's ear that has wires running to a grid of 16 electrodes affixed to the output layer of the retina. The video processor wirelessly transmits a simplified picture of what the camera images to the box, and then the retinal implant stimulates cells in a pattern roughly reflecting that information.

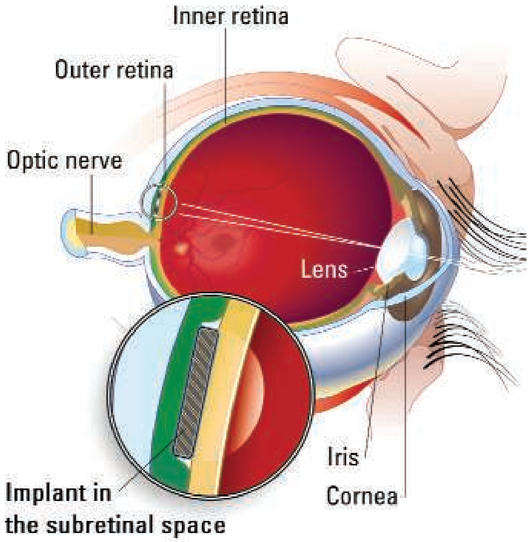
In normal vision, the rods and cones at the back of the retina detect light, and the retinal ganglion cells (RGCs), which actually sit closest to the vitreous—the eye's gelatinous interior—relay the visual signal to the brain. The electrodes of Second Sight's prosthesis directly excite RGCs—a so-called epiretinal approach—by sitting between them and vitreous. The stimulated RGCs then send signals along their axonal fibers, which make up the optic nerve.

Since 2002, Humayun's group, now at the University of Southern California in Los Angeles, has implanted its array into six people blinded by RP. After some training with the device, all of them could distinguish between the light patterns given off by a plate, cup, and spoon by moving their head-mounted cameras to scan the objects, the group reported at ARVO this month. Some of the people could also detect motion when a bar of light was moved in different directions in a darkened room. Their perceptions are crude, admits Weiland, "but for them, it's a pretty big deal."

CREDIT: A. CHOW/OPTOBIONICS

Weiland, Humayun, and their colleagues are now working on epiretinal implants containing hundreds of electrodes, which they hope will provide enough points of light to enable patients to recognize faces and read large print. The group is also developing a tiny video camera that would be embedded in an artificial lens and implanted in the eye. That lens would replace the eye's natural lens and would enable scanning using natural eye movements instead of awkward head shifting. In the meantime, Second Sight plans to start testing a 60-electrode implant by the end of the year.

That technology will compete head-to-head with IMI's 49-electrode array, also implanted in the epiretinal space. Next to the IMI electrodes is a tiny infrared receiver, which enables the chip to receive video input from a glasses-mounted camera and "pocket processor," the size of a small paperback book. In August, the company will begin implanting this upgraded device into 10 people. The prosthesis should enable them to find large objects in a room such as a table, chair, door, and perhaps even a cup of coffee, according to Hans-Jürgen Tiedke, an electrical engineer who heads the IMI group.



Silicon sandwich. A silicon-based subretinal implant is wedged (*inset*) into the photoreceptor layer of the retina at the back of the eye, near the eyeball's perimeter. An epiretinal implant would sit on the other side of the retina, facing the eye's gelatinous interior.

Under the retina

Whereas epiretinal devices such as IMI's and Second Sight's require extraocular cameras and video processors to capture images, other teams elect to use light-sensitive chips designed to tap into more of the retina's image processing. In the retina, about 125 million rods and cones connect, through intermediate cell layers, to just 1.2 million optic nerve fibers, a 100-to-1 compression of information. Placing electrodes directly where photoreceptors are being lost, against the lining of the eyeball, enables the electrodes to excite the retina's intermediate cell layers and allows those layers to perform their normal processing of visual signals. These so-called subretinal implants also have the advantage of stimulating the retina in its natural topography, theoretically provoking more natural perceptions.

Ophthalmologist Alan Chow and his team at Optobionics in Naperville, Illinois, were the first to try this approach in people in 2000. In 30 people so far, they have implanted in one eye a silicon disk the size of a nail head that is studded with 5000 microscopic solar cells, or photodiodes. The solar cells capture ambient light and translate it into pulses of electricity intended to stimulate the retina's intermediate layer of cells.

Most of the implant recipients, including all 10 in the first clinical trial, have reported moderate to significant improvements in at least one aspect of visual function, such as light sensitivity, size of visual field, visual acuity, movement, or color perception. One of the first subjects, for example, had virtually no light perception before the surgery but could see human shadows after receiving the implant. A person in a more recent trial, who had very poor central vision and was legally blind, could thread a needle 6 months after the surgery, Chow says.

Such improvements pose a mystery to some. Many of them are unlikely to be a direct result of the chip's electricity on retinal cells, according to William Heetderks, who directs extramural sciences at the National Institute of Biomedical Imaging and Bioengineering in Bethesda, Maryland. "The amount of current you need to actively stimulate retinal ganglion cells is known," he notes, "and it is not in the same range as the amount you get off a photodiode."

Chow insists that some of his patients do see light at the implant site, but he agrees that the visual improvements are too widespread and complex to come solely from electrical stimulation of retinal cells by the tiny chip. He suggests that the implants somehow induce the release of growth factors that improve the function of remaining retinal cells. In rats with a genetic disorder that causes retinal degeneration, both active and inactive retinal implants delayed the degeneration of photoreceptor cells, Chow, Machelle Pardue of Emory University School

Solar-powered sight. Optobionics co-founders, and brothers, Alan and Vincent Chow work on their silicon eye implant (*above*), an array of 5000 microscopic solar cells (*below,* magnified). These are implanted in the human eye (*center*).

of Medicine in Atlanta, Georgia, and their colleagues reported at ARVO.

Retina Implant GmbH in Reutlingen, Germany, the company founded by Zrenner and his colleagues, has created its own subretinal implant, a 40 × 40 array of microscopic solar cells. Each photodiode links up with a small amplifier, to boost the power of incoming light. In October, ophthalmic surgeons spent 7 hours putting the Tübingen team's chip into a blind person and have since repeated the surgery on a second patient. So far, Zrenner's team has only revealed data from the use of the chip's 16 test electrodes, which can be controlled externally via a cable that leaves the body behind the ear. Activating those electrodes elicited predictable images in both patients. Stimulating single electrodes produced pea-sized spots of light an apparent arm's length away. Switching on all 16 electrodes created a square; flipping on four in a row lit up a line the size of a large match, Zrenner and his colleagues reported at ARVO. "In principle, if you have enough electrodes working, you can put together an object," he says.

Looking ahead

Although Zrenner's and Chow's prostheses are designed to work without cameras, subretinal devices don't have to operate solo. Physicist Daniel Palanker of Stanford University in California and his colleagues have developed an array of photodiodes that receive infrared input from goggles displaying a projection from a video camera. In this setup, the infrared "scene" changes as the eyes move inside the goggles' virtual reality display. This may provide more natural visual input than people can get from ordinary head-mounted displays, in which the view stays static unless a patient moves his or her head.

The Stanford team's chips, which are not yet in human trials, also have unique structures that enable electrodes to get closer to retinal cells. That enables each electrode to stimulate a narrow area of tissue distinct from that triggered by a neighboring electrode, an advance that could be critical for developing high-resolution artificial vision. In one of the chips, cells migrate toward electrodes through pores. In another, cells travel between pillars such that electrodes at the tips of the pillars penetrate into the retina without apparent harm. When implanted in the retinas of blind rats with an RP-like disorder, both chips put retinal cells within just a few micrometers from electrodes. That should be close enough for 20/80 vision, enabling a person to read large print, the group reported at ARVO. By comparison, other groups' chips are basically flat, and their electrodes are typically tens to hundreds of micrometers away from retinal cells, limiting resolution to about 20/400, the level of legal blindness, or worse.

Brindley's strategy of bypassing the eye completely also continues to be studied. IIT's Troyk and his colleagues are developing an array of 1000 microelectrodes that they hope eventually to implant in the visual cortex of a blind person. Such an implant could, in theory, help the many blind people who do not have intact optic nerves or retinas. One challenge is finding the best way to use an electronic link to put visual information into the brain, Troyk says.

There are still big hurdles to cross before any of the prosthetic eyes under development can be put to everyday use. For example, no one knows for sure how much of the retina remains intact in the late stages of RP and similar retinal disorders, or what happens to neural tissue after it's stimulated repeatedly over months or years. In addition, researchers still don't have devices that can illuminate any of the world's fine print—details of faces or the texture of a flower. Nor do they have eye chips that can adapt to variations in natural lighting as the eye does. Stimulating color perception remains an even more distant dream. "One of the realizations I've come to is that artificial vision is not a restoration of natural vision," Weiland says.

Still, Suchert remains optimistic that IMI's chip or a similar device will one day help his sons. Matthias, who is 30, sees the world through a narrow tunnel, as if he were looking through the bore of a paper-towel roll. Andreas, 32, has a wider field of view but has lost his peripheral and night vision. "I insist on being successful," says Suchert.

–INGRID WICKELGREN

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