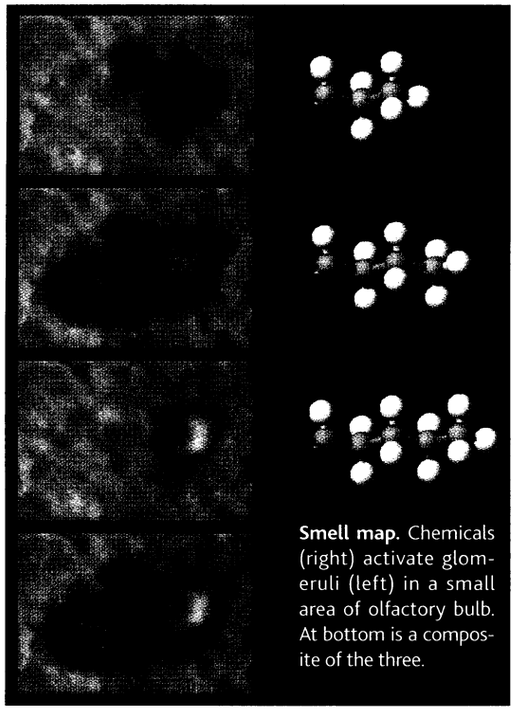
NEUROBIOLOGY

Mapping Smells In the Brain

A whiff of perfume or the smell of wood smoke may dredge up complex memories, but every smell starts as a simple code. Now, a team at Duke University Medical Center in Durham, North Carolina, has developed a powerful new tool for reading the brain's smell code.

Each sensory system has a code for the information it receives. For example, hearing uses a frequency code, while the olfactory system encodes odors by chemical composition. There are over 1000 different olfactory receptor proteins found on neurons in the nose, each of which recognizes a particular chemical feature of some odor molecules. The neurons send their signals to the brain's olfactory bulb, where each of thousands of little clusters of neurons called glomeruli receives input from olfactory neurons with just one receptor type. That means each smell should activate a unique pattern of glomeruli—the "code" for that smell.



Smell map. Chemicals (right) activate glomeruli (left) in a small area of olfactory bulb. At bottom is a composite of the three.

Researchers want to know how the brain uses that code to process olfactory information further, and now Duke neuroscientist Lawrence Katz and graduate student Benjamin Rubin have developed an essential tool for doing so. In the July issue of *Neuron* they report that they have used an optical imaging technique to see the patterns of glomeruli that respond to particular odors in rat brains—the first time that's been done in living mammals.

"This is really a breakthrough," says Randolf Menzel of the Free University of Berlin, who studies olfaction in honeybees. He and others note that because the olfactory system is so well characterized molecularly and structurally, the technique should offer neurobiologists a rare opportunity to examine and manipulate the ways the brain processes specific sensory information.

Katz and Rubin decided to try a technique on the olfactory bulb that had been used for years on the visual system. Developed by Amiram Grinvald of the Weizmann Institute of Science in Rehovot, Israel, the method, called intrinsic signal imaging, involves shining light on a patch of brain surface of a living animal. An analysis of the light bouncing back can reveal changes in blood oxygenation (via changes in light absorption by hemoglobin) or changes in the light-scattering properties of neural membranes, both of which reflect changes in neural activity.

Rubin tried the technique on rats, removing or thinning the part of the skull lying over their olfactory bulbs, then measuring the pattern of optical signals in the bulbs when the anesthetized animals were exposed to different odors. The technique worked beautifully, says Katz, with a resolution "10-fold better than in the visual system," enabling Rubin to clearly visualize individual glomeruli. Each odor produced a unique pattern of active glomeruli.

The optical imaging is a vast improvement over earlier methods, which entailed exposing a rat to an odor for 45 minutes (an unnaturally long time), then killing it and looking for changes in the uptake by the olfactory bulb of a labeled form of glucose, which also indicates neuronal activity. That approach can test only one odorant per animal, and, Menzel adds, "one never knows whether the neuronal ... code might not change" under such long stimulation. Katz and Rubin, he says, "used stimulation which is rather natural" in concentration and timing.

That advantage, coupled with the high resolution and the flexibility of being able to expose a single animal to many odors at different concentrations and under various conditions, is what has researchers so excited. What's more, the imaging can be used to guide other techniques. For example, once researchers identify the glomeruli that respond to a particular odorant in a living animal, Katz says, it is "not that difficult" to use electrodes to examine how the glomeruli interact, enabling researchers to check the hypothesis that active glomeruli turn up the contrast in their signal by inhibiting the responses of their neighbors.

Olfaction is also "perfect for looking at learning and memory," Katz says, "because one thing rodents learn very well is odors." He and others are eager to ask how the glomerular code for an odor may change if the rat learns to associate a smell with, say, food, something Menzel has already shown to be the case in honeybees. The possibilities don't stop there.

Katz's team now has the technique working in mice, and because the mouse odorant receptors have been cloned, researchers can use genetic engineering to generate receptor molecules tagged with a fluorescent protein, enabling them to associate specific glomeruli with specific receptors, or even genetically change the receptors or their neurons to see how that affects olfactory processing. What's more, optical imaging can likely be done on higher olfactory processing areas in the cerebral cortex, where smells may interact with other perceptions or memories, to ask how the patterns from the olfactory bulb are translated and transformed in those areas.

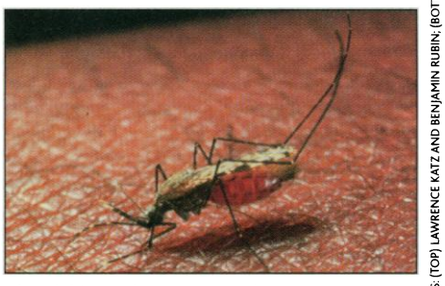
Indeed, says Grinvald, the possibilities opened by Rubin and Katz's result are already drawing new participants into the field of olfaction. "I know of two very good groups that jumped on this project as soon as they heard that the imaging is working so well," he says. Others are bound to follow.

–MARCIA BARINAGA

INFECTIOUS DISEASES

Gene Sequencers Target Malaria Mosquito

A group of insect geneticists, genome researchers, and funding officials has put together a plan to open a new front in the war against malaria: the sequencing of the genome of *Anopheles gambiae*, the mosquito primarily responsible for spreading the disease in Africa. "*Anopheles* would be the first insect disease vector to be sequenced," says Carlos Morel, director of the United Nations' Special Program for Research and Training in Tropical Diseases, which hosted a meeting earlier this month in Geneva to discuss strategy. The participants will submit proposals to major biomedical agencies in Europe and the



Bloodthirsty bug. *Anopheles gambiae* is the leading malaria vector in Africa.

CREDITS: (TOP) LAWRENCE KATZ AND BENJAMIN RUBIN; (BOTTOM) OSF/ANIMALS, ANIMALS

United States to fund the project, which would take an estimated 5 years and cost between $50 million and $90 million.

Malaria researchers say that sequencing the mosquito's genome—which, at 260 million base pairs, is about the size of one large human chromosome—should lead to a better understanding of interactions between the insect and the parasite. "Having the genome sequence would be fantastic," says molecular entomologist Robert Saunders of the University of Dundee in the United Kingdom.

Malaria kills more than 1 million people worldwide each year, and an estimated 86% of those deaths occur in Africa, where it is the second leading cause of mortality after AIDS (*Science*, 14 May, p. 1101). The disease is caused by the protozoan parasite *Plasmodium*, which infects red blood cells and causes them to burst when progeny parasites are released. Since 1995, an international team of researchers has been sequencing the genome of *Plasmodium falciparum*, the species responsible for the most serious form of malaria. The proposed *Anopheles* sequencing project would complement this work.

To enter its human host, *Plasmodium* needs the help of the *Anopheles* mosquito, which injects the parasite into the host's bloodstream while it ingests blood. Some strains of *Anopheles*, however, are resistant to the parasite, mounting an immune response that kills off the protozoan before it can mature. What some researchers call the "Holy Grail" of malaria control would be to create a genetically modified mosquito incapable of transmitting *Plasmodium*, an aim that would be greatly aided by knowing the sequence of the mosquito's genome.

Although the project's supporters have yet to raise the funding, they were encouraged by the fact that the meeting was attended by emissaries from major genome research agencies as well as leading gene sequencing centers. "I'm not really worried" about getting the money, says Fotis Kafatos, director of the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, who initiated the project together with *Anopheles* expert Frank Collins of the University of Notre Dame in Indiana. The participants included representatives of NIAID—the infectious disease institute of the U.S. National Institutes of Health (NIH)—and the Wellcome Trust, Britain's mammoth biomedical research charity. Also attending were gene sequencing jockeys from the Wellcome Trust–funded Sanger Centre near Cambridge, France's Genoscope, and The Institute for Genomic Research in the United States.

Kafatos points out that a lot of research has already been done on the *Anopheles* genome, including genetic mapping and preliminary sequencing at Genoscope, EMBL, the University of Iowa, and other centers. "We have really already started, and as the money comes in that will determine how fast we go," Kafatos says. NIH has already said it will consider grants of up to $1.5 million per year for at least the first 2 years of the project. Wellcome director Michael Dexter told *Science* that although there is "excitement" at the trust about the proposal, funding decisions will have to wait until a replacement is found for outgoing Sanger director John Sulston.

Anopheles researchers argue that recent advances in efforts to create transgenic mosquitoes have added urgency to the plan. Mosquitoes have long proved awkward to modify genetically, in part because their eggs are hard and difficult to inject with foreign DNA. Last year, however, two research groups, one led by Collins and the other by Anthony James of the University of California, Irvine, succeeded in injecting foreign genes into embryos of *Aedes aegypti*, the mosquito vector for the viruses that cause yellow fever and dengue fever. This raised the hope that *Anopheles* might be similarly modified. "People will say that it's science fiction until the day you do it," comments Morel. "The human genome is already being sequenced, and so is *Plasmodium*. Once we have *Anopheles*, we will have all three actors in the malaria cycle." **–MICHAEL BALTER**

IMAGING

X-ray Crystallography Without Crystals

For much of his career, David Sayre has been seeing spots and doing everything he can to get rid of them. Sayre, an x-ray crystallographer now retired from IBM, makes images of materials using x-rays, which can reveal fine detail down to the arrangement of atoms in a molecule. But this ultrahigh-resolution imaging technique only works on crystals, in which many copies of a molecule are lined up in a regular array. When x-rays are targeted at such a crystal, they bounce off the atoms and interact to produce a set of diffraction spots, which researchers can mathematically reconstruct into an image of the molecule. Now Sayre and colleagues in the United States and the United Kingdom have done away with the need to form molecules into a crystal and diffract x-rays into spots. In this week's issue of *Nature* they report creating the first diffraction image from a noncrystalline sample, a feat that could revolutionize the imaging of the vast array of materials that cannot be crystallized, providing ultrahigh-resolution images of everything from cells to individual protein molecules.

"It's really a brilliant experimental

CONGRESS

U.S. Science Advocate George Brown Dies

Scientists have lost one of their leading advocates in Congress. Representative George E. Brown Jr. (D–CA), the oldest member of the House of Representatives and a leader of its Science Committee, died 15 July of an infection following open heart surgery. The physicist-turned-politician was 79.

Brown studied physics and engineering at the University of California, Los Angeles, in the 1940s and entered politics in 1954, winning a congressional seat in 1962 which he held ever since, except for a 2-year hiatus after losing a Senate race in 1970. He joined the House Science Committee in 1965, rising to chair in 1990. After Republicans won control of the House in 1994, Brown became the committee's senior Democrat. That post is now expected to pass to Representative Ralph Hall (D–TX), a Science Committee veteran and a former chair of its space science subcommittee. Observers say Hall's ascension is not likely to change the committee's direction.

One of the few House members with scientific training, Brown was an outspoken and often wry advocate for government spending on basic research and a booster of crewed and uncrewed space exploration. He was also a force behind the 1976 strengthening of the White House science adviser's office and the 1972 creation of Congress's Office of Technology Assessment, which the Republican leadership disbanded in 1995.

Brown was Congress's "wise man of science," says Rita Colwell, head of the National Science Foundation. "Even after sitting through hundreds of presentations by researchers, George never lost a genuine delight in hearing of new breakthroughs," recalls Representative F. James Sensenbrenner Jr. (R–WI), the current chair of the Science Committee. D. Allan Bromley, dean of engineering at Yale University and a science adviser to several Republican presidents, says Brown "will be very much missed." **–DAVID MALAKOFF**