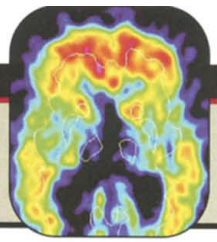
PAGE 752
Genes and violence



752
Marker for Alzheimer's disease

DRUG-ABUSE RESEARCH

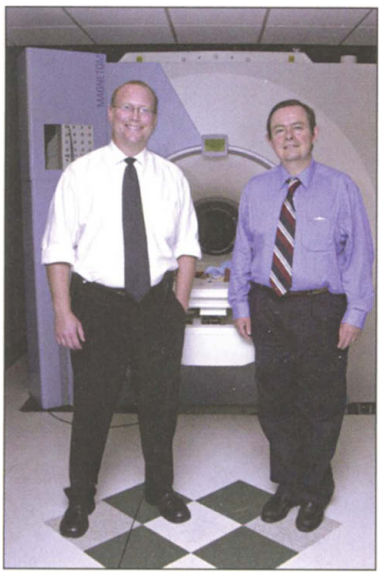
White House Stirs Interest in Brain-Imaging Initiative

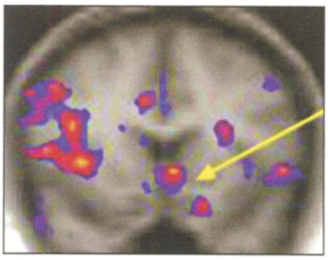
BOSTON—Thanks to drug-war money, Massachusetts General Hospital just dedicated one of the most sophisticated magnetic resonance imaging machines around. With a whole-body magnet and a 460-ton steel shield, the multimillion-dollar device promises to give researchers new insight into the brain circuitry of drug craving and euphoria. The device is one of dozens of neuroimaging machines planned for labs across the country, all paid for by White House drug czar John Walters's office. Their debut is creating a euphoria of its own among researchers. They are putting together a major initiative to use the machines in concert with advances in genetics and animal research to vault the field into the forefront of neuroscience—what Walters calls "a bold new model for drug-abuse research."

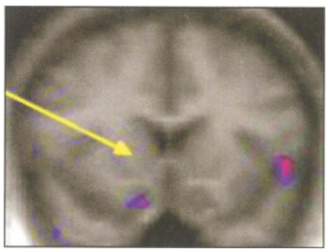
The idea for a brain-imaging initiative—seen as a decade-long, $100-million-plus effort—is generating excitement among policymakers such as Walters, officials at the National Institute on Drug Abuse (NIDA), and academic researchers, many of whom gathered here last month at a White House–sponsored meeting on reducing drug demand. By gathering data from thousands of human subjects, they hope to understand the genetic and physiological underpinnings of drug abuse. But skeptics warn that the ambitious effort must be carefully designed, lest it produce reams of unusable data—and damage neuroimaging's already mixed reputation.

Researchers involved in the effort say that the technology is ready: "I'll do everything I can to kick this off," says Albert Brandenstein, chief scientist for the Counterdrug Technology Assessment Center (CTAC), which is part of the White House Office of National Drug Control Policy. "We want the best people in the world—and our carrot is the best equipment in the world."

The U.S. government is spending nearly $19 billion this year on treating and preventing drug abuse and interdicting illicit drugs; the vast majority goes for law enforcement. NIDA, part of the National Institutes of Health, has a $933 million budget, but that money pays for research, not infrastructure. So Brandenstein's office stepped in a few years ago to provide imaging facilities and technical support; $14 million is allocated for 2002. Almost a dozen machines are completed or under construction—including three at NIDA—and CTAC hopes to fund 40 to 50 over the next 5 years, officials say. This growing network would form the basis for the proposed initiative.







Brain power. Mass General's Breiter (*left*) and Gasic propose to use a powerful new imager in a major study of drug abuse. They aim to link DNA studies to brain scans such as these, which contrast the effects of cocaine (*top*) and saline.

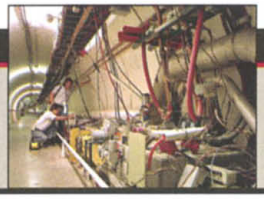
Mass General neuroscientists Hans Breiter and Greg Gasic will submit a grant proposal to Brandenstein's office this month for a pilot program, the first step toward a national program. CTAC would pay for the pilot project; NIDA would then take over to run a full research initiative. "This would be no smaller than the genome project, once full blown," says Gasic, who foresees "a concerted effort by many institutions." The Mass General imaging center, which houses the new machine, is a cooperative venture with nearby Harvard and the Massachusetts Institute of Technology (MIT).

The Mass General team envisions a three-phase effort. A 1-year pilot project would recruit more than 100 subjects—mostly siblings—divided into four groups: nicotine addicts, cocaine addicts, depressives, and a healthy control group. Using the imager, researchers would test their reactions to a handful of exercises involving perception of beauty, monetary rewards, and pain. To date, the largest neuroimaging studies have been limited to about 50 people. Phase two of the Mass General effort, lasting 3 to 4 years, would recruit up to 4000 people from the New England region and collect images and DNA from each. The third phase would fund multiple centers in a national effort involving an estimated 8000 to 20,000 human subjects. The costs could be about $2.5 million for the pilot program—borne by Brandenstein's office—and could top $100 million in NIDA funding for phase three, according to officials familiar with the long-term plans.

The first two phases—if approved by peer reviewers at CTAC—would test whether links could be established between genetics and neuroimaging data. "Two years of work will give us the confidence to step forward to see if there is enough data for a major initiative," says Brandenstein. Ultimately, "a goal of this effort is to develop the genotypes and phenotypes of the addicted human brain," which will lay the foundation for better treatment and prevention programs, adds Richard Millstein, NIDA's deputy director. NIDA likely would farm out work on the third phase to a variety of labs. Such an interdisciplinary collaborative effort, insists Walters, "is the best hope for a better future in the struggle against drugs."

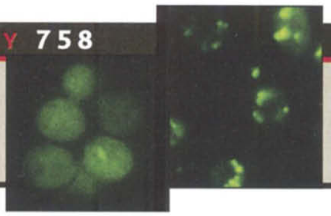
Many researchers are enthusiastic. "This sounds wonderful; we've learned a great deal with longitudinal studies," says Eric Kandel, a Nobel laureate and neuroscientist at Columbia University in New York City.

CREDITS: (LEFT) PAUL BATISTA/MASS GENERAL; (RIGHT) H. BREITER/MASS GENERAL



757 Prospects brighten for Tevatron

LEAD STORY 758 A more benign view of prions



764 Sedatives as chemical weapons?

"This could be a Framingham study on mental health," referring to a long-term examination of heart disease in that Massachusetts town. Others, however, are cautious about promising too much. "You may end up with data that is uninterpretable," warns Nora Volkow, a neuroscientist at Brookhaven National Laboratory in Upton, New York. "There's a consensus [that] we need to do our homework before embarking on such a program." She says that brain images from the same person can vary from day to day, and others note that drug users typically use several substances, complicating efforts to sort out variables.

The genetics portion will pose its own challenges, researchers say, particularly attempts to link specific genes with physiological changes. "Sure, we should try," says Harvard provost and neuroscientist Steven Hyman. "But we need to have the greatest humility as to where we are." Many agree, however, that neuroimaging and genetics demand collaboration. "There is no question about the importance of these two forces in understanding cognitive issues," says Phil Sharp, who heads MIT's McGovern Institute for Brain Research. The challenge, he adds, is to come up with studies that can pass muster in peer review, be replicated, and build up large databases for future researchers.

Breiter acknowledges that neuroimaging has had a reputation for producing "pretty pictures" but not replicable data. "It has been characterized as pseudocolor phrenology, but thanks to very rigorous animal neuroscience, we know how [neural] circuits work." Responding to colleagues, he revamped his proposal to include a slow scale-up. "The worst-case scenario," he says, is that it would end with the pilot studies, giving "a neural circuitry–based picture of nicotine and cocaine use and depression."

Such a picture would aid drug-abuse research, which Harvard University psychiatrist Perry Renshaw says has long suffered from a lack of good clinical studies using neuroimaging. Larger studies, he says, hold the key to making use of the technology's possibilities. They also require more money and are certain to raise controversial issues about confidentiality, gender, and ethnicity. "If this is not well thought out, it will hurt us," adds Volkow. But given new facilities, funding, and the strong support of the White House, drug-abuse researchers might have a good shot at riding to the forefront of neuroscience. **–ANDREW LAWLER**

CREDIT: DENNIS COOK/AP

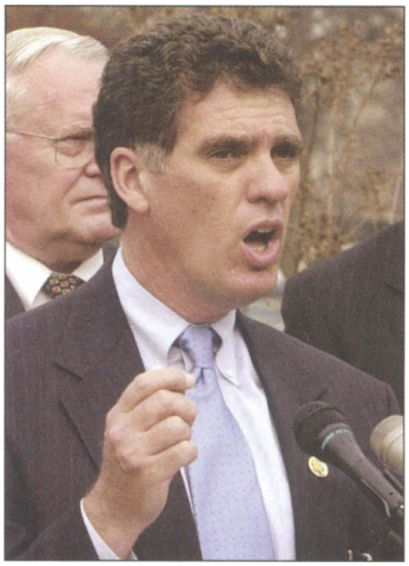
BIOTERRORISM

A Call for Restraint On Biological Data

Two events last week are prompting a public debate over a hot-button issue that has quietly been discussed in the scientific community since last fall's anthrax attacks: Should unclassified research that might conceivably help bioterrorists be openly published?

A handful of members of Congress filed a resolution criticizing the publication by *Science* of a paper on poliovirus and calling on journals, scientists, and funding agencies to take more care about releasing such information. Separately, the American Society for Microbiology (ASM), which represents 40,000 scientists, sent a letter to the National Academy of Sciences (NAS) 22 July requesting a meeting of biomedical publishers to discuss whether and how to publish research that might be co-opted by terrorists. NAS plans a meeting this fall.

The *Science* paper, published online 11 July (www.sciencemag.org/cgi/content/abstract/1072266), describes the assembly of poliovirus from stretches of DNA obtained by mail from specialty reagent suppliers. The publication troubled Representative Dave Weldon (R–FL). Along with seven other Republicans, Weldon introduced a resolution 26 July criticizing *Science*'s publisher, the American Association for the Advancement of Science (AAAS), for publishing "a blueprint that could conceivably enable terrorists to inexpensively create human pathogens." The resolution, which has been referred to three congressional committees, also calls on government funding agencies to reconsider how they classify research. The polio study, funded by the Department of Defense and led by Eckard Wimmer at the State University of New York, Stony Brook, was unclassified.



Critic. Rep. Dave Weldon took AAAS to task for publishing a paper on poliovirus.

Many microbiologists say that they see no threat to national security in the polio paper, because the virus's DNA sequence is available over the Internet and techniques for building it have long been known. "The colleagues that I have spoken with … do not feel there was any information presented in the publication that was national security information," says Andrew Onderdonk, a microbiologist at Harvard and editor-in-chief of the *Journal of Clinical Microbiology*, one of 11 journals published by ASM. At the same time, some biologists have condemned the publication for needlessly raising public fears (see Letters, p. 769).

Alan Leshner, AAAS's chief executive, defended the decision to publish: "The technique reported in *Science* is neither a practical nor efficient method for making more complex, lethal viruses," he said, noting that methods used in this research had been previously published and that the virus Wimmer's group produced is less virulent than natural poliovirus.

Weldon's call for rethinking open publication of potentially sensitive microbial work, however, echoes months of conversation among biologists. "Everyone is walking on eggs," says Sam Kaplan, chair of the ASM publications board. Editors of the ASM journals, which frequently publish research on dangerous pathogens, have been mulling over policies since last December. The Department of Defense, meanwhile, is funding a workshop of journal editors and national security experts on 12 August in Washington, D.C., on the publication of research it funds that is potentially related to biological warfare.

Absent clear guidance, some scientists are taking matters into their own hands. Ronald Atlas, president of ASM, says that the group's journals have received "a dozen or two dozen inquiries" from scientists afraid to publish their work in full. ASM's answer: Incomplete papers are not eligible for publication. In at least one case, though, a gutted paper did slip through: a report on smallpox sent to the