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Also in the works are plans for Gordon and for Mildred Dresselhaus, a Massachusetts Institute of Technology engineer and the new head of the Office of Science, to host "science days" at the Sandia, Los Alamos, and Livermore weapons labs. The events, says an aide, would emphasize Gordon's belief that "security must not jeopardize DOE's science mission." That goal also underlies the new commission, to be stocked with high-profile independent scientists and security experts appointed by Richardson.

Such initiatives, however, may not be enough to win back researchers' confidence. Dorfman "is reserving judgment" but says he is "impressed with Gordon's commitment to science." A Los Alamos scientist quoted in the Baker report urged DOE officials to be guided by common sense rather than political expediency. "If you give nerds absurd guidance, it won't work," said the anonymous researcher. "Give them sensible and consistent guidance, and they'll do their best." Scientists are hoping that DOE will meet that standard.

—DAVID MALAKOFF

LABORATORY ANIMALS

Researchers Fight Plan To Regulate Mice, Birds

The U.S. government has decided that laboratory mice are animals. This week a federal judge is expected to accept an agreement between the U.S. Department of Agriculture (USDA) and animal-welfare advocates to regulate the use of mice, rats, and birds in scientific research. The pact, which would settle a pending lawsuit, would reverse a 30-year-old policy that exempts 95% of all experimental animals from the federal government's legal definition of "animal."

Biomedical research groups are furious. They predict that new rules will drive up animal-care costs, force small colleges to stop using live animals in classes, and spawn more lawsuits. "Settling this suit without taking into account the deep concerns of the research community is a serious mistake," says Jordan Cohen, president of the Association of American Medical Colleges (AAMC), one of several groups that fought unsuccessfully to sink the deal.

The controversy stems from a 1972 decision by the USDA's Animal and Plant Health Inspection Service to exempt mice, rats, and birds from Animal Welfare Act (AWA) regulations that spell out everything from annual

inspections to cage sizes. That decision came under legal attack in 1992 after a federal judge ruled that USDA's justification for the exemption—that Congress never intended the law to apply to the three animals—was "strained and unlikely." But an appeals court later threw out the case, ruling that the Humane Society of the United States and other plaintiffs lacked standing to sue since they had not been directly harmed by USDA's action.

In 1997 the Alternatives Research & Development Foundation (ARDF) of Eden Prairie, Minnesota, sought a way around that ruling by suing on behalf of an undergraduate student who claimed she suffered emotional and aesthetic harm from working with mistreated rats in a college psychology lab. This summer, after a judge ruled that the student had standing, USDA moved to negotiate an out-of-court settlement (*Science*, 21 July, p. 377).

The decision alarmed biomedical research advocates, including AAMC, the National Association for Biomedical Research (NABR), and the Federation of American Societies for Experimental Biology. In a blizzard of faxes, they asked Agriculture Secretary Dan Glickman to intercede, arguing that researchers should not be frozen out of negotiations. They also worried that USDA's refusal to challenge the decision could lead to dozens of new animal-rights cases.

Their pleas fell on deaf ears. On 29 September, USDA officials agreed to "initiate and complete a rulemaking on the regulation of birds, rats, and mice within a reasonable time." A jubilant John McArdle of the ARDF says that "we wanted to be certain that alternatives are considered for all laboratory animals," as required by the AWA. He also

notes that the process will allow "everyone to have their say."

Observers are divided over the practical impact of any new rules, which could take years to finalize. Animal-care experts say large breeders and research universities, which typically already meet widely used voluntary standards and other government requirements, should have little trouble complying with new regulations. But NABR has estimated that compliance could cost researchers \$280 million or more, in addition to requiring a bigger USDA budget for enforcement. Smaller teaching institutions won't be able to afford to keep rats in mazes in psychology classes or raise chicks in development courses, the

group predicts. Research funds, says Cohen, will be "frittered away on senseless and duplicative bureaucratic hoops that are driven by ideology and not reality."

Opponents have vowed to fight any changes. NABR and the Johns Hopkins University in Baltimore, Maryland, have asked to be included in the case so that their voices can be heard. If the judge signs off, however, the groups may seek a statement from

"We wanted to be certain that alternatives are considered for all lab animals."

—John McArdle



"Settling this suit without taking into account the deep concerns of the research community is a serious mistake."

—Jordan Cohen

Congress on whether it intended to regulate mice, rats, and birds when it passed the AWA. Any final rule could also be challenged in court. "The battle will now be joined in the regulatory and legislative arenas," says Cohen.

—DAVID MALAKOFF

NEUROSCIENCE

A Possible Target for Better Benzodiazepines

Valium and other benzodiazepines are among the world's most prescribed drugs. They ease anxiety, relax muscles, control epilepsy, and help people sleep—but so far it's impossible to enjoy just one of the drugs' benefits without the rest of the package. Benzodiazepine users also risk some

troubling side effects, such as scrambled memories and clumsiness. The problem, says behavioral neuroscientist David Stephens of the University of Sussex in the United Kingdom, is that the drugs "shut down the brain fairly generally." Pharmacologists have tried for years to distill the drugs' desirable effects from the bad; now a team of neuroscientists has shown that such a strategy could well succeed.

Benzodiazepines work by amplifying the action of the neurotransmitter GABA, the brain's main "off" switch. They do this by binding to and sensitizing some of the receptors that register GABA's inhibitory signal. Now, in work described on page 131, a group led by Uwe Rudolph and Hanns Möhler at the University of Zürich in

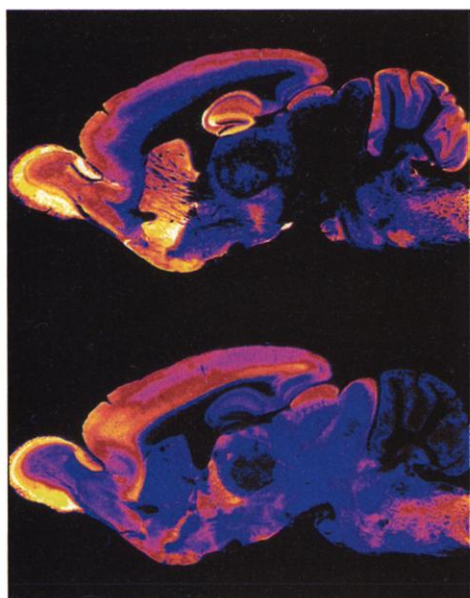
that the α subunit's identity might influence the type of effects the drug produces came last year. In work reported in the 21 October 1999 issue of *Nature*, Rudolph's team reported that when they mutated the gene encoding the $\alpha 1$ subunit in mice, Valium no longer bound to the receptors that should have embraced it. What's more, the mice weren't sedated by the drug, even though it retained its ability to reduce anxiety and relax muscles in the animals. Those results were subsequently confirmed by Ruth McKernan and colleagues at Merck Sharp & Dohme Research Laboratories in the United Kingdom.

In the current work, Rudolph's team has tracked down the site of Valium's anxiety-reducing action. The researchers focused on receptors composed of the $\alpha 2$ and $\alpha 3$ variants of that protein because of where the receptors are located in the brain—in regions that previous research has shown participate in fear.

Karin Löw, a former graduate student in Rudolph's lab who is now at the University of California, San Diego, created mice with a point mutation in the gene for the $\alpha 2$ receptor subunit; meanwhile Ruth Keist of the University of Zürich bred mice with mutated $\alpha 3$ genes. "What's really clever about these mice," says Stephens, who was not involved in the research, is that the mutations affect only the receptor's sensitivity to benzodiazepines.

Indeed, the mice appeared to be perfectly normal. Their GABA receptors continued to respond to the neurotransmitter, and the mice also responded to other anxiolytic drugs that act on non- α -dependent binding sites. Administering Valium produced a different picture, however. In standard lab tests of anxiety, which measure how much an animal explores new wings of a maze or ventures into the light, the animals with $\alpha 2$ mutations—although not those with the $\alpha 3$ mutation—acted as though they hadn't received a dose of the drug. Thus, it appears that only the $\alpha 2$ receptor is needed for Valium's antianxiety effects, even though $\alpha 3$ receptors are also located in fear areas.

Stephens isn't prepared to rule out $\alpha 3$ as a mediator of Valium's anxiolytic effects, however. The tests the Zürich group chose, he points out, measure unconditioned fear. Other sorts of fear, such as learning to avoid a certain place or scent, might be better models of human anxiety and could rely on different receptor subtypes. Even so, Stephens says, drugs that target $\alpha 2$ receptors are a good bet for stopping anxiety. The $\alpha 2$ receptors tend to be clustered around the base of a neuron's axon, a region through which any nerve signal must pass, and so they are well positioned to inhibit neuronal firing. "There's nothing subtle about" $\alpha 2$ receptors, he says; they're an "emergency off switch." —LAURA HELMUTH



Focusing anxiety relief. $\alpha 2$ receptors (light, top) ease a mouse's anxiety if it's given Valium. $\alpha 3$ receptors (bottom) don't appear to help.

Switzerland has pinpointed one particular subtype of the GABA receptor as the source of benzodiazepines' anxiety-reducing powers. Knowing this, says neuroscientist Richard Olsen of the University of California, Los Angeles, "we can and should be able to design drugs that selectively lower anxiety without putting you to sleep or impairing learning and memory."

An individual GABA receptor contains five different protein subunits, which come in a variety of shapes. Benzodiazepines bind between the α and γ subunits, changing the receptor's shape subtly so that it responds more enthusiastically to GABA. There are six possible α subunits, just four of which allow a receptor to respond to Valium.

"We knew about the diversity of [GABA receptors] in the brain, but it was unclear whether that would correspond to functional diversity," says Rudolph. The first indication

ScienceScope

The Secret's Out The algorithm is dead; long live the algorithm. After a 3-year competition, the National Institute of Standards and Technology (NIST) this week revealed the cryptographic standard that will replace the aging Digital Encryption Standard (DES), the mathematical recipe used to safeguard everything from digital records to communications.

The new standard will be based upon an elegant algorithm, called Rijndael, designed by Belgians Vincent Rijmen of the Catholic University of Louvain and Joan Daemen of smartcard company Proton World International. Rijndael got the nod because it is fast and compact, and it sets up cryptographic keys quickly, said NIST director Ray Kammer. And it's so secure that even the government spies at the National Security Agency plan to use it.

Coincidentally, Rijndael also was the only algorithm among the five finalists not to face a potential patent-infringement lawsuit from Hitachi, which earlier this year made broad claims to an array of mathematical techniques used by ciphers (*Science*, 19 May, p. 1161).

Into the Unknown Marine researchers want the U.S. government to send them where no scientists have gone before. A White House advisory panel last week recommended spending at least \$750 million over the next decade on a new ocean exploration program that would expand research into uncharted waters.

It's "easier to get ship time to go back to places we've already been than explore new areas," says Marcia McNutt, head of the 15-member President's Panel on Ocean Exploration and chief of the Monterey Bay Aquarium Research Institute in California. The new program would reverse those priorities by providing scientists with the ships, submarines, sensors, and data banks they need to document unknown ocean ecosystems. Priority targets would include U.S. coastal waters and arctic and antarctic seas.

The report may help push a marine science initiative into the Administration's 2002 budget request, currently under discussion, says James Baker, head of the National Oceanic and Atmospheric Administration. "We're trying to make something happen," he says. The fate of that effort, however, rests in the hands of the next president.

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