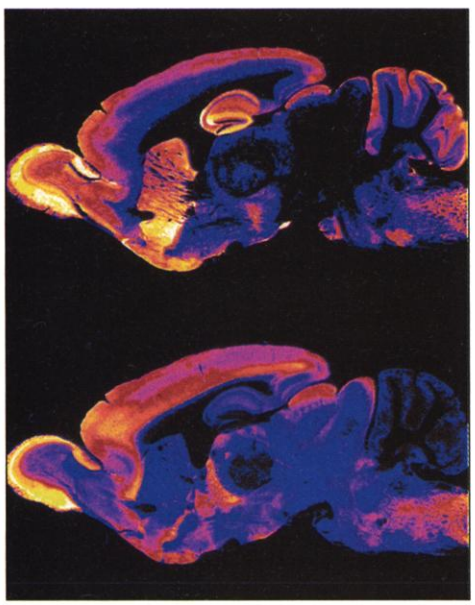
troubling side effects, such as scrambled memories and clumsiness. The problem, says behavioral neuroscientist David Stephens of the University of Sussex in the United Kingdom, is that the drugs "shut down the brain fairly generally." Pharmacologists have tried for years to distill the drugs' desirable 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 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."



Focusing anxiety relief. α2 receptors *(light, top)* ease a mouse's anxiety if it's given Valium. α3 receptors *(bottom)* don't appear to help.

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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 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 α1 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 α2 and α3 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 α2 receptor subunit; meanwhile Ruth Keist of the University of Zürich bred mice with mutated α3 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 α2 mutations—although not those with the α3 mutation—acted as though they hadn't received a dose of the drug. Thus, it appears that only the α2 receptor is needed for Valium's antianxiety effects, even though α3 receptors are also located in fear areas.

Stephens isn't prepared to rule out α3 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 α2 receptors are a good bet for stopping anxiety. The α2 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" α2 receptors, he says; they're an "emergency off switch." **–LAURA HELMUTH**

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.

Contributors: Charles Seife, David Malakoff