el's response to increasing greenhouse gases, nor, for that matter, in any model-based claims that the greenhouse warming is here.

Most current models have a positive cloud feedback, that is, changes in clouds under a strengthening greenhouse amplify the warming. The inclusion of this positive cloud feedback seems largely responsible for the doubling in recent years of model sensitivity to greenhouse gas increases. The feedback can be traced to a decrease in the model of low and middle cloud cover and an increase in high, cirrus-type cloud cover, which produces a proportionately greater trapping of infrared emissions.

Whether that is the way real clouds will react is unclear. Researchers are not even sure whether the real world cloud feedback will be positive or negative, much less what size it will be. "You have every right to be very, very skeptical of the results" of today's models, says Michael Schlesinger of Oregon State University, himself one of the leading American modelers. "But this is the best that we're doing."

While the state of the art of climate modeling is not what anyone would like, there are signs that, for whatever reason, the current estimates of the warming for a carbon dioxide doubling may not be all that bad. Michael MacCracken of Lawrence Livermore National Laboratory recently compared model and real world responses to various climate forcings. Models reproduce the cycle of the seasons, in which regional energy inputs vary by 100 watts per square meter, as well as the climate of the most recent glacial maximum, in which latitudinal and seasonal variations differ by 20 to 40 watts per square meter. The models also generate the greenhouse warming that has kept Earth from freezing over during the past few billion years.

Other comparisons can be made. The sensitivity of the models is consistent with the small to negligible climate effect of a veil of volcanic aerosol in the stratosphere. Given a number of uncertainties, the model responses, or at least those toward the lower end of the range, are consistent with the 0.5°C global warming of the past century.

MacCracken concludes that the global average temperature increase under a carbon dioxide doubling would be a few degrees Celsius plus or minus 50%. It would not be 10° nor a few tenths of a degree. For policymakers, MacCracken suggested, perhaps that is all they need to know about the magnitude of the global warming. That and that feedbacks can only amplify or damp a forced climate change, not negate it. Consistent forecasts of regional changes of any kind will likely be out of reach for many years. ■ RICHARD A. KERR

Neurotoxicity Creates Regulatory Dilemma

New, more sensitive tests that detect damage to brain neurons in animals are leading researchers to reexamine the potential toxicity of some drugs already on the market

WHEN SHOULD A COMPOUND be classified as a neurotoxin and a health hazard? The answer is not always clear and fenfluramine, an appetite-suppressing prescription drug, is a continuing case in point. The current dilemma is this: people have been taking fenfluramine for nearly 20 years without any observable toxic effects, but new studies show that, in rats, fenfluramine selectively damages the fine endings or terminals of nerve cells in the brain that release serotonin as a transmitter.

The issue of fenfluramine toxicity is not new. Ten years ago the Food and Drug Administration (FDA) investigated reports that it killed groups of nerve cells in the brain, but the results could not be confirmed. Today, however, new tests are available that can detect more subtle damage to specific brain regions and neurotransmitter pathways. It is these new tests that point to fenfluramine toxicity in rats given five or more times the daily human dose.

Fenfluramine belongs to a class of amphetamine-related drugs that also includes ecstasy (3,4-methylenedioxymethamphetamine or MDMA), which is designated as an illegal drug (see *Science*, 19 February 1988, p. 864), and Ritalin, which is used to treat children who are hyperactive. Using similar criteria for determining neurotoxicity, researchers have preliminary data indicating that in rats fenfluramine is more neurotoxic than ecstasy and that Ritalin is not toxic, even at very high doses. The FDA has a new program to reevaluate this class of drugs for potential toxicity and is not targeting fenfluramine or any other drug in particular.

Nevertheless, the seemingly conflicting data about the safety of fenfluramine in humans and its toxicity in rats leave FDA officials in something of a quandary. "When we talk about the neurotoxicity of drugs, what exactly do we mean?" asks Joseph Contrera of the FDA. "What are the appropriate criteria? Is it long-lasting depletion of a neurotransmitter, selective damage to a particular population of neurons, or a visible lesion in the brain?" Until recently when new techniques became available, FDA used the latter criterion, which indicated that a large number of nerve cells in the brain had died.

Despite extensive studies on fenfluramine, scientific opinion on the drug is currently divided. Many clinical researchers are strong proponents of its continued use for patients who need to lose weight, citing the drug's effectiveness and the lack of clinical data showing evidence of toxicity. For example, Michael Weintraub of the University of Rochester in New York and his colleagues have just completed a 4-year study of people taking fenfluramine in combination with another diet drug. "The drugs were far superior to a combination of diet, behavioral modification, and exercise in producing weight loss," says Weintraub, adding that no one reported toxic side effects. But most clinical studies, including this one, were not designed to assess neurotoxicity.

"When we ask about the neurotoxicity of drugs, what exactly do we mean? What are the appropriate criteria?"

At least part of the reason is that damage to serotonin neurons in the brain is difficult to measure in people. Early studies of fenfluramine showed that it causes a decrease in overall brain levels of serotonin and its metabolite (5-HIAA) in cerebrospinal fluid, but these decreases were thought to be transient and an indication of the drug's efficacy, not its potential toxicity. Furthermore, behavioral tests of serotonin depletion in people simply do not exist. "Serotonin helps to regulate sleep, sexual behavior, mood, and the perception of pain," says Lewis Seiden of the University of Chicago in Illinois. "These factors are very subtle and hard to test for." Precisely how fenfluramine curbs the appetite and how this effect may be related to its actions on serotonin neurons in the brain is also not fully resolved.

So in the absence of good assays for evaluating potential toxicity in people, some researchers have turned to experiments with animals. At the Society for Neuroscience meeting, held 13 to 18 November in Toronto, Ontario, several groups of investigators reported that fenfluramine is toxic to serotonin neurons in the brains of rats. All find that fenfluramine is neurotoxic at lower doses than MDMA.

"In rats, fenfluramine is three times more toxic than MDMA," says Stephen Peroutka of Stanford University. He and John Warner, also of Stanford, report that giving rats a single high dose of fenfluramine (about ten times higher than the daily human dose of 1 milligram of drug for every kilogram of body weight) causes a 50% depletion of the membrane sites that recycle serotonin back into nerve cells. This indicates a form of toxicity because the effect is ultimately to deplete the releasable supply of serotonin in the brain. The researchers label these serotonin uptake sites with paroxetine, a newly developed marker.

Not everyone is comfortable with the comparison between fenfluramine and ecstasy, despite their chemical similarity. "It's not fair to compare fenfluramine to MDMA," says Errol De Souza of the National Institute on Drug Abuse's Addiction Research Center in Baltimore, noting that fenfluramine has demonstrated clinical usefulness, whereas MDMA does not. MDMA is also classified as a substance that people abuse, but fenfluramine is not.

In their new studies, however, De Souza, Robert Zaczek, also of the Addiction Research Center, and George Battaglia, now at Loyola University in Maywood, Illinois, report that injected doses of fenfluramine about ten times more than the equivalent human dose deplete the number of serotonin uptake sites by more than half. In addition, they find that this relatively high dose may cause physical damage to serotonin nerve terminals that are stained with a fluorescent label. Using similar techniques, the researchers have also screened Ritalin for neurotoxicity. "We went to horrendous doses of Ritalin and found no damage to serotonin, norepinephrine, or dopamine neurons," says De Souza.

Other researchers reported further aspects of fenfluramine neurotoxicity last year (*The Journal of Pharmacology and Experimental Therapeutics*, vol. 246, p. 822). "We found long-term decreases in brain levels of serotonin and also in serotonin uptake sites," says Lewis Seiden of the University of Chicago. Seiden, Mark Kelven, also of the University of Chicago, and Charles Schuster, director of the National Institute on Drug Abuse, report that a 4-day regimen of fenfluramine significantly diminishes serotonin levels in the hippocampus, neocortex, and striatum of rats for 8 weeks. Several groups of researchers, including De Souza's, are currently investigating whether these toxic effects of fenfluramine can be reversed over longer periods of time.

None of this is good news for Servier, the French company that makes fenfluramine, or A. H. Robins, its American licensee and distributor. The drug is sold in the United States under the name Pondimin and is available only by prescription as a diet medication. It is used much more widely in Europe than in this country. Servier could not be reached for comment.

The historical precedent for reevaluating fenfluramine and other amphetamine-derived compounds is that MPTP, a neurotoxin and sometime contaminant of synthetic heroin, can cause a Parkinsonian-like movement disorder. The evidence is now irrefutable that MPTP selectively destroys a group of dopamine-containing neurons in the brain, but it is only after 80% to 90% of these nerve cells are destroyed that people show signs of Parkinsonism. To date, there is no evidence that fenfluramine is comparably toxic in humans. Nevertheless, a gnawing concern is that as people lose brain neurons during the normal aging process, any toxic effects of fenfluramine or its chemical relatives, however subtle when they first occur, might be enhanced.

Still, no one is ready to pass final judgment on fenfluramine. "There are a number of questions in extrapolating the new rat data to the human situation," says Neil Rowland of the University of Florida in Gainesville. "One is the dose issue, another is the metabolite issue, and a third is the route of administration." Researchers have learned that the so-called D-isomer of fenfluramine and norfenfluramine, its metabolite, are the biologically active compounds that cause all of the drug's effects—both good and bad. Rowland finds that animals injected with fenfluramine metabolize it more quickly to norfenfluramine than do humans who take it orally. This might help to account for the drug's toxicity in animals and its apparent lack of toxicity in people, he suggests.

"What really needs to be done now to assess toxicity is to give animals the drug orally at lower doses, as people take it," says De Souza. Ultimately, more human studies with long follow-up periods will be required. Another consideration will be deciding what level of risk is acceptable for a diet medication.

Contrera and De Souza are now directing an FDA-sponsored study to examine the potential neurotoxicity of fenfluramine and other related amphetamine-like compounds, including MDMA. "We are using state-of-the-art techniques to see how the amphetamine drugs affect specific neurotransmitter pathways in the brain," says Contrera.

■ DEBORAH M. BARNES

Getting a Grip on Elliptic Curves

A combination of research by mathematicians in the United States, Canada, and the Soviet Union has made important progress with a class of equations known as elliptic curves

FOR MATHEMATICIANS, seeing is not necessarily believing. At the same time, mathematicians sometimes believe things they have not necessarily seen.

Belief is no substitute for mathematical proof in either case, but an instance of blind faith has recently been vindicated. A combination of research by mathematicians in the United States, Canada, and the Soviet Union has taken a solid bite out of a pair of long-standing conjectures about an important class of equations known as elliptic curves. One of the conjectures had been verified for many individual curves already. But until 2 years ago not a single instance of the other conjecture had ever been seen.

The equations known as elliptic curves are cubic polynomial equations in two variables, typically of the form $y^2 = 4x^3 + Ax + B$, with integer coefficients A and B. An elliptic curve is actually the set of solutions to such an equation. Elliptic curves play a key role in many problems in number theory. They are the basis for a powerful factoring algorithm and some related cryptography systems. They have also been recognized as a possible key to proving Fermat's Last Theorem.

Number theorists are particularly interest-