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-

ed in the *rational* points on an elliptic curve—that is, the solutions for which x and y are both rational numbers. Some curves have an infinite number of rational points, others have a finite number, and some have none at all. However, it is very hard to tell by looking at the equation just how many rational points to expect—there is no easy formula for it. The hardest part is knowing when to stop looking.

In 1963 and 1965, Bryan Birch and H. P. F. Swinnerton-Dyer published a series of conjectures regarding the "arithmetic" of rational points on elliptic curves, together with the results of extensive numerical computation. Their basic idea was to relate information about rational points to the behavior of a certain analytic function that is defined for each elliptic curve. This analytic function, conventionally called a zeta function, is a complex-valued function of a complex parameter, usually denoted as s. (Complex numbers are numbers of the form $a + b\sqrt{-1}$; why analytic functions should enter into number theory is one of those sweet mysteries of life.)

Based on heuristic arguments and numerical evidence, Birch and Swinnerton-Dyer conjectured that the set of rational points for an elliptic curve is finite if and only if the curve's zeta function is nonzero at $s = 1$. The conjecture is somewhat audacious in that the zeta function is not even necessarily defined at $s = 1$. Nevertheless, it has been verified for many individual curves. Needless to say, no counterexample has ever been found.

In 1977, John Coates and Andrew Wiles at Cambridge University proved half of the Birch–Swinnerton-Dyer conjecture for a family of elliptic curves possessing a property called complex multiplication. They showed that if the zeta function of such a curve is nonzero at $s = 1$, then there are only finitely many rational points on the curves. The converse statement, that finitely many rational points implies a nonzero zeta function, is still unproved as a general theorem, although many examples of it are known.

How does a mathematician know when to stop looking for rational points? There are sophisticated techniques for determining the complete set of rational points. In addition to sitting on the elliptic curve, the rational points reside abstractly in an algebraic structure called the Selmer group. Mathematicians look at pieces of the Selmer group to get an upper bound on how many rational points to look for. Computing rational points gives a lower bound. If the two bounds happen to agree, the job is finished.

Unfortunately, there is an obstruction sitting inside the Selmer group, called the Tate-Shafarevich group. Loosely speaking, any piece of the Selmer group that contains a piece of the Tate-Shafarevich group will never give a bound agreeing with the lower bound of the rational points. Consequently, the larger the Tate-Shafarevich group is, the harder it is to determine the complete set of rational points.

Number theorists would therefore prefer the Tate-Shafarevich group to be small. This preference led to the conjecture that, whatever else might happen, the Tate-Shafarevich group is finite. Conjectures are usually based on examples where they are known to be true. But in this case not a single example of a finite Tate-Shafarevich group had ever been identified.

The situation changed dramatically in 1986. Karl Rubin at Ohio State University proved the Tate-Shafarevich conjecture in the setting of curves with complex multiplication. Specifically, he extended Coates and Wiles's result by showing that if the zeta function of a curve with complex multiplication is nonzero at $s = 1$, then not only is the set of rational points finite, but so is the Tate-Shafarevich group. Rubin got both results because the rational points and the Tate-Shafarevich group both belong to the Selmer group; what Rubin really proved is that the *Selmer* group is finite when the zeta function is nonzero.

Belief is no substitute for mathematical proof in either case, but an instance of blind faith has recently been vindicated.

Rubin's result has now been widened considerably to a family that conjecturally consists of *all* elliptic curves with nonzero zeta function. In 1987, V. A. Kolyvagin, now at the Steklov Institute in Moscow, found a purely algebraic condition under which the Selmer group is finite. Kolyvagin assumed only that the elliptic curve be "modular," which in effect means that the zeta function of the curve obeys a certain set of symmetries. There are infinitely many such curves, including all curves with complex multiplication, and the condition can be checked for any given curve.

Conjecturally, *all* elliptic curves are modular, but it will be a red-letter day when this conjecture is proved: mathematicians have shown that if all elliptic curves are modular, then Fermat's Last Theorem is true (*Science*, 3 June, p. 1275).

Kolyvagin's proof does not make direct use of the zeta function or its value at $s = 1$. However, earlier work by Benedict Gross at Harvard University and Don Zagier at the University of Maryland and the Max Planck Institute for Mathematics in Bonn shows that Kolyvagin's algebraic condition is equivalent to two analytic conditions on the zeta function. One condition is that the zeta function be nonzero at $s = 1$. The other condition is that at least one "twisted" form of the zeta function have a nonzero derivative at $s = 1$.

The last nail has just recently been driven home—twice. Three mathematicians in the United States and two mathematicians in Canada have shown that Gross and Zagier's first condition actually implies the second. Daniel Bump at Stanford, Solomon Friedberg at the University of California at Santa Cruz, and Jeffrey Hoffstein at the University of Rochester have shown that if the zeta function of a modular elliptic curve is nonzero at $s = 1$, then in fact there are infinitely many twisted forms of it with nonzero derivative. They do so by showing that the twisted derivatives occur as the coefficients of yet another type of zeta function that is known to require infinitely many nonzero coefficients.

Ram Murty at McGill University in Montreal and V. Kumar Murty at the University of Toronto have proved the same result by a different approach. The Murtys prove that a certain average value of the twisted derivatives is nonzero, and hence infinitely many of the individual values must be nonzero.

When fed into Kolyvagin's result, the new theorem proves that for modular elliptic curves, if the zeta function is nonzero at $s = 1$, then the set of rational points and the Tate-Shafarevich group are both finite.

More recently, Kolyvagin has proven that the Tate-Shafarevich group is also finite for modular elliptic curves when the zeta function itself is zero but its derivative is nonzero at $s = 1$. Gross and Zagier had already proved in this case that the set of rational points is infinite, in accordance with the Birch–Swinnerton-Dyer conjecture.

The Birch–Swinnerton-Dyer conjecture goes on to predict the value of the zeta function (or its first nonzero derivative) at $s = 1$ by a formula that includes the size of the Tate-Shafarevich group. (It also states a precise relation between the structure of the set of rational points and the number of times the zeta function must be differentiated before it has a nonzero value at $s = 1$.) In spite of recent progress, much of the mystery of elliptic curves remains. Number theorists must continue to keep the faith.

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