Doubts about Fermat solution

Careful scrutiny of a recently proposed proof of Fermat's last theorem (SN: 3/19/88, p.180) has turned up several flaws that cast doubt on the proof's validity. Japanese mathematician Yoichi Miyaoka, who is presently working at the Max Planck Institute for Mathematics in Bonn, West Germany, last week admitted that his proof has a serious problem. He is now studying how to revise his proof.

"That doesn't mean it's irreparable," says Barry Mazur of the Institut des Hautes Etudes Scientifiques near Paris, who has been discussing the proof with Miyaoka. "But it certainly means there's more work to do. It's a rather complex proof. If you change some things in one part of the proof, then all the other parts may be subject to change."

Fermat's last theorem concerns equations of the form $x^n+y^n = z^n$. More than 300 years ago, amateur mathematician Pierre de Fermat stated that such equations have no positive-integer solutions when n is greater than 2, but he left no proof of his theorem. Ever since, innumerable mathematicians have tried to prove this conjecture. Although these attempts proved fruitless, they sometimes led to important new mathematical techniques that could be applied to other problems. And gradually, the potential for solving Fermat's theorem became linked with other questions in mathematics.

To solve the Fermat problem, Miyaoka, a specialist in algebraic geometry, which concerns the relationship between geometric surfaces and solutions of equations, ventured into a relatively new field known as arithmetic algebraic geometry. In this discipline, mathematicians look at surfaces that result when only integer solutions of equations are considered. Miyaoka tried to show that an inequality, or bound, that applies in algebraic geometry also fits an analogous case for equations with integer solutions.

That Miyaoka's initial attempt failed is hardly surprising or unusual in mathematical research. Normally, mathematicians privately circulate proposed proofs and discuss possible errors or oversights for months before gaining enough confidence to announce a proof publicly. In Miyaoka's case, the fact that Fermat's last theorem was such a famous unsolved problem put him in a spotlight that he had not sought.

Mathematicians are quite confident that someone, if not Miyaoka, will eventually come up with a proof of Fermat's last theorem. It's a little like waiting for an earthquake, says mathematician Ronald L. Graham of AT&T Bell Laboratories in Murray Hill, N.J. "All you know is that the longer you wait, the sooner the next one is going to be." — *I. Peterson*

Searching for the better clot-buster

With a variety of blood-clot-dissolving agents vying for a lucrative market, scientists are trying to optimize the effects of these so-called fibrolytic drugs. Several new studies indicate that, by combining the agents with other therapies such as monoclonal antibodies or aspirin, researchers can fine-tune fibrolytic treatment to prevent repeat heart attacks during the crucial weeks following the initial attack.

British researchers at Radcliffe Infirmary in Oxford report that giving aspirin and the fibrolytic agent streptokinase within four hours after the first chest pains can reduce mortality from heart attacks in the first five weeks by up to 60 percent. But even if delayed up to 24 hours after the first symptoms, the combination treatment reduces the number of deaths by at least 20 percent, say the scientists, making it potentially superior to fibrolytic agents like tissue plasminogen activator (tPA) that should be administered much earlier for beneficial effect.

The study, released last week at the American College of Cardiology meeting in Atlanta, involved more than 17,000 patients and 400 hospitals worldwide. Those patients not randomly assigned to the placebo group received a single dose of streptokinase (a bacterial product), or half an aspirin tablet daily for one month, or both. Clots in coronary arteries can lead to heart attacks, and aspirin interferes with the clotting mechanism. The researchers concluded that, although the two drugs alone had a beneficial effect, using both "appears best of all" in cutting heart attack deaths.

Newer than streptokinase and without its bacteria-related side effects, tPA is a product of genetic engineering, fashioned after a substance normally found in the body that eats away blood clots. Federally approved late last year, tPA was hailed for its specificity (SN: 11/21/87, p.325). But tPA has certain drawbacks, some of which are shared by other fibrolytic agents. Among these common faults is the return of the clot.

Reformation of clots, called reocclusion, occurs in an estimated 20 to 45 percent of patients after fibrolytic therapy is discontinued. Three studies published in the March CIRCULATION attempt to clarify post-tPA reocclusion and suggest solutions.

At the Washington University School of Medicine in St. Louis, Charles L. Lucore and Burton E. Sobel found that 47 percent of those heart attack victims studied had "markedly elevated" blood levels of the plasminogen activator inhibitor (PAI-1) that inactivates tPA, and that those levels stayed high for 24 hours after tPA treatment stopped. Sobel said in an interview that the body's allotment of PAI-1 apparently is saturated with tPA during treatment, but then exerts its inhibitory effects in some patients after tPA infusion stops. "We're hinting strongly that part of the reason for early reocclusion in a minority of patients . . . is the inhibitor tipping the balance in favor of thrombosis [clot formation]," says Sobel. To prevent this from happening, he says, researchers need to find ways to inhibit the inhibitor, as well as consider giving higher doses of tPA later in the treatment regimen.

Another approach seeks to lower the amount of expensive tPA necessary. By attaching tPA to a monoclonal antibody, scientists at Massachusetts General Hospital and Harvard Medical School in Boston and the State University of New York in Stony Brook say they have speeded clot breakdown and prevented reocclusion during dog experiments. The tPA/antibody binds receptors on platelets, the blood cells that release chemicals needed for clotting.

Other researchers at the University of Texas Health Science Center in Dallas and the University of Cincinnati School of Medicine report that, by blocking platelets' release of the blood-vessel-constricting compounds thromboxane and serotonin, they prevented or markedly delayed reocclusion in dogs after tPA treatment. As for the dangers of interfering with general platelet function, Texas' James T. Willerson told SCIENCE NEWS that bleeding "did not appear to be substantial in these studies." He does caution that, as with any fibrolytic agents, patients treated with such blockers would have to be closely monitored for signs of excess bleeding.

Given the uncertainties and caveats for tPA treatment, the Health Care Financing Administration (HCFA) announced last week that the drug "should not be singled out as a special case requiring special treatment" and that specific Medicare/Medicaid reimbursement for tPA would not be approved at this time. According to HCFA official William Winkenwerder, the decision "was prompted by requests from the hospital industry to have [HCFA] consider special additional payment for tPA." He told SCIENCE NEWS that the cost of tPA (about $2,300 per treatment) would have to be included in the lump sum already paid hospitals based on diagnosis. That may change in the future, he says, but he adds that there still are questions as to whether tPA should be used in older patients, the main beneficiaries of HCFA funding.

— *D.D. Edwards*