erations "are several orders of magnitude slower than what enzymes can do."

The relative slowness of the antibody-catalyzed reactions is not a major barrier to the eventual development and application of catalytic antibodies. Restriction enzymes do not work particularly fast either. Moreover, the work on catalytic antibodies is just beginning. Future investigations by the Schultz group, for example, will be directed at a better understanding of how the amino acids in the substrate binding site of the antibodies contribute to their catalytic activities. This information can help in the design of more effective "abzymes."

In addition, antibody genes are especially subject to mutations, which is one of the factors contributing to the generation of the large diversity of antigen-binding sites. Lerner suggests that it may be possible to apply genetic selection techniques to antibody-producing cells as a way of obtaining mutations that lead to the production of catalytic antibodies with the desired characteristics.

More chemical approaches might also be used to generate catalytic antibodies, Schultz points out. The Berkeley group is attempting to produce semisynthetic catalytic antibodies by chemical modification of the antigen-binding site. If this approach proves successful, the result would be a combination of the specificity and high binding affinity of an antibody with the activity of a synthetic catalytic compound not normally found in antibodies.

At least for now the major goal for the future is the production of catalytic antibodies that can break the peptide bond, which is the bond that joins together the amino acid building blocks of proteins. The catalytic requirements for breaking this bond will be more difficult to meet than those for ester or carbonate hydrolysis, however. "The problem is to get the appropriate chemistry into the binding pocket to carry out the more difficult reactions," Lerner says.

This situation is the converse of another current approach to making enzymes with particular specificities. Researchers are also trying to modify existing enzymes by using site-directed mutagenesis to change the amino acids in the substrate-binding sites, but in these circumstances they are usually trying to alter the range of substrates on which the enzyme will act, rather than the reaction catalyzed. With the antibodies, the specificity comes first. The trick then is to develop the catalytic activity. ■ **Jean L. Marx**

ADDITIONAL READING

A. Tramontano, K. D. Janda, R. A. Lerner, "Chemical reactivity at an antibody binding site elicited by mechanistic design of a synthetic antigen," *Proc. Natl. Acad. Sci. U.S.A.* **83**, 6736 (1986).

Math Proof Refuted During Berkeley Scrutiny

A highly publicized proof of a famous math problem—the Poincaré conjecture—has a gap, which might be unbridgeable

On Monday, 3 November, mathematician Colin Rourke of the University of Warwick got up in front of a cluster of mathematicians at the University of California at Berkeley to defend his claim that he and his colleague Eduardo Rego of the University of Oporto in Portugal had proved the Poincaré conjecture—a famous and difficult problem that has taunted mathematicians for 80 years. It was not an easy proof, and the mathematicians in attendance had already put in dozens of hours reading Rourke and Rego's work and trying to understand it. Now Rourke was about to start the first of several 3-hour seminars to explain the proof.

Because the Poincaré conjecture is such a famous problem and such a challenge to mathematicians and because Rourke and Rego had already gained a great deal of publicity for their proof, Rourke's seminars drew an impressive audience. In attendance were Berkeley's mathematical stars, including Andrew Casson and Robion Kirby. Well-known mathematicians from elsewhere came too, among them David Gabai and William Kazez of the California Institute of Technology. A few mathematicians who could not make it, including Fields Medal winner Michael Freedman of the University of California at San Diego, sent senior graduate students who served as emissaries.

But it was not to be the triumphant vindication that Rourke sought. By the end of the week, Rourke's audience pointed out what Rourke calls "a gap" that he cannot fill. Rourke says he is confident that he will be able to fix the proof, but others are not so sure. "My opinion is that what remains to be done is at least as difficult as what's been done already," says Casson. The opinion of the mathematicians at the seminars is that Rourke and Rego do not have a proof.

It is a familiar story in mathematics. The history of famous problems is littered with false proofs, some of them by eminent mathematicians who published proofs and only years later realized that they were incorrect. But what makes Rourke and Rego's proof stand out is the attention they received from nonmathematicians. Their work has been publicized in *Nature*, the *New Scientist*, and the *New York Times*, for example, at a time when the mathematics community was saying it remained to be convinced that the proof was real. The story of the decline and fall of this proof is more a story of the sociology of mathematics than of advances in math research.

The Poincaré conjecture was proposed at the turn of the century by French mathematician Henri Poincaré and it grabbed topologists' attention because, says Barry Mazur of Harvard, it is "so basic. If you are interested in geometry, the first thing you want to know are the simplest spaces." The Poincaré conjecture tells what they are.

The original conjecture applies to geometrical objects in three dimensions, but mathematicians generalized it to all dimensions. Freedman won his Fields Medal this year in part for his proof, in 1982, that the conjecture is true in four dimensions. In 1959, Stephen Smale of the University of California at Berkeley proved it is true for all dimensions higher than four. And it is fairly straightforward to prove it is true for dimensions one and two. So only the three-dimensional case remains unsolved.

The three-dimensional Poincaré conjecture is about the nature of the structures of three-dimensional objects, called three-manifolds. These are structures in four-dimensional space with the property that, says Kirby, "if you stand at one point and look around, it looks like ordinary three-dimensional space." An analogy is to a two-manifold, says Mazur. A doughnut and a balloon are two-manifolds. "If you are an ant on the surface of a doughnut and you look around, it looks like you are in a two-dimensional space," Mazur explains.

The Poincaré conjecture says that if you take a string, make a noose, and draw it closed on a three-manifold, and if the noose does not catch on anything as it is shrinking down to a point, then the three-manifold must be what topologists call a three-sphere—the four-dimensional analog of an ordinary sphere. In other words, only an object that is either a three-sphere or that can be stretched and pushed into a three-sphere has no holes that could snag the noose or leave it dangling.

Although no one has yet been able to prove the three-dimensional Poincaré conjecture, most mathematicians believe it is true. "It would be *astounding* if it were false," says Mazur. But, lacking a proof of it, topologists have simply worked around it. They try never to state a hypothesis that is true if and only if the Poincaré conjecture is true. For that reason, if a proof of the conjecture finally came, it would not in itself affect much of the work topologists have already done. But, says Kirby, mathematicians expect that a proof of the conjecture will almost certainly involve new methods that may help them to solve other problems.

Rourke's proof, however, did not involve new methods, according to Kirby, and, in fact, the method Rourke and Rego used "is not much different from methods that were tried in the past." That is not in itself a reason not to believe the proof, but mathematicians say they had other reasons to be skeptical of it all along.

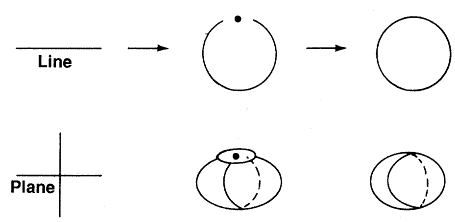
Rourke announced his proof last March in a press release. He and Rego had discovered the proof 11 months previously and, by March, were absolutely convinced that it was correct. Then Rourke's colleague, Ian Stewart, wrote about the work in *Nature* and the spotlight was on.

Rourke's tactics, although common in other fields of science, are virtually unheard of in mathematics. Mathematicians almost never put out press releases, for example, and rather than publicize their work themselves, they pass their manuscripts to their friends and colleagues who then proclaim the work significant. Only later, if at all, does the press learn of the work.

A number of mathematicians were peeved by the way Rourke proceeded. "The publicity has upset a fair number of mathematicians," says Kirby. Members of the mathematics community had not verified that this was in fact a proof of the conjecture and, says Kirby, "mathematicians figure that a piece of mathematics does not make the *New York Times* much more than a few times a year. The feeling was that when it does make it, it should be right. Many mathematicians felt embarrassed. Mathematicians just don't do things like this."

"Usually, mathematicians don't have any sense of public relations," says Freedman, who himself initially shunned publicity for his Fields Medal–winning work. "We have no sense of how to communicate to the outside world. I don't think it's particularly good that we take that posture. That's just the way we are."

Although many mathematicians have claimed to have proved the Poincaré conjecture, "usually, the claims stay within the mathematics community," says Freedman. But why not publicize a proof that you think is significant and correct? Are mathematicians falsely modest? Freedman thinks not. Instead, he says, they are afraid that the proof might be wrong. It can be extremely difficult to pick out an error in a long and difficult proof. The safest course is to wait until people you know and trust have verified the proof and then rely on them to spread the word. Actual publication in a mathematics journal usually comes months or even years after the math community agrees that an important new proof is correct.



How to make a sphere in four-dimensional space. *The idea is to do it by analogy. A circle, or a "one-sphere," can be formed by rolling up a line and adding a point at the top to close it off. An ordinary sphere, or a "two-sphere," can be made by rolling up the plane and adding a point to close it off. In the same way, say mathematicians, a "three-sphere" can be made by rolling up three-dimensional space and adding a point to close it off.*

In the case of Rourke and Rego's proof, it seemed that virtually no one believed it. Mathematicians complained that it was not written in a way that would enable others to follow it. "I guess I was one of the everybody who didn't believe the proof," says Casson. "It was too vague to follow in detail. I kept coming across parts that were ambiguous." Freedman agrees, adding, "it looks like a program for a proof rather than a proof."

Another reason for doubting the proof, says Freedman, is that it does not take advantage of new developments in the area of three-manifolds. These discoveries, which were advanced in the past decade by William Thurston of Princeton and Richard Hamilton of the University of California at San Diego, have revolutionized the field, leading to the solution of problems that everyone thought were impossible.

"Rourke, as far as I know, was not affected by this revolution," says Freedman. "He could have looked at the problem in this way in 1976 instead of 1986. I'd put a higher probability on an argument being correct if it involved the new ideas." This is not to say that it is impossible that Rourke's approach could work. Instead, says Freedman, the new ideas are "so powerful" that most mathematicians are betting that if anything will enable them to prove the Poincaré conjecture, these ideas will.

Basically, the new ideas relate topology and geometry. In topology, says Freedman, you are not studying shape. "Instead you are studying properties that don't change if you stretch and bend an object. That indicates that you shouldn't think about shape too rigidly." But what Thurston and Hamilton found is that, contrary to mathematicians' intuition, the best way to look at these topological problems is to "put rigid structures on the shapes." Says Freedman, "it was totally unexpected."

With the new ideas in topology, the way to prove the Poincaré conjecture would be essentially to blow up the objects that you think are like spheres and make them round. "You would take this baggy old thing and blow air into it like blowing up a balloon. You would do it by geometry," Freedman explains. "Rourke did it by topology. The argument has nothing to do with shape."

But the new methods are not exactly in common use. "They are very difficult to master. Only a few people can exploit them. Most people find it much easier to keep on doing things the way they always did them," Freedman remarks. And, of course, the new methods do not immediately lead to a proof of the Poincaré conjecture. If they did, Thurston or Hamilton would have proved the conjecture by now.

Still, says Casson, Rourke is certainly a reputable mathematician. "He has done good work and he probably is capable of doing something this good." No one was ready to dismiss out of hand the possibility that he and Rego actually proved the Poincaré conjecture.

Is it possible that Rourke and Rego really do have an outline for a proof? Is it at least a partial proof? Kirby stresses that a proof is either correct or it is not a proof at all. "There is no such thing as a '90% true proof' or an 'almost theorem,' " he says.

Does their approach at least seem promising? Mathematicians say there is no way of knowing. "A lot of things *could* work," says Freedman. "The thing is to find a line that does work. Until there is a complete proof, there is no point in making too much over approaches. There are half a dozen good approaches." In fact, Freedman notes, "what seems to make a good problem is that intelligent plans for attacking it come to naught."

So, for now, mathematicians are not holding their breath waiting for Rourke and Rego to fill in the gap in their proof. Nonetheless, says Rourke, "I will not withdraw the proof until I've thought about it some more." ■ GINA KOLATA