Diego, "we can now visualize how the enzyme interacts with [RT inhibitors], which provides new insights into the mechanisms of resistance." Adds virologist Jaap Goudsmit of the University of Amsterdam, "This is a good paper, and it's very helpful."

Successfully blocking RT is critical to antiviral strategies because the enzyme catalyzes a vital early step in HIV infection: the copying of the virus's RNA genome into DNA, which is then integrated into the host cell's chromosomes. To do this, RT first copies its RNA strand into a DNA strand and then, using the DNA strand as a template, recopies it to make a DNA-DNA double helix. Although other groups have made x-ray structures of RT, no one had ever captured it as it acts on its natural substrates.

The Harvard team began by trying to crystallize a three-part complex made up of the RT protein; a DNA template, to which a short additional piece of DNA "primer" was bound; and a deoxynucleoside triphosphate (dNTP), a precursor building-block molecule that is repeatedly added onto the end of the primer to make the second DNA strand. Many RT inhibitors work by taking the place of dNTP and acting as DNA "chain terminators," gumming up RT function by bonding to the end of the growing DNA chain and barring the addition of new dNTPs.

Several groups, including Harrison's, had tried to crystallize this ungainly molecular complex for many years without success, apparently because the DNA primer–template combination associates only loosely with the RT protein. Harrison then asked Verdine's lab to help out, and Huang, after engaging in what Verdine calls "chemical biology heroics," succeeded in tethering the primer-template to RT with a disulfide chemical bond. The resulting complex was stable and uniform enough to form crystals, which the team took to two U.S.–based synchrotron sources to determine the structure of the enzyme, with all its substrates in place, to the detailed resolution of 3.2 angstroms. "This puts them all together and adds a critical piece to the puzzle [of resistance to RT inhibitors]," says biochemist Bradley Preston of the University of Utah, Salt Lake City.

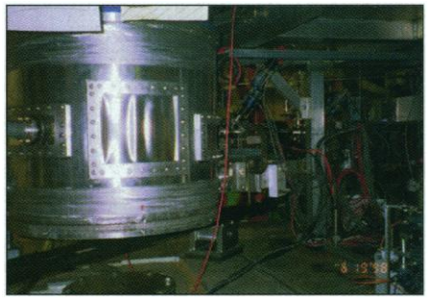
This three-dimensional view of RT in action, combined with earlier studies of the location of drug-resistant mutations along its polypeptide chain, is already yielding new information about how RT foils the inhibitors. For example, those mutations already known to confer resistance directly to the drugs are all clustered around the dNTP site, which the inhibitor occupies when it terminates DNA chain growth. The authors propose that these mutations interfere with the drug's ability to attach to the DNA, either by making it harder for the inhibitor to get into the right position or by reducing its stability or reactivity once it is bound.

According to the Harvard team, the new structure also points to at least one possible target for new RT inhibitors: a small "pocket" in the enzyme near one portion of the dNTP site. Researchers say that drug companies are unlikely to wait long before following up these and other hints provided by the RT structure. "This opens a path to structure-based drug design," says Preston. "It really wasn't feasible before." **–MICHAEL BALTER**

NUCLEAR PHYSICS

Experiment Stopped After Safety Concerns

Nuclear physicists will have to wait a bit longer for long-sought data on the structure of the neutron. In a decision that has stunned members of an international research team, the United States' flagship nuclear science center, the Thomas Jefferson National Accelerator Facility in Newport News, Virginia, has pulled the plug on a major experiment to chart the distribution of the charged particles—quarks—that make up the neutron. The cancellation, announced 12 November, came after an accident last month that heightened tensions between visiting researchers and managers of the 2-year-old facility. The decision, which reflects a growing attention to safety, "has left grown men crying," says team spokesperson Donal Day, a physicist at the University of Virginia, Charlottesville.



CREDIT: DONAL DAY

Fatal attraction. Magnet pulled a tripod through the aluminum window of this target device.

Day is one of several dozen researchers working on the $2 million G_{EN} experiment, seen as a key to proving decades-old theories about how the neutron—the neutrally charged particle in an atom's nucleus—is put together. It involves smashing a beam of electrons accelerated through a kilometer-long circular tunnel against a barrel-shaped target containing supercooled ammonium atoms. By monitoring the collisions, researchers hoped to tease apart the configuration of the neutron's quarks. Indeed, conducting the experiment was one of the main reasons the Department of Energy (DOE) built the $600 million, state-of-the-art lab. "It wasn't the only experiment scheduled to address the question, but it was extremely important," says Don Geesaman, a physicist at DOE's Argonne National Lab in Illinois and head of the Jefferson lab's user committee.

However, that experiment had been plagued by delays since it began earlier this year. And its undoing came on the morning of 7 October, after a surveying team entered the experimental hall to make sure that the electron beam was correctly aligned before the next run. A powerful magnet that is part of the particle-scattering target had been accidentally left on, and its force pulled a surveyor's metal tripod through a thin aluminum window into the target. The collision caused an explosive release of the supercooled helium and damaged the sensitive machine. Although nobody was hurt, and the target was repaired, the mishap prompted an investigation into safety practices.

That investigation—and the researchers' reaction to the findings—prompted Jefferson Lab Associate Director Lawrence Cardman to call off the experiment. In a 12 November memo widely distributed to lab users, Cardman wrote that he had uncovered a potentially dangerous design flaw in the target's helium release valve, as well as numerous violations of safety procedures. But he was most troubled by signs that the visiting scientists and Jefferson staff "had not developed a good working relationship." In particular, he cited reports that a senior scientist had "ridiculed" a recent safety memo and that the researchers had been slow to submit a safety plan.

By the time the plan was done in early November, he says, it was "too late. Experiments like this require cooperation, and they weren't taking their share of the responsibility," although he also faulted his own staff. Another factor in his decision, he says, is that DOE has taken "a lot harder line" on safety in recent years.

Cardman and Day say that such friction between visiting researchers and lab management is not uncommon at a large user facility and can usually be worked out given enough time. In this case, however, the researchers were up against a tight deadline: The target is scheduled to be shipped to the Stanford Linear Accelerator Center in Palo Alto, California, at the end of the year for experiments there aimed at understanding how quarks behave. "We were running out of time," says Day, who notes that his team had safely operated the target in the past.

It is not clear when Day's team will get a chance to complete its work. The target is scheduled to return to Virginia late next year, but the lab's experimental schedule is full. On the bright side, Cardman believes Day's group should be able to demonstrate that it can operate safely and says he doesn't hold a grudge: "We haven't banned them for life."

–DAVID MALAKOFF