BREAST CANCER GENE

Many Mutations May Make Test Difficult

The cloning in September of a strong candidate for the breast cancer gene known as *BRCA1* triggered a whirlwind of activity as cancer researchers rushed to verify the finding (*Science*, 23 September, p. 1796 and 7 October, p. 66). A bare 10 weeks later, three articles in this month's issue of *Nature Genetics* have confirmed *BRCA1*'s identity.

But while those articles have nailed *BRCA1*, they've also raised problems that may further cloud the development of the much-anticipated test for susceptibility to breast cancer caused by mutations in *BRCA1* (*Science*, 22 July, p. 464). The articles report that *BRCA1* mutations occur in many different forms, scattered throughout the gene, making it technically challenging to develop an accurate test. What's more, they hint that mutations in the gene may account for fewer cases of hereditary breast cancer than previously thought.

In the *Nature Genetics* papers, teams led by Steven Narod of McGill University in Montreal (a member of the team that isolated *BRCA1*), Barbara Weber of the University of Pennsylvania, and Mary-Claire King of the University of California, Berkeley, describe 22 different *BRCA1* mutations in 31 families. As the *Science* paper describing the cloning of *BRCA1* identified five mutations in the gene, including one also found in the current work, the total number of published *BRCA1* mutations now stands at 26. Because these mutations are scattered throughout the gene, which at about 100,000 base pairs is exceedingly long, development of a test that will detect all mutations with certainty may be difficult. Indeed, Weber calls the results "bad news for testing."

Still, the problem may be less formidable than it looks right now, says Narod. He notes that some mutations have been detected again and again in different families, suggesting that a relatively small number of mutations may account for most *BRCA1*-related cancers, a situation that may help make screening possible. His team, for example, found two mutations, each of which turned up in four Canadian families. In addition, says Narod team member David Goldgar of the University of Utah, who is busy categorizing all known mutations, published or otherwise, the two Canadian mutations have also been detected in families in the United Kingdom and the United States, and several other mutations have been found two or more times.

"We'll probably be able to identify mutations 75% of the time ... and if it turns out that the majority of [*BRCA1*-associated breast cancers] are caused by 10 or fewer mutations, it could still be a relatively simple screening test," says Narod. Such a test, he adds, "will be very helpful" for screening women from families with a high incidence of breast and ovarian cancer, because the mutation can first be sought in a family member with cancer. But, he says, widespread screening of the general population for *BRCA1* defects is not feasible unless all the mutations can be detected, because it would be uncertain whether a negative result could be trusted.

Both Weber and Narod also point out that about two thirds of the *BRCA1* mutants detected so far cause the protein produced by the gene to be shorter than normal, effectively crippling it. Therefore, measuring the length of *BRCA1*'s protein product could be the basis of a rapid screening test for predisposition to breast cancer. Such a test would avoid the technical difficulty of screening for all types of mutations, but it would also miss more subtle—yet equally dangerous—mutations that don't shorten the protein.

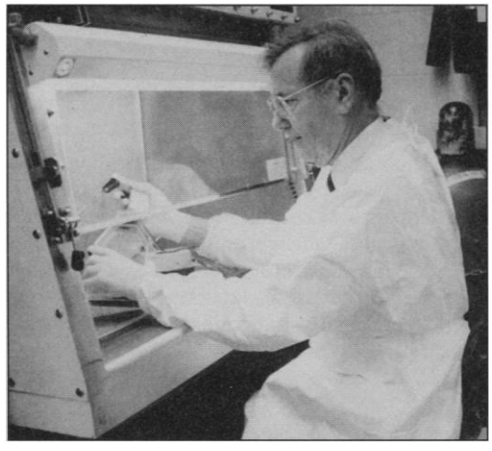
But even if detection of *BRCA1* mutations does one day become practical for widespread population testing, its usefulness for predicting susceptibility to breast cancer may be limited. Hereditary susceptibility accounts for up to 10% of the 180,000 breast cancers that occur in the United States each year. But the discovery of a second breast cancer gene, *BRCA2* (*Science*, 30 September, p. 2088), and hints of others, restrict the number of breast cancers that can be attributed to *BRCA1* defects. Moreover, the three groups failed to detect *BRCA1* mutations in 69 breast cancer families, suggesting either that the tests used were too insensitive or that *BRCA1* accounts for fewer breast cancers than expected. "We are already talking about fairly small numbers," says Weber. "If *BRCA1* accounts for even less, it will further limit the clinical usefulness of a test."

–Rachel Nowak

EPIDEMIOLOGY

Yale Arbovirus Team Heads South

As a source of knowledge about the strange and deadly viruses carried by such creatures as ticks and mosquitoes, nothing rivals a small research center tucked away at the Yale University School of Medicine. Since 1964, the Yale Arbovirus Research Unit (YARU) has been the central repository for the world's arboviruses—shorthand for arthropod-borne viruses—and the place that puzzled scientists have sent their samples. In addition, the unit's director, virologist Robert E. Shope, travels the world to lend his expertise on everything from outbreaks of encephalitis in China to the dengue virus now afflicting U.S. soldiers in Haiti.



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Lone Star–bound. Yale's Robert Shope is expected to join new Texas center.

But as of next year, researchers should plan to send their samples to Shope at a new address: the University of Texas Medical Branch at Galveston. Shope, who is retiring from Yale next year, and virologist Robert B. Tesh, a senior scientist with the unit, have decided to leave New Haven to join a new center for tropical medicine at Galveston—and they hope to take the virus collection with them. Tesh and Shope, who were traveling abroad and could not be reached for comment, disclosed their plans 2 weeks ago at a meeting of the American Committee on Arbovirology in Cincinnati. The University of Texas verified the move after a report appeared in *The Hartford Courant*. A Yale spokesperson says officials have confirmed the departure of Tesh but "have had no conversation with" Shope.

Outside scientists say they aren't surprised the two are leaving Yale. Shope has faced "an uphill battle finding money," says Thomas Monath, former director of the Fort Collins, Colorado, vector-borne infectious diseases laboratory run by the U.S. Centers for Disease Control and Prevention (CDC) and now research director for Oravax Inc. in Cambridge, Massachusetts. After researchers paid by the unit's dwindling original endowment from the Rockefeller Foundation began to retire in the late 1970s, says James Meegan, head of the extramural arbovirus program at the National Institute of Allergy and Infectious Diseases and a former YARU scientist, Shope came to rely increasingly on

researchers on loan from the U.S. military and visiting scientists. The unit has also struggled to maintain grant support, especially as a shrinking defense budget has squeezed funding for arbovirus research.

In addition, says Monath, "it has been difficult for Shope to sustain strong support for this effort within his own department." U.S. Army hantavirus researcher Connie Schmaljohn describes the situation more bluntly: "The people above them just didn't recognize their value," she says. "Half the higher level administrators didn't know it existed." A Yale spokesperson disputes that charge, saying that the university "has been supportive of the unit for 30 years." Recent instability at the Department of Epidemiology and Public Health, which oversees the unit, has aggravated the situation, according to several sources.

YARU, which operates mostly on grants from the National Institutes of Health (NIH), the U.S. Army, and the World Health Organization (WHO) that totaled about $2 million in 1993, houses some 450 virus cultures, as well as reagents, antibodies, and antigens for studying arboviruses. In addition to Shope and Tesh, the lab employs three investigators who will not be moving to Galveston. A lot of history will be going with it. Begun with a grant from the Rockefeller Foundation, YARU has "a long, glorious history," notes Meegan. "It has been at the front line [of infectious disease research] for 30 years."

The unit's most recent media splash, however, was an embarrassment. In August, visiting scientist Jean-Paul Gonzalez didn't report that he had broken a vial of the dangerous Sabia virus until 12 days after he showed symptoms of the disease. Gonzalez has recovered, and a CDC report on the accident is due out this month. But the origins of the move to Galveston predate this incident, say Texas officials, who began negotiating with Tesh last year.

Galveston sought the Yale unit to bolster its new Center for Tropical Diseases, opened last year with help from the Texas-based Kleberg Foundation. The center, part of WHO's network of tropical disease centers, will focus on intracellular diseases, particularly in Latin America. The YARU recruits will help "expand the depth of the center" and build international collaborations, says Assistant Director Michael McGinnis.

Tesh will arrive in March or April, McGinnis says; Shope has not yet made a formal agreement to come to Galveston, but university officials expect him to join them sometime next summer. The status of the collection is also up in the air: Yale officials are prepared to discuss with Shope and Tesh the transfer of YARU's virus collection and some of the unit's grants to Galveston, says a university spokesperson.

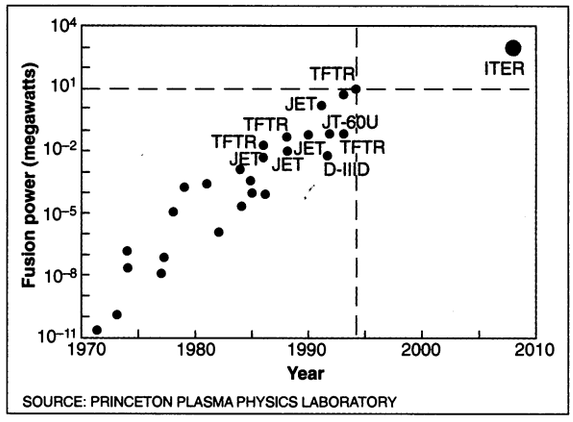
–Jocelyn Kaiser

PLASMA PHYSICS

Magnetic Fusion Tops Limit at Princeton

MINNEAPOLIS—Like race car mechanics grinding valves and polishing cylinders to squeeze out a few extra horsepower, physicists and engineers at Princeton University's Tokamak Fusion Test Reactor (TFTR) have pushed their machine beyond its design specifications to set a new record for fusion energy output. Even better, said TFTR researchers when they announced the latest results here on 7 November at a meeting of the plasma physics division of the American Physical Society, their fusion machine is running more smoothly than ever.

In a packed hall so large that his transparencies had to be shown on three separate screens, Princeton physicist Kevin McGuire announced that a hot, magnetically confined plasma in TFTR had produced 10.7 megawatts of fusion power, surpassing the 6-megawatt mark set late last year (*Science*, 24 December 1993, p. 1966). Along the way to the new record, McGuire added, the Princeton group found that the deuterium-tritium plasmas they have been testing—the same mixture of hydrogen isotopes likely to fuel the first working fusion power reactors—are "better [behaved] in almost every respect" than plasmas of pure deuterium, the staple of fusion experiments until last year. TFTR recently won a 1-year reprieve from the funding cutoff that would have shut down the facility at the end of this year, and Steve Eckstrand, TFTR program manager in the Department of Energy's (DOE's) office of fusion energy, says "the results have certainly borne out [the decision]."



On track. The rising output of magnetic fusion experiments in Princeton (TFTR), the United Kingdom (JET), Japan (JT-60U), and San Diego (D-IIID) is raising hopes about the proposed International Thermonuclear Experimental Reactor (ITER).

If TFTR had been kept within its design specifications, the machine would have been limited to about 9 megawatts of power. But after re-evaluating the machine's earlier performance and its safety criteria, TFTR physicists decided this fall that they could turn up the heat. They pushed the doughnut-shaped device's magnetic field 8% beyond the specifications and its neutral-beam injectors—which heat the plasma trapped within the field to hundreds of millions of degrees—to 20% over the specs. The result was the unprecedented burst of power, which peaked for a tenth of a second.

All the while, the plasma remained gratifyingly well-behaved. In fact, McGuire said at the meeting, the amount of thermal energy stored in the plasma, the length of time the energy could be confined, and the temperature and density of the plasma have all gone up over the past year as researchers wrung more power from TFTR in successive tests. And the levels of radioactivity leaking out of the reactor from the deuterium-tritium reactions were surprisingly low, according to Richard Hawryluk, head of the TFTR project. Part of the reduction reflects a lower-than-expected rate of tests, but the reactor's structure also cut radioactivity leakage by at least a factor of 10 below the original conservative projections, said Hawryluk.

The TFTR team will have at least a year to build on these successes. The facility had been scheduled to be shut down at the end of 1994 to make way for Princeton's next major fusion experiment, the Tokamak Physics Experiment (TPX), which is meant to sustain fusion reactions for minutes on end. In August, however, Congress reapportioned the fusion budget, reducing TPX's share and freeing up enough money for TFTR to continue operating. Hawryluk says TFTR scientists will use the extra time to study physics issues such as instabilities in the plasma and the behavior of the alpha particles, or helium nuclei, that are the "ash" of fusion. These high-energy particles would play a crucial role in a working reactor: keeping the plasma hot enough to sustain fusion when the external heating is turned off.

Keeping TFTR running is a good investment, Hawryluk adds, because except for the Joint European Tokamak in the United Kingdom, which is expected to break Princeton's records by 1996, experiments with reactor-grade plasmas will be scarce once TFTR shuts down. "We have a facility that is really running well," says Hawryluk. "I think it's important to get the maximum out of it."

–James Glanz

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