crobe's diabolical modus operandi.

Using a tissue culture system in which the microbe causes the same type of damage as in humans, the researchers found that two toxic substances produced by *B. pertussis* work together to kill the ciliated cells. One of those molecules, tracheal cytotoxin (TCT), has long been a suspect, but the other, endotoxin, is somewhat of a surprise. It is usually known for causing widespread immune system stimulation, which can lead to shock. "This is different," says Drusilla Burns, a microbiologist at the Food and Drug Administration's Center for Biologics Evaluation and Research in Bethesda, Maryland. "Endotoxin is not normally associated with specific pathology."

Even more surprising, the two toxins do not launch a direct attack on the ciliated cells. Instead, they work together to incite neighboring cells to produce a noxious molecule, nitric oxide (NO), which kills the ciliated cells by an as yet unknown mechanism. "This work might explain some of the pathology of *pertussis*," says Ferric Fang, a molecular biologist at the University of Colorado Health Sciences Center in Denver. And, he adds, it might also "provide strategies for intervention."

Such strategies are badly needed. In developed countries, vaccination largely holds whooping cough in check, but the incidence of the disease in adults appears to be increasing; in nondeveloped countries, *B. pertussis* still kills from 300,000 to 500,000 people every year. And although antibiotics eliminate the bacteria, by the time the characteristic cough develops, the microbes are often already gone, having set a cascade of destructive events in motion. Drugs that inhibit NO production might allow the tracheal epithelium to recover more quickly.

Earlier work by Goldman's group had shown that NO is involved in the attack on the ciliated cells and suggested that TCT acts as a trigger. But when the team tested whether TCT causes epithelial cells in cultured hamster tracheal tissue to activate production of an enzyme called inducible NO synthase (iNOS)—which makes NO—they got what Goldman describes as a "surprise result." TCT had no effect at all on iNOS production in epithelial cells. The researchers concluded that something in addition to TCT may be required to coerce the epithelium to produce NO.

Goldman and Flak suspected that this coculprit might be endotoxin, because the team had previously uncovered another case of TCT-endotoxin cooperation, in preventing the growth of a single type of respiratory epithelial cell in culture. It prompted the researchers to add endotoxin along with TCT to their culture system. The combination worked.

Because not all the cells in the tracheal epithelium are ciliated, the team wondered whether the ciliated cells themselves or their neighbors produce the NO. As Goldman recalls asking, "Are the ciliated cells committing suicide, or are they being assisted by other cells in the epithelium?" Further studies provided an answer: TCT and endotoxin induce the nonciliated, mucus-secreting cells to produce the toxic gas.

Goldman notes that both TCT and endotoxin are made by many other bacteria in addition to *B. pertussis*, although most of the other microbes recycle TCT rather than release it. "You've got almost an ironic situation," he says, "where you have this extraordinary specificity of pathology and of nitric oxide production" spurred by two extremely common molecules. Endotoxin and TCT might collaborate to kill other ciliated cells in the body as well. Work by Raoul Rosenthal's group at Indiana University School of Medicine in Indianapolis and collaborators suggests that *Neisseria gonorrhoeae* destroys ciliated cells of the reproductive tract using these same two molecules.

The researchers do not yet understand how NO kills the ciliated cells without harming the secretory cells that produce it. But, as Goldman points out, the strategy might be "exactly what [*B. pertussis*] needs," because it allows mucus to accumulate while eliminating the normal way for expelling it. The result is a hacking cough—an ideal way to transfer the bacteria from one person to another.

Many questions remain about how both NO and the TCT-endotoxin partners produce their effects. Researchers also need to find out whether *B. pertussis* operates the same way in humans. This might be addressed, says Erik Hewlett, a *B. pertussis* expert at the University of Virginia, Charlottesville, by seeing whether the iNOS expression patterns in trachea specimens from children who died from whooping cough mimic those seen in Goldman's experiments. If so, it might indicate that *B. pertussis* is putting its subversive tactics to work in environments other than the culture dish. **–EVELYN STRAUSS**

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RESEARCH FUNDING

House Panel Cuts Space Science, NSF Budgets

Two weeks ago, NASA's leaders were popping champagne corks to celebrate the 30th anniversary of the "giant leap for mankind" on the moon and the recent launching of the x-ray telescope Chandra. Then last week, the atmosphere in NASA's Washington, D.C., headquarters turned funereal: On 26 July, the House Veterans Affairs–Housing and Urban Development (VA-HUD) appropriations subcommittee cut $1.4 billion, or more than 10%, from NASA's current budget. This carved a massive $640 million slice out of space science, threatening future Mars missions and the

ScienceScope

High-Tech Whipping Boy A federal program that funds high-risk industrial R&D is back in the congressional doghouse. Last week, House appropriators voted to zero out the 2000 budget of the Department of Commerce's Advanced Technology Program (ATP). House Science Committee chair James Sensenbrenner (R–WI) then piled on, calling reform efforts at ATP "a sham."

After much prodding from Congress, ATP in 1997 rewrote its rules to fund only those R&D proposals at companies that failed to secure private money for projects. But according to a new report from the Government Accounting Office, ATP officials still review initial proposals in which the prospects for private sector funding aren't spelled out.

ATP project for making semiconductor chips.

To Sensenbrenner, that means the reforms aren't working. ATP associate director Marc Stanley, however, says the program hews to its new line: Regardless of which projects ATP ends up reviewing, only those shunned by corporate financiers get federal dollars. The Senate has given ATP an easier go, allotting the program $226.5 million, nearly the full White House request; a House-Senate conference later this year will resolve the differences.

Darwin-Free Biology Kansas authorities are poised to approve a new set of science standards that eliminates most references to evolution. The decision is expected on 11 August, when the Kansas State Board of Education meets to approve wording of a text that has been the focus of a prolonged public battle.

Several members of the 10-member elected board have fought to keep evolution out of the document, which will be the basis for statewide achievement tests. Religious fundamentalists on the board have recruited a six-member majority in favor of a version that deletes most references to evolution from the biology curriculum, says John Staver, director of the Center for Science Education at Kansas State University in Manhattan and co-chair of the committee that drafted the standards. If approved, the curriculum will leave individual school districts free to decide whether to include evolution in biology classes. "It's a sad day for public education and an embarrassment for the state of Kansas," Staver says.

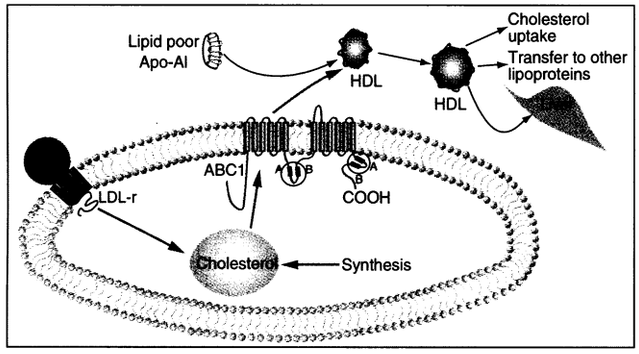
The search for the Tangier culprit was a sprint to the finish after a very long marathon. Donald Frederickson, then at the National Institutes of Health in Bethesda, Maryland, discovered the disease in 1961. Not until 1998, however, did longtime Tangier researcher Assmann—formerly a postdoc in Frederickson's lab—and his colleagues finger a region of chromosome 9 as the location of the Tangier disease gene. But that still left the major job of finding the gene itself.

Enter Hayden's group in Vancouver. The researchers pinned down the approximate location of the gene by looking to see which chromosome 9 "markers" were consistently found in Tangier patients, but not in unaffected family members—an indication that the gene and marker are close to one another. Once they found such a link, the researchers had help from nature in pinpointing the exact gene: One patient was the child of two first cousins, and thus, Hayden's team reasoned, he likely had the same mutation in both copies of the gene. That conjecture, together with their analysis of FHA families, led the team to the *ABC1* gene, which had been cloned in 1994 by Giovanna Chimini's group at the French research agency INSERM-CNRS in Marseille Luminy, but whose function was then still unknown. "Basically, we squeezed as much juice as we could from the genetic data we had," Hayden says.

Meanwhile, Schmitz's group in Regensburg was using a more biochemical approach to pinpoint the gene. They looked for genes that were expressed differently in the cholesterol-laden cells of Tangier patients than in normal cells. This search also fingered the *ABC1* gene as the most likely candidate—an identification that was confirmed when the gene turned up mutated in all five Tangier patients that the Schmitz team studied. In addition, Chimini's group had already inactivated the gene in mice, and when Schmitz and his colleagues examined those animals, they found that they had developed symptoms similar to those of Tangier disease. Finally, Assmann's group found *ABC1* through a combination of the techniques used by the other groups.

Evidence from Hayden's and Schmitz's groups indicates that ABC1 normally transports cholesterol out of the cell. For example, Schmitz found that cells engineered to make extremely high amounts of the protein were so depleted of cholesterol that they died, while cells in which ABC1 synthesis was inhibited accumulated more, much as cells from Tangier patients do.

So far, however, the research has not resolved a conundrum about Tangier disease: Even though all the patients have low HDL cholesterol concentrations in their blood—a condition thought to predispose to the artery-plugging lesions of atherosclerosis—some seem to escape coronary disease. That puzzle is heightened by the Hayden group's results linking *ABC1* mutations to FHA, an HDL cholesterol problem in which patients do show an increased risk of heart attack. The Vancouver group has so far screened 20 FHA families for *ABC1* mutations and found them in eight.



The way out. ABC1 normally carries cholesterol out of the cell for uptake into HDL particles. But if *ABC1* mutations prevent that, cholesterol may build up in cells while blood HDL levels go down.

CREDIT: S. CLEE, G. LIU, AND M. HAYDEN

One possible explanation for the apparent paradox, Schmitz says, is that the transporter has a dual role—both ferrying cholesterol out of the cell and directing cells such as macrophages, a type of immune cell, to specific locations in the body. His hypothesis is that a mutation in one spot may send cholesterol-laden macrophages off to the spleen, lymph nodes, or tonsils for processing—hence the oversized tissues characteristic of Tangier disease—whereas a different *ABC1* mutation may cause the macrophages to stick to the vessel wall, in that case leading to atherosclerosis and heart disease.

Further work will be needed to test those ideas, as well as to see how common *ABC1* mutations are in FHA. But the new findings raise the possibility of developing drugs that protect against heart disease by raising blood HDL levels—a feat no one has yet accomplished. Even if ABC1 doesn't pan out as a target for such drugs, researchers may yet find other potential targets. "This should open the doors to a general research effort into what regulates cholesterol coming out of cells," Fielding says. "There may be other mechanisms, but this is the first one, and it is a good place to start." **–TRISHA GURA**

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ScienceScope

Pet Projects The Japanese government is preparing to give science a hefty 9% raise in next year's budget. But researchers aren't quite ready to celebrate: Much of the increase appears slated for projects that will be hand-picked by Prime Minister Keizo Obuchi's office.

Agency spending guidelines, adopted by the Cabinet last week, include a new $2.17 billion account for R&D in information, life, and environmental sciences deemed to have potential for a high economic payoff. Science spending in usual accounts for the fiscal year starting in April 2000 will be nearly flat, says Nobuhiro Muroya, deputy director of planning for the Science and Technology Agency. The majority of the increase will go to the new category; to vie for funds, each ministry must propose projects to the prime minister's office, which will assess the projects—likely ones already on the drawing board—according to yet-to-be-defined criteria.

"This came up so suddenly, I don't think anyone in the science community knows anything about it," says one senior scientist. But they will soon: It should become clear by the end of this month which projects are on the funding fast track.

Beyond the Numbers A new report offers stern advice for academic mathematicians: Pay more attention to the world around you, or at least to the other departments in your university.

To learn how math departments view themselves—and how they're viewed on campus—a task force of the American Mathematical Society (AMS) spent 7 years interviewing the chairs of half the nation's Ph.D.-granting math departments and 30 of their deans. They found a dramatic dichotomy in perceptions. "There wasn't a dean who didn't say math was the leading cause of complaints" at his university, says AMS executive director John Ewing. And whereas most mathematicians saw their discipline as central to the sciences, says Ewing, most deans viewed mathematics as one of the most "insular" departments on campus.

The report recommends that department chairs reward faculty members who focus on instruction, forge collaborations with other departments, and devote more resources to outreach and to remedial education. The payoff may well be more money for research, says Ewing: "Their life as a research department depends on ... their teaching."

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