The chiefs of the Department of Energy (DOE) weapons labs, called to testify before the Senate Armed Services Committee on 7 October, didn't provide their political bosses with much ammunition, either. Bruce Tarter, director of the Lawrence Livermore National Laboratory, said that simulated weapons testing under DOE's $4.5 billion-per-year Stockpile Stewardship Program "has an excellent chance of ensuring that this nation can maintain the safety, security, and reliability of the stockpile without nuclear testing" but that "it is not a sure thing." C. Paul Robinson, director of the Sandia National Laboratory, said the best guarantee of security is to continue testing weapons. "To forego that validation ... [is] to live with uncertainty," Robinson warned. Los Alamos National Laboratory chief John Browne said the reliability of nuclear weapons requires a "national commitment"—in other words, generous funding of the stewardship program and less criticism of lab management.

The CTBT did receive a technical vote of confidence last week from a joint AGU-SSA review panel, which had examined the plan for detecting low-yield nuclear tests. The CTBT allows for on-site inspections covering no more than 1000 square kilometers of any alleged test site. This is the area within which current technology can pinpoint the location of a magnitude 4 seismic event (equivalent to a 1-kiloton blast). The AGU-SSA panel, chaired by seismologist Terry Wallace of the University of Arizona in Tucson, concluded that the CTBT verification network, when complete, "can be relied upon" to detect and locate 1-kiloton tests. Members of the panel—including Gregory van der Vink of the Incorporated Research Institutions for Seismology in Washington, D.C., and Jeffrey Park of Yale University—said they didn't think it would be difficult to spot a weapons development program, even if the tests were very small.

The AGU-SSA group acknowledged a major uncertainty, however: No one has reliable data on a blast deliberately "decoupled" from the environment. Some research suggests the seismic signal would be nearly cut in half by decoupling, a process in which a damping substance (or air) is introduced between a bomb and the surrounding structure to reduce the transmission of blast waves. But doing this would require "extraordinary technical expertise," according to the AGU-SSA statement, and in any case, "the likelihood of detection is high." Van der Vink said that decoupling a bomb might increase the risk of radionuclide release, which would be picked up by an independent set of sensors. "No nation could rely upon successfully concealing a program of nuclear testing, even at low yields," the panel concluded.

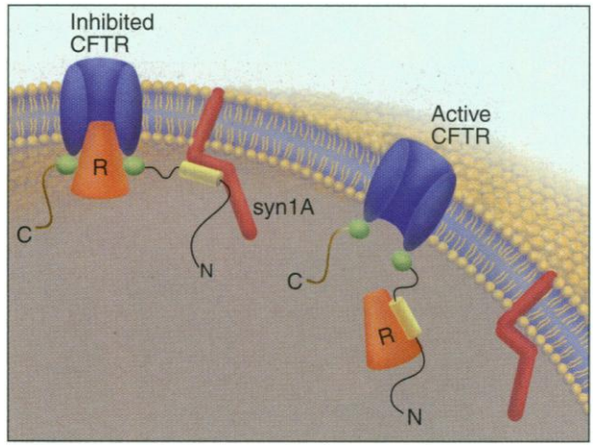
Whatever the Senate does, the test ban is likely to be discussed at election time. And that may mean an encore for the scientists who appeared in last week's drama.

–ELIOT MARSHALL

CELL BIOLOGY

New Insights Into Cystic Fibrosis Ion Channel

For commuters all over the world, a broken traffic light can be a nuisance. But when the proteins that regulate the traffic of molecules into and out of cells malfunction, it can spell disaster. Take the protein encoded by the gene at fault in cystic fibrosis, which strikes about one in 3000 newborns every year in the United States alone. Known as the cystic fibrosis transmembrane conductance regulator (CFTR), this protein channels chloride ions through the cell membrane, thereby regulating the water and salt balance in cells that line organs such as the lungs and intestines. Mutations that prevent the CFTR from doing its job disrupt this chloride transport, which in turn causes the lungs and certain other organs of affected individuals to fill up with thick, sticky secretions, setting the stage for life-threatening lung infections.



Unplugged. By interacting with the R domain, the CFTR tail may help keep open one of the cell's chloride channel.

New insights into how the CFTR works may now help researchers design drugs that regulate the operation of this vital cellular channel. On page 544, physiologist Kevin Kirk of the University of Alabama, Birmingham, and his colleagues report that they've identified an interaction between two parts of the CFTR molecule that seems to help keep the channel open. Drugs directed at the CFTR regions involved in that interaction might therefore serve to either enhance or inhibit chloride transport through the channel.

Although few cystic fibrosis patients are expected to benefit from any channel-activating drugs—most CFTR mutations prevent the protein from even getting to the membrane—channel inhibitors may have a wide application. Various forms of watery diarrhea, including those caused by the cholera bacterium and pathogenic *Escherichia coli*, are due to toxins that kick the CFTR into overdrive. Such infections kill far more people than cystic fibrosis, mainly children in developing countries. "This is a solid step forward, one of the more important insights into CFTR regulation in recent years," says biochemist and CFTR co-discoverer Jack Riordan of the Mayo Clinic in Scottsdale, Arizona.

The new findings stem from a discovery Kirk, Anjaparavanda Naren, and their colleagues made about 2 years ago. They found that a membrane protein called syntaxin 1A shuts down the CFTR channel by holding on to one of the channel protein's "tail" regions, which protrude into the cell interior. This suggested that the tail somehow controls CFTR function. To find out more about what it does, the team performed a series of experiments in which they either mutated specific amino acids in the tail region that binds syntaxin 1A or deleted the tail altogether.

The researchers introduced the mutant genes separately into frog eggs, where the protein products were made and inserted into the cell membranes. Because chloride transport affects the cell's electrical properties, the team assessed CFTR function by measuring the overall current across the membrane in response to signals known to activate CFTR. The researchers found that the tail had to be present for normal channel opening to occur. And they identified four negatively charged amino acids, all clustering on the same side of a predicted helical region of the tail, as crucial to that operation. "This suggested that the tail probably interacts with some other part of the CFTR," Kirk says. Fishing for the partner region, the researchers came up with "the most obvious candidate," as Kirk puts it. This is the so-called R domain.

Previous work has shown that the R domain keeps the CFTR channel closed until it is decorated with chemical tags called phosphate groups in response to CFTR activation signals. At that point it seemingly "swings out" of the way and sets the stage for a second incoming signal, the binding and subsequent cleavage of a small molecule called ATP, which provides the energy necessary to pop the channel open. Kirk now proposes that the tail binding to the R domain helps keep the channel unlocked. He and his team

CREDIT: MODIFIED FROM KEVIN KIRK; ILLUSTRATION: CARIN CAIN

found, for example, that a CFTR with mutations in the presumed R-binding region opens at about the same rate as the normal CFTR but, once open, closes much faster. This, "of course, reduces the total amount of chloride ions" a cell can shuttle in and out, Kirk says.

In the past, the CFTR tail had attracted little attention, but that is now likely to change. "The tail is a new player in the game, and this suggests a new way of regulating the gating of CFTR which may involve other proteins that can bind to the tail," says William Guggino, a cell physiologist at the Johns Hopkins School of Medicine in Baltimore. One of these other proteins is likely syntaxin 1A, which may keep the tail from interacting with the R domain until activating signals somehow disrupt syntaxin binding and release the tail to capture the R domain.

What's more, says Richard Boucher, a physiologist at the University of North Carolina, Chapel Hill, the newfound tête-à-tête between the tail and the R domain "gives you a clear-cut target" for drugs against cholera or for drugs to treat the 10% to 20% of cystic fibrosis patients whose CFTR makes it to the cell surface but is crippled by mutations. And though it's unclear whether such compounds will work, specific CFTR blockers, for instance, should help clarify the intricate workings of the CFTR, which even today—10 years after its discovery—still holds many secrets. **–MICHAEL HAGMANN**

MATERIALS SCIENCE

Words Writ—Very—Small by a Nanopen

In 1959, physicist Richard Feynman gave a speech that inspired later generations of scientists. Titled "Plenty of Room at the Bottom," the talk foreshadowed one of today's hottest trends in material sciences: nanotechnology, assembling chosen molecules into tiny materials that can be used for everything from fluorescent dyes to solar cells. He did take some seemingly wild flights of fantasy, however, such as wondering whether crafty researchers would one day find a way to write an encyclopedia on the head of a pin. Now, chemists at Northwestern University have memorialized a paragraph of Feynman's speech in a most appropriate way: They've used a nanoscale pen and ink set to write it in an area just one-thousandth the size of a pinhead.

The work, performed by postdoc Seunghun Hong and graduate student Jin Zhu along with group leader Chad Mirkin, is described on page 523. It isn't the first example of nanoscale writing, but it is the first time researchers have accomplished the job with multiple "inks" that line up with one another to produce features as small as 5 nanometers.

More than just a gimmick, the achievement could pave the way for applications, ranging from testing novel catalysts to creating nanoscale electronic devices, that might reveal whether the dream of making electronic devices with the dimensions of molecules could ever succeed. "It seems like a real enabler" of nanotechnology, says Clifford Kubiak, a chemist and nanotechnology expert at the University of California, San Diego.

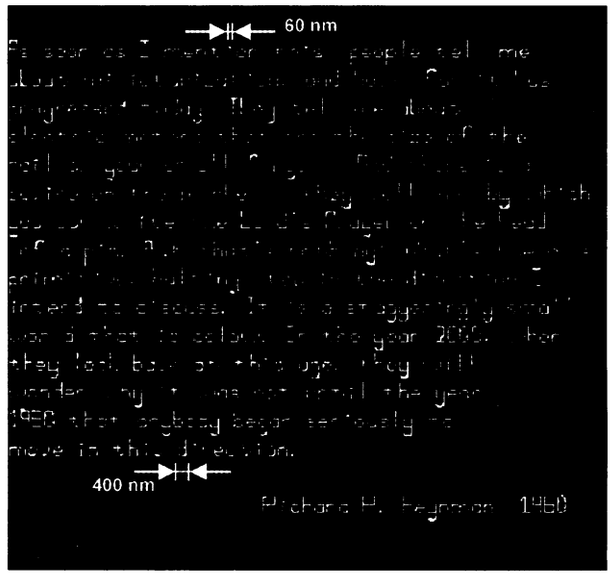
Previously, researchers have used either electron beam lithography or, more recently, the tiny styluslike arm of an atomic force microscope (AFM) to create nanometer-sized features on a surface. But these techniques can damage the surface, particularly if it's already been patterned with an organic ink, or leave behind molecular contaminants, making it hard to add new, pristine layers that line up in perfect registry with the ones below, a typical requirement for making electronic devices.

To get around these problems, Mirkin and his colleagues came up with a technique called dip pen nanolithography (*Science*, 29 January, p. 661). It takes advantage of another problem encountered by researchers trying to write features with a conventional AFM: water from the air that condenses between the tip and sample, interfering with the tip's motion and thereby the resolution of the image. Rather than being stymied by this problem, Mirkin's team used the water layer to transport organic ink on the AFM tip to a surface. Thus, dragging the tip over the surface produces well-defined lines.

With just one ink, they could write simple structures, including letters. But making an electronically active nanostructure requires positioning different organic conductors, insulators, and semiconductors in different regions. The Mirkin team hasn't yet accomplished that, but it has taken a step in that direction by figuring out how to align a second set of ink marks with the first.

They began by coating one AFM tip with an ink consisting of 16-mercaptohexadecanoic acid (MHA), an organic molecule capped with a water-attracting carboxylic acid group. They then used this ink, along with their computer-controlled AFM, to write a set of parallel lines 70 nanometers apart. Because they feared that their second AFM pass would damage these lines if they used it to locate them directly, they also put in cross-shaped alignment marks, which sit 2 micrometers on either side of the lines.

Next, the researchers changed their AFM tip to one dipped in a second ink called 1-octadecanethiol (ODT), which is capped with a water-repelling methyl group, and scanned this tip across the surface to find the alignment marks. The computer then positioned the tip near the original set of parallel lines and wrote another set alongside the first. Alternatively, the researchers simply use the second ink to fill in the space around the first set of features, because the two inks they chose don't mix.



Tiny tribute. Text from a speech by physicist Richard Feynman, which was first delivered in 1959 and published in 1960, now comes nanosized.

Finally, to view the patterns they created, the team switched to an uncoated AFM tip, which they used to scan the entire surface. Since the tip encountered higher friction with the MHA than with the ODT, it could tell the two materials apart and create an image of the pattern.

All this tip-changing sounds slow and tedious, but the team has recently automated the procedure, enabling them to write letters reasonably quickly. Indeed, the 115-word paragraph from Feynman's speech took 10 minutes—"about the same amount of time it took us to print it out on our color printer," says Mirkin.

While nanowriting could generate some interest among spies, Kubiak believes its real value will be in making numerous nanoscale electronic devices in a highly reproducible fashion. That would benefit researchers trying to understand how well such small devices operate. Mirkin adds that the technique could also be used by researchers trying to understand catalyst behavior, since it would enable them to place catalysts and reactants in precise locations, just a few nanometers apart, and

CREDIT: S. HONG, J. ZHU, AND C. MIRKIN/NORTHWESTERN UNIV.