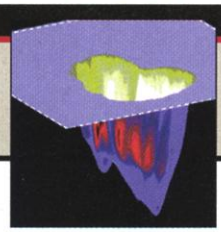
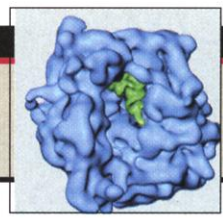


PAGE 25
Detecting a subway from space

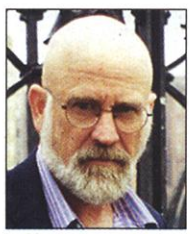


25
Looking ahead to 2000

CHRONIC FATIGUE SYNDROME

CDC Struggles to Recover From Debacle Over Earmark

Crossing Congress can be bad for an agency's health. That's the painful conclusion that the Centers for Disease Control and Prevention (CDC) has drawn as it tries to recover from a self-inflicted wound: the diversion of millions of dollars budgeted for chronic fatigue syndrome (CFS) into work on other diseases. In addition to angering patient advocacy groups and some legislators, the CDC has now been forced to tax other programs to replenish the CFS account. And even though the agency has apologized and sought extensive comment on a new CFS research agenda, officials face another round of investigations—as well as a complaint from an employee alleging that he was persecuted for revealing the misallocation.



> "Now that we have complete and unfettered control over the money, the program is going very well."
>
> —William Reeves

At the root of the controversy is $22.7 million that Congress earmarked for CFS research in 1995. In 1998, William Reeves, the agency's top CFS researcher and director of the Viral Exanthems and Herpesvirus Branch, filed a whistle-blower complaint charging that his superior, Brian Mahy, who heads the Division of Viral and Rickettsial Diseases, had used a large part of the special funds for other purposes. He also alleged that CDC officials tried to cover up the reallocation during oversight hearings before Congress. His claims were backed up by the inspector general of the Department of Health and Human Services, who in May 1999 found that only $9.8 million had definitely been spent on chronic fatigue research. Some $8.8 million had gone to poxvirus, human papillomavirus, measles, polio, and other research within Mahy's division, she reported, and it was impossible to tell how the remaining $4.1 million was spent. The report also said that CDC's acting director, Claire Broome, had provided lawmakers with "inaccurate and potentially misleading" data about the program.

In July, CDC's new director, Jeffrey Koplan, acknowledged the diversion, apologized to Congress and CFS patient groups for a "breach of CDC's solemn trust," and vowed to restore the disputed $12.9 million for CFS research over the next 4 years. To prevent future episodes, CDC has mandated financial training for all its managers, and Mahy's divisional budget will be handled by Koplan's office until 2001. CDC says the corrective measures are "the most far-reaching in the half-century history" of the agency. Mahy has declined to comment on any aspect of the controversy.

CFS, also known as myalgic encephalopathy, is a mysterious, debilitating disorder that robs patients—mostly adult Caucasian women, according to an as-yet-unpublished CDC study—of the energy needed for even the most basic tasks. Although it has been called chronic fatigue syndrome since the late 1980s, records of related afflictions go back more than a century. However, researchers have so far failed to link the disease to an infectious agent or another organic cause.

Patient groups such as the Chronic Fatigue and Immune Disorder Syndrome Association of America (CFIDS) say that the lack of clear etiology has led many researchers to see CFS as a psychosomatic disease, which has reduced scientific interest. "There is an element of bias at CDC," says CFIDS executive director Kimberly Kenney. "They feel that if there was something to be found, they would have found it by now, and therefore it doesn't warrant much more intensive research."

Agency officials disagree, saying that the reallocation of funds was mostly the result of poor accounting practices. "We have many brilliant scientists who are, frankly, not very good managers," says CDC spokesperson Barbara Reynolds. In addition, Joseph McDade, deputy director of the National Center for Infectious Diseases (NCID), says that public health emergencies such as last summer's West Nile virus epidemic in New York City can require CDC to reshuffle resources suddenly. "When you have large outbreak investigations, it's sometimes difficult to fund those and continue other programs as well." Indeed, some researchers both within and outside CDC say that there may well have been sound scientific reasons to emphasize diseases known to be infectious rather than something as elusive as CFS. "Of course you shouldn't break the rules," says Jack Woodall, a former CDC researcher who now directs the Center for the Study of Emerging Infectious Diseases at the Federal University of Rio de Janeiro in Brazil. "But I'm sure [Mahy] did what he thought was in the best interest of public health."

In the wake of the government inquiry, CDC has drawn up a "reinvigoration plan" to understand the disease. The new strategy, to be finalized in February after a series of hearings, includes a nationwide study of the prevalence of CFS and efforts to increase awareness of the disease. It will also pursue a new approach to finding a cause, comparing gene expression patterns between patients and healthy people and using advanced techniques to detect new pathogens. "Now that we have complete and unfettered control over the money, the program is going very well," says Reeves, who manages the effort.

> "We have learned a valuable lesson through this experience, which will not be forgotten."
>
> —Jeffrey Koplan

But although the CFS program may be back on track, other research programs may be knocked off balance. Most of the money will come from the $217-million-a-year

CREDITS: CDC

26 The plight of postdocs

28 The travails of archaeology in the Holy Land

budget of NCID, which includes Mahy's division. Reeves says CDC as a whole should absorb the loss. "This is going to severely compromise NCID's ability to do important infectious diseases research," he warns. But McDade predicts that things will work out. "Every year there are many things that need to be done, and there are always challenges about resource allocation," he says. "This is just one more challenge."

Finances aren't the only obstacle to full recovery for CDC. Reeves, who is protected by a federal whistle-blower law, has filed a complaint with the U.S. Office of Special Counsel in Washington, D.C. It claims that Mahy, upset at his speaking out, issued him an unjustified reprimand, reduced his performance appraisals, and removed staff from his supervision. Reeves says he wants those actions undone and is also asking for recovery of attorney fees and $300,000 in damages. McDade says CDC hasn't been officially notified of the case and declined to comment.

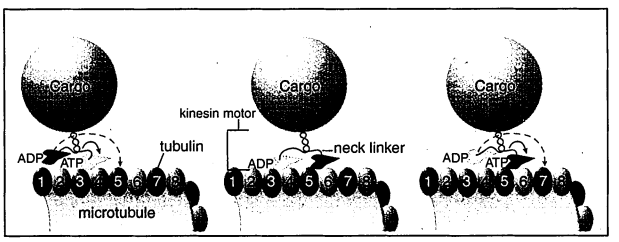
Meanwhile, the General Accounting Office (GAO), Congress's financial watchdog, is taking a closer look at chronic fatigue research at CDC and its sister agency, the National Institutes of Health. That study, to be completed in the spring, "will be a qualitative assessment of the [scientific] program," says GAO researcher Janet Heinrich. The study was requested by Senator Harry Reid (D–NV), a champion of CFS patient groups who helped obtain the special funding.

Whatever these investigations and studies conclude, CDC isn't likely to make the same mistake twice. "We have learned a valuable lesson through this experience, which will not be forgotten," said a statement that Koplan sent to patient groups this summer. For Woodall, that lesson is elementary: "As we all know, you have to be careful with what you do and how you deal with the people who control the money." **–MARTIN ENSERINK**

CELL BIOLOGY

Kinesin Movements Revealed

Edwin Taylor and Nobutaka Hirokawa are not your average mechanics. Instead of tinkering with grease and iron, they study the cell's molecular motors. And unlike ordinary mechanics, who know that all engines are basically alike, Taylor and Hirokawa are finding an unexpected diversity in molecular motor design. Take kinesins, motor proteins that drag protein-laden vesicles along microscopic tracks called microtubules to the cell's periphery. Last month, at the annual meeting of the American Society for Cell Biology, which was held in Washington, D.C., Taylor, a cell biologist at the University of Chicago, and Hirokawa, a cell biologist at the University of Tokyo, described new results showing that two different kinesins move in very different ways.



Forward, march! When ATP binds to kinesin's front "foot," it causes the neck linker to swing the rear "foot" forward, allowing the motor protein to take a step.

The classic "double-headed" kinesin studied by Taylor and his colleagues plods systematically step by step along the microtubules, whereas the single-headed variant kinesin studied by Hirokawa ambles forward, relying on random movements to make progress. What's more, both kinesins move differently from myosin, a motor protein involved in muscle contraction. Some cell biologists had expected that the two-headed kinesin in particular would work in a similar fashion, partly because it and myosin both consist of two subunits, each with its own business end, or "head."

Cell biologists had learned that myosin moves when one head swings out like a lever and pulls the protein along the actin filaments of the contractile machinery. But Taylor found something quite different when he became part of a team led by Ron Vale, a biophysicist at the University of California, San Francisco, and Ron Milligan, an electron microscopist at The Scripps Research Institute in La Jolla, California. By attaching fluorescent probes or gold beads to each kinesin subunit, the researchers were able to use a variety of techniques, including electron microscopy, to monitor the molecule's shape and movements. In some experiments, for example, they treated the protein with altered versions of ATP, the energy-rich molecule that is the "fuel" for motor proteins, which caused it to freeze at various stages in the movement cycle.

The researchers found that the kinesin moves one foot at a time. First, ATP binds to the front foot, causing a 15–amino-acid region called the neck linker to zip up with a nearby part of the molecule and stiffen. This stiffening yanks the back foot off the microtubule, swinging it ahead of what was the front foot. Then, ATP can bind to the new front foot, and as this process is repeated, the kinesin motor plods along, with cargo in tow. "The motion here is a much smaller change" than the one seen with myosin, Taylor said in his talk at the cell biology meeting. (The work also appeared in the 16 December 1999 issue of *Nature*.) Or as Thomas Pollard, a cell biologist at The Salk Institute in La Jolla, puts it, "The myosins are dancing while kinesin is hiking, steadily chugging along step by step."

Hirokawa found that the kinesin called KIF1A works quite differently, however. In early 1999, the group reported a preliminary clue: They found that KIF1A moves on its own, without pairing off (*Science*, 19 February 1999, p. 1152). Now the researchers have an idea of how it does that.

The starting point for the new work was their finding that although the *KIF1A* gene is quite similar to other kinesin genes, it has extra bases that code for a sequence of six lysine amino acids. Thinking that the lysines might be the key to this kinesin's ability to move solo, the researchers synthesized the part of the protein containing the sequence and used cryo-electron microscopy, in which samples are stabilized in glassy ice, to examine how it interacts with microtubules. They also made other versions of this part of KIF1A, varying the number of lysines to see whether that affects KIF1A's movement.

The electron microscopy studies revealed that KIF1A grasps the microtubule both with its foot and the stretch of lysines, which form part of a positively charged loop that is attracted to the negatively charged tubulin protein in microtubules. Based on that finding, Hirokawa proposed that the loop acts as a sliding clamp that holds KIF1A to the microtubule as it moves.

The studies of KIF1A with altered numbers of lysines bore this idea out. "If we take the lysines out, [the motor] doesn't work," Hirokawa's Tokyo colleague Masahide Kikkawa said when he presented some of the

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