But some members of the Lyons-based European Center for Research in Virology and Immunology (CERVI)—a federation of teams associated with the BSL-4 facility—are left wondering how their plans will be affected. "None of the directors [of the CERVI research units] were consulted, and we do not know what [Pasteur's] scientific program is going to be," says CERVI member Jean-Luc Darlix, head of a human virology lab run by the biomedical research agency INSERM.

In the hot seat. Europe's premier pathogens lab is about to come online with the Pasteur Institute—not Susan Fisher-Hoch (*right*), it appears—at the helm.

Fisher-Hoch is even less certain about her future at the lab. Confidential documents from CERVI and the foundation obtained by *Science* indicate that Pasteur and foundation officials intend to appoint Pasteur virologist Vincent Deubel as the new director, effective this fall. Deubel has searched in Africa for reservoirs of the deadly Ebola virus, although Darlix and others say that he has no experience in a BSL-4 lab. Deubel declined to comment, but Kourilsky defends the putative appointment of a Pasteur scientist: "If the Pasteur Institute is associated with the [BSL-4 facility]," he says, "it is normal that the scientific direction would be assured by a Pasteurian."

Fisher-Hoch sees darker forces at work. For the past several months, articles in Lyons newspapers and in the national press have suggested that the lab might pose a health threat to the local community. A story in the 30 March issue of the weekly magazine *L'Express*, for example, reported that Fisher-Hoch last fall was given a number of possibly virally infected blood samples from Sierra Leone by her husband, Joseph McCormick, and that she violated safety procedures by putting them in a freezer in a BSL-2 lab, which has fewer safeguards than a BSL-4 lab. (McCormick, also a former CDC virus hunter who works at the Lyons-based drug company Aventis-Pasteur, has had his own troubles with Pasteur; see *Science*, 13 November 1998, p. 1241.) Charles Mérieux refers repeatedly to this alleged incident in letters to the WHO's Heymann this spring, in which he asks for help in replacing Fisher-Hoch. Mérieux also complained about Fisher-Hoch in letters to Kourilsky. (Heymann says he did not respond to the request, and Kourilsky declined to comment, saying the issue is an internal foundation matter.)

Fisher-Hoch and McCormick dispute the press accounts. They say the samples were from healthy Western donors, including themselves, and were drawn during a workshop they conducted in Liberia—not Sierra Leone—to teach medical personnel how to perform diagnostic tests for Lassa fever. Fisher-Hoch says she laid this out in an 11 April letter to Mérieux, explaining that she intended to use the uninfected samples as controls in future work on lethal viruses. Mérieux, 93, told *Science* that whether or not the alleged incidents were true, they "created a bad image of the [BSL-4 facility]" in the press which "I cannot tolerate." Fisher-Hoch's contract to direct the lab runs until February 2002, although foundation officials say she will now be asked to accept a lesser role. But she speculates that once the lab was ready to come online it was too tempting a prize: "As the French say, the cake was too beautiful, everyone wanted to eat it." –MICHAEL BALTER

CREDITS: R. BENALI AND R. CAILLARDE/GAMMA LIAISON

OBESITY

Enzyme Blocker Prompts Mice to Shed Weight

When it comes to body fat, the laws of thermodynamics hold weight: Take in more calories than the body burns to produce energy, and the excess will be shunted into fat. To regulate this thermodynamic system, the body somehow keeps the brain apprised of the energy balance so it can dampen our appetites if we are overeating. Now, a multidisciplinary team from Johns Hopkins University may have discovered an important new clue about how the body performs this feat of calorie—and thus weight—control.

The team, led by pathologist Francis Kuhajda, chemist Craig Townsend, bio-

ScienceScope

Money Trouble Scientists are blasting the South African government for offering expense-paid trips to 45 members of a controversial advisory panel that is revisiting HIV's role in AIDS. South African President Thabo Mbeki—who has said his government can't afford the relatively cheap drugs that prevent mothers from infecting their babies with HIV—was lambasted by critics in May when he expressed doubts that HIV caused AIDS and convened a review panel that includes prominent HIV skeptic Peter Duesberg of the University of California, Berkeley (*Science*, 28 April, p. 590). Now, even some panelists who live outside South Africa are enraged that the government is offering generous per diems, business-class air tickets, and swank hotels to the group for its final meeting in Johannesburg on 3 to 4 July, before a major international AIDS conference in Durban.

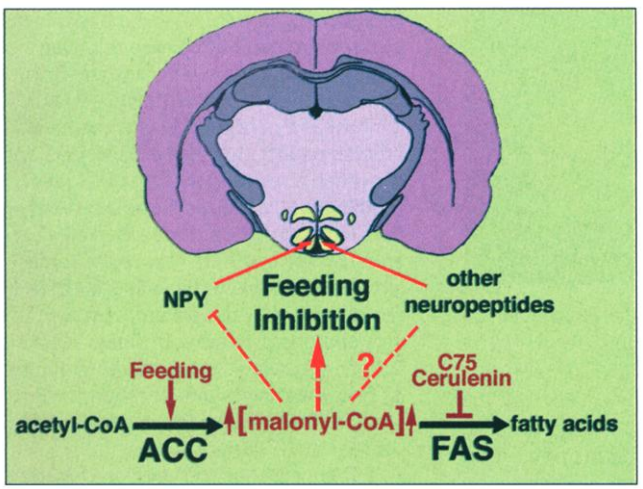
But panelist Stefano Vella, president-elect of the International AIDS Society, believes that the money will be well spent if the panel convinces Mbeki that HIV causes AIDS. "We can't skip dealing with him," says Vella. "South Africa is seen as a leading country in Africa." A government official who sent the invitation did not respond to *Science*'s inquiries.

Genetic Variety Forty Japanese drug firms will fund a $10 million program to explore single-nucleotide polymorphisms (SNPs), the single-base variations in a person's genetic code that influence disease risk and treatment reactions. University scientists involved in the program, set to begin next year, will analyze blood samples from 1000 Japanese individuals and make the data freely available to other researchers.

The project will run in parallel with two existing efforts funded by the government and an international consortium. Backers of the $45 million SNPs Consortium, supported by European and U.S. firms, hoped that Japanese companies would join their effort (*Science*, 16 April 1999, p. 406). But a spokesperson for the Japan Pharmaceutical Manufacturers Association said that the group felt it needed its own program, although future cooperation is possible. And how the private effort, which has an applied focus, will coordinate with Japan's more basic research–oriented public program isn't clear, says Yusuke Nakamura of the University of Tokyo, who heads the government-funded effort. But he agrees that Japan "definitely needs its own [SNPs] database."

Contributors: Christine Mlot, Michael Balter, Jon Cohen, Dennis Normile

chemist M. Daniel Lane, cell biologist Thomas Loftus, and neuroscientist Gabriele Ronnett, reports on page 2379 of this issue that a molecule called malonyl–coenzyme A (malonyl-CoA), which is needed for fat synthesis in the body, may play a key role in appetite signaling in the brain. Moreover, the investigators produced a synthetic inhibitor that prevents this molecule from being converted to fat, causing it to build up in the body. In mice, the inhibitor spurs a dramatic, but reversible, drop in appetite and weight.



Feedback. Feeding stimulates production of acetyl-CoA carboxylase (ACC), which results in elevation of malonyl-CoA levels. This, in turn, may alter regulation of NPY and other neuropeptides in the brain to inhibit feeding. By blocking fatty acid synthase (FAS), C75 and cerulenin prevent the removal of malonyl-CoA, keeping levels elevated and appetite suppressed.

"This is provocative and exciting, and I think we will see an avalanche of work to see if it has validity," says Dennis McGarry, a fat metabolism researcher at the University of Texas Southwestern Medical Center in Dallas. Indeed, with an estimated third of Americans now grappling with obesity and its subsequent health problems and costs, any drug that could safely and effectively block appetite and lead to weight loss could be a big money-spinner.

The discovery was sparked by Kuhajda's studies of an enzyme called fatty acid synthase (FAS). When the body wants to store excess fuel, this enzyme makes the long-chained fatty acids that are the building blocks of fats by transferring two-carbon units from malonyl-CoA to the growing fatty acid. Thirty years ago, Nobel Prize–winner Konrad Bloch had shown that cerulenin, an epoxide produced by fungi, inhibits FAS. But epoxides are notoriously unstable and reactive, so Kuhajda teamed up with Townsend, who synthesized a cast of cerulenin derivatives that might be a less reactive, and therefore safer, FAS inhibitor.

Of the hundreds of compounds tested, one, dubbed C75, looked especially promising. It easily latched onto and blocked FAS with the same potency as cerulenin, but without the toxicity problems. It had a dramatic effect when given to mice: The treated animals began losing weight almost immediately. Because blocking FAS causes a buildup of the enzyme's target—malonyl-CoA—in the liver, the investigators wondered whether that compound might be somehow signaling the brain to dampen appetite.

To explore that possibility, Kuhajda teamed up with Lane and Loftus. Loftus quickly confirmed that C75 suppresses appetite, showing that treated animals eat just 10% of the food their untreated littermates consume. The animals dropped, on average, almost a third of their body weight. Even more surprising, the treated animals lost 45% more weight than untreated mice fed the same reduced amounts of food. Fasted animals normally turn down their metabolic activity to compensate for their reduced food intake—that's one reason losing weight can be so difficult—but C75 may prevent this metabolic slowdown.

The researchers also found that malonyl-CoA concentrations remained high in the livers of the C75 animals but not in those of the fasted mice, lending further weight to the idea that the compound might mediate the physical and metabolic changes. And tests with another inhibitor, a compound called TOFA that blocks the enzyme that makes malonyl-CoA, bolstered the hypothesis. The investigators reasoned that if malonyl-CoA is the key signal that tells the brain to quench appetite in response to C75, then TOFA should block the drug's effect by preventing malonyl-CoA synthesis. When they injected mice with TOFA before giving them the C75, the appetite suppression was indeed attenuated.

"This lends some degree of credibility to the results," says McGarry, although he says he still questions whether malonyl-CoA in this pathway is the sole signal orchestrating the feeding effects. "The question now is how is malonyl-CoA doing this and in which neuronal compartment?"

With the help of neuroscientist Ronnett, the group set out to answer that question. The researchers showed that C75 works when pumped directly into the brains of mice. Surprisingly, however, the well-known antiobesity hormone leptin did not appear to conduct C75's effects: The drug quelled the appetites of mutant mice lacking the fat-busting hormone. But another peptide—the appetite-stimulating neuropeptide Y (NPY)—did prove to be involved.

The investigators found that levels of the messenger RNA (mRNA) for NPY rose quickly in the brains of fasted animals—an indication that they were making large amounts of the protein, presumably to stimulate feeding. But even though C75-treated mice were eating very little, NPY mRNA levels plummeted in the rodents' brains. What's apparently happening, Loftus suggests, is that C75, by keeping malonyl-CoA concentrations high, is "fooling the system. We are making the system think that it has fuel when it actually hasn't." Thus, NPY levels fail to rise, keeping appetite down.

Longtime NPY researcher Michael Schwartz says that C75 may affect more than just NPY levels, though. "Simply blocking NPY is not likely to cause that profound of an inhibition of food intake," he notes. Indeed, obesity researchers have identified plenty of candidates for C75 partners besides leptin and NPY (*Science*, 10 March, p. 1738).

Beyond pinning down exactly how C75 works, there's the multimillion-dollar question of whether the drug or chemical derivatives of it will ever prove useful in curbing human obesity. "That would be the hope," says McGarry, who cautions that such a scenario is still a long way off, especially as C75 is rather draconian in its suppression of appetite. It might be possible, though, to design milder versions. "We may have in our hands a mechanism that works at the level of the brain for the control of feeding behavior," Lane says. If researchers can target it safely, he adds, "I think it has the potential to deal with obesity and all the consequences thereof."

–TRISHA GURA

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NUCLEAR ESPIONAGE

Report Details Spying On Touring Scientists

Foreign spies apparently find traveling U.S. nuclear scientists irresistible. A congressional report released this week details dozens of sometimes clumsy attempts by foreign agents to obtain nuclear secrets, from offering scientists prostitutes to prying off the backs of their laptop computers. The report highlights the need to better prepare traveling researchers to safeguard secrets and resist such temptations, say the two lawmakers who requested the report and officials at the Department of Energy (DOE), which em-

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