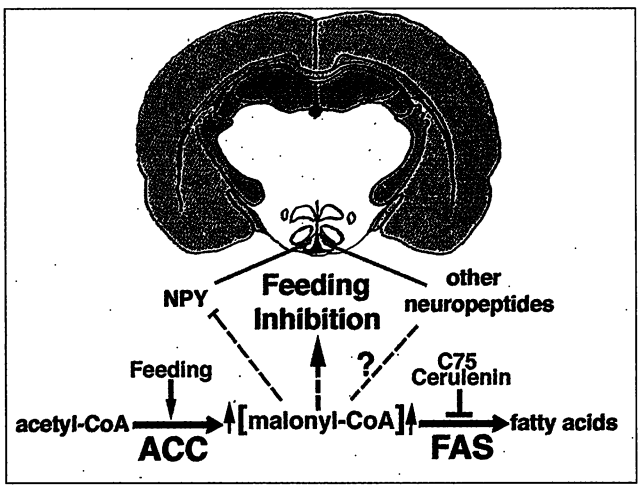
chemist M. Daniel Lane, cell biologist Thomas Loftus, and neuroscientist Gabriele Ronnett, reports on page 2379 of this issue that a molecule called malonyl–coenzyme A (malonyl-CoA), which is needed for fat synthesis in the body, may play a key role in appetite signaling in the brain. Moreover, the investigators 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**

Trisha Gura is a science writer in Cleveland, Ohio.

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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ploys the scientists.

The study by the General Accounting Office (GAO), Congress's investigative arm, reviewed DOE reports on nearly 5000 foreign excursions by scientists from four national laboratories: Sandia and Los Alamos in New Mexico; Livermore in California; and Oak Ridge in Tennessee. It found more than 75 incidents between 1995 and 1999 in which researchers reported the possibility of eavesdropping and luggage tampering or said they were offered sexual favors. The report does not identify specific researchers, laboratories, or the nations visited, and DOE officials say no secrets were revealed. Some of the travel involved the 25 nations on DOE's "sensitive" list, which includes Russia, China, and Ukraine.

The report makes for racy reading. In one case, a scientist visiting a sensitive nation was repeatedly propositioned by women who called his hotel room and knocked on his door. Another DOE researcher, in a post-trip debriefing with security officials, admitted to having sex with at least four women, including a prostitute, a waitress, and two employees of a laboratory he was visiting. Security officials were "particularly concerned about these activities because of the potential for blackmail," the report notes. There were also reports of tampering with personal equipment, including riffling through and then locking a previously unlocked briefcase, turning on a previously shut-down computer, and trying to pry open the back of a laptop.

Some of the incidents were almost comical. One researcher who telephoned his wife at home and chatted about her upcoming plans to play the game Bingo at a social gathering was later asked in the hotel bar about those plans. The next day another host asked him: "What is Bingo?" Some researchers even used the suspected eavesdropping to their advantage. After talking to their hotel walls about the desire for an extra roll of toilet paper or a television set, two scientists were pleasantly surprised to see the items appear within hours. Other episodes included "maids" interrupting a meeting to move potted plants closer to visiting U.S. scientists, and a technician who entered a conference room to change the tape in recorders previously hidden behind a wall. Dismayed U.S. officials hadn't been told the meeting was being recorded.

GAO investigators say the episodes highlight the need to brief researchers more carefully and to review all travel plans, because spies "can operate worldwide." They recommend that the weapons laboratories consult with counterintelligence agents and other scientists, who would be able to spot potentially sensitive information in planned presentations. Livermore and Oak Ridge currently conduct such reviews, which have prompted some scientists to alter or cancel travel plans.

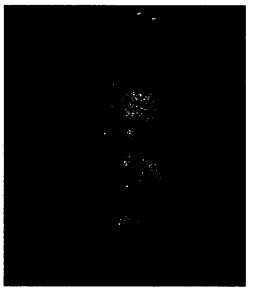
DOE officials agree with the findings and say they are expanding reviews and paying more attention to activities involving nonsensitive nations. But given limited funds, says one official, the agency "will probably continue to target the primary threat, and that is the sensitive nations."

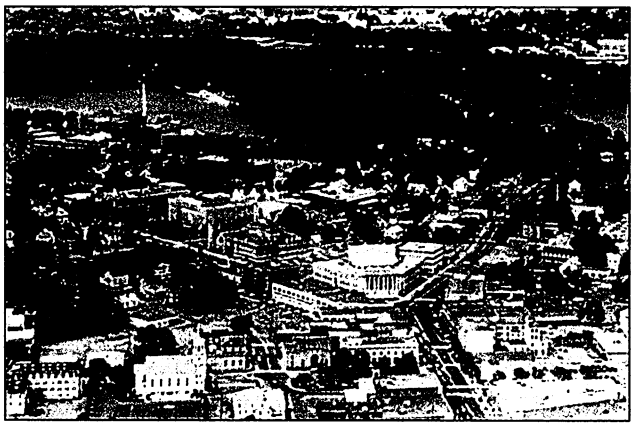
–DAVID MALAKOFF

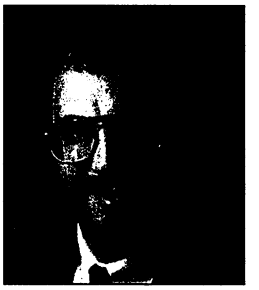
GENOMICS

University Company to Exploit Heart Data

BOSTON—As a boy growing up in the small town of Framingham, Massachusetts, medical ethicist Arthur Caplan remembers watching excitedly as distinguished scientists from nearby Boston visited his father's drugstore. They came to inspect the pharmacy's records of patients enrolled in the federally funded Framingham Heart Study, a massive government effort begun in 1948 to monitor the cardiovascular health of more than 10,000 townsfolk. "It was a great event," recalls Caplan, 50, who has long since left town for the University of Pennsylvania in Philadelphia. But the Framingham study, which helped establish a link between cigarette smoking and heart disease and between high blood pressure and stroke, continues to chart new territory—and Caplan is poised to play a role in its future development.







Heart of the matter. The longitudinal heart study in Framingham (*above*) has great commercial value, says Fred Ledley (*right*), but must be done properly, says medical ethicist Arthur Caplan (*top*).

This month, Boston University (BU), which directs the study and maintains the records, announced plans to form a bioinformatics company that will mine the data. The university will own 20% of Framingham Genomic Medicine Inc., which hopes to raise $21 million to begin modernizing the immense database and packaging it in a format that will be valuable to the pharmaceutical industry. The plan raises a host of difficult ethical issues, including patient privacy, academic conflicts of interest, and reciprocal value to the Framingham residents whose medical data will form the basis for the new enterprise. "These are all choppy waters," says Caplan, who may become a paid ombudsman for the community in its dealings with the company and the university. But he thinks it's a voyage that may be worth taking: "We're talking about the gold standard of epidemiology."

Fred Ledley, chief scientist for the new company and its only full-time employee to date, also sees a golden opportunity to use what is now largely gathering dust in warehouses. "There's an enormous amount of data that's never been pulled out of boxes," he says, "and I don't think the government has the money to do it." However, the university's actions touch on issues similar to those raised by a controversial decision by the government of Iceland to provide a private company with health records on all its residents in return for an upgraded record-keeping system and free access to any new drugs the company develops (*Science*, 30 October 1998, p. 859). The University of Utah, Salt Lake City, also has provided private companies with genealogical data from Mormon church records, says Richard Koehn, Utah's vice president of research, after taking steps to ensure confidentiality and requiring involvement by faculty members.

The Framingham company's first move will be to build a comprehensive electronic database over the next several months. Its second, more ambitious, step will be to correlate clinical records with DNA analyses from blood samples on file, with the goal of

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