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news&notes

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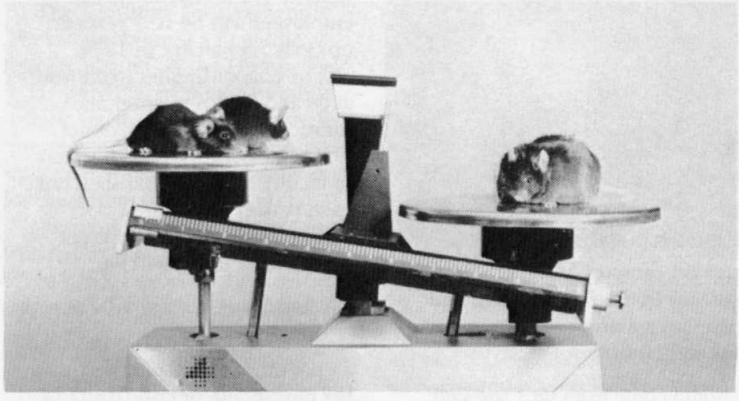
Researchers identify and clone a gene that regulates weight

John Sholtis



Mice with mutations in the *ob* gene cloned by Associate Professor Jeffrey Friedman gain excess weight *(right)*. The human version of this gene, also cloned by Friedman, may play a major role in obesity.

by Susan Blum

Body weight is a highly heritable characteristic. Indeed, various studies have shown that from 60 to 90 percent of the differences among people's weights is due to their genes. Now, Associate Professor Jeffrey Friedman and his colleagues have taken a step toward identifying one of the genetic contributors to body weight by cloning—or pulling out from the chromosomes—a gene, called *ob*, that plays a central role in weight control in the mouse. Because the physiology of mice and humans is very similar, the gene may play a major role in humans, too—and the researchers have already cloned the human version of the gene. Their report is the cover story in yesterday's *Nature* (Dec. 1).

The cloning of the *ob* gene—and the insights it may provide into the biochemical pathways regulating body weight—holds great promise for a better understanding of and, potentially, treatment for, a variety of pathological conditions.

One such condition is obesity, defined as the state of being 20 percent or more over ideal weight. Much attention has rightfully been focused on obesity and its associated health problems such as heart disease, high blood pressure, and diabetes. Less well known, but equally dangerous, are the consequences of being profoundly underweight, a condition that often occurs as a result of serious illnesses such as cancer and AIDS. By revealing the mechanisms that regulate body weight, Friedman's stud-

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Rockefeller author to lecture on book

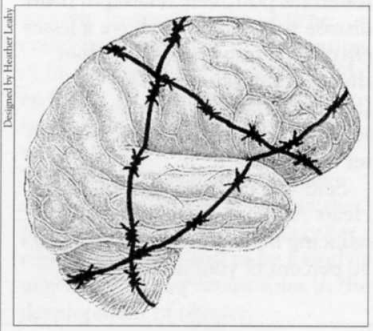
Professor Bruce McEwen, head of the Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology, will give a special presentation Wed., Dec. 7 on his new book, *The Hostage Brain*, co-authored with Harold M. Schmeck Jr., recently retired national science correspondent at *The New York Times*.

The book illuminates for a lay audience the nature of the brain as a vulnerable and everchanging organ of the body. Published in November by The Rockefeller University Press, the book has sixty-two color plates drawn by medical illustrator Lydia Kibiuk.

The presentation, to take place at 5:00 P.M. in Caspary, will be followed by a reception in Abby Lounge with McEwen and Schmeck. All are welcome.

McEwen will discuss the book in an upcoming issue of *News&Notes*.

Designed by Heather Leahy



From the cover of *The Hostage Brain*; RU Professor Bruce McEwen will lecture on the new book Dec. 7.

Rockefeller Professor Alexander Tomasz was the guest speaker at a Regency Hotel luncheon on the dangers of antibiotic-resistant bacteria. The Nov. 16 event was organized by the Public Health Research Institute and sponsored by Lederle Laboratories.

Biophysicist to speak on motor protein kinesin

Jonathon Howard, Associate Professor of Physiology and Biophysiology at the University of Washington, will speak on "Force Generation by the Motor Protein Kinesin" at the Friday lecture today (Dec. 2).

Howard studies the workings of motor proteins. These proteins are enzymes that convert the chemical energy contained in adenosine triphosphate, or ATP, into the mechanical work used to power intracellular transport. Today Howard will discuss his work on kinesin, a ubiquitous microtubule-based motor protein found in all eukaryotic organisms.

"Joe Howard's work addresses the important issue of molecular mechanisms: How do proteins work?" said Associate Professor Sanford Simon, who will introduce Howard today. "These studies are an important bridge between our understanding of protein structure and cellular function."

Howard received a B.Sc. (1979) and a Ph.D. (1983) from Australian National University (A.N.U.) in Canberra. After serving as a postdoctoral fellow at A.N.U. and as a postgraduate research assistant at the University of Bristol, Howard went to the University of California in San Francisco (U.C.S.F.) in 1985 as a visiting postdoctoral fellow. Working in the laboratory of Albert Hudspeth (who recently joined the Rockefeller faculty), he studied the mechanoelectrical transduction of sound in hair cells of bull frogs. In 1988 he became an assistant research physiologist at U.C.S.F., and in 1989 joined the faculty of the Department of Physiology and Biophysics at the University of Washington as an assistant professor. He was promoted to associate professor this year.

Howard has received many honors, including the Australian Commonwealth Postgraduate Research Scholarship, the Fondation pour l'Etude du Système Nerveux Fellowship, and the Alfred P. Sloan Research Fellowship. From 1990 to 1994, he was a Pew Scholar in the

See **Howard**, *page 4*

Confused about cholesterol? Lecturers offer advice

While heredity plays a role in obesity, there is much evidence indicating that the American high fat, high cholesterol diet contributes to heart attacks, disease, and death. And while many of us are aware of this danger, sources of cholesterol and fat and ways to reduce them are confusing. Two recent lectures in the Employee Health Office's Health and Wellness series shed some light on this matter.

Elizabeth de Oliveira e Silva, an associate physician and research associate in the Breslow lab, pointed out that although cholesterol is often vilified, it is vital for survival. Among its essential functions is transporting triglycerides, and it is the precursor of bile acids, which help the body process fat.

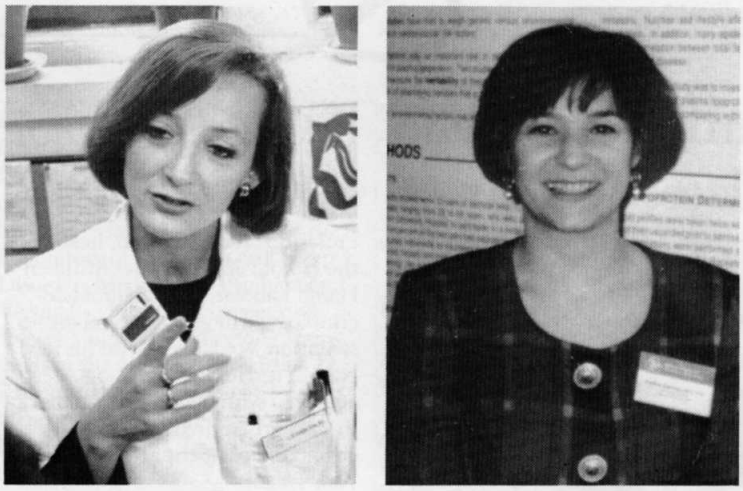
Yet high cholesterol levels are "a major cause of atherosclerosis, leading to heart disease," de Oliveira e Silva said. Cholesterol is highly insoluble in plasma and must be carried by molecular complexes called lipoproteins, of which the best known are low density lipoproteins (LDL)—"bad cholesterol"—and high density lipoproteins (HDL)—"good cholesterol."

"There is a lot of evidence that HDL has a protective effect on your heart," she said. "This comes from the ability of HDL to remove cholesterol from peripheral tissues and take it to the liver, where it can be metabolized and excreted."

After a cholesterol screening, such as the one still going on at Rockefeller, the total cholesterol level (T.C.L.) is usually reported. This is the number that most people think of as their "cholesterol." The National Cholesterol Education Program has deemed T.C.L. of less than 200 as desirable, and anything above 240 as having a high risk for coronary heart disease.

However, T.C.L. tells only part of the story. "A lot of people think that there is a threshold below which you will not develop heart disease," said de Oliveira e Silva. "You can have a T.C.L. of 185 but still be at a high risk if you have a low HDL." The ratio of T.C.L. to HDL, used with T.C.L., is often used as an indication of atherosclerosis risk: A ratio above five is usually associated with higher risk for heart disease.

What can you do to reduce the risk if you have a high T.C.L. or not enough good cholesterol? Cynthia Seidman, director of the Dietary Service at the Hospital, stressed one proven method: reduce total fats, saturated fats, and dietary cholesterol.



In two recent complementary lectures on campus, Elizabeth de Oliveira e Silva (*left*), associate physician in the Breslow lab, and Cynthia Seidman, director of the Hospital's dietary service, gave information and advice on dietary fat and cholesterol.

Dietary fat serves many important functions, as does cholesterol. But, also like cholesterol, too much is harmful. "Federal agencies as well as private organizations concur that excess fat is the villain in the promotion of several chronic diseases," Seidman said. "While cholesterol is positively related to heart disease risk, it tends to have a lesser effect on serum cholesterol than the intake of saturated fats." (Saturated fats are those that are solid at room temperature, like butter and lard.)

Seidman outlined the American Heart Association guidelines for reducing fat in the diet. "Less than 30 percent of your daily calories should come from fat," she said. On average, this means 65 to 107 grams of fat, depending on your daily calorie requirement, which for most people is 2500 to 3000. Reducing saturated fats and limiting portions at meals is also recommended. "Beef and dairy products contribute the most saturated fat," she said. Drug therapies are available to reduce cholesterol, but most physicians suggest a six-month trial diet before prescribing drugs.

Although fat consumption in America is declining, Seidman says there is still a long way to go before we reach the 30 percent mark. Only by making informed choices about what we eat can we reverse the incidence of heart disease.

Fred Hechinger (left), currently a senior advisor at the Carnegie Corporation of New York and a former education editor at The New York Times, *lectured at Rockefeller on "Fateful Choices: From Birth to Adolescence." Organized by Bonnie Kaiser, director of the Science Outreach Program, the Nov. 15 lecture was attended by about three dozen professionals concerned with science education.*

Health insurance rates to rise slightly in January

This week, the university administration advised faculty and staff of an increase in employee contributions to cover the costs of health and dental insurance. As of January 1, the cost borne by employees will be 10.1 percent, up from 7.5 percent in 1994.

The change applies to all insurance and health maintenance organization plans. The Personnel Office has sent individual letters to faculty and staff that spell out each person's new rates.

Employee contributions per month as of Jan. 1 will be:

- For those making under $30,000: single coverage, $13 (an increase of $3 per month); couple (staff member plus spouse or child), $32 (a $12 increase); family, $43 (an $18 increase);
- For those making between $30,000 and $59,999: single, $25 (a $5 increase); couple, $58 (an $18 increase); family, $77 (a $27 increase);
- For those making between $60,000 and $99,999: single, $39 (a $9 increase), couple, $92 (a $32 increase), family, $120 (a $45 increase);
- For those making over $100,000: single, $53 (a $13 increase), couple, $120 (a $40 increase), family $160 (a $60 increase).

For more information about individual rates, contact Kristin Gross or Ginny Hansen, x8300.

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Obesity gene product may be a hunger hormone

(continued from page 1)

ies may ultimately lead to ways to boost or diminish the body's fat stores as appropriate for each individual case.

Searching for the homeostatic signal

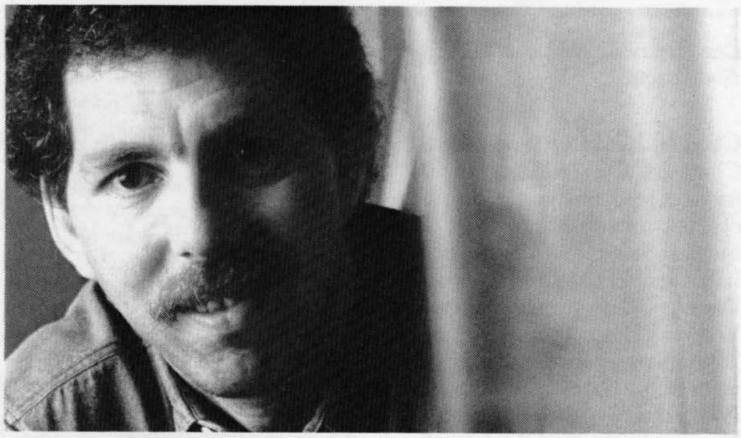
The scientists' achievement is the culmination of a long line of research based on the premise that body weight is regulated by a homeostatic feedback system. This premise, Friedman explained, has its roots in the earliest considerations of the nature of energy and the function of biological systems in the natural world.

In 1783, Lavoisier and Laplace provided the first evidence that the energetics of respiration were no different from those of combustion—thus showing, Friedman said, "that living organisms obey the same physical laws that govern inanimate objects." For those creatures, energy in (in the form of nutrients) must equal energy out (in the form of heat, waste, carbon dioxide, and physical work).

Confirmation of this law of nature, combined with observations that an individual's weight seldom changes dramatically over a lifetime despite a lifetime's worth of food consumption, eventually led scientists to posit the existence of a regulatory system that continuously measures energy intake and output against one another and fine tunes them accordingly.

One model for such a system hypothesized a homeostatic feedback mechanism that maintains body weight at a particular "set point." Such a system would involve signals from the body's periphery (the fat cells, for instance) that reach receptors at control centers in the brain (perhaps a region known as the hypothalamus) to report on how much the body currently weighs and how well it has recently been nourished. The brain then might regulate various physiologic and behavioral responses, such as energy expenditure and food intake, to maintain the size of the body fat depot and, thus, body weight. In a complex system like this, problems anywhere along the pathway—a faulty signal, for instance, or a defective receptor—could lead to obesity.

"Data suggested that such a system is hard wired, and is the consequence of the genes," Friedman recounted. In the 1950s and 60s, for instance, researchers found at least five different single genes that lead to obesity in various strains of mice.



Associate Professor Jeffrey Friedman has cloned a mouse gene that codes for a protein secreted by fat cells. He and members of his lab are now working to confirm that the protein is a signal that plays a central role in maintaining body weight.

Two of these genes—*ob* (for obesity) and *db* (for diabetes)—appeared to be central players in the system. Animals with mutations in either of these genes eat more food early in life, have decreased energy expenditure, and increased insulin levels—all of which, acting in concert, lead to profound obesity and diabetes.

Various lines of evidence suggested that the *ob* gene coded for a signaling molecule and the *db* gene coded for its receptor. But before that possibility could be tested, scientists had to have the actual genes in hand. To that end, Friedman and his colleagues began experiments in positional cloning, a technique that allows scientists to snare genes of unknown function. This time-consuming and arduous technique was even more difficult eight years ago, back when the Rockefeller researchers began their project and before the Human Genome Project had generated creative techniques to speed the process along. But the researchers' persistence paid off in their recent cloning of the *ob* gene.

Subsequent analysis of the gene has provided much evidence suggesting that *ob* may indeed code for a signaling molecule produced by fat cells. For instance, the gene is turned on only in these cells, and codes for a protein with a tell-tale signaling region. In obese mice, the types of gene mutations found are consistent with the hypothesis that the *ob* signal tells the hypothalamus to reduce food intake and or/prompt more energy expenditure once a certain level of protein is reached, thus indicating that the fat cells have grown to a certain mass.

Two crucial experiments will confirm *ob*'s signaling role: the ob protein must be shown to circulate in the blood, and injections of a normal version of the ob protein must reduce the weight of animals with mutations in their *ob* genes. Such experiments are now under way in Friedman's lab, as are studies to positionally clone the *db* gene in a first step toward confirming its role as a receptor molecule.

If *ob* is found to encode a signal picked up by a receptor, then, Friedman said, "one could imagine multiple ways in which an individual could become obese." In one case, the *ob* gene might be mutated, leading to a defect in the signaling protein. In another, the *ob* gene could be normal, but the regulation of its expression, or readout, could be faulty. In still another, there could be a problem with the receptor gene, or with its regulation. Thus, while the *ob* and *db* genes appear to be the key players in the pathway, mutations in many other regulatory genes, still to be found, may also play important roles in the development of obesity.

Gathering the evolutionary evidence

Using the mouse *ob* gene as a probe, Friedman and his colleagues have found that it is highly conserved among many vertebrates from eels to humans, whose *ob* gene shares an 84 percent similarity, or homology, to that of the mouse. Such conservation suggests that a feedback system for weight maintenance has been in place for eons, and that the genes controlling this system have been subjected to intense selective pressure.

"Humans evolved in a much different and harsher environment than we currently live in. In that environment, where getting enough calories was difficult, we might have been selected for genes that allow us to deposit food efficiently as fat," Friedman said. Once highly adaptive, these genes would now be maladaptive in environments such as the United States, where sufficient calories are available to many—and where the rate of obesity has soared to 30 percent.

Some of the strongest evidence in support of an evolutionary role for obesity genes comes from studies of aboriginal populations, such as the Pima Indians in the U.S. and the Pacific Islanders of Micronesia, who now have extremely high rates of obesity and diabetes. "In general, the more severe the environmental conditions throughout history, the more profound the obesity in modern times," said Friedman.

The study of such populations offers extraordinary opportunities to answer the fundamental question that must be asked about genes such as *ob*, to wit: is their role in human obesity as clear as their role in the rodent form of the disease? Friedman and his colleagues are now collaborating with the residents of the Micronesian Island of Kosrae to answer just this question. Not only is the incidence of obesity and diabetes on Kosrae exceptionally high, but the genetic histories of its residents are exceptionally interesting, a wave of colonization by Europeans in the 1800s having led to much intermarriage between members of previously separated groups. Thus, by comparing the *ob* genes of those who are obese and those who are of normal weight, much may be learned about the role *ob* plays in weight regulation.

Opening up possibilities

The confirmation of *ob*'s role in human weight maintenance would open up many exciting possibilities to raise or lower body fat stores as appropriate for individuals suffering from pathophysiologic states such as obesity or profound underweight. The exact nature of the problem might be pinpointed through analysis of the *ob* gene, or assessment of the amount and the nature of circulating ob protein. Then, strategies such as administration of the ob protein (much as insulin is administered for diabetes), gene therapy (to correct the gene defect), "antisense RNA" (to intervene in the process of ob protein production), or pharmaceuticals (to stimulate or block *ob*'s signaling function) might be employed as appropriate. In addition, a better understanding of the role of *ob*, as well as of *db* and the many regulatory genes in the weight maintenance pathway, will help scientists understand the control of body weight in the healthy population that tips the scale at various weights between the two extremes of weighing too much or too little.

Potpourri

In memoriam
The university community mourns the passing of Alan Lipton, a former engineer in the Electronics Department, who died last month. Lipton, a member of the department for 13 years, worked closely with Professor Emeritus Frank Field in the mass spectrometry lab. He left the university in 1986.

Tri-Institutional Noon Recital
The Miami String Quartet will perform the works of Alberto Ginastera at The Tri-Institutional Noon Recital today (Dec. 2). The quartet—violinists Felicia Moye and Cathy Meng Robinson, violist Chauncey Patterson, and cellist Keith Robinson—won first prize in the 1992 Concert Artists Guild New York competition. The concert, to be held in Caspary Auditorium at noon, is free. All are welcome.

Friday film
Ju Dou (China, 1990), directed by Zhang Yimou, will be shown today (Dec. 2) at 8:00 P.M. in Caspary Auditorium. The film, which is in Mandarin with English subtitles, is free. All are welcome.

Health and Wellness lecture
Sonia Austrian, director of the Employee Assistance Program Consortium, will speak on "Getting the Bah Out of the Humbug: Dealing with the Stresses of the Holidays" at the Health and Wellness lecture Wed., Dec. 7 at noon in Caspary Auditorium.

Clinical Research Seminar
Charles A. Czeisler, associate professor of Medicine in the Division of Endocrinology at Harvard Medical School and director of the Laboratory of Circadian and Sleep Disorders Medicine at Brigham and Women's Hospital, will speak on "Neurobiology and Photic Entrainment of the Human Circadian Pacemaker: Regulation of Sleep, Neuroendocrine and Behavioral Rhythms" at the Clinical Research Seminar Wed., Dec. 7 at noon in Nurses Residence 110B.

Statistical Physics Seminar
Lyonia Bunimovich, professor at the Georgia Institute of Technology, will speak on "Space–Time Dynamics in Networks of Interacting Elements" at the first Statistical Physics Seminar, Mon., Dec. 12 at 2:00 P.M. in the B Level Conference Room in Smith Hall Annex. The seminar, which will be offered at irregular intervals on Mondays, is organized by Professor E.G.D. Cohen, x8855.

Discussion on art and science
The Lincoln Center Theater is presenting "A Roundtable Discussion about Art and Science" Wed., Dec 14 in the Mitzi E. Newhouse Theatre, an event suggested by the Tom Stoppard play *Hapgood*. Participants in the hour-long discussion, which will begin at 5:00 P.M., are: poet Diane Ackerman, microbiologist Sharyn Endow, painter Andrew Forge, physicist Melissa Franklin, theatre director Adrian Hall, and poet and Nobel laureate Roald Hoffman.

Admission is free but as seating is limited, reservations are required; contact Mari Eckroate at 362-7600.

Honor
Frederick Henry Leonhardt Professor Jan Breslow received the Basic Research Prize from the American Heart Association at its 67th Scientific Sessions in Dallas last month. Breslow was honored for his research into the genetics of lipoprotein metabolism.

Donations
The Rockefeller University Children's School and Infant-Toddler Center is collecting food and toys for contribution to the Yorkville Common Pantry. Donations may be brought to the Children's School in GSR until Dec. 14.

Book sale
A book sale to benefit The Rockefeller University Children's School and Infant-Toddler Center will be held today (Dec. 2) from 8:30 A.M. to 3:30 P.M. in Tower lobby. Adult and children's books will be available.

Howard

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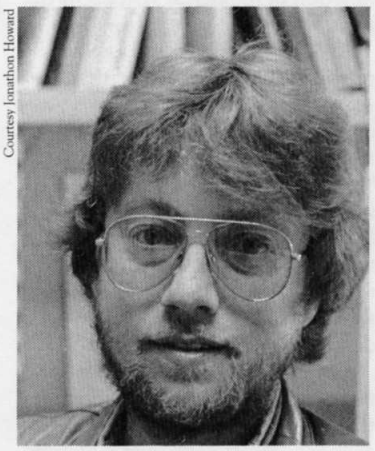
Biomedical Sciences. He is a member of the American Association for the Advancement of Science, the Biophysical Society, and the Society of General Physiologists. He has been an invited lecturer to more than a dozen conferences, and is the author or coauthor of more than 35 papers.

The lecture will be held in Caspary Auditorium at 3:45 P.M. and preceded by tea at 3:15 P.M. in Abby Aldrich Rockefeller Lounge. All are welcome.

Courtesy Jonathon Howard



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Lenny Cohen

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Christian Steiner

Renowned soprano Kathleen Battle will perform at Rockefeller Thurs., Dec. 8 at 8:00 P.M. in Caspary Auditorium. For ticket availability and prices, contact Cathy Rogers, x8971.