of the turnover-pulse hypothesis. So far the fit between environmental cooling, which fragments the bovids' habitats, and increased rate of species turnover looks good at 5 and 2.4 million years ago. These two dates, incidentally, coincide suggestively with the possible origin of hominids and the subsequent origin of *Homo*. A third peak in bovid speciation occurs around 0.5 million years ago, which coincides with the probable first appearance of *Homo sapiens* and follows a climatic cooling, mainly recorded in the north, initiated at about 0.9 million years ago.

By themselves, the hominid data cannot be used to test the turnover-pulse hypothesis, because they are so sparse. But, to some eyes at least, they do fit the requirement of turning over in concert with other lineages.—**ROGER LEWIN**

Reference

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Why Do People Get Fat?

A group of researchers at Rockefeller University has evidence that the signals to overeat may come from the fat cells themselves

Living on the ward at Rockefeller University is a man who weighs 500 pounds. He has numerous medical problems, and when these get overwhelming, he "is available for study at the clinical research center," says Jules Hirsch of Rockefeller, "where we take a couple of hundred pounds off of him." That is why he is there now. But after reducing his weight somewhat, he returns home, only to put the weight back on again.

The question is, Why is this man so fat? And why are 34 million Americans at least 20 percent above their desirable weights? Few people want to be obese, but it is inordinately difficult for overweight people to get their weight down to normal and keep it there. The recidivism rate in obesity treatments is estimated at more than 95 percent for the morbidly obese and about 66 percent overall.

After decades of research on the causes and effects of obesity, Hirsch is certain that it is not just a matter of slovenliness or poor eating habits or a lack of good nutritional information. Nor is it a problem that just requires some behavioral modification. "We are absolutely convinced that when a person says he can't control his eating, there is a biological basis for it," Hirsch says.

And, at last, Hirsch and his associate Rudolph Leibel believe they are on the right track to specifying just what that biological basis is. The signals to eat seem tied to the biochemical status of the fat cells themselves, Hirsch and Leibel find. They emphasize that they do not have a way to chemically prevent people from wanting to overeat. But they do think they can tell when a person's fat cells are in a state that will result in overeating, and they do think they can explain, in biochemical terms, why some people put on weight primarily in their hips and others tend to gain weight in their abdomens. In addition, Hirsch suspects that it is the metabolic state of fat cells that makes obesity a health hazard and that those fat people whose cells are biochemically normal may be healthier if they stay obese than if they reduce and make their cells metabolically abnormal.

The story begins with an observation that has been made by numerous researchers over a period of decades: most animals seem to have stable weights. If they are given all they want to eat, they somehow eat just enough to maintain their weights at their own particular ingrained levels. If they are force-fed, they get fatter, but the moment the force-feeding is stopped, their weights return to normal. If they are semistarved, they lose weight, but the moment they are given free access to food again, their weights return to normal.

Then researchers began to investigate whether an animal's stable weight, sometimes called its set point, has something to do with the fat cells in its body. Fat cell number is not necessarily fixed, says Irving Faust of Rockefeller, although once an animal gains fat cells it never loses them. But what does seem to be closely regulated is how large fat cells become. "Fat cell size is elastic and the cells can store very small or very large amounts of lipid," Faust remarks. "An animal with neurological lesions [that cause it to grossly overeat] has fat cells that are 4 to 5 times larger than normal. On the other hand, we can push the fat cell size in any animal to a bare minimum by depriving it of food. Knowing this, it is interesting to observe that if you leave an animal or a person alone, their fat cells will stay constant in size. It suggests to us that there is some sort of regulation in effect. We feel that there are signals between the fat tissue and the central nervous system." In obesity, these signals may be perturbed, Hirsch and Faust point out, because obese people tend to have fat cells that are two to two and a half times larger than normal.

The Rockefeller University researchers did two kinds of experiments to look at the influence of fat cell number on total body fat. In one, they looked at what happens when rats have double the usual number of fat cells. These rats, Faust and Hirsch found, regulated the size of their fat cells so that they were always the same size as the fat cells of control rats fed similar diets. But, since they had twice as many fat cells, they were twice as fat as the controls.

Faust also tried the reverse experiment. He took young rats and cut fat out of them so that they had only half as many fat cells as their littermates. Once again, these experimental rats seemed to regulate their fat cell size, not total body fat, when they were given high-fat diets, normal diets, or were deprived of food. In all circumstances, they were half as fat as the controls.

Now, says Hirsch, take a look at people. "We can take obese people and reduce them in the hospital so that their body weight is perfectly normal. But then we discover an astonishing thing. They are not normal. They need fewer calories than people who weigh the same as them but who were never obese. Their caloric need is 25 percent below normal and it persists that way forever. There is also abundant evidence that when you get normal volunteers to gain weight, they start to burn more calories." It is as though the body adjusts its metabolism to encourage a particular fat cell size.

Hirsch and Leibel are following a group of women and one man who belong to Overeaters Anonymous. All are formerly obese, weighing more than 200 pounds before they dieted and got their weights down to normal. But although

they look normal, their body chemistries are deranged. Their fat cells are tiny and, to a person, the women do not menstruate. They have low levels of thyroid hormone, they consume 25 percent fewer calories than would be expected on the basis of their weights and heights, they have low white blood cell counts, they have low pulse rates of about 50 to 60 beats per minute and low blood pressure of about 100/60 mmHg. They complain of cold intolerance and they are obsessed with food. In short, they look like people with anorexia nervosa.

Leibel proposed that the way fat cells signal the brain might have something to do with the peculiarities of fat cell metabolism. Ninety-nine percent of the fat in fat cells is stored as triglycerides. The triglycerides are formed when glucose enters the cell, is converted to glycerol phosphate, and is esterified with free fatty acids to form triglycerides. But the triglycerides in a fat cell are in a constant state of flux, being continually formed and degraded. When a triglyceride is broken down, all of its glycerol is released from the cell but only some of its free fatty acids. Those free fatty acids that are not released are used to make new triglycerides. It was possible, Leibel reasoned, that free fatty acids and glycerol might be controlling appetite.

Leibel developed an in vitro assay to measure how much free fatty acid relative to glycerol is released from fat cells. This assay, which involves double-labeling, is sensitive enough to be used on the amount of fat that can easily be obtained by a single needle puncture. And he discovered that the extent of reesterification of free fatty acids—the percent that remain in the cell to make new triglycerides—varies according to the state of the fat cells.

Normal, well-fed subjects, Leibel finds, have 50 percent reesterification. If these subjects then fast for 4 or 5 days, their percent of reesterification drops to only 10 percent, meaning that virtually all of their free fatty acids are released from their fat cells along with glycerol. Then he looked at obese subjects who were not trying to diet. They, like the normal subjects, had about 50 percent reesterification, which, says Leibel, "fits with our notion that fat people may not be in an abnormal state when they are obese." Finally, he looked at obese people who had lost weight. Only 35 to 40 percent of their free fatty acids were reesterified—a pattern that resembles the pattern he saw with the volunteers who had fasted.

Leibel notes that many formerly obese people have up to three times as many fat cells as people who were never overweight. "We're talking about a lot of glycerol and free fatty acids," he says. "This may relate to the clinical observation that obese people who reduce have symptoms that resemble semistarvation and that they tend to regain their lost weight with an almost mathematical precision. They are driven to get to some plateau. Their cells are not necessarily subnormal in size. But they exhibit very strange behavior. It is not like what cells do when a person is obese nor what a normal person's cells do."

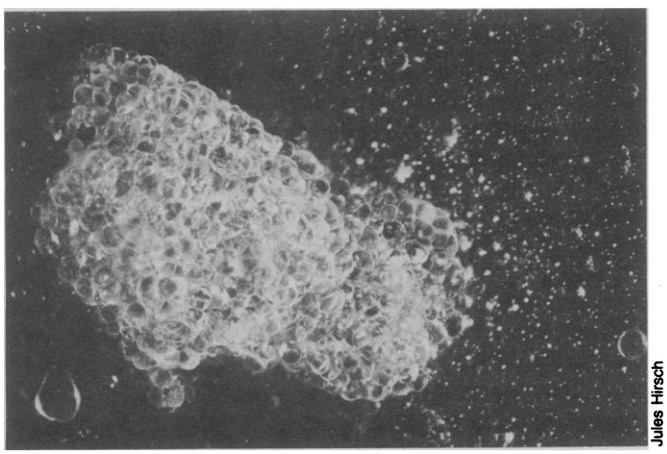
This does not mean, however, that the Rockefeller University researchers know yet how to alter people's eating habits. They tried the obvious—giving subjects glycerol. "It didn't make a damn bit of difference," Hirsch says. Possibly, the signals to eat or not eat are tied to sensitive ratios of glycerol to free fatty acids in the peripheral tissues, and such a gross measure as giving glycerol was simply insufficient.

The same assay that measures the percent of reesterification in fat cells can also be used to look at a fat cell's tendency to accumulate fat or break it down. Human fat cells have both α_2- and β-adrenergic receptors on their surfaces; the β receptors stimulate fat degradation through cyclic AMP and the α_2 receptors stimulate fat accumulation, also acting through cyclic AMP. (In rats, which are the usual experimental animal for obesity research, the α_2 receptors do not have the same biological influence.) Leibel finds that the preponderance of α_2 and β receptors vary in fat from different parts of the body and in fat from different people. Subcutaneous abdominal fat tends to have proportionately more β receptors, which means it releases more glycerol and free fatty acids. This may account for the epidemiological observation by several groups that people whose fat accumulates in their abdomens are at greater risk for heart disease than people whose fat accumulates in their hips and thighs.

Gluteal fat, Leibel finds, tends to have a preponderance of α_2 receptors. And individuals who have enormous difficulty reducing their hips or abdomens may have too many α_2 receptors in the fat cells from these areas. One woman he studied, for example, had extremely responsive α_2 receptors in her gluteal fat and, even though she lost 15 percent of her body weight, she lost virtually no fat from her hips and thighs. This woman also exercised vigorously but was unable to affect the pattern of her weight loss. A man had the opposite problem—overly responsive α_2 receptors in his abdominal fat. He halved his weight but kept his paunch.

For now, there is no established way to make a person's α_2 receptors less responsive. But, in vitro, drugs that block α_2 receptors or that stimulate β receptors make fat cells from even the most intransigent patients metabolize fat furiously. Drugs that block β receptors make cells accumulate fat. Whether these drugs alter fat metabolism in vivo is unknown. But millions of people take them. The frequently prescribed drug propranolol, is a β blocker. Hirsch is intrigued by the fact that propranolol and other β blockers, in addition to their effects on the heart, may be acting to slow the metabolism of abdominal fat, which has been linked to excess risk of heart disease.

These recent findings on the metabolism of fat cells will not yet make much difference to the 500-pound man under study at Rockefeller nor to the hordes of overweight people looking for a way to shed their excess pounds. But at least it should give them hope that, with a further understanding of how fat cells signal the brain, the problem of obesity may someday be solved.—GINA KOLATA



Jules Hirsch

Human gluteal fat

In the best clinical tradition, Jules Hirsch tried out on himself his needle puncture method of getting fat cells. These cells are the result.