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# The Fat's In The Fire: [Dr. Jules Hirsch]

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# RESEARCH PROFILES

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*It's a very odd thing —*
*As odd as can be —*
*That whatever Miss T. eats*
*Turns into Miss T.*
—WALTER DE LA MARE

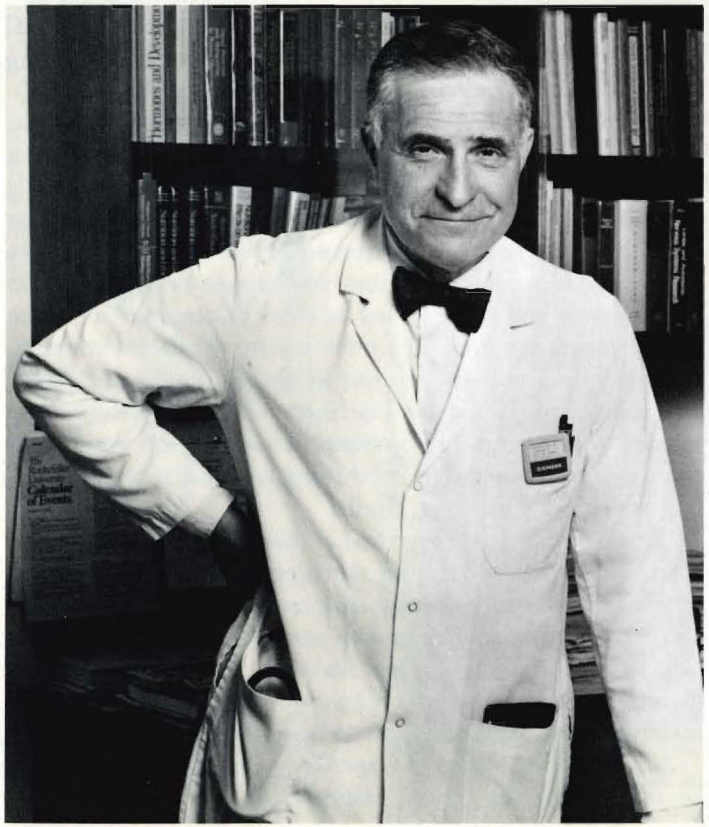
## The Fat's in the Fire

Despite the billions of dollars Americans spend each year to achieve slimmer silhouettes, we are getting fatter. This has been going on at least since the Civil War. Statistics on army inductees in each of the wars fought by this country show that Americans have grown progressively taller and fatter.

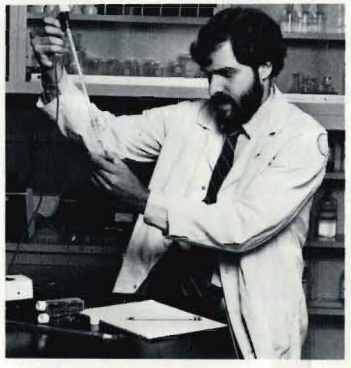
Jules Hirsch, a professor at The Rockefeller University and a senior physician in its research hospital, wonders whether we "have done ourselves such a favor by becoming taller and fatter and accelerating in growth." He asks: "Is this a factor in coronary disease? Is this why Americans in their forties and fifties get the diseases we used to get in our seventies and eighties?"

Earlier this year, Dr. Hirsch sounded a public alert. "We want the average American and his physician to know that obesity is a disease," he told reporters at a news conference called by the National Institutes of Health. "It's not just an adverse cosmetic condition. Obesity is a killer." He was speaking as chairman of a consensus panel on the health implications of obesity. The consensus report, released after a day-and-a-half of expert testimony, was one of the strongest indictments of overweight ever to come from a scientific group. It touched off a spirited debate.

"The question of what is too much fat is a matter of lively argument," Dr. Hirsch says, "but most people will agree that



*Jules Hirsch*



*Irving Faust, a member of Dr. Hirsch's laboratory since 1973, sampling cultured pre-adipocytes to determine the activity of the enzymes that signal cell differentiation.*

roughly thirty million Americans would profit by having less fat. They would have less diabetes and less hypertension, they certainly would have less stress upon weight-bearing joints afflicted with arthritis, and they would have a lot less hyperlipidemia and hypercholesterolemia and therefore less heart disease. So the NIH conference declared that obesity is a biologic hazard.

"The panel has gotten some flack," he notes. "Since there's no ready way of treating obesity, some critics have said that we're doing people an injustice by telling them about it." He acknowledges the extreme difficulty people experience in attempting to control their weight: the recidivism rate in obesity reduction programs is more than ninety-five percent for the extremely obese and about sixty-five percent overall. He also is troubled by what he calls "an enormous business in diets, nostrums, and pills, of things that are not effective in the long rm and often fall over into what I can only call quackery."

Since the NIH report, Dr. Hirsch's phone is seldom silent. "When someone calls me and says, 'I'm fat, what am I going to do?' I can't give them a speech about the need for biological research. They're calling me for direct help as a physician. What I tell those people is that everyone can lose weight, and there are four rules for doing it. First, you have to have a diet that's as reasonable and sensible and as close to one you can be on forever as you can find. The more bizarre the diet, such as all grapefruit or pistachios, the less likely it is to succeed. Then, if possible, you must become more active physically. That appears to be extremely important in maintaining weight loss and staying on a diet. The third thing is to realize that controlling obesity is a life-long process.

"Finally, what I tell everyone is that many people fail, but if you fail don't stop treating the hypertension or the diabetes or whatever else may develop that must be taken care of." He also advises against "perennially searching for the next great help over the horizon." Then he adds: "It may well be that there are some individuals who are, in our present state of understanding, better advised to leave the situation alone."

At this point, a note of impatience creeps into his voice as he admits that the current strategies of weight reduction are only a holding action. "I've just told you all I know about the treatment of obesity, and I certainly do that with our patients here. But to talk about slimming diets is looking at the problem from the outermost of many concentric circles. The other part of what we are doing—the central reason for my being at Rockefeller—is to examine how and why people get fat as a biological phenomenon, and to see how I can transmit what I learn into the treatment or prevention of obesity."

## GETTING TO THE FAT

Obesity is just the kind of problem The Rockefeller University Hospital, seventy-five years old this year, is organized to explore in depth. At the hospital, investigators can combine observations of patients with laboratory studies at the basic scientific level. The hospital staff can also collaborate freely with colleagues in other University laboratories on research projects that call for the insights and techniques of a number of disciplines.

Dr. Hirsch, who was born in New York City, came to the hospital after two years in the U.S. Coast Guard and the Public Health Service. He had attended Rutgers and received the M.D. degree from the Southwestern Medical School of the University of Texas in 1948. He then interned at Duke Hospital in Durham, North Carolina, and served his residency at the Upstate Medical Center of the State University, in Syracuse, New York. He had planned to teach cardiology after leaving the service. He decided to spend a year or two at Rockefeller at the suggestion of a friend who had worked there. The year was 1954, and as he explains, "the rage in those days, the new thing, was serum cholesterol and the relationships of blood fats to heart disease. I came to learn something about fats in the blood."

He came and he stayed. Except for service as a consultant to medical centers in Israel, a cause very close to his heart, The Rockefeller University Hospital, where he now heads the Laboratory of Human Behavior and Metabolism, has remained his base for thirty-one years.

He began in the laboratory of Edward H. (Pete) Ahrens, which was doing research on the metabolism of lipids. Since

the 1940s, Dr. Ahrens' work on these fats and fatlike compounds, particularly cholesterol, has brought him international recognition. "I was well trained clinically," Dr. Hirsch says, "so I became one of Pete's people taking care of the patients admitted to the hospital for study."

For several years, he also worked with Dr. Ahrens on the development of reliable methods for separating lipids. The laboratory made several major contributions to the refinement and invention of chromatography techniques, whereby a complex mixture is separated into its various constituents by percolating it through glass columns containing a selectively adsorbing liquid or solid medium.

The new research tools made it possible not only to separate, rapidly and precisely, all major types of lipids in a mixture but also to divide a lipid into the fatty acids and other chemicals it was made of. Dr. Hirsch and his colleagues were thus able to explore the effects of diet on concentrations of fats in the blood. Their observations were particularly important at a time when scientists were beginning to evaluate the relationship of diet to heart disease.

At the close of the 1950s, Dr. Hirsch began to switch his attention to adipose tissue, which is made up of billions of fat cells deposited under the skin and around certain organs. These cells contain energy stored as fats called triglycerides, which are constantly being formed and broken down. They are formed when glucose (blood sugar) enters a cell, is converted to glycerol phosphate, and is chemically linked to free fatty acids. When a triglyceride is broken down, all of its glycerol and some of its fatty acids are released into the blood. The remaining fatty acid are used to make new triglycerides. Our weight depends on the balance between energy (calories) we take in and the energy we burn up.

Though researchers at Rockefeller and elsewhere had evidence that adipose tissue played a central role in many phases of lipid and carbohydrate metabolism, they had made few studies of the biochemical processes involved. One reason was the limitation of analytic techniques, which required tissue samples of a size obtainable only by surgical excision. The new chromatographic methods made it possible to analyze the composition of the fatty acids in less that a milligram of tissue. "The question," Dr. Hirsch says, "was how can you get adipose tissue easily.

"I devised a ridiculously simple method that's like doing a bad venepuncture. If you take a needle and you want to get blood, and if you keep missing the vein and sucking back, you may get a little fat. It's practically microscopic, but it was enough for our purposes. So I began putting needles into my own fat tissue and that of my friends and we started getting samples for study."

Once perfected, adipose aspiration, as the method is called, afforded virtually painless tissue sampling. This research deepened Dr. Hirsch's interest in adipose tissue and led him to studies of obesity.

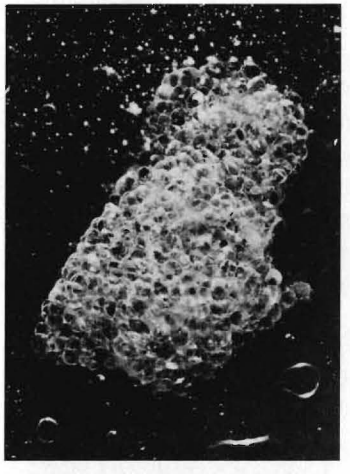
## SWELLING CELLS, MULTIPLYING CELLS

"Obesity was a logical thing for me to work on," Dr. Hirsch says, "because I've always been interested in the interactions of behavior and metabolism. Rockefeller Hospital was a congenial setting because Vincent Dole, one of the leaders here in metabolism research, had also been studying obese patients. He was interested in caloric exchange and did some pioneering work with formula diets."

Dr. Hirsch and his colleagues conducted several studies of adipose biochemistry and showed that this tissue has enzymatic machinery for processing glucose and fatty acids and releasing them into the blood to supply energy. "Which brings us to the mid-sixties or a little later," he recalls, "when the following issue came up: If you want to compare the adipose biochemistry in the fat person versus the lean person, how would you do it?

"Well, presumably, what you really need to know when you take out one of those little pieces of tissue is how many cells there are, so that you can say how much glucose a cell takes up or metabolizes on a per cell basis. When you take samples, you get more or less tissue and the customary ways of dealing with this were not satisfactory. We really needed some denominator, a way of doing our tests per cell.

"So I spent some time examining techniques for doing that, and it turned out that there was on the scene then a relatively



*Fat cells, where fat is made, stored, and released into the body to provide energy.*

new instrument called a Coulter Counter, which is now in common use in hospitals for counting blood cells. We found that we could make a suspension of fat cells and run them through the counter." Using this method, Dr. Hirsch and his colleagues then made a number of findings about adipose cells that have influenced the study of obesity since.

When people become obese their fat cells blow up in size. But there is a limit to how big they can get, and very obese people, who weigh one hundred and seventy percent or more of their ideal weight, develop more fat cells. Although a person may be able to add fat cells at any point in life, so-called juvenile-onset obesity is more likely to result in an increase in fat cells. This type of obesity appears to be the most difficult to treat. Some scientists have theorized that at various "critical" periods during development, alterations in food intake will permanently affect adipose tissue, but whether this is so is not yet known with certainty.

"It's not at all clear," says Dr. Hirsch, "what the factors are that lead to more fat cells. What seems to happen when people lose weight is that their fat cells shrink in size but the number of cells remains the same. So however they became obese, if they've made more fat cells, the mark of obesity remains with them. This leads us then to the idea that maybe something about this irreversibly high fat cell number is involved in the whole issue. Perhaps the reason why a person who was once obese so frequently regains weight is that those fat cells, as someone put it poetically, cry out to be filled again."

During studies of fat metabolism and cellularity, the Hirsch laboratory recorded clinical and behavioral changes in their patients. They discovered that some patients undergoing weight loss reacted in ways reminiscent of the reactions of victims of starvation. "As a matter of fact," Dr. Hirsch says, "although these individuals are in some respects much better off if they reduce, in other respects they're not. Women may lose their menstrual periods and feel unwell. There's a body of literature we've produced on the effects of dieting, such as depression, obsession with food, intolerance to cold, and low blood pressure and low white-cell counts, that are also seen in people with anorexia nervosa. It's not a uniformly happy event to take obese people and have them reduce down to what we consider normal weight."

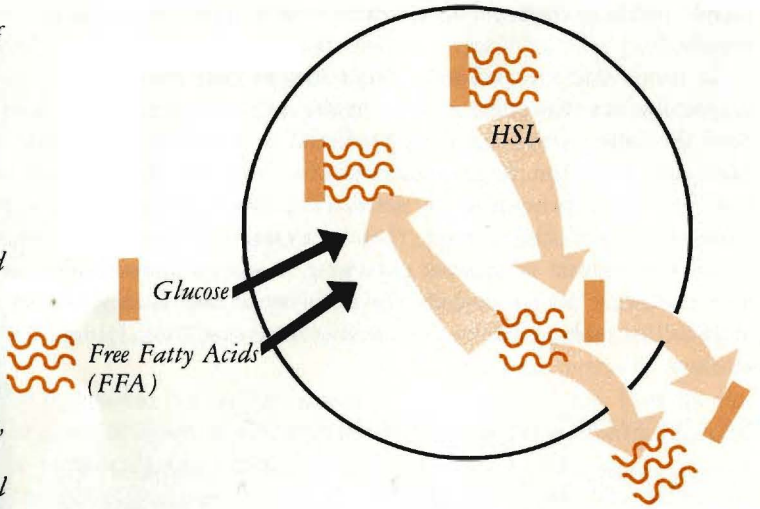
To compound the problem, recent studies have revealed the surprising fact that obese persons in the reduced state actually need *less* energy than would be predicted on the basis of their body size. For some, to maintain their lower weight they must restrict their caloric intake by about twenty-five percent more than anticipated. By contrast, there is a good deal of evidence that when normal volunteers gain weight, they start to burn *more* calories. "It's as though the body were modulating its metabolism to keep its fat cells at a certain size," Dr. Hirsch observes.

## SEARCHING FOR A SIGNAL

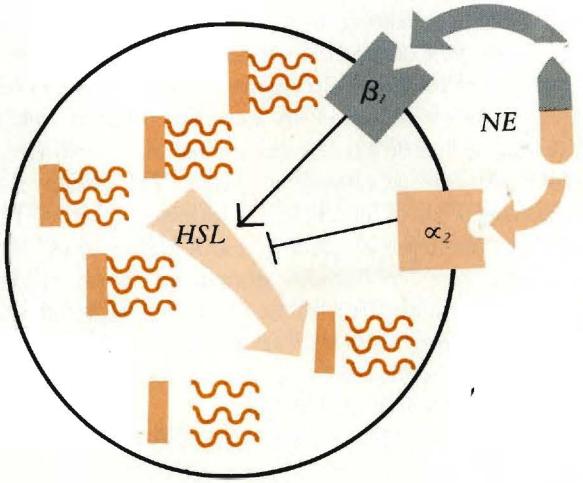
After three decades of research, Jules Hirsch is convinced that obesity is not just a "disorder of hedonism." "A person," he says, "who comes waddling down the street weighing fifty or a hundred pounds more than the next person is not that way because of some unique lack of will power or nutritional understanding. My feeling is that the amount of adipose tissue in the body is a controlled variable like blood pressure or pulse rate. All of us have some degree of propensity to become obese; it appears to be easier to store fat than to lose it. During evolution, starvation has been a far more common fact of life than our current society of surfeit. Fat storage is useful and lifesaving, which is why it is jealously guarded by the body, and the obese person guards it at a higher level." Irving Faust, a member of Dr. Hirsch's laboratory, further explains that in times of food scarcity, as fat stores are depleted and the body begins to feed on itself, fat cells, like nerve cells, are fully spared. "In the hierarchy of cells critical for survival, the adipocytes appear to be quite high."

The level of fat storage, Dr. Hirsch believes, is to some degree genetically determined. Studies of identical twins show that sixty to eighty percent of the risk of obesity is attributable to genetic factors. That is not to say that fat storage may not also be influenced by early events in life such as feeding experiences or chronic childhood infections, which lead to reduced food intake.

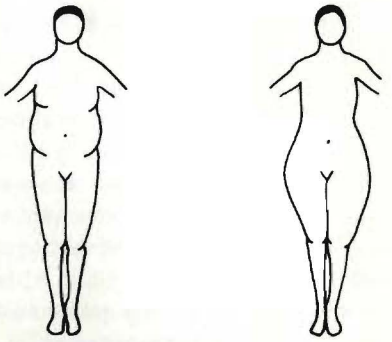
*Rudolph Leibel, a pediatrician who came to The Rockefeller University Hospital under its clinical scholars program to learn more about the processes leading to obesity. Here he collects radioactively labeled fat cells, which have been incubating in the two flasks. The amount of radioactivity incorporated into tryglycerides in the cells provides a measure of metabolic activity.*




*A diagrammatic representation of a fat cell. The activity of fat cells involves many complex interactions. Triglycerides, the energy stores, are made in fat cells from glucose (sugar) and free fatty acids. In the drawing, the triglyceride compound is represented by three wavy lines (the fatty acids) attached to a backbone called gycerol. When the enzyme hormone-sensitive lipase (HSL) breaks triglycerides apart, a process called lipolysis, some of the fatty acids attach to glycerol newly made from glucose and some are released outside the cell.*




*Important in the control of HSL are receptors on the cell's surface which read "signals" from norepinephrine (NE), a chemical secreted by nerve cells. When norepinephrine stimulates the beta-1 receptor, HSL is activated. When alpha-2 is engaged, HSL is inhibited. The balance of receptor activity is believed to influence where adipose tissue accumulates in the body.*



*Where adipose tissue is deposited in the body appears to be an important health factor. The type of fat distribution in the figure on the left is typically male, that in the figure on the right is typically female, but either type can appear in either sex. People who store fat in the abdominal region have been shown to be at considerably greater risk for hypertension, diabetes, strokes, and coronary artery disease. How fat becomes concentrated in particular body areas is one of the subjects under investigation in Dr. Hirsch's laboratory.*

"At any rate," he concludes, "the food-intake-related behaviors we have observed and the metabolic events we have analyzed are all in favor of a regulatory or signaling system controlling this fat storage. The things that drive a person to eat may in some way relate to the state of the fat cell. Trying to look at that is a major part of our work."

In this work, Dr. Hirsch is closely associated with Rudolph Leibel, who explains that he was drawn into research partly because he realized, as a pediatrician, that treatment of obesity in children was made difficult, if not impossible, by scientists' lack of understanding of the underlying biology. A few years ago, he read a paper in *Science* written by Drs. Hirsch and Faust in which they described a series of studies with rodents that had led them to hypothesize a feedback signaling system between adipose tissue and the brain. "It was an idea that had also occurred to me," Dr. Leibel says. "I wrote a letter about it to *Science,* which they published, and I wrote to Jules. Within a few months I had given up my clinical and teaching responsibilities to come here and do research full time."

Dr. Hirsch and Dr. Leibel have developed a sensitive new assay for the study of metabolic cycles in fat tissue. One area of investigation is the mechanism by which the fat cell regulates the release of fatty acids and glycerol to the rest of the body.

The ratios of each as they leave a cell may somehow signal either the liver or the brain as to the size of that cell, or provide other information about its metabolic state.

One discovery has been that the percent of free fatty acids remaining in a cell to make new triglycerides varies according to the state of the subject from whom the cell is taken; for instance, whether the subject was fasting. Dr. Leibel studied the fat cells of three groups of patients. In normal, well-fed volunteers, fifty percent of their fatty acids remained in the cells to become new triglycerides. When the same group fasted for four or five days, virtually all the fatty acids were released from their cells. Obese subjects who were not on a diet, like the normal subjects showed about fifty percent retention of the fatty acids. But the fat cells of obese people who had lost weight released an amount of fatty acids similar to what was recorded in the normal subjects who had fasted. The data, Dr. Leibel reports, "support our notion that some formerly obese people may be in an abnormal metabolic state."

A second area of investigation that may point the way to why people lay down adipose fat in different areas of the body is the analysis of receptor molecules found on the surface of fat cells. These receptors are the routes through which certain hormones and neurotransmitters stimulate or inhibit fat release. When triggered by a hormone, one type of receptor, called beta-1, stimulates fat breakdown and release; a second type, alpha-2, inhibits fat release and favors fat build-up. Drs. Hirsch and Leibel have found that the numbers of alpha-2 and beta-1 receptors in fat tissue vary from place to place in the body and in different people. Abdominal fat tends to have more beta-1 receptors. Fat in the hips and thighs has more alpha-2 receptors.

It has been shown that people with large bellies are at greater risk for heart disease and diabetes than those with big hips. The reason is not clear. Could it be because fat cells in the abdomen are more active metabolically, releasing more glycerol and free fatty acids? This is but one of the questions that Drs. Hirsch and Leibel are seeking to answer. One of their objectives is to be able to manipulate the receptors with drugs and hormones, and at least moderate some of the health-threatening effects attributed to obesity.

Another major endeavor of the laboratory in which Dr. Faust is engaged, is the investigation of factors that lead to the multiplication of fat cells and their differentiation. As he explains: "If you culture fibroblasts—connective tissue cells—from the cheek or tail of an animal, they multiply and form sheets of fibroblasts. But if you culture what appear to be fibroblasts from parts of the body where fat is developing, multiplication is often followed by differentiation of the cells into typical fat cells. It's very important to know the determinants of this differentiation and why it occurs in cells from some parts of the body but not others."

## A RICHNESS OF RESOURCES

"With obesity," says Jules Hirsch, "there is a braiding of psychosocial and environmental forces, genetic endowment, and metabolism all changing and interacting. When we approach the problem, we often have a fixed theory because of our own disciplines. The psychologist sees it one way, the chemist or molecular biologist another. One of the reasons I'm a spokesman for clinical investigation is because the physician-researcher is in a unique position to observe the natural phenomenon; he sees an individual over the whole developmental sequence, and he can use everything—psychology, biochemistry, whatever—to study human disorder.

"We began from the purely chemical standpoint, studying fat, and got interested in obesity. We looked at the psychological aspects and concluded that whatever they may be, obese individuals behave as though they have a major metabolic or chemical disorder. That's what we're looking at now. Fortunately, we are in an institution that's rich in resources for doing this kind of research."

This December, Dr. Hirsch begins a collaborative venture with Dr. Theodore van Itallie, who directs nutritional studies at St. Luke's Hospital Center, in New York. They will be the principal investigators of the only NIH-sponsored obesity research core center, in a five-year study that will involve scientists from a number of institutions and disciplines. "Our objective," says Dr. Hirsch, "is to mount a concerted, broad-scale effort to understand the nature of human obesity." □

*Dr. Hirsch and Dr. Leibel in front of the Rockefeller Hospital.*

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