

# THE LIVER'S WEIGHTY PROBLEM

As obesity rates soar, a sometimes fatal liver disease is becoming epidemic *By Mitch Leslie*

**T**he patient who walked into Joel Lavine's office at the University of California, San Diego (UCSD), medical center one day in the mid-1990s didn't know how sick he really was. He was morbidly obese. A brownish blemish known as acanthosis nigricans sprawled over the nape of his neck and into his armpit, signaling that he probably had developed insulin resistance, a condition in which cells don't respond normally to the hormone that controls blood sugar.

A biopsy revealed striking damage to the patient's liver: so much fat crammed into

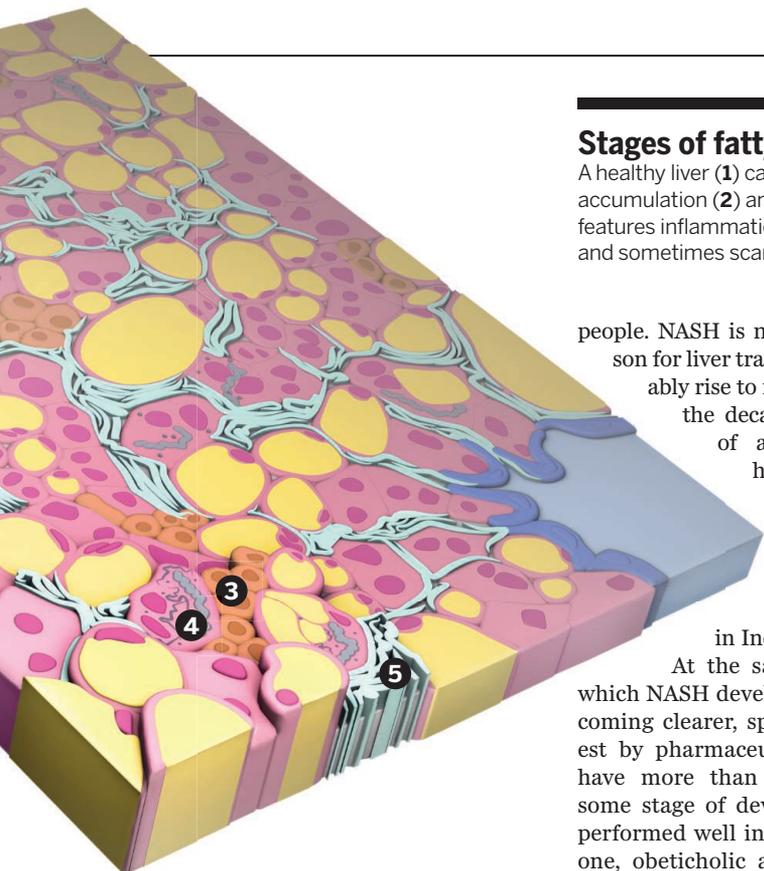
the cells that it squashed their nuclei and other contents. Cirrhosis, or severe liver injury, was beginning as scar tissue ousted healthy cells. The patient essentially had the liver of a middle-aged alcoholic. Yet he was only 8 years old.

To Lavine, a pediatric hepatologist, it was clear the boy was suffering from non-alcoholic steatohepatitis (NASH). A condition usually associated with obesity, NASH results from excess fat in the liver and, as the name indicates, doesn't stem from the alcohol abuse that causes many cases of severe fatty liver disease. Because NASH can destroy the liver, patients can require

a liver transplant or even die.

Although Lavine had come across a few kids with NASH earlier in the 1990s when he worked at Boston Children's Hospital, he found "it was rampant" in San Diego among the large Hispanic population. A dozen children suspected of having the illness were coming to his office every week for diagnosis. "It was clear we had an epidemic of sorts," says Lavine, who is now at Columbia University's College of Physicians and Surgeons.

That epidemic has now spread throughout the country as our livers pay the price for our calorie-rich diets and sedentary



## Stages of fatty liver disease

A healthy liver (1) can progress to fat accumulation (2) and then to NASH, which features inflammation (3), cell swelling (4), and sometimes scarring (5).

people. NASH is now the number two reason for liver transplants, and it will probably rise to number one by the end of the decade as a new generation of antiviral drugs controls hepatitis C, currently the largest cause of liver failure, says hepatologist Naga Chalasani of the Indiana University School of Medicine in Indianapolis.

At the same time, the paths by which NASH develops and worsens are becoming clearer, sparking a surge of interest by pharmaceutical companies, which have more than 20 potential drugs in some stage of development. Several have performed well in early clinical trials, and one, obeticholic acid, recently impressed researchers by reducing the amount of liver scarring, a serious consequence of NASH. “We are at a pivotal time” in the history of NASH, Lavine says. “In 5 years we will have at least one treatment approved,” Ratziu predicts.

**NASH WENT UNRECOGNIZED** for decades, mainly because doctors confused it with alcoholic steatohepatitis, or ASH, which also involves fat buildup in the liver but results from heavy drinking. Although some people who had fat-flooded livers denied being alcoholics, doctors were convinced they were boozing in secret, says hepatologist Stephen Caldwell of the University of Virginia in Charlottesville. The assumption was “if you had liver disease, you

were a drinker,” he says.

Then in 1980, pathologist Jurgen Ludwig of the Mayo Clinic in Rochester, Minnesota, and colleagues put the “N” in “NASH,” describing a cluster of people with fatty, damaged livers who were not alcoholics. The large number of kids subsequently found to have NASH helped dispel any lingering doubts that the illness wasn’t alcohol-related, Lavine says.

Extra fat in the liver is now fairly easy to spot with imaging techniques. Gauging how many people have the severe form of fatty liver disease, NASH, is trickier. “The only way to know if your patient has NASH is a liver biopsy,” says gastroenterologist Stephen Harrison of the Brooke Army Medical Center in San Antonio, Texas. Although he describes the procedure as “a nick in the skin” that doesn’t involve surgery, people often refuse, which makes it hard to determine NASH’s prevalence; researchers’ estimates generally run between 2% and 5% of the population.

Ultimately, says molecular biologist Jay Horton of the University of Texas Southwestern Medical Center in Dallas, fatty liver “is a disease of caloric excess.” The imbalance between calories consumed and burned triggers a complex series of changes that transform the organ’s character. Many of the diet-derived fatty acids in the bloodstream make their way to the liver, which directs them to other parts of the body. “The liver is your traffic cop” for these building blocks of fats, says Elizabeth Parks, a nutritional physiologist at the University of Missouri in Columbia. But the organ itself typically holds onto little fat. For instance, Parks says, a fairly fit 70-kg man will carry about 14 kg of body fat—and only 125 g will reside in the liver. “It’s such as small pool, and there are lots of options that the liver uses to get rid of it,” she says.

In some people, however, the liver becomes a hoarder and starts stockpiling

lifestyles. About 20% to 30% of people in the United States who don’t abuse alcohol carry extra fat in their livers, a precursor to NASH. The condition is even turning up in unlikely places such as rural India. “It’s becoming an important problem everywhere,” says hepatologist Vlad Ratziu of the Pitié-Salpêtrière Hospital in Paris.

That’s worrying, doctors and researchers say, because although such liver fat accumulation is usually benign, NASH develops in about 30% of people with fat in the liver. It can lead to liver failure, liver cancer, and death, and no drug treatments exist yet. A new liver is the only option for many

## The culprits

The liver stores excess fat in fatty liver disease, and these five contributors help determine how much.



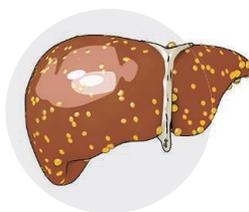
### Diet

Fats that we eat can travel to the liver, which may stash some of them.



### Adipocytes

These fat-storage cells release fatty acids, which can travel to the liver.



### Fat producer

In fatty liver disease, the liver can turn up its production of fatty acids.



### VLDL

The liver sheds some—but not enough—excess fat by producing these particles.



### Insulin resistance

This condition causes adipocytes to spill fats and the liver to make them.

triglycerides, a fat variety, sometimes accumulating so much that the organ “can look like butter,” Lavine says. In addition to dietary fatty acids, fat in the liver can come from two other sources, researchers have found. Outside the liver, fat-storing cells known as adipocytes continually release some of their contents, which end up in the organ. And the liver itself synthesizes some fat.

All three sources ramp up in fatty liver disease. Parks and her team recently showed how the liver contributes to its own woes. They fed volunteers meals that contained stable isotopes, enabling them to track the synthesis of free fatty acids, precursors of triglycerides. People who had fatty liver disease manufactured three times more free fatty acids in their livers than did healthy subjects, the group reported last year in *Gastroenterology*.

Of the many metabolic abnormalities that could drive accumulation of fat in the liver, insulin resistance seems key, Chalasani says. It develops when cells become less responsive to the hormone, usually because of a surfeit of nutrients from food, and it promotes fat buildup in the liver in several ways. For example, insulin normally prompts adipocytes to stop releasing fatty acids. But as Parks and her team showed in their study last year, insulin-resistant adipocytes continue to spill fatty acids into the blood. The liver can usually rid itself of some fat by exporting triglycerides, but insulin resistance prompts the organ to synthesize more triglycerides, overwhelming the disposal mechanism.

Other factors, from the types of microbes living in the intestine to genetics, may also induce fat accrual in the liver. Having a particular variant of the metabolic gene *PNPLA3* boosts the risk of developing a fatty liver, for instance.

**A RAFT OF HEALTH PROBLEMS** typically accompanies the fat buildup, including obesity and diabetes. But the liver’s extra heft doesn’t normally kill, Harrison says. Chances are, “you are going to grow old with your fatty liver,” he says.

The odds are worse for people who progress to NASH. About 25% of them eventually develop cirrhosis that devastates the liver. Compared with individuals with more benign fatty livers, NASH patients typically show two distinctive characteristics. The inflammation in their livers is more intense as white blood cells infiltrate the organ. And hepatocytes, the most abundant liver cells,

swell to as much as twice their normal size, a condition known as ballooning that heralds their demise.

These two phenomena can segue to an insidious problem: fibrosis, or the buildup of scar tissue rich in the protein collagen. As scarring progresses, it takes over more and more of the liver, and fewer and fewer healthy cells remain, sometimes resulting in liver failure. Cirrhosis can also trigger liver cancer, although researchers haven’t worked out exactly how.

The biggest question—why about one-third of people with fatty liver disease develop NASH—remains unanswered, notes UCSD hepatologist Rohit Loomba. Some scientists posit that the fat itself is poisonous to liver cells, whereas other evidence points to inflammation and oxidative stress.

Whether scar tissue accumulates in a fat-laden liver may depend on the organ’s ability to heal itself. Hepatologist Anna Mae Diehl of the Duke University Medical Center in Durham, North Carolina, and her colleagues have found evidence that repair goes awry in the livers of NASH patients because of excessive activity by a molecular signaling pathway normally prominent in develop-

ment. In an embryo, a protein called hedgehog and its partners help sculpt the brain, kidneys, intestines, and other parts of the body. The pathway all but shuts down in the livers of healthy adults, but it can ramp up again if the liver is injured. The pathway then spurs certain liver cells to transform into cells that produce scar tissue. The bal-

looned hepatocytes that accrue in the livers of NASH patients could be the culprit, Diehl and her team suggest. The bloated cells pour out proteins that activate the hedgehog pathway, the researchers revealed in a 2011 paper in *The Journal of Pathology*.

**DOCTORS NOW HAVE LITTLE TO OFFER** NASH patients apart from the recommendation to eat less and exercise more. If a patient worsens to the point where the liver starts to shut down, a transplant becomes a possibility. But at the moment, “the ability to rescue someone who is getting really sick is limited,” Caldwell says.

That grim outlook may soon change. Many biotech and pharmaceutical companies have launched NASH drug development efforts, enticed by the potentially huge demand for a chronic medication—a \$35 billion annual market by one estimate. The drugs researchers have tested against NASH or hope to test include vitamin E, the diabetes treatment pioglitazone, and a

raft of new compounds. “What’s interesting is that almost all of them have a different mode of action,” Ratziu says.

One drug, aramchol, combines a synthetic fatty acid and bile acid; it is now in a phase II trial to determine how well it reduces fat accumulation in the liver. In contrast, cenicriviroc, also in a phase II trial, originated as an antiviral candidate because it blocks certain receptor molecules on immune cells that viruses use as entryways. But it also may stem inflammation and liver fibrosis.

At least two phase III clinical trials of potential NASH treatments are likely to begin this year, although one them is already starting with a strike against it. In March, the French pharmaceutical firm Genfit announced that GFT505, which stimulates cellular receptors that promote insulin sensitivity and spur fatty acid breakdown, didn’t reduce the amounts of liver fat or fibrosis overall in a phase II trial of 274 NASH patients. But the most serious cases did show improvement, and Ratziu says the company plans to launch a phase III trial in 2500 patients with advanced NASH.

The most promising NASH treatment so far, several researchers say, is obeticholic acid. The liver produces bile acids to help the intestine absorb fats, which help manage fat and sugar metabolism. Obeticholic acid is a modified bile acid, and it prods a cellular receptor that promotes sensitivity to insulin and reduces the amount of triglycerides in the blood.

Last November, hepatologist Brent Neuschwander-Tetri of the Saint Louis University School of Medicine and colleagues reported the results of the FLINT trial, a phase II study that found that obeticholic acid reduced the amount of fibrosis in NASH patients, suggesting the drug can reverse the disease. “That’s something that’s never been seen for a drug before,” says Lavine, who was on the trial’s steering committee.

Still, researchers—and drug company investors—remain cautious. As Loomba points out, none of the drugs tested so far has benefitted more than 50% of NASH patients. And although obeticholic acid reduced fibrosis, it also increased the levels of LDL cholesterol, which promotes cardiovascular disease. That’s worrying, Chalasani says, because “these people are already at greater risk for coronary artery events and cardiovascular disease.” Even so, a phase III trial of obeticholic acid in 2500 patients with severe liver fibrosis is scheduled to start later this summer. And the scientific community studying NASH is hopeful for the first time. Preventing or even reversing NASH, Neuschwander-Tetri says, finally seems “a reachable goal.” ■

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**Vlad Ratziu,**  
Pitié-Salpêtrière Hospital