

# MEDICAL MYSTERY



Catherine Zonsky first noticed the bump on the back of her right hand in 1995, when she was a college student. About the size of a marble, it was on tendons near the knuckles, though not painful. She didn't think much of the growth, attributing it to the time she smashed her hand against the porch railing during

a moment of anger. But it didn't go away.

Several years later two similar bumps appeared, one on each of her ankles. Catherine saw a doctor who suggested that the growths might be due to ill-fitting shoes. By 2001 she decided to have all three bumps removed because they were unsightly.

The bump on Catherine's hand was excised, but those on her ankles were left untouched because of a potential risk to the joints. When biopsied, the lump — a rare growth called a xanthoma — was found to contain inflammatory cells and fat deposits that were assumed to be cholesterol. Xanthomata (the plural form of xanthoma) typically attach to tendons in the hand, elbow, and ankle.

Over the next five years, the lump in her hand slowly grew back. Her mother became worried; Catherine's father had died of heart disease at age 65. She convinced her daughter to see Patrick J. Lamparello, M.D., Associate Professor of Surgery, who had treated her father at NYU. Because Catherine's lumps may have contained cholesterol, he referred her to the NYU Lipid and Treatment Research Center, which had opened recently. (It has since been renamed the NYU Center for the Prevention of Cardiovascular Disease.) Catherine was examined by its director, Edward A. Fisher, M.D., Ph.D., (75) the Leon H. Charney Professor of Cardiovascular Medicine and Professor of Cell Biology and Pediatrics.

Dr. Fisher's initial thought was familial hypercholesterolemia (FH), an inherited disease of high cholesterol. People with FH have abnormally high levels of LDL cholesterol, the so-called bad cholesterol, but previous tests had revealed that Catherine's levels were normal. So he rechecked her LDL levels and ordered specialized tests for other lipopro-

tein particles that also carry cholesterol. He suspected that Catherine could have some unusual type of hyperlipidemia in which cholesterol is carried on a non-LDL particle, leading to accumulations of cholesterol in the tendons. Once again the results were completely normal.

Weeks passed. "Her case was on my mind," recalls Dr. Fisher, "when all of a sudden I remembered the rare causes of recurrent xanthomata that aren't from elevated LDL levels — sitosterolemia and cerebrotendinous xanthomatosis (CTX). I didn't think of these diseases right away; it was an epiphany."

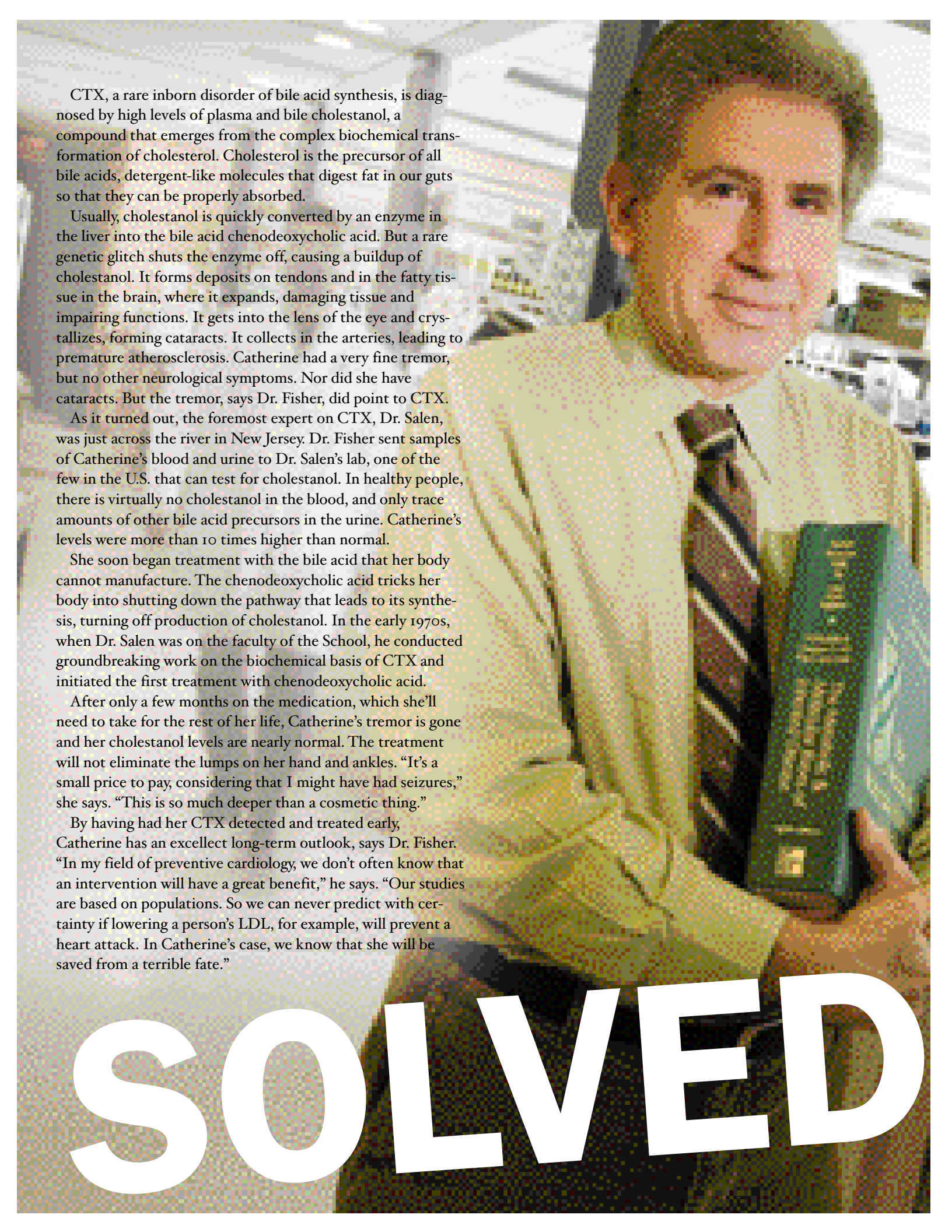
Dr. Fisher regularly attends meetings of the New York Lipid Research Club, where about 10 years ago he had heard Gerald Salen, M.D., and Steven Tint, Ph.D., both affiliated with the University of Medicine and Dentistry of New Jersey, discuss sitosterolemia and CTX.

Dr. Nadeem Ahmed, a Fellow in Preventive Cardiology, helped Dr. Fisher search the medical literature on the diseases. Dr. Fisher first thought that Catherine had sitosterolemia, which, although rare, is still more common than CTX. Sitosterolemia is caused by the abnormal absorption of plant sterols, cholesterol-like molecules present in many foods, including processed foods. Our intestines don't absorb plant sterols, and they cause no harm. But in people with a certain genetic mutation they are absorbed, causing advanced atherosclerosis at an early age.

Catherine underwent a test called intima-media thickness (IMT) to measure the amount of plaque in her neck arteries. Yet again, the results were normal; she had no evidence of premature atherosclerosis. With sitosterolemia less likely, Dr. Fisher believed he had finally found the culprit: CTX.

Left untreated, Catherine could expect dementia and death by the age of 50 or so. At the time, Catherine was 31. Before it kills, CTX can bring about cataracts, mental retardation, and a host of neurological problems, as well as Achilles tendon xanthoma, atherosclerosis, and other symptoms.

IN HIS SMILOW LAB, DR. EDWARD A. FISHER WITH A COPY OF *THE METABOLIC & MOLECULAR BASIS OF INHERITED DISEASE*. THIS BIBLE OF METABOLIC DISORDERS CONTAINS A CHAPTER ON CTX, WHICH SOLVED THE RIDDLE.

A man in a light-colored suit and striped tie is smiling and holding a large, dark green book. The background is a blurred office or laboratory setting with shelves and equipment.

CTX, a rare inborn disorder of bile acid synthesis, is diagnosed by high levels of plasma and bile cholestanol, a compound that emerges from the complex biochemical transformation of cholesterol. Cholesterol is the precursor of all bile acids, detergent-like molecules that digest fat in our guts so that they can be properly absorbed.

Usually, cholestanol is quickly converted by an enzyme in the liver into the bile acid chenodeoxycholic acid. But a rare genetic glitch shuts the enzyme off, causing a buildup of cholestanol. It forms deposits on tendons and in the fatty tissue in the brain, where it expands, damaging tissue and impairing functions. It gets into the lens of the eye and crystallizes, forming cataracts. It collects in the arteries, leading to premature atherosclerosis. Catherine had a very fine tremor, but no other neurological symptoms. Nor did she have cataracts. But the tremor, says Dr. Fisher, did point to CTX.

As it turned out, the foremost expert on CTX, Dr. Salen, was just across the river in New Jersey. Dr. Fisher sent samples of Catherine's blood and urine to Dr. Salen's lab, one of the few in the U.S. that can test for cholestanol. In healthy people, there is virtually no cholestanol in the blood, and only trace amounts of other bile acid precursors in the urine. Catherine's levels were more than 10 times higher than normal.

She soon began treatment with the bile acid that her body cannot manufacture. The chenodeoxycholic acid tricks her body into shutting down the pathway that leads to its synthesis, turning off production of cholestanol. In the early 1970s, when Dr. Salen was on the faculty of the School, he conducted groundbreaking work on the biochemical basis of CTX and initiated the first treatment with chenodeoxycholic acid.

After only a few months on the medication, which she'll need to take for the rest of her life, Catherine's tremor is gone and her cholestanol levels are nearly normal. The treatment will not eliminate the lumps on her hand and ankles. "It's a small price to pay, considering that I might have had seizures," she says. "This is so much deeper than a cosmetic thing."

By having had her CTX detected and treated early, Catherine has an excellent long-term outlook, says Dr. Fisher. "In my field of preventive cardiology, we don't often know that an intervention will have a great benefit," he says. "Our studies are based on populations. So we can never predict with certainty if lowering a person's LDL, for example, will prevent a heart attack. In Catherine's case, we know that she will be saved from a terrible fate."

# SOLVED