Lipids are essential for good health, but they contribute to major diseases when harmful forms overwhelm beneficial ones. Researchers are exploring why the balance shifts for the worse around midlife and are searching for therapies to counteract that tendency. Along the way, they’re uncovering hints that lipids influence mental agility and longevity as well.

Lipids—fatty molecules such as cholesterol and triglycerides—are two-faced characters. They bolster cell membranes, offer insulation against cold, provide energy, and promote healthy brain and nerve function. But as flab accumulates with age, lipid quantities escalate. With this rise, lipids turn evil: The molecules spur a host of health problems including heart disease, stroke, obesity, diabetes, and dementia.

Researchers are exploring why lipids run amok as people grow older and are hunting for ways to intervene. They’re cataloging and characterizing the 1000-odd lipids within a cell, exploring the Jekyll-and-Hyde personalities of lipids called fatty acids, engineering animals that gorge without gaining an ounce, and teasing apart connections among lipids, longevity, and mental sharpness—all with the aim of exploiting the molecules’ better qualities and thwarting their destructive tendencies.

**The Good, the Bad, and the Gunky**

Lipids’ changing proclivities are influenced by lipoproteins, key actors in this midlife melodrama. These conglomerations of fat and protein chauffeur cholesterol, fatty acids, and other lipids through the body and come in several varieties. Low density lipoprotein (LDL) and very low density lipoprotein (VLDL) play the villains because of their propensity for depositing cholesterol in artery walls, thus contributing to atherosclerosis, a stiffening of blood vessels that leads to blockage and raises the risk of heart attack and stroke. High-density lipoprotein (HDL), the hero, protects against these dire developments by shuttling excess cholesterol to the liver for recycling or disposal.

Another lipoprotein with rogue-like propensities, chylomicron, makes cameo appearances after fat-rich meals to escort dietary fats such as cholesterol and triglyceride from the intestine into the bloodstream. Soon after entering the bloodstream, chylomicron particles unload much of their triglyceride cargo to muscle and adipose tissue—the body’s fat warehouse. The resulting scraps, known as chylomicron remnants, normally exit from the bloodstream to the liver within a few hours after a meal.

But problems arise as midlife flab replaces youthful muscle, a transformation that might occur because older people aren’t as active as they once were or because a genetic program prompts the aging body to fatten up. Although scientists aren’t sure what causes the change in body composition—which occurs even in seniors slender enough to fit into the clothes they wore in college—they do understand how the shift brings out chylomicron’s evil side. As fat supplants sinew, the body’s capacity to break down chylomicron declines because the process requires an enzyme that’s more active in muscle tissue than in fat, says endocrinologist Ernst J. Schaefer of Tufts University School of Medicine in Boston, Massachusetts. In addition, the liver’s ability to take up chylomicron remnants wanes. As a result, the particles—which still carry cholesterol—accumulate; as with LDL and VLDL, they contribute to atherosclerosis.

Concentrations of VLDL and LDL also rise when aging bodies gain blubber, says endocrinologist W. Virgil Brown of Emory University School of Medicine in Atlanta, Georgia. VLDL reshelves fatty acids in adipose tissue, and swelling adipose tissue releases a surplus of fatty acids. To deal with the rise of evil. As bodies fatten, lipid processing turns sour. After unloading triglycerides (TGs), cholesterol-bearing chylomicron remnants (CMRs) aren’t cleared efficiently by the liver. VLDL quantities rise to cope with extra fatty acids (FAs) released from bloated fat tissue. LDL concentrations soar as extra cholesterol (C) blocks liver cell receptors that dispose of LDL. Cholesterol-bearing chylomicron, LDL, and VLDL lodge in blood-vessel walls, spurring atherosclerosis.

**Greasing Aging’s Downward Slide**

Counteracting the midlife shift in fat processing might improve seniors’ health—and forestall decrepitude.

Nancy Ross-Flanigan

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overflow, the liver increases production of VLDL. Expanding adipose tissue also releases copious amounts of cholesterol in addition to fatty acids. The excess blocks receptor proteins that normally allow liver cells to dispose of LDL.

In addition, concentrations of HDL plummet when triglyceride amounts are large—which results when the liver converts overflowing fatty acids to triglycerides as well as when chylomicron processing falters. An enzyme called CETP swaps triglyceride from VLDL and chylomicron with cholesterol from HDL; normally, the transfer benefits organisms by providing additional vehicles for disposing of cholesterol. But when triglyceride concentrations soar, CETP produces an abundance of HDL tagged with triglyceride. Further processing makes the lipoprotein smaller and denser. Because the compact particles are removed more rapidly from the blood than their normal-sized kin are, HDL amounts drop. As this melodrama unfolds, harmful lipoproteins run amok and the heroes are captured, setting the stage for atherosclerosis, heart disease, and stroke.

**The Insulin Connection**

In addition to crippling circulation, lipid imbalances encourage diabetes. Ballooning fat numbs tissues to insulin, the hormone that prods cells to take up glucose. Insulin resistance is associated with a cluster of symptoms—high blood pressure, high triglyceride concentrations, small HDL quantities, and obesity—known as metabolic syndrome, which increases the risk of diabetes and heart disease.

Metabolic syndrome strikes 25% to 30% of middle-aged people, and in older populations, the percentages are even higher. The fatter a person is, the earlier metabolic syndrome strikes, and the sooner health problems are likely to develop, Brown says. Free fatty acids, which are liberated as triglycerides break down, seem to drive the development of insulin resistance, says Schaefer: The more fatty acids there are in the bloodstream, the more likely insulin resistance becomes.

Researchers are exploring how fatty acids—which are essential for growth, hormone balance, and immune function—start causing trouble. The sites in the body at which they are broken down might play a role, says endocrinologist Clay Semenkovich of Washington University School of Medicine in St. Louis, Missouri. Some researchers posit that fatty acids can be safely stored in fat cells but become harmful when they break down in blood vessels. And proteins that process the fatty acids might promote diabetes and hypertension. “So what we’re pursuing,” says Semenkovich, “is the general hypothesis that abnormal fatty acid metabolism contributes to the degenerative diseases of Western society.”

**Lowering Lipids**

As scientists clarify the health implications of creeping corpulence, they’re also exploring ways of controlling escalating lipid quantities. One approach has already succeeded: lowering LDL concentrations with statins, a family of compounds that inhibit an enzyme known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase. These drugs also decrease triglyceride concentrations. Because of their dual effect, they dramatically reduce the risk of coronary heart disease and stroke in people from middle age on.

Statins aren’t perfect, however: They don’t deplete bad lipids equally well for everyone, and elevated LDL and triglyceride quantities aren’t the only alterations that spur disease. Other therapeutic tactics might therefore be useful. “The most common thing you find in patients with heart disease is low HDL,” Schaefer notes, “and the statins don’t correct that abnormality.” He considers HDL-raising drugs—currently in clinical trials—“the next frontier.” One type of HDL-raising drug works by inhibiting CETP; the enzyme that slaps triglyceride onto HDL and sets up the lipoprotein for rapid removal from the bloodstream. Clinical trials indicate that CETP blockers raise HDL quantities by 60% to 70%, says Schaefer.

But lipid-adjusting drugs are no substitute for a healthy diet and daily exercise, and Semenkovich’s research underscores that message. In one set of studies, he and co-workers showed that vigorous exercise induces production of the chylomicron-dismantling enzyme LPL in skeletal muscle. But, he says, “the effect was extremely transient. By the next day, LPL output was down again.” Hence the hard truth: “If you’re going to use exercise as a treatment for lipids—which I think is good—you have to do it nearly every day,” he says.

Plenty of people would love to get the fat-burning benefits of working out without the exertion, and other research in Semenkovich’s lab points to that possibility. In a study published in *Nature Medicine* in 2000, the researchers altered mouse metabolism so that animals burned excess calories instead of storing them as fat. They engineered the rodents to produce uncoupling protein (UCP), a molecule that disconnects cellular respiration—the process by which cells harvest energy stored in food—from the production of ATP, the cellular energy currency. As a result, cells produce heat instead of repackaging energy as ATP. The mice don’t become obese or develop diabetes, even on high-fat diets. Still, too much of a good thing is not good: Mice that produced large amounts of UCP were so weak they could hardly walk. Those that made less, however, showed no ill effects, while still avoiding diabetes.

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**Source:** A. SOMA DISSEPTOR, ILLUSTRATION: JULIE WHITE

**Image:** sageke.sciencemag.org/cgi/content/full/sageke;2003/41/ns6
and obesity. Now the researchers are working on methods for injecting the gene for UCP into muscle, hoping to develop a treatment that will let people eat as much as they want without gaining weight.

**Linking Lipids and Longevity**

Semenkovich also wonders whether his engineered mice will outlive their normal counterparts, and he’s optimistic. Mice whose adipose tissue lacks a component of the insulin signaling pathway can devour oodles of calories without turning corpulent—plus they survive longer than normal animals do (see “Lasting Without Fasting”).

Some studies have also coupled lipid processing and longevity in humans. Gerontologist and endocrinologist Nir Barzilai of Albert Einstein College of Medicine in New York City and his colleagues have studied lipid concentrations in people who live well into their 90s and beyond. In particular, Barzilai has measured HDL—the “good” cholesterol carrier—in centenarians and their children and found high concentrations in both groups. The results, published in the *Journal of the American Geriatric Society* in 2001, suggest that beneficial lipid profiles run in families and contribute to unusual longevity. More recent work reveals genetic underpinnings of the lipid-longevity link. In a paper published in the 14 October 2003 issue of the *Journal of the American Medical Association*, Barzilai’s team showed that a particular mutation in the CETP gene was three times more prevalent in people between the ages of 95 and 107 than in the general population. The mutation, which likely reduces CETP protein quantities and raises amounts of HDL, also appeared in the long-lived subjects’ offspring. In addition, the mutation leads to significantly larger HDL and LDL particles, which appear to protect an individual’s health: Those with larger particles less frequently developed high blood pressure, cardiovascular disease, and metabolic syndrome, the study also showed. Identifying the genes that modulate lipid amounts and deciphering ways to manipulate them might result in therapies that counter the shift from lean to lard and simultaneously increase longevity.

**Greasing Mental Gears**

Favorable lipid profiles go hand in hand not only with long life but also with better brainpower in later years. When Barzilai tested centenarians’ cognitive function, those with the highest HDL amounts performed better on memory tests and were at lower risk for developing dementia.

Early hints of a connection between lipids and cognitive function came from studies of apolipoprotein E (ApoE), a protein that helps the liver absorb lipoproteins. A variant of ApoE, known as ApoE4, which occurs in 21% of the population, is associated with larger LDL amounts and increased risk of heart disease, Alzheimer’s disease, and dementia. Recent work has documented the link in other ways. For example, a study last year showed that women who carried the largest LDL and total cholesterol amounts were more likely to lose brainpower than were those with smaller quantities. Furthermore, individuals whose LDL cargo dropped over the course of that 4-year study—either naturally or through medication—were less likely to show signs of dementia than were those whose LDL concentrations increased or stayed the same. In addition, subjects who took LDL-lowering statins scored better on cognition tests than did their untreated counterparts.

Another large study bolsters the idea that statins preserve brain function. Researchers analyzed the records of more than 57,000 hospital patients over age 60 and revealed that statin users showed signs of Alzheimer’s disease significantly less often than did patients who weren’t taking that drug. The reviews are still mixed, however: A human study published last year found no evidence that treatment with the drug prevents cognitive decline. Other compounds show promise: A study published last month in *Neuroscience* showed that Probrucol, a cholesterol-lowering drug that works by a different mechanism than statins do, raises ApoE protein amounts in aged rats and keeps their neurons supple. Although the relation between ApoE quantities and Alzheimer’s disease is controversial (see “Apoplectic From ApoE”), the study suggests that boosting ApoE might protect brains from deterioration. For now, the effect of cholesterol-lowering drugs on brain function remains fuzzy.

Research in the coming years should bring lipids’ role in disease into sharper focus. In August, the U.S.
National Institutes of Health announced a 5-year grant, expected to total $35 million, to fund the Lipid MAPS Consortium. This collaborative effort led by researchers at the University of California, San Diego, will unite scientists from various fields in an effort to identify and measure quantities of all the lipids within a cell, estimated at 1000 different types.

Knowledge of how newly discovered lipids change with disease, combined with novel information about how old stalwarts such as cholesterol turn against the elderly, might lead researchers to new treatments for age-related diseases. Such progress could help old people triumph over evil lipids and stick around for a few extra curtain calls.

Nancy Ross-Flanigan writes from Belleville, Michigan. She wonders whether having good lipids is worth giving up Edy’s Chocolate Caramel Swirl ice cream.

**Further Reading**
Lipid Maps Consortium. www.lipidmaps.org
Lipids Online. www.lipidsonline.org

**References**