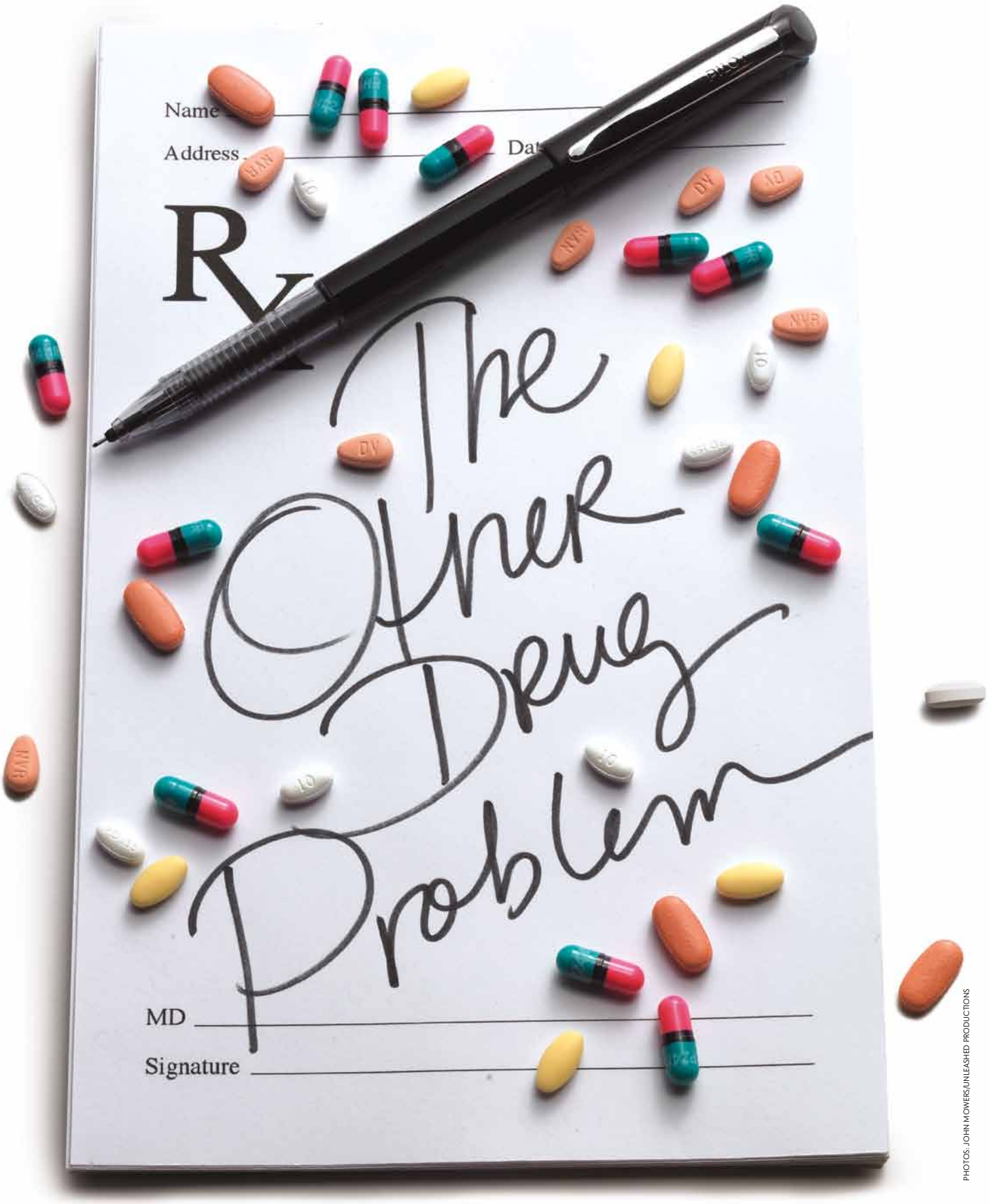

PHOTOS: JOHN MOWERS/UNLEASHED PRODUCTIONS

The prescriptions we take to regulate cholesterol, blood pressure and stomach acid are supposed to make us healthier. **But could these medications be doing us more harm than good?**

By Pamela Weintraub

He had been a faculty member in three departments of a major university with an IQ north of 180. Over time, the professor lost the ability to recognize people he'd known closely for decades and to read more than a page of text at a time. He'd repeat the same thing over and over, not recalling he'd already said it. The diagnosis: rapidly progressive Alzheimer's. When he went to his 50th college reunion, he wore a sign around his neck with his name and the statement, *I have Alzheimer's.* Old friends needed an explanation for why he couldn't recognize people he'd known for decades or repeated himself endlessly throughout the night.

His condition seemed hopeless when he applied to enter a clinical trial testing a new Alzheimer's drug at Duke University.

Before he started the clinical trial, his wife took him off his cholesterol-lowering statin drug, simvastatin. By the time he got to Duke, he was no longer qualified to participate; he didn't have Alzheimer's, doctors said. Instead, he entered another study: The Statin Study Group, directed by University of California at San Diego (UCSD) physician and scientist Beatrice Golomb, MD, PhD. "There are people with extremely severe functional deficits caused by statin drugs," Golomb says. Two years after he stopped taking simvastatin, the patient reported his recovery was complete. His mind was clear and he was back to reading three newspapers daily.

Statin's side effects are rarely so severe, but they are far more common — and numerous — than generally thought. And statins aren't the only popular drug with unpredictable side effects. Three common classes of prescription drugs in the United States — statins for reducing cholesterol, angiotensin II antagonists for lowering blood pressure, and proton pump inhibitors for reducing stomach acid — can all cause side effects worse than the problems they aim to treat. And the symptoms caused by one drug may necessitate the use of the others.

For large numbers of people with questionable risk factors, these drugs deliver little or no benefit, but that hasn't stopped pharmaceutical manufacturers from aggressively marketing them as preventive treatments. Underlying their marketing strategy is a host of scientific studies that "exaggerate positive results and bury negative ones," says Shannon Brownlee, author of *Overtreated: Why Too Much Medicine Is Making Us Sicker and Poorer* (Bloomsbury USA, 2007). "The science on which so much of prescribing is based is biased, shaky, overmarketed and misinterpreted. These are excellent drugs when used on the right people. The problem comes when they're marketed to everyone on the planet. There's benefit to a few people, but when you start giving them to everybody, they may do more harm than good."

Cholesterol Conundrum

The rise in widespread use of statins coincided with lifestyle changes in post–World War II America. As the population gradually migrated to car-friendly suburbs and became increasingly sedentary, the food industry began filling supermarket shelves with more processed "convenience" foods packed with high-fructose corn syrup, trans fats and other pro-inflammatory ingredients. Before long, coronary heart disease (CHD) became a major cause of death.

At first, many experts attributed the problem to a single, simple cause: A high-fat diet thought to fuel high levels of a molecule called cholesterol in the blood. In optimum quantities, cholesterol is essential for cellular health, but in excess, the experts said, it coated and hardened the arteries, preventing blood from circulating and causing heart attacks and strokes.

That view has changed in recent years: The problem is not cholesterol, per se, but a low-density lipoprotein (LDL) that carries cholesterol through the blood and deposits it in arterial plaque, where it can do the most damage to the body. Also at fault ➞

are triglycerides, another type of fat circulating in the blood and coating arterial walls. (A protective cholesterol-carrying molecule, high-density lipoprotein, or HDL, lowers CHD risk.) Elevated levels of the offending molecules may not be a problem for the fit and healthy, but for those at risk due to obesity, diabetes, hypertension or smoking, they increase the likelihood of disease.

Scientists are beginning to revise the dietary factors once thought to underlie CHD. Instead of placing saturated fat at the root of the disease, some of the newest studies point to processed carbohydrates like white bread, sugar and rice, which are known to increase triglycerides and boost insulin production. The surging insulin causes diabetes and obesity, increasing inflammation along with the unfavorable LDL cholesterol known to damage arterial walls.

Despite an increasingly clear connection between diet and heart disease, pharmaceutical companies in the 1990s saw a burgeoning market for a class of drugs called statins, which block production of LDL in the liver, reducing its levels in the blood. And, by 1994, they had the research they needed to argue that these drugs could prevent heart disease.

The Scandinavian Simvastatin Survival Study, sponsored by pharmaceutical giant Merck, showed that the cholesterol-inhibiting drug, simvastatin (brand name: ZOCOR), could lower LDL levels by 25 to 35 percent and reduce myocardial infarction (heart attack) by 25 to 30 percent in those with normal cholesterol but who have other risk factors, like hypertension, smoking or diabetes.

With the advent of statins, our Big Mac nation was given license to stay the course: We kept consuming processed foods through the rollout of lovastatin, simvastatin and atorvastatin — otherwise known as Lipitor — which for many years has been the top-selling drug in the world. Just last year, rosuvastatin (brand name: Crestor) was approved as a preventive for healthy individuals with low cholesterol counts and no risk factor beyond an elevated level of C-reactive protein (CRP), a sign of inflammation in the body. Once prescribed statins, these people were advised to take them for life.

That's when cardiologists and epidemiologists adept at reading statistics finally began breaking ranks. Their concerns about statins' side effects were well placed. A study published in *The Lancet* in February 2010 showed statins could increase the risk of type 2 diabetes by 9 percent. Other recent studies have traced statins to headache, joint pain and abdominal pain, as well as linked the drugs to peripheral neuropathy, the sense of tingling and numbness or burning pain, often in arms and legs.

At UCSD, Golomb has been studying a series of lesser-known (but not less common) neuropsychiatric and cognitive side effects. Her interest began when, as a medical student in the late 1980s, she became aware of two studies linking cholesterol-lowering drugs to violent death. "In these studies, the decrease in death from heart disease was fully offset by increases in violent death from suicide, homicide and accident," she says. Golomb's neurobiology research told her the reports made sense. "Cholesterol is a very high fraction of the dry weight of the brain," she says, and aids the function of neurotransmitters — the molecules of emotion and cognition that help the brain do its job. Force cholesterol levels down by artificial means, and brain infrastructure suffers. Her own paper on low cholesterol and violence was published in the *Annals of Internal Medicine* in 1998.

> "In these studies, the decrease in death from heart disease was fully offset by increases in violent death from suicide, homicide and accident."

As word got out, Golomb's lab received a steady stream of email from statin users with a wide range of problems neither reflected in the literature nor taken seriously by their doctors. The effects, documented in her multi-year study, include reduced energy and a lack of interest in activity, increased fatigue after exercise, erectile dysfunction, and a significant reduction in the ability to achieve orgasm. "Half the people who reported any symptom reported more than one," Golomb adds.

This reflects what the evidence shows — a common mechanism based on statin disruption of the mitochondria, the energy-producing parts of cells. "We are conditioned to think of cholesterol as a nefarious substance that courses through the blood for the sole purpose of congealing in our arteries and causing cardiovascular disease, but there is a reason why evolution mandates that every cell in our body produces it, and that it circulate through our blood," Golomb says.

So what's a statin-taker to do? If you are experiencing troublesome side effects, but have heart disease or serious risk factors and can't stop taking the

drugs entirely, you may still want to consider taking a brief break from the med to see if it seems to be causing your symptoms. If so, you should ask your doctor to prescribe a different drug or lower your dose.

If you've been prescribed the drugs prophylactically, it may be time to talk with your doctor about getting off statins entirely. According to internist and clinical pharmacologist James M. Wright, MD, PhD, professor at the University of British Columbia, statins have no proven net health benefit as a preventive. As managing director and chair of the Therapeutics Initiative, a group that evaluates drug studies in Canada, Wright is an expert on meta-analyses — the large "studies of studies" — that take every last bit of data into account. His latest review of the data — and the most comprehensive to date — was published in the *Therapeutics Letter* in 2010: "Statins do not have a proven net health benefit in primary prevention populations," he wrote, adding that the "claimed mortality benefit" for this group is "more likely a measure of bias than a real effect."

The data is especially murky for people with elevated cholesterol but no other risk factors. "This is a gray area," he notes. In short, there's little credible evidence that attempting to lower a high cholesterol count with drugs is beneficial unless other risks are elevated as well.

Walter Willett, MD, chair of the department of nutrition at the Harvard School of Public Health, adds that even for those who need the drug, "statins only reduce risk of heart disease modestly, about 30 percent, and thus are not sufficient." Lifestyle changes (see "Many Problems, One Cure," page 65) are required to take patients the rest of the way. For many, making the right lifestyle changes is *all* that's required.

Halting Hypertension

Similar criticisms have emerged regarding the conventional treatment of high blood pressure, the measurement indicating how hard circulating blood pushes against arterial walls. Pressure may rise and fall throughout the course of a normal day, but if it stays too high for too long, it damages blood vessels, the kidneys and the heart. Hypertension, while asymptomatic, is a major cause of heart failure, heart attack and stroke.

Anyone who's been to a doctor knows that blood pressure consists of two separate readings — systolic pressure (the higher top number, measured as the heart is beating) and diastolic pressure (the lower bottom number measured between beats when the heart is at rest). It is the higher, systolic pressure that is most often used to determine risk.

For many years, physicians have treated even slightly high blood pressure with drugs that counteract the vessel-contracting hormone, angiotensin. First, the pharmaceutical industry introduced angiotensin-converting enzyme (ACE) inhibitors; later, when ACE inhibitors went off patent, drug companies began selling angiotensin II antagonists, also called angiotensin receptor blockers, or ARBs. But the data has not held up, says Wright, who also serves as coordinating editor of the Hypertension Group at The Cochrane Collaboration, whose systematic reviews of healthcare studies are considered the gold standard of evidence.

"Our job is to systematically review all the evidence related to blood pressure and hypertension, and what we are discovering is that the evidence for blood pressure treatment at more moderate levels is not as strong as we had previously thought," he says. Indeed, while doctors routinely treat patients with mild to moderate systolic pressure of 140 to 160, it is only for those with moderate to severe hypertension — people with blood pressure over 160, the top 5 percent of the curve — that "we get a modest bang for our buck. Between 140 and 160 there is no good evidence that the benefits outweigh the harm," he says.

Wright especially takes issue with marketing efforts to push ARBs rather than the less-expensive ACE inhibitors. The drug companies claim their studies showed better health outcomes with ARBs, he says, but recent research challenges that claim. A 2010 study published in *The Lancet Oncology*, for instance, reported an increase in cancer diagnoses among ARB users. Other side effects include headache, dizziness, lightheadedness, nasal congestion, back and leg pain, and diarrhea. And, while rare, side effects such as kidney failure, liver failure, allergic reaction, a drop in white blood cells and localized swelling of tissues (angioedema) can all be fatal. ➔

> "What we are discovering is that the evidence for blood pressure treatment at more moderate levels is not as strong as we had previously thought."

The Acid Erasers

Another popular class of drug, generating more than $13 billion a year in the United States alone, is the proton pump inhibitor (PPI). These drugs reduce between 90 and 100 percent of acid in the gut by shutting down a system known as the proton pump.

The PPIs, including Prevacid, Nexium, Aciphex and Prilosec, originally were used to manage ulcers, a condition in which acid coursing over open stomach sores caused incapacitating pain. But research later confirmed that most ulcers are caused by the spiral bacteria *Helicobacter pylori* and could be effectively treated with a brief regimen of antibiotics. Use of PPIs then shifted to common conditions like ordinary heartburn (the burning sensation behind the breastbone) and the far more painful and persistent gastroesophageal reflux disease, or GERD (which results when muscles between the stomach and esophagus stay partly open, allowing stomach acid to leak up, or reflux, into the esophagus, causing pain).

PPIs can, in fact, effectively treat some noninfectious ulcers and severe cases of reflux, but it's increasingly clear that long-term use can be dangerous, according to a series of studies published last year:

- Research from the National Institutes of Health, published in *Current Gastroenterology Reports*, shows that long-term use of PPIs can limit the body's absorption of essential nutrients, including calcium, magnesium, iron and vitamin B12, which require gastric acid to be absorbed. Risks include not just osteoporosis, but also anemia, fatigue, seizures and cardiac events.
- The *Annals of Internal Medicine* reports that long-term use of proton pump inhibitors increases cardiovascular risk for those already suffering myocardial infarction or stroke.
- The *Archives of Internal Medicine* reveals that PPIs substantially increase the risk of infection from a particularly hardy bacteria called *Clostridium difficile*. The study also linked long-term PPI usage with spine, lower arm and total fractures in postmenopausal women. Perhaps even more alarming was the finding that as many as 69 percent of people taking PPIs don't need them to effectively treat their symptoms.

> "When gastroenterologists go to their annual meeting and there is a purple bus paid for by the maker of the purple pill, it is time to worry."

While almost no one should be using these drugs for years at a time, once someone has been taking them long enough, the habit can be hard to break. It's been suggested that when patients stop PPIs, a rebound effect increases acid production for a while, causing painful reflux symptoms again. "People should hold out until the excess acid dissipates and the symptoms go away," says pharmacologist Wright.

Having appropriate levels of acid in the stomach is the healthiest situation of all. Eating high-fiber whole foods (such as beans, veggies and nuts), taking digestive enzymes and probiotic supplements, and decreasing chronic stress can all help to bring your gut back into balance.

Changing Course

If there's any silver lining in this cloud of overmedication, it's that Americans have been programmed to at least consider their risk factors for chronic disease. "We have this culture of 'let's catch it before it's too late,'" says Brownlee. Unfortunately, she notes, rather than encourage people to make proactive adjustments in the way they eat, move and manage stress, the drug and medical industries have largely encouraged them to take medication. "What it has done is create a whole nation of perfectly well people who have been turned into patients," she says. "Most of these people just have risk factors. They are not sick."

But many doctors rely on pharmaceutical reps and materials for the latest information on treatment options. And they're inundated with reports — that may or may not be credible — about the latest research. As Golomb notes, clinical studies designed to prove the efficacy of a certain drug have inherent limitations, particularly as it relates to examining safety.

"The people most likely to allow adverse effects to be identified, like the elderly or those on multiple drugs with health problems, are often excluded from participating in trials but not from receiving the drug in the real world," Golomb says. "This occurs in part for sound reasons like minimizing risk to those in the study, but it also reduces the ability to identify an increase in problems if there is one. Because studies are designed in a way that obscures the harms associated with drugs, serious problems

often show up only years after a drug has been fully approved by the FDA."

So it's up to doctors to practice some healthy skepticism when pharmaceutical reps promote studies heralding the next miracle drug, says Brownlee. "While physicians are now aware that the information they are getting from the drug industry is not unimpeachable, the bigger issue is that they often aren't trained to tell good data from bad."

And they should avoid continuing-education conferences paid for by the drug industry, she adds. "When gastroenterologists go to their annual meeting and there is a purple bus paid for by the maker of the purple pill, it is time to worry. One of the problems we have is that many physicians are not aware of the poor evidence for efficacy, and they also are not aware of side effects, because most of their information is not coming from unbiased sources. It is coming from the manufacturer, who has every reason to downplay the negative and emphasize the positive."

For patients seeking unbiased information, two credible resources are The Cochrane Collaboration (www.cochrane.org) and Clinical Evidence (clinicalevidence.bmj.com/ceweb/index.jsp), both of which feature summaries of valid pieces of research that provide important, relevant, more accessible information to patients and doctors.

At the very least, patients should ask their doctors to explain the pros and cons of every drug in a way they can understand, so patient and doctor can share the decision about treatment, says Brownlee. "If your primary-care doctor says, 'I'm ever so busy, I'm not going to do that,' you might need to find a new doctor who will help you be informed and who will share treatment decisions with you," she says.

Patients must be "assertive, smart consumers" to make sure they are not being overmedicated or getting drugs they do not need, says Joseph T. Hanlon, PharmD, MS, professor of medicine in the University of Pittsburgh's Division of Geriatrics and Department of Pharmacy and Therapeutics, and health scientist at the VA Pittsburgh Health Care System. "Make a list of every drug you are on and make sure you can answer five questions: What is it called? What are you taking it for? How and when are you taking it? What are the common side effects? And when will the treatment stop?" Hanlon says. "Medical schools don't always do the best job of teaching prescribing. You are your own best advocate."

Pamela Weintraub *is features editor at* Discover *and author of* Cure Unknown: Inside the Lyme Epidemic *(St. Martin's Press, 2008).*

Many Problems, One Cure

You've probably heard the line in plenty of pharma ads: "When lifestyle changes aren't enough . . . " But changing your life *can and does work*, even in tough cases — as long as you're making the changes that really count.

In fact, research shows that basic shifts in nutrition, activity, stress and other lifestyle factors can be more effective than drug protocols in treating inflammatory health conditions — dramatically improving overall health and fitness in the process.

Unfortunately, most people (including many primary-care physicians) don't know what kinds of lifestyle factors actually work, or how to go about embracing them. So we've gathered articles from our archives that cover effective interventions for tackling chronic health problems. Get all 11 in one downloadable PDF by scanning this barcode with your smartphone (you'll need Microsoft TagReader, available for free at http://gettag.mobi or at your phone's app marketplace) or by clicking on the "Get the PDF!" link in the online version of this article.

TIPS FROM THE ARCHIVES at ExperienceLife.com

Eliminate processed carbs
("3 Simple Shifts," March 2011)

Avoid sugars and alcohol
("Sugar Breakdown," July/August 2006)

Emphasize healthy fats
("All About Oils," April 2007)

Pack in phytonutrients
("Phyto Power," November 2007)

Get more food-based fiber
("Fiber: Why It Matters More Than You Think," April 2010)

Aim for a blend of activity — high and low
("Just-Right Fitness," March 2007)

Get plenty of rest
("Getting to Sleep," November 2004)

Set boundaries around work
("Back on Schedule," January/February 2010)

Meditate regularly
("Learning to Sit Still," December 2007)

Manage stress
("Put Stress in Its Place," March 2007)

Minimize inflammation
("Fighting Inflammation," July/August 2004)

WEB EXTRA!

For information on the downside of drug interactions, see "Slippery Slope" in the online version of this article at **experiencelife.com.**