



"EXPLOSIVE."—PEOPLE

BITTER PILLS

INSIDE THE
HAZARDOUS WORLD
OF LEGAL DRUGS

BITTER PILLS "COULD SAVE YOUR LIFE."—THE SAN DIEGO UNION-TRIBUNE

STEPHEN FRIED

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Inside the Hazardous
World of Legal Drugs

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BITTER PILLS is a work of investigative and personal journalism. Although it raises some frightening questions about legal drugs—I know they scare me—the book is meant to help reform the system and inform your choices when using medications, not to scare you out of taking them at all.

Suddenly halting the use of a safe drug can be more deadly than taking a so-called “dangerous” drug. Please do not do it. Read the book, talk to your doctors, and if they don’t seem to understand why you want to know more about your own medical care, get new doctors. Get to know your pharmacists and nurses, consider a consultation with a clinical pharmacologist. And when asked what drugs you take, make sure you include all nonprescription medicines. Improperly used, they can kill you, too.

But always remember that we as medical consumers are part of the problem. Drug companies and doctors often make decisions based on the assumption that we are too dumb to understand the medications we’re given. Don’t prove them right.

“Fortunately, a surgeon who uses the wrong side
of the scalpel cuts his own fingers and not the patient.
If the same applied to drugs, they would have been
investigated very carefully a long time ago.”

DR. RUDOLPH BUCHHEIM,
the father of pharmacology, 1847

“Here was the medicine, the patients died
And no one asked: Who thrived?
So have we with hellish electuaries
In these valleys, these mountains,
Raged worse than any plague.
I have myself given the poison to thousands.
They withered, I must live to see
The impudent murderers praised.”

FROM *FAUST* BY
JOHANN WOLFGANG VON GOETHE (1831);
*as recited by Widikund Lenz—the German physician who
first linked thalidomide to birth defects—at the
Kyoto International Conference against
Drug-Induced Sufferings, April 1979*

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PROLOGUE

It began with a pill. One pill.

My wife's gynecologist gave her samples of a new antibiotic to treat a urinary tract infection so minor, she didn't even know she had it. The doctor told her to take this new wonder drug twice a day for three days.

Your doctor gives you a pill, you take it. When I left for work the next morning, I said good-bye to Diane as she swallowed the first pale yellow oval tablet with breakfast.

Six hours later I was bringing her, delirious, to the emergency room. Our lives haven't been the same since.

Diane called me at work several hours after she took that pill and said she felt strange. I knew something was *really* not right, because my wife comes from a long line of "it's just a flesh wound" stoics who underreact to all physical discomfort. She said she was disoriented and hallucinating. Her mouth was dry, and she felt tingling in her left arm and hand. She was having trouble talking.

After we spoke, she found herself wandering around in her small home office, and when she located her desk, she couldn't figure out how to turn off the computer she writes on every day. When she went to lie down, she started shaking uncontrollably and then saw white. She was sure she was dying.

Then she heard the phone ring. It was me, calling to see if she was feeling any better. Luckily, she was able to reach over, pick up the receiver and mumble to me about what was going on. I called her gynecologist.

cologist, who told me to take her to the hospital. When the cab got me home from the office, I found Diane lost in her closet. She stammered that she wanted to get dressed to go out but couldn't find her white shirt. I looked down and saw that it was an inch from her hand.

Married people can afford to panic only one at a time, so I pretended I was not scared as I helped her on with the shirt and took her to the hospital closest to where we live in Philadelphia, which happens to be Pennsylvania Hospital, the oldest hospital in America and one of the very best. As Diane spoke—haltingly, elliptically—to the ER doctors, more symptoms emerged. Her jaw was terribly sore from clenching against what we assumed had been a seizure. Her pupils were fixed and dilated, like blobs of black ink. She said she felt as though something were “melting” just behind her green eyes.

It was late Friday afternoon at the ER, just before the weekend rush, so we got a good, slightly private, curtained-off area. An emergency medicine specialist and several neurology residents tag-teamed in and out of our space. Each one asked a slightly different version of the same questions. I worried that we weren't being clear because there didn't seem to be any accumulation of knowledge taking place. They all had tests they wanted Diane to perform.

“Spell the word ‘world’ backwards,” one asked. She did it and was then asked to name the U.S. presidents in reverse chronological order.

“Can you spell ‘world’ backwards?” the next one asked. Then he requested that she touch her finger to her nose.

“I'd like you to try to spell—” the next one began.

“—yeah, yeah,” Diane said, “‘world’ backwards.” But she was bobbing in and out of full lucidity. Only seconds after cracking a joke, her mind would be sluggish again, and she would barely respond when I stroked her cheek or her shoulder-length brown hair.

After nearly five years of marriage, this was the first medical emergency we ever had to face. The only thing that kept me from really losing it was a woman in the next cubicle who already *had* lost it. Dragged in by the police in the middle of a major psychotic episode, she screamed continually in English and Chinese about everything from her husband's homosexuality to her close personal friendship with the president of the United States. Her screams pierced the crackly trauma calls from ambulances all over the area, which were being broadcast on a loudspeaker system for the ER staff to monitor. The combined noise was oddly stabilizing, a constant reminder that things could be considerably worse.

After several hours of neurological exams, the word came back—from a place called the Poison Control Center—that all of Diane's symp-

toms had been previously reported as reactions to the antibiotic she took. The drug is called Floxin. She had, as we now say, been “Floxed.”

My wife took a pill. It made her sicker than she was before.

World backwards. Tell me about it.

The ER doctors, however, were not through with us. They still wanted to run more tests. Even though Diane’s symptoms, such as “acute delirium,” were consistent with a reaction to the Floxin, they could also be caused by a brain tumor, a stroke or a big horrible infection with larger neurological implications, like spinal meningitis. They wanted to do a CT scan.

I got to sit in the CT control room and watch the machinery visually slice and dice. There is nothing quite so frightening as watching your loved one’s brain being scanned for tumors, especially when you’re not exactly sure what a normal brain looks like. But it is also very moving to peer directly into your wife’s mind. What spouse hasn’t at one time or another wished to be able to do that?

Back in the ER after a clean scan, we were then told the prevailing wisdom about all adverse drug reactions: that the effects would subside when the medication left her system. And we were sent home—with a supply of the milder, cheaper antibiotic she probably should have taken in the first place for her urinary tract infection (UTI)—to wait for that to happen. On our way out, we walked past the main ER desk. On the wall behind it was a light box for reading X-rays, which was still illuminating pictures from the inside of Diane’s brain. To the left of the viewer was a shiny metal towel dispenser. It was adorned with Floxin advertising magnets that had been left by some enterprising drug sales rep.

At that moment I thought the Floxinalia would actually make a nice detail for our emergency room horror story, the recitation of which would commence as soon as Diane was fine, ostensibly in a couple of days. But her symptoms did not disappear as promised. Some waned, but new ones developed. Besides the “melting” and the fixed pupils, she had really aggressive, buzzy insomnia, visual distortions that made the world seem six-dimensional and aphasia: she would get halfway through a sentence and just couldn’t get the rest of the words out. For a woman with a high school trophy for “best negative debater” sitting on a shelf behind her desk, this was probably the scariest symptom of all.

Over the next two weeks, she endured an electroencephalogram (EEG), which tests electrical function in the brain; a magnetic resonance imaging (MRI) of her head, which offers more structural detail than the

CT scan; and a spinal tap, to check the cerebrospinal fluid for infections, as well as some blood work. All these tests just to rule out any other possible explanation for her continuing symptoms than an adverse reaction to the drug—the same drug that was supposed to be long gone from her system. While the tests themselves were creepy, what they were testing *for* was absolutely horrifying. I found myself weighing which awful result would be most acceptable, watching the life we had planned to have pass before my eyes.

The tests all came back on a Thursday, one of the most harrowing days of our lives. As we were read the results over the phone by our internist, I found myself mentally checking off all the nightmares that had been eliminated by the process—“brain tumor, no; stroke, no; AIDS, no.” But Diane still wasn’t well. The doctors concluded that the drug reaction had triggered some genetic predisposition to neurological illness. Since her body hadn’t been able to correct the situation naturally, she would need to take a combination of heavy-duty drugs, each with its own possible side effects, to do it. If, in fact, it could be done at all.

But at least that urinary tract infection had cleared up.

It has now been five years since Diane got Floxed. In that time, we have learned more than we thought we’d ever want to know about what has been called “the *other* drug problem.” The one with *legal* drugs.

Since that day in the emergency room, I have been on a quest. An investigative journalist and exasperated husband, I am trying to find out if my wife was the victim of a pharmacological foul-up or just a statistically acceptable casualty of “friendly fire” in the war on disease. I am also trying to find meaning in our experience, a married couple searching for each other through a medical emergency that never seems to end, the siren never completely quieted.

Along the way, I have met the people behind the studies, the statistics, the press releases and the lawsuits: heroes, scoundrels, geniuses and idiots, victims and victimizers, the amorphous “less than one percent” of the population who have the adverse reactions you read about in the fine print on your drug labels and even the people who massage the numbers to get them under one percent. I have seen close up what happens at that moment when science officially becomes commerce, when exciting new drugs are handed over from the lab nerds to the marketing types. I have watched everyone in the pharmaceutical food chain describe everyone but themselves as unhealthily arrogant. I have seen the world’s top drug cop, the head of the U.S. Food and Drug Administration (FDA), excori-

ated as a “thug,” a “bully” and even a “killer” by an industry-friendly legislator. And I have listened to the head of one of America’s largest drugstore chains turn to me and growl, “These drug companies always hide under the cloak of ‘We’re these great research and development houses and without us there would be no medications.’ I think they’re full of shit.”

The Europeans have a very elegant word for a certain type of drug safety research. The word is *pharmacovigilance*, and it refers to research that is supposed to be done *after* a drug has been approved and we’re taking it. Because the people who do this work are the sole link between the pharmaceutical world and the real world and are often the bearers of unwelcome news, they sometimes seem like pharmacovigilantes. Over these years, I have been doing my own form of pharmacovigilantism. I use my press credentials to move effortlessly between the camps warring for control of your medicine cabinet.

My quest began with tracking down everything I could find about Floxin. But I realized that the only way to understand what had happened to Diane was to see beyond one pill and journey to the heart of the legal-drug culture: the international pharmaceutical industry, the government drug police in countries large and small, the physicians, the researchers, the pharmacists, the nurses, the consumer advocates—and the patients who unwittingly place their blind faith in this system. In college there was a book we had to read for political science class called *The Dance of Legislation*, about how a bill becomes law. Since Diane’s drug reaction, I have been investigating politicized science and watching “the dance of medication”—how a *pill* becomes law.

Much to my surprise, I found that the world of legal drugs is actually far more fascinating than its illicit counterpart, where we journalists generally focus our attention. It can also be more dangerous. While pharmaceutical science has made some medical miracles almost routine, the sheer size of the legal-drug world means that its problem areas are bigger than the entire illegal-drug problem.

For example, far more people die each year from adverse reactions to prescription and over-the-counter medications than succumb to *all illegal drug use*. Illicit drugs kill anywhere from 5,000 to 10,000 Americans a year. The estimates for U.S. deaths from *legal* drugs have ranged from 45,000 to over 200,000 per year, which represents 2 to 9 percent of the 2.3 million people who die annually, thereby qualifying as at least the sixth leading cause of death in America, and possibly as high as the third—behind only heart disease and cancer. Of course, many people take many medications without experiencing such problems, which are

referred to as “adverse drug reactions” in the United States, “medication misadventures” in the U.K. and “drug-induced sufferings” in Japan. But according to studies in the *Journal of the American Medical Association* (JAMA), as many as 11 percent of all hospital admissions are the result of adverse drug reactions, or ADRs, as they are often called. More than one-quarter of all inpatients have adverse reactions to the drugs they are given *in the hospital*—many the result of preventable medication errors—which makes ADRs the leading cause of in-hospital injury.

In America more people die each year from reactions to the drugs they get in the hospital than are killed in automobile accidents. (Some 10 percent of all auto accidents involve drivers impaired by medications.) Outpatients are victimized in greater numbers in another way by drug reactions: they stop taking their pills after being spooked by annoying side effects, neglect to tell their doctors, and are then hurt or killed by the untreated illness.

Before Diane got Floxed, I thought of medicines as pretty much idiot-proof. You take them assuming that the worst that can happen is that they won’t work. It turns out the *worst* that can happen is that you drop dead. The next worse is that your body is permanently damaged. Less worse, but still not very good, is that you suffer for hours, days or weeks with something your doctor may or may not recognize as a drug reaction—anything from a skin rash to heart failure to a sudden inability to have an orgasm. The symptom may or may not go away by itself, but until it does, your doctor may mistake it for another illness and give you more drugs for that, leading to a cascade of prescribing. And your drug experience may affect how the next medication you take works in your body—or how well your body is able to fight infection in the future.

Adverse drug reactions are clearly a huge international health problem. A few enlightened pharmacologists also see them as an enormous learning opportunity, a “gift” that accidentally offers a chance to deepen understanding of drugs and the human body. For me, they have been both. Understanding drug reactions has been a way to explore what is wrong with the entire international pharmaceutical business—a \$250 billion enterprise (\$700 billion if you count all the other products sold by drug companies) that has managed to repel scrutiny more effectively than almost any other major industry, while remaining the world’s most profitable business through many changes in economic climate.

Asking questions about what government regulators were doing about the drug reaction problem also became my way of infiltrating the

FDA, an agency so misunderstood that it is easy to overlook its omnipresence in our lives. The FDA is responsible for regulating 25 percent of America's entire gross national product and its policies are the benchmark for world regulation of drugs and medical devices.

The work done by understaffed national agencies like the FDA has never been more important, because in all too many cases, the new economics of health care have transformed drugs from one possible treatment into the *only* possible treatment—or at least the only reimbursable treatment. In the past five years, drug sales in U.S. pharmacies and outpatient clinics have risen more than 50 percent and the total number of prescriptions dispensed, more than 2 billion a year, has risen over 25 percent. The vast majority of those increases are attributable to managed care's growing use of drugs to avoid hospitalization.

Drugs have become not only the tail that wags the dog but the tail that feeds the dog, trains the dog and makes the dog do tricks. And the growing power of the pharmaceutical industry is being controlled by a shrinking base of owners. Not only are the huge “drug houses” merging with each other and streamlining, but they are buying the firms that decide which drugs will be made available to patients in HMOs and other managed health care organizations. The companies also control the flow of information about medicines. The drug industry now funds, directly or indirectly, almost all the research done on drug products and almost all the drug education doctors get after medical school. Most of the destigmatizing public-awareness advertising campaigns about illnesses are paid for by the companies whose drugs are used to treat or in some cases *define* those illnesses. And more than ever, drug companies are end-running physicians' authority by advertising directly to consumers, which is why your magazines and newspapers are overflowing with pharmaceutical ads, your favorite TV shows are interrupted by pleas to “ask your doctor” about drugs and your doctor is quietly wincing every time he or she is “asked.”

It's a situation that can easily turn unhealthy and too often does. Companies can't always be counted on to do “the right thing” when they're faced with a tough choice between profit and public safety. Experts in the field are growing worried about where the in-house “conscience” of these companies will be found, especially when firms with sterling reputations merge with their less high-minded competitors.

While drug therapies grow stronger and more profitable every day, the system that is supposed to assure the safety of those drugs is getting relatively weaker, an economic and bureaucratic liability easily targeted for downsizing. Even as computers and easier international communica-

tion make *more* drug safety efforts possible, the chasm between what *can* be done and what *is* being done to keep us safe grows constantly larger.

Ten years ago, the bottom-line business practices of the pharmaceutical companies were considered by many to be the dark underside of health care. Today, all of health care is being run like a drug company.

It's no wonder that, more than ever, patients and their doctors feel—well, pillaged.

How unhealthy is the legal-drug culture? I put that question to two of the world's leading minds in drug research during a big clinical pharmacology cocktail party. The two disagreed on the extent of the risks to everyday medicine-takers: one thought patients were too scared, while the other thought we might not be scared enough. But they shared a general perspective on the state of the pharmaceutical art.

"The amazing thing about this world," one said, sipping his drink, "is that everybody in it is really trying to do the right thing. If you look hard, you won't find many real villains. Yet the whole thing is still so messed up."

This is a book about how it got so messed up. It is what I wish I had known about drugs before my wife took that one pill.

In 1979 an international conference that some consider the Woodstock of drug safety was held in Kyoto, Japan. Its goal was to make some sense of a legal drug disaster that most people have never heard of, even though it affected as many patients as thalidomide. It was an outbreak of an irreversible neurological condition, sometimes leading to blindness and degeneration of the spinal cord, that was caused by an over-the-counter medication for intestinal disorders and diarrhea so widely used that some people sprinkled it over their breakfast cereal as a preventive measure. There were some 10,000 cases in Japan, and smaller numbers in twenty-five other countries where the drug was sold. It took nearly fifteen years to finger the drug as the culprit. And even though the epidemic in Japan stopped almost immediately after the drug was banned, one of its three manufacturers continues to insist the condition was caused by a virus.

During the course of this five-day conference, a call went out for a New International Pharmaceutical Order. Almost twenty years later, with all our advances in medical treatment, we are still waiting for that New Order. While pharmaceutical science has obviously made great strides since 1979, it is amazing and horrifying how many of the complaints about pharmacovigilance brought up at the conference are just as

valid today. Some are actually *more* valid, because recent economic pressures have dramatically narrowed what was once a comfortably broad margin of error in all matters medical. Back then, fewer illnesses were treated *only* with drugs and fewer strong drugs were available over the counter, allowing people to haphazardly self-medicate.

If something isn't done, the price we will pay could be far more than the health of the patients who get the drug reactions listed on the impenetrable, mind-numbing package inserts that come with our medicines. A growing number of experts are worried how the casual, often irrational use of antibiotics will affect our ability to treat infectious disease. They believe our refusal to take drugs seriously will eventually unleash untamable viruses that could kill huge numbers of people—perhaps the planet's entire population. Their fears were recently confirmed with the discovery of a new strain of staph, one of the first infections ever conquered by medicine, that is impervious to even our strongest intravenous anti-infectives. It was caused, researchers believe, by stupid, unwarranted use of antibiotics.

That's how you spell world backwards, doctor.

