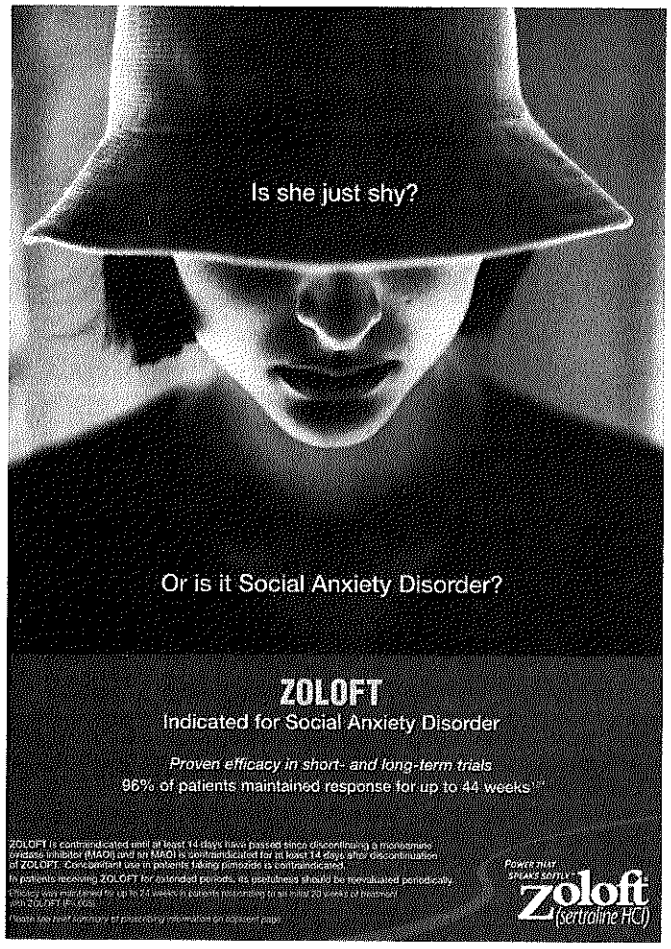


(Zoloft, *American Journal of Psychiatry* 160, August 2003)

Such banality is the point. The phrase *social anxiety disorder* was so commonplace by 2003 that this last ad didn't bother to gloss it. Apparently, the public no longer needed to know it was suffering in vast numbers from a "debilitating medical condition." The PR firms and marketing departments, bludgeoning us repeatedly with this constant refrain, had already done their job.

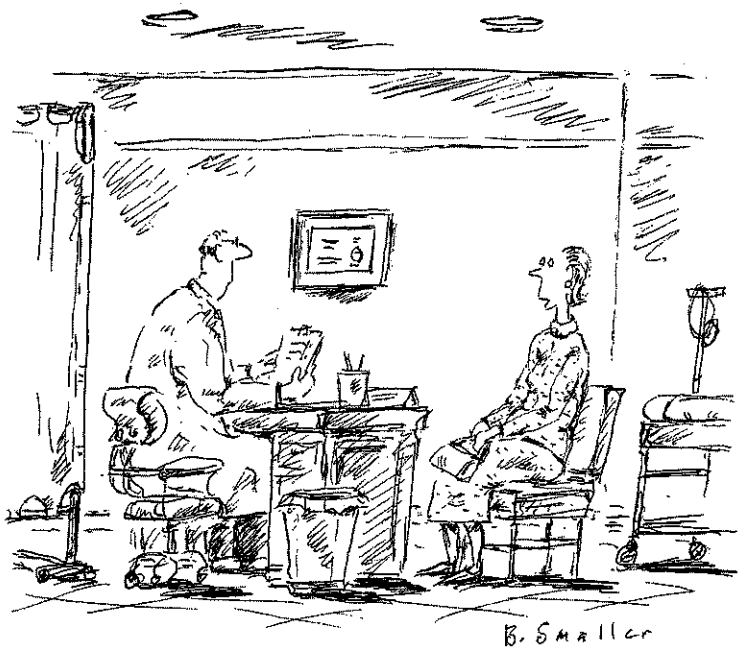
5

REBOUND SYNDROME: WHEN DRUG TREATMENTS FAIL

Robert Spitzer's task forces paved the way for the drug companies, creating seven new anxiety disorders that supposedly required medical attention. But the drugs approved to treat these disorders turned out to be as indiscriminate in their effects as Spitzer's colleagues were in their initial judgments.

By failing to distinguish clearly between shyness and social anxiety disorder, the task forces made every anxiety reaction fair game for medical attention. They lumped together routine traits that do not belong in a manual of mental disorders. And they quietly ignored the fact that shyness was once thought a positive characteristic, whereas anxiety can be a rational, even necessary, response to stress. Ironically, the drug the FDA licensed to treat social anxiety disorder, Paxil, is similarly all-inclusive, often blanketing the nervous system so completely it prevents the brain and nervous system from distinguishing between routine stress and chronic anxiety. The result is all manner of health risks that GlaxoSmithKline (GSK) now reluctantly acknowledges. Paxil's side effects also explain why a substantial number of patients (16.1 to 20 percent) discontinue treatment after several months and why, after doing so, they often feel worse than before.[1]

The hasty, overmedicated handling of anxiety is a direct result of *DSM-III* and the large number of new disorders it created. But an alarming medical problem now faces many patients taking Paxil, in particular. Doctors call it "rebound syndrome," because its symptoms—which stem from discontinuing drug treatment—can have a boomerang effect more intense



"I think the dosage needs adjusting. I'm not nearly as happy as the people in the ads."

and dangerous than the turmoil the patients first experienced. So many Paxil users are in fact struggling with this syndrome that they have formed support groups to share information, swap advice, and manage a health crisis that GSK for many years tried to ignore.

Fueled by new research, health scares, and mounting skepticism about GSK's promotional campaigns, public concern about rebound syndrome has led many to ask whether drugs are the optimal or necessary way of treating anxiety. This reevaluation is now sufficiently widespread and accepted among medical experts that the *Los Angeles Times* and *Newsweek,* adjusting their earlier emphasis, ran parallel stories about it on the same day in March 2006. "The nation's heady romance with antidepressant medication appears to be over," the *Los Angeles Times* declared, while *Newsweek* insisted, in a cover article, "Freud Is *Not* Dead. The Couch Is Out, But the Culture of Therapy Is Everywhere—And Science Is Taking a New Look at His Theories."[2]

I do the same in this chapter, to provide a clear medical explanation for why some patients have an adverse reaction to drugs such as Paxil. Considering the many side effects of medications, I also assess different ways of viewing shyness and more effective ways of handling anxiety. Because therapists view anxiety less mechanistically than do neuropsychiatrists, they restore the phenomenon's complexity and reverse the impoverishment of human experience that dates to *DSM-III.* And though I focus partly on cognitive-behavioral theories, because they are considered a popular and efficient alternative to psychotherapy, like *Newsweek* I take a fresh look at Freud's theories of anxiety, because they point to more deep-seated conflicts that resist our culture's stress on quick fixes.

Kate is one of many patients who wishes a specialist had told her about potential withdrawal symptoms long before she began taking Paxil. "Ironically," she tells me, "I did ask for Paxil because I thought I had social anxiety disorder."[3] After enduring anxiety and bouts of menopausal depression, she responded well to the drug for three years, then carefully tapered her dose when she felt better. Hers would seem to be a simple success story. But as Kate stepped down her prescription, a new wave of problems hit her. "I immediately had a whopping reaction," she despaired. "Three months of quasimania, which made it seem as if I was very active and confident, followed by six months of anxiety, insomnia, periodic brain zaps, and total uninterest in sex."[4] Other drugs, such as trazodone, prescribed by "well-meaning psychiatrists," only worsened her anxiety, weepiness, and hopelessness. Coping with Paxil's aftereffects, she now feels worse than she did before starting treatment.

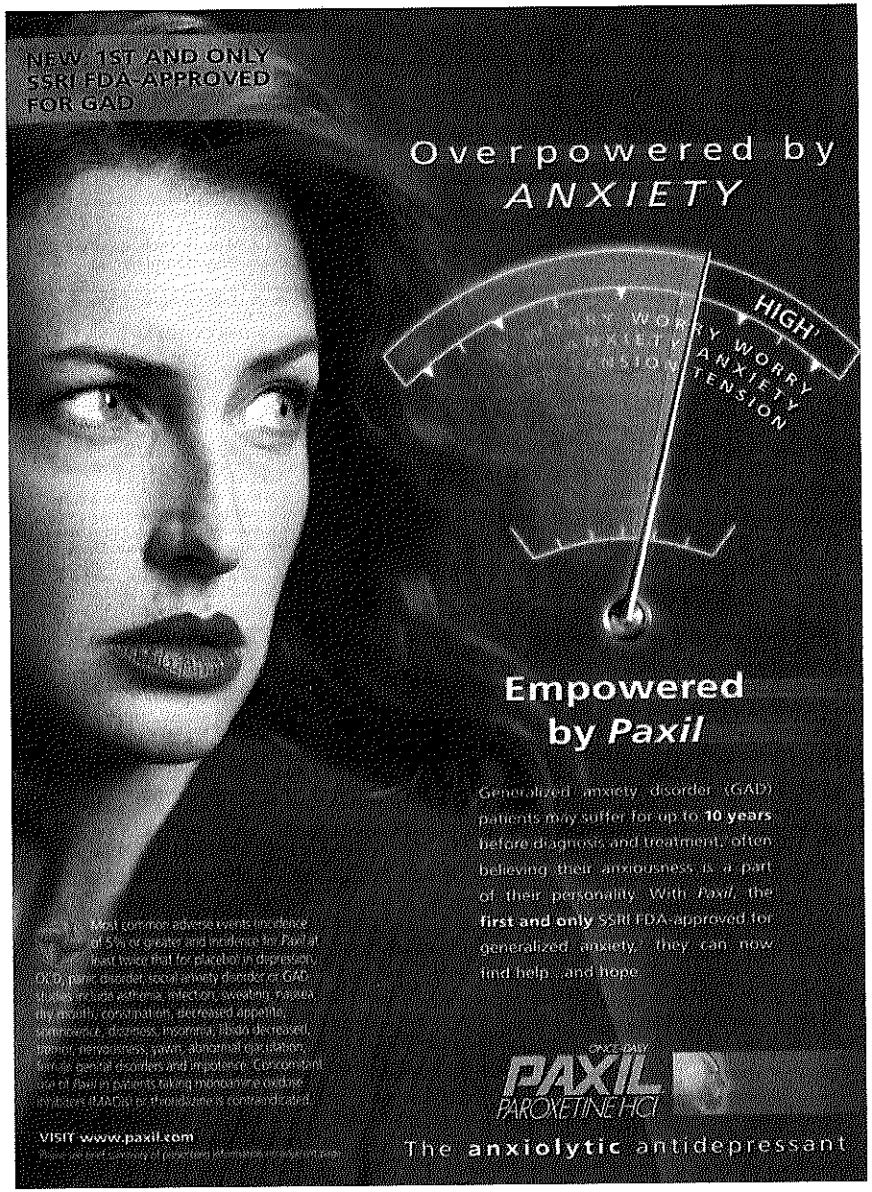
Kate does not represent every patient who has taken Paxil. She is, however, one of a disturbingly large number who are documenting their problems online because the drug companies, eager to promote remedies for the new anxiety disorders, are painfully slow in investigating the health-related side effects. The many expert pharmacologists I consulted when researching this chapter, who verified its medical claims and whose careers as researchers partly depend on the amount of external funding they can attract, are loath to bite the hand that feeds them by publishing findings at

odds with the drug companies' largely upbeat reports. Consequently, it is extremely difficult to find articles about SSRI-related rebound syndrome in the nation's top peer-reviewed medical and psychiatric journals. For many years, moreover, doctors and psychiatrists would tell patients like Kate they were re-experiencing their original anxiety and should either raise their dose or change to another medication. Now they are more likely to recognize that she and many others are experiencing side effects stemming entirely from the drugs.

Of all the antidepressants and antianxiety remedies now available, Paxil has the worst track record for rebound syndrome, because it has additional side effects as an anticholinergic, a term I explain shortly. Indeed, the chorus of outrage, litigation, and bad press in 2005 became so deafening that GSK decided to revise the drug's "product monograph." It warned healthcare professionals about "adverse reactions" and "discontinuation symptoms" that include "agitation, anxiety, headache, tremor, confusion, diarrhea, nausea, vomiting and sweating."[5] These, the booklet stressed, supplement a litany of already well-known side effects: "dry mouth, constipation, decreased appetite, somnolence, tremor, decreased libido, yawn [*sic*], abnormal ejaculation, female genital disorders, and impotence."[6]

As GSK's altered rhetoric broke the dam, patients finally could account for the side effects deluging them. The company felt obliged to note "serious, sometimes fatal, reactions" to the drug, including "mental status changes that include extreme agitation progressing to delirium and coma." Other disturbing reports receiving brief, scattershot attention concerned newborns with serious birth defects, most of them heart related, when pregnant mothers continued taking Paxil into their third trimester. And GSK admitted that patients on Paxil had experienced seizures, kidney failure, and abnormal bleeding because of "impaired platelet aggregation."[7]

As if these revelations weren't shocking enough, the company stressed, in boldface type, that "recent analyses" of the drug's effect on patients under the age of 18 recognized "behavioral and emotional changes, including an increased risk of suicide ideation." GSK couldn't generalize about these "small denominators," it hastened to add. But since the list of "severe agitation-type adverse events" in children ***and*** adults included "self-harm or harm to others," as well as "disinhibition, emotional lability



(Paxil, *American Journal of Psychiatry* 158, July 2001)

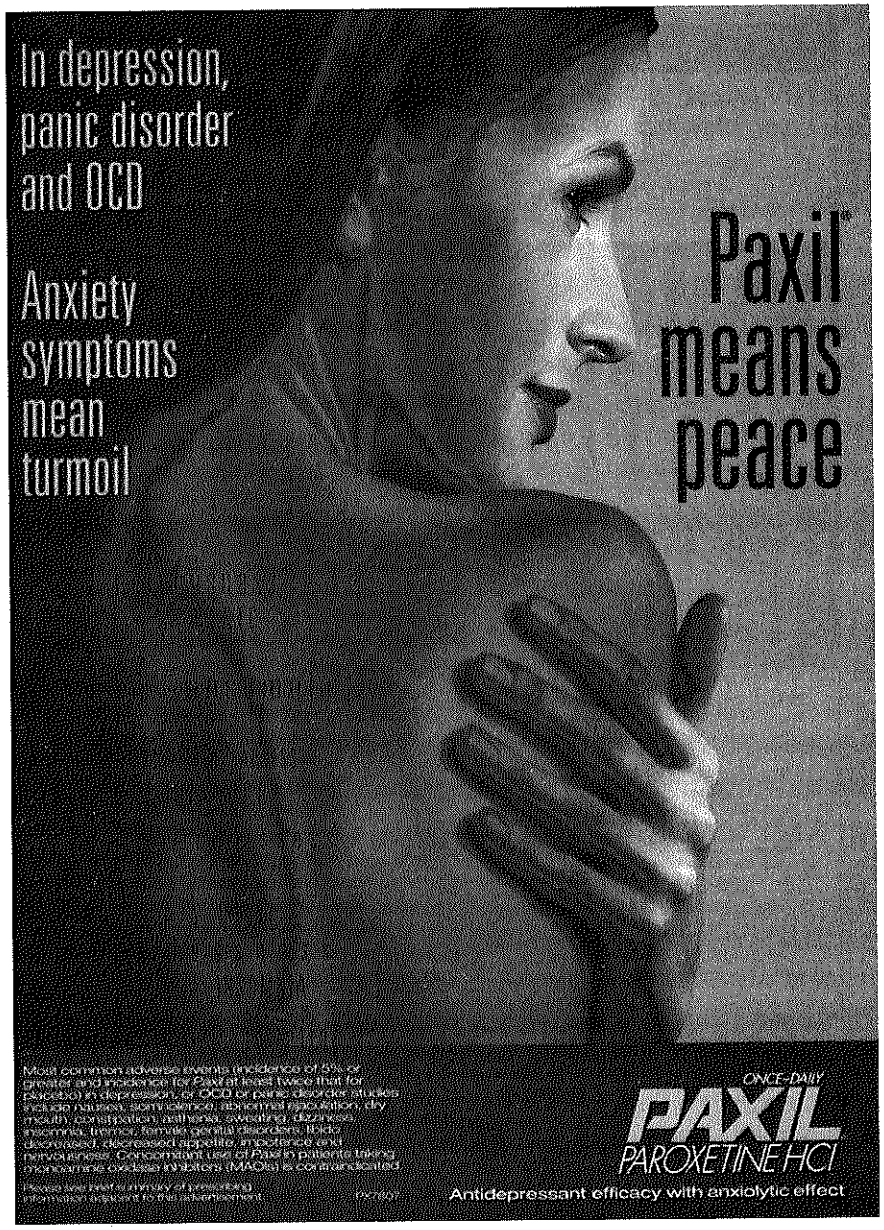
[unpredictable mood swings], hostility, aggression, depersonalization, [and] akathisia," a serious condition marked by extreme motor restlessness, apparently none of the several million people taking the drug could safely be said *not* to require "rigorous clinical monitoring for suicidal ideation"[8]—an almost unbelievable outcome, voiced by the drug manufacturer itself, for a company still encouraging the public to take Paxil for anxiety about going to parties and fear of being criticized.

If, according to our drug companies and psychiatrists, this list of side effects represents progress, then something is terribly wrong with their vision of mental health. The upshot of GSK's multimillion-dollar "awareness campaign"—certain to intensify the anxiety it was meant to quell—is mind-boggling, yet in the brochure, at least, the company scarcely breaks its stride. It continues to represent the drug as a key treatment "for the symptomatic relief of generalized social phobia (social anxiety disorder)," as well as depression, panic disorder, and premenstrual dysphoric disorder.[9]

It would have been better, of course, if the scale and gravity of Paxil's side effects had been broadcast long before millions of people began taking the drug. Even in 2002, the list of associated health problems GSK was required to mention was still relatively easy to downplay: "Paxil is generally well tolerated. As with many medications, there can be side effects. . . . Most people who experience [them] are not bothered enough to stop taking Paxil. . . . Talk to your doctor about non-habit-forming Paxil today. So you can see someone you haven't seen in a while . . . Yourself!"[10]

GSK's careful qualifiers ("generally well tolerated"; "most people"; "there can be side effects") give the company so much legal and clinical wiggle room that by the time one reaches its final, vacuous statement about seeing oneself, the copy might be advertising a window cleaner, not a powerful psychotropic with a laundry list of side effects.

The problem facing GSK today is that it knew about most of these problems years ago—a key reason the company is plagued by litigation charging gross negligence. It is well known among experts, as *USA Today*'s website still reports, that fully "20 percent of patients treated with Paxil in worldwide clinical trials in major depressive disorder and 16.1 percent of patients treated with Paxil in worldwide trials in social anxiety disorder . . . discontinued treatment due to an adverse event."[11] You will still hear



(Paxil, *American Journal of Psychiatry* 156, March 1999)

some psychiatrists, many of them paid consultants, question the significance of these figures while urging more people to seek treatment. Doing so must take real nerve: the fact that one in five patients has an adverse reaction to Paxil is, proportionally speaking, a staggering number. Even a small incidence of serious side effects would be cause for alarm, but the sheer scale of the problem facing the drug companies makes their unwillingness—and psychiatry's—to study it systematically a grave concern.

Fed up with GSK's half-truths, New York State Attorney General Eliot Spitzer decided to sue the company for fraud in June 2004, claiming it had concealed crucial information about the drug's track record.[12] The full extent of Paxil's side effects, Spitzer alleged, hadn't been disclosed to physicians—no real surprise when GSK advised its pharma reps not to discuss such matters with them.[13] The company said the charges were unfounded but decided to settle anyway, paying the State of New York $900,000 and promising to post on its website summaries of all its clinical trials since December 2000.[14]

In April 2006 the company also "agreed to pay U.S. states $14 million to resolve allegations it illegally blocked generic entry to the market of its antidepressant Paxil, which caused state healthcare plans to pay inflated prices for the drug." Indeed, GSK has "paid a total of *$165 million* under similar settlements stemming from class action lawsuits brought by pharmacies, consumers, and health insurers."[15]

Although the settlement with the attorney general's office paves the way for further industry reforms, $900,000 is but a fraction of GSK's revenue for the drug. And despite promises that it would disclose key information to the public and to researchers, GSK and other drug companies continue to withhold major documents and results.[16] Neither settlement nor promise is especially reassuring to Kate, whose full recovery from Paxil seemed so elusive fourteen months after ending treatment that she decided to learn more about the drug she had taken. What she read horrified her.[17]

Paxil, she discovered, is unusual among SSRIs in being a potent anticholinergic. That means, technically, that the drug tends to block receptors in our cholinergic system, an aspect of our central nervous system controlling many involuntary activities such as fight-or-flight reactions, the amount we sweat, and our ability to produce saliva and tears.[18] It is no surprise, then, that many taking the drug experience dry mouth and feel mildly sedated.

But Paxil doesn't just frequently jam the cholinergic system, to prevent it from going into overdrive. Because the drug is *not* sufficiently selective to distinguish between extreme and routine stress, it often blocks almost all signals from this system, including those that would alert us to undue stress and overexertion. Nor does the cholinergic system stand by and accept its altered condition. Sensing that something internally is wrong, it often tries to compensate for the false neuronal picture by sprouting new receptors, a process that in psychiatric jargon is called upregulating. The whole nervous system is thrown out of kilter, making it more difficult than ever for the body to distinguish between stress and anxiety.

Paxil's other deliberate and unintended effects can be equally erratic. Like all SSRIs (including Prozac, Zoloft, Effexor, and Lexapro), Paxil is meant to block the uptake of the serotonin that neurons normally discharge, thereby storing a greater amount of this messenger to activate neighboring neurons. Some neuropsychiatrists believe that over the long term a large amount of serotonin in the brain can stabilize extreme fluctuations in mood—a belief, we'll see shortly, that many of their colleagues have discredited.[19] Still, the serotonergic system doesn't ignore the artificially raised quantities of this messenger. It normally needs more 5-HT2 receptors to soak up the excess, a situation some researchers link to patients' widespread sexual dysfunction, because these receptors send saturation signals to the brain.[20] The system's excess serotonin has the opposite effect on our 5-HTIA receptors, however, which assume they're in less demand and downregulate accordingly. The combined effect of these alterations, as our body tries to adjust or compensate, is a key reason the drugs lose their kick (Lauren Slater calls this SSRI "poop-out") and patients are urged either to up their dose or to switch to another brand.[21]

Those trying to quit Paxil face an especially difficult dilemma, with few really equipped to guide them. For if they taper their dose when the drug stops working, they may experience an intense "cholinergic rebound."[22] Why?

There are three reasons. First, as the receptors in our cholinergic system try to outpace the drug, more of them will put the body in a state of permanent red alert, leaving patients at the mercy of hair-trigger symptoms

such as intense anxiety, aggression, and insomnia. This is exactly what Kate endured. "I have never been prone to anxiety attacks," she reports, "but in April 2005, shortly after reducing my dose, I experienced an anxiety attack so severe I thought I would have a heart attack."

Second, although most people's nervous systems eventually adjust, the receptors in our serotonergic system—saturated artificially for several months—experience the drop to predrug levels as starvation. Kate puts it memorably, "Once well-fed, they're now like hungry baby birds, bitterly squawking for food."[23]

Third, our 5-HTIA receptors aren't as malleable as other kinds and take longer to sprout anew, delaying the return to neuronal health. Indeed, studies have found that in some patients these receptors fail to grow back at all, in effect leaving the patients worse off than before.[24]

Among medical experts, including the many I consulted, none of these statements is especially controversial. GSK's revised product manual even acknowledges the existence of rebound syndrome and other discontinuation symptoms. But it sugarcoats this process by saying "a gradual reduction in the dose rather than abrupt cessation" will minimize the problem.[25] That is misleading. Like many other patients, Kate was scrupulous in lowering her dose. She followed her doctor's recommendations to the letter. But that's when she experienced her worst difficulties.

When patients are at the mercy of such unpleasant mood swings, it's easy for harried doctors to misdiagnose the problem, insisting that the original anxiety has returned with a vengeance. For a long time, these assumptions masked rebound syndrome and put anxiety in a chronic light. Rather than tolerating such symptoms, perhaps for weeks or even months at a time, some patients understandably want to end them by switching to a new drug or taking an even higher dose of Paxil. Unfortunately, in most cases that simply prolongs the inevitable.

While for years the drug companies and their consultants blamed these problems on the disease, not the drug, the counterevidence pointing to SSRIs is now too massive—and widely accepted—to ignore.[26] Nevertheless, many experts still broadcast the discredited notion that our serotonin levels drop when we feel down, and underreport the neuronal crises besetting those who are trying to discontinue treatment.

Although the drug companies often suggest otherwise, there is no correlation between anxiety or depression and low levels of serotonin. Some people with symptoms of either have ordinary levels of serotonin, others high, and others low. Flooding the brain with this messenger therefore doesn't end, or even swiftly reduce, depression or anxiety. That interested clinicians and lobbyists for the pharmaceutical industry repeatedly claim otherwise is, as David McDowell of Columbia University says, "part of modern neuromythology."[27] Doubtless it is easier to accept that our suffering derives from faulty neurotransmitters than it is to concede that numerous factors—psychological, biological, social, and environmental—influence our states of mind.

If we are to understand why anxiety blights so many lives, we need a comprehensive picture of its causes and effects. Yet even after a century of wrangling, clinicians are no closer to agreeing about them.

Neuropsychiatrists favor drug treatments because they say anxiety stems largely, if not exclusively, from our nervous system's overreacting to situations that do not warrant extreme fight-or-flight responses. If a work-related presentation paralyzes us with dread, apparently it's because our nervous system has misread external cues as threatening or even dangerous. The office is suddenly a battleground; the meeting becomes a torture chamber, as GSK's year 2000 advertisement for Paxil tried to convey. The arguments—psychological, social, even ethical—for preventing these mistakes and the suffering they cause seem unambiguous, indeed commendable.

Yet this limited picture of our body's behavior tells us nothing about how the mind processes such information. After all, the office problem concerns *perception* as well as biology. The relationship between consciousness and our nervous system is far more open-ended and unpredictable than many neuropsychiatrists allow; it involves also family history, hereditary traits, our most vivid memories, and behavioral qualities we might loosely call temperament. Just as some people seem relatively untroubled by catastrophes while others find them traumatic, our perceptions are not limited to biological factors. Though our mental landscapes may be sufficiently resilient to influence us for years, our minds form new associations all the time, especially with the help of therapy—a point to which I'll return.

SHYNESS

How Normal Behavior Became a Sickness

Christopher Lane

Yale University Press
New Haven & London