

4. Events in Kentucky^x

Joseph Wesbecker's father died in 1943, leaving the one-year-old to be brought up by his sixteen-year-old-mother. His poor and difficult childhood included time in an orphanage. In his twenties he began work as a printing press operator in the Standard Gravure plant in Louisville, Kentucky. Working his way up the trade to a journeyman's card, he married and had two sons. When the printing industry ran into difficulties in the 1970s, pressure increased on Wesbecker and his colleagues as more work was asked of fewer employees. When Mike Shea bought Standard Gravure, using money from the workers' pension fund to defray the purchase cost, employees began carrying guns to work, and threats became commonplace. Wesbecker's marriage broke down.ⁱ

Wesbecker began to see psychiatrists and was diagnosed as having depression. After a suicide attempt, he was put on a number of different medications. In the summer of 1988, his physician, Lee Coleman, prescribed the recently released new wonder drug Prozac. Wesbecker stopped Prozac after two days, claiming it didn't suit him. He went on disability in the spring of 1989. He had begun to dread his job and was concerned about going back. Then his disability payments were cut.

On August 10th 1989, Coleman suggested trying Prozac again. When he saw Wesbecker a month later Coleman found him much more agitated and volatile. Coleman wanted to stop the drug and made a note to this effect, but Wesbecker, who had fifteen days of pills left, refused to stop. It had helped, he claimed. When Coleman asked how, Wesbecker said it had helped him to remember an incident at work where he had been required to perform an act of oral sex with one of the foremen while his co-workers watched. According to Wesbecker this had been the price of getting off a particular printing press he hated.

Coleman later testified: "I knew that Prozac in some people could cause nervousness—can cause agitation, can cause sleep problems, plus I had

started him on it three or four weeks before. When you start a new medication and something different happens, you tend to suppose that it's the medication that is causing it within that period of time."ⁱⁱ

A number of Wesbecker's friends later reported that over the next few days he was agitated, his sleep was poor, his appearance was unkempt, and he was pacing endlessly. On the evening of September 13th, he went for a meal with his ex-wife Brenda, who said, "He was just more nervous. He paced more. While we were eating, he got up two or three times and went to the bathroom in the middle of the meal. He didn't finish all of his meal. I didn't either, because he just kept doing that. I finally said, 'I'll just get a go box.'"ⁱⁱⁱ His son James said that on the morning of the 14th, "he really wasn't the same person."^{iv}

Later that day, Wesbecker went to the printing presses with an AK47 and other guns and walked through the plant, killing eight people and severely wounding twelve before shooting himself dead.

Did Wesbecker's Prozac play a part in the events of September 14th? On the one hand, he was at risk for suicide, and the printing press was an accident waiting to happen. On the other hand, his history shows prior intolerance to Prozac and evidence of decompensation when he was re-exposed to it. The almost psychotic developments where he talked of non-existent sexual abuse during his final course of treatment had been reported in other settings, was found in Lilly's trials with Prozac, and has since been reported on Prozac.^v Something similar led to the discovery of the first tricyclic antidepressant, imipramine.

Facing a Jury

Almost from its launch, Prozac generated legal actions. By 1990, 54 cases were pending. By the mid-1990s Lilly faced a series of civil suits, 160 of which were consolidated in a Federal MultiDistrict Legislation (MDL) case. The Californian firm of Kannanack, Murgatroyd, Baum, and Hedlund had 15

cases, one involving Del Shannon, the singer of the 1960s hit single “Runaway.” The drug was also cited in a number of crimes.

A group of attorneys involved in these cases met in 1992 and agreed the first case to go to trial should be clear-cut and winnable. Leonard Finz, Leonard Ring, and Paul Smith were the most prominent lawyers involved. One of the clearest cases was Paul Smith’s Biffle case in Texas and one of the most difficult the Wesbecker case in Kentucky. Smith sent a letter to the other lawyers outlining the agreement to move forward with Biffle first.^{vi} “Obviously, it is my preference to get this case tried at that time, especially in the light of the fact that Judge Finz has the Kentucky litigation set for trial immediately behind this and that case is the weaker case.”

Martin Biffle had been on Prozac only for a matter of days. The drug was present in his body at autopsy after his suicide. His prescribing physician was willing to testify that he had not been suicidal prior to being given Prozac and a series of friends and co-workers were agreed that none of them would have expected him to commit suicide. The Biffle trial was scheduled for the end of 1993. But it took till the end of 1994 before a case reached court—and then it was the Wesbecker rather than the Biffle case.^{vii}

The lead attorney for the plaintiffs in the Wesbecker case in Louisville, Kentucky was Leonard Ring. But one month before the trial was scheduled to take place, Ring had a heart attack that compromised the blood supply to his brain. Nancy Zettler, his junior counsel, felt unable to take on the case alone. She sought help from Paul Smith, who in addition to taking the Biffle case had become the lead attorney in the MDL cases. Zettler and Smith got an extension on the case and spent half a year taking depositions from 56 people, mostly from Lilly, which took 83 days and filled almost 21,000 pages of print.

When Zettler first applied to Lilly for internal documents, she was told there was nothing on the computer. It turned out 4 million pages worth of documents in hard copy had been downloaded from the computer. She was

told she could have them.^{viii} This is common practice in cases involving large corporations. A reasonable expectation might have been that plaintiffs' lawyers would call off the hunt, but Zettler and a colleague, Monica Putnam, set about the documents. Their willingness to do so may now mean that documents are increasingly likely to be routed through a company's lawyers, with the company then withholding them on the basis of attorney-client privilege. The documents from the Wesbecker case therefore shine a unique light on some of the normally hidden operations of large corporations.^{ix}

Zettler and Putnam hit on a strategy to ease their task as they worked through the material. They persuaded trial judge John Potter that Lilly should provide the relevant documents for each of the company's employees three weeks before that employee was due to be deposed.^x Smith and Zettler finally took twelve boxes of documents which Lilly claimed were covered by attorney-client privilege to Judge Potter for a decision. He decided in favour of the plaintiffs.

Among those deposed were David Wong and Ray Fuller, involved in making the drug, and Charles Beasley and John Heiligenstein, who ran the clinical trials programs from the late 1980s and were responsible for assessing reports of adverse events. Zettler and Smith also deposed other key people such as Paul Stark and Dorothy Dobbs, clinical trial monitors, and Catherine Mesner, a clinical research associate. A range of other people from clinical past and present included Irwin Slater, Robert Zerbe, Dan Massica, David Wheadon, Joachim Wernicke, Max Talbott from regulatory affairs in Lilly, and others. Clinicians from Lilly Germany were brought over, including Hans Weber and Nick Schulze-Solce. They also deposed the bosses, including the heads of sections such as Leigh Thompson and Gary Tollefson up to Vaughn Bryson, Melvin Perelman, and Richard Wood from the boardroom and chief executive level.

Lilly employees denied being trained by lawyers but gave standard responses to the effect that randomized controlled trials were accepted as the gold standard in the field, and that there were no trials to show Prozac had

negative effects. Depression was said to be a terrible disease that could lead to suicide. Prozac was frequently described as the most studied drug in history. The responses raise the possibility of brainwashing rather than coaching.

The depositions have either a Jesuitical or pedantic tone. Key players, asked whether they had seen a certain document, would say “no,” perhaps on the basis that this was almost certainly a photocopy of something they had seen rather than the actual thing. They would deny remembering anything without crystalline recall of the event. Charles Beasley couldn’t remember the number of studies in the meta-analysis on which he had spent more than a year.

Here is an excerpt from the deposition of Catherine Mesner by Nancy Zettler:

Q. Did you ever see any meeting minutes generated from any of the division meetings that you attended regarding Fluoxetine?

A. I don’t remember.

Q. Catherine, you understand that you’re sworn to tell the truth?

A. Yes.

Q. You understand that to a certain extent saying you don’t remember when you do have a vague memory is not telling the truth?

Larry Myers (for Lilly) She’s not going to be governed by a definition that you apply, Nancy.^{xi}

Or John Heiligenstein, who after extensive difficulties remembering, is asked:

Q. So it’s your testimony.. that in this phone conversation between yourself and four scientists at Eli Lilly and Company and the medical examiner who was responsible of the autopsy in connection with Joseph Wesbecker’s death, you can remember nothing about

that phone conversation other than the medical examiner was frustrated about the Scientologists being involved.

A. Yes, yes, sir.

Q. Have you ever had trouble with your memory Doctor Heiligenstein.... Have you ever seen a physician for problems with your memory?

A. Have I ever seen a physician for problems with my memory. Yes, as I recollect.

Q. When did you first see a physician for problems with your memory?

A. Probably sometime in 19—, I didn't see it specifically for that.

(After spelling out that he had consulted for possible adult ADHD and was prescribed Ritalin)

Q. Have you ever been criticized by any of your colleagues for memory problems?

A. It's ironic because I think for the most part I've only received compliments for my memory.^{xii}

The plaintiff's attorneys had a further obstacle. Even though they had been offered a room full of documents, sensitive documents had been routed through the legal department or even to outside attorneys, and were then withheld. Catherine Mesner was asked about the challenge-rechallenge study Lilly had undertaken to do:^{xiii}

Q. Would you have turned over the final copy of the protocol and any other documents you had in your file related to the rechallenge study to the legal department in Lilly in one of these quarterly document collections?

A. Yes.

Q. Were those documents that were returned to you either in original or in copy form?

A. Usually I received a copy back.

- Q. Do you have a specific recollection of receiving a copy of the final protocol in the rechallenge study back from the legal department?
- A. No, I don't remember.

Smith's folksy, humorous style in these depositions may have disarmed some of his witnesses more than they intended. Zettler was far more combative. Between them they were deposing witnesses for a series of trials, including Smith's MDL cases, his Biffle and Welch cases, the Crossett case, the Reves case, the Saines case, the Huslig case, and others in addition to the Fentress (Wesbecker) case. Other attorneys sat in on some of the depositions, including William Downey of Kannanack, Murgatroyd, Baum and Hedlund.

One of the fascinating things about the depositions and subsequent trial is how much time Smith, clearly intrigued by the implications, spent on the question of the interface between neurochemistry and free will. But with no science background he was unable to see that the rudimentary state of neuroscience in the 1990s, let alone the 1970s when Prozac was made, permitted little or nothing to be said about any such interface.

Smith and Zettler completely missed the issue of how relatively ineffective Prozac was for depression. No one asked the simple question: If Prozac was a better serotonin reuptake inhibitor than older antidepressants and if serotonin was lowered in depression, why wasn't Prozac bringing about recoveries in hospital depressions quicker than older drugs? They focussed on early clinical reports that schizoaffective patients had done particularly badly on Prozac because some labelled Wesbecker as schizoaffective. In the attorneys' efforts to land a punch on this target they missed the fact that Prozac couldn't be shown to work at all in hospital depression.

Smith and Zettler ran into yet another obstacle when they tried to call an expert witness. It seemed all the psychopharmacologists they approached were either retained by, or consultants to, Lilly—or were just unwilling to get involved. Jonathan Cole was unavailable because seriously ill for much of

1993 and 1994. Martin Teicher seemed uncomfortable with all the documents unearthed and too nervous to get involved,^{xiv} claiming that a lot of pressure had been brought to bear on him.

In the end they went with two experts. One was Nancy Lord, who had both medical and legal qualifications and who had worked in the pharmaceutical industry with Abbott Laboratories on the development of a hypnotic. Lord knew a lot about how clinical trials should be conducted.

The other expert was Peter Breggin, a notable critic of psychopharmacology who was closely associated with the famous antipsychiatrist Thomas Szasz. Since the publication of his 1991 book *Toxic Psychiatry*, Breggin had all but taken on Szasz's mantle.^{xv} *Toxic Psychiatry* is powerful rhetoric, which many psychiatrists find unsettlingly good, on the marketing of psychiatric disorders and a medico-pharmaceutical complex. But at the heart of the book is an argument for the moral superiority of psychotherapy to pharmacotherapy that few biological psychiatrists could endorse. In 1994 Breggin brought out a new book, *Talking Back to Prozac*,^{xvi} based on his role as an expert witness in this and other cases, but which descends into romantic argument about the superiority of psychotherapy over drug treatments.

A few years before the Wesbecker case came to trial, Lilly had hired a new chief executive. Through the 1980s the company experienced a number of setbacks. Lilly's painkiller Orflex had led to many criminal convictions, and the company had developed a reputation for weak moral values. Profits were sliding. Chief executive Vaughn Bryson was ousted in a boardroom battle and the company turned to their first outsider as chief executive, Randall Tobias. Tobias came from AT&T and had no background in pharmaceuticals. He aimed to downsize the company. Furthermore, he had heard a message: depression was costing the workplace millions of dollars. Businesses and other organizations should know that in the longer run, diagnosing depression and getting treatment for their employees could save them money.^{xvii}

Fentress et al. versus Eli Lilly^{xviii}

After five years the Wesbecker case finally came to trial in Louisville on September 28th, 1994. Lilly made it clear from the outset that the company would fight rather than settle this case. Wesbecker offered the perfect opportunity to play the “disease, not the drug” card. Here was a man with an extensive psychiatric history, including a suicide attempt five years earlier, working in a plant that was an accident waiting to happen. Lilly argued he came from a family with three generations of nervous troubles. Lilly’s attorneys deposed 400 people, making Wesbecker, as one witness put it, “one of the most studied serial killers in history.”

At trial, Smith and Zettler faced various disasters. After an impressive performance on examination from Smith, Breggin was faced with Joe Freeman, the attorney for Lilly. Freeman let Breggin launch into his hobbyhorse—how psychotherapy was to be preferred to pharmacotherapy. A psychotherapeutic approach let people build better principles for living.^{xix}

Freeman then faced Breggin with material he had written in 1980. “Have you written ‘that permitting children to have sex among themselves would go a long way toward liberating them from oppressive parental authority?’” Breggin stumbled forward into a left uppercut: “Did you accept money for putting these ideas in writing and selling them to the general public of the United States of America?” Freeman went on to quote: “The difference between believing in the divinity of Christ and believing in oneself as Christ is merely a difference in religious point of view.” Holding a copy of *Penthouse*, he challenged Breggin to explain why he had written an article for that magazine blaming American and British psychiatrists for the Holocaust. It might have been possible to explain these points to a jury with enough time, but not on the witness stand. These guys didn’t take hostages.

Lee Coleman also failed Smith and Zettler. State jurisdictions vary, and according to Kentucky rules, Lilly was not debarred from retaining Coleman.

So although he had previously been one of the main proponents for the argument that it was Prozac that caused Wesbecker's symptoms, he effectively became a witness for Lilly. Questioned by Smith about his earlier views, he testified that his views had changed after he had been made aware of further material by Lilly.

The real success for Smith and Zettler was Nancy Lord.

When I looked at the Lilly data, I didn't find it was adequate to study this drug. The data was flawed for a number of reasons. First of all, the protocols were not well designed... Not only did they permit the use of concomitant medications, but they permitted the use of psychotropic concomitant medications... If someone came on to a trial and got, say, insomnia, they couldn't sleep, or they became jumpy and agitated, instead of having them withdraw and counting that person as someone who couldn't handle the drug, they simply gave them Dalmane to go to sleep, which had a lingering anxiolytic effect during the next day.^{xx} [...]

It looked like they did everything possible to kind of tone down the problems with the drug rather than give them a rigorous, systematic and comprehensive evaluation to define what the problems were and then put it in the package insert so that doctors could be warned not to use the drug in certain types of patients, or to use it more carefully.^{xxi} [...]

In my opinion, this drug has not been approved. It's been approved with sedatives, but taking fluoxetine all by itself has never been studied.^{xxii}

Some patients in trials were recorded as having severe agitation but in the summaries of side effects this became nervousness, or was not recorded as a drug side effect "as the investigators were instructed not to record as adverse experience symptoms of depression."^{xxiii} Patients who dropped out for "patient decision" were not followed up to establish whether it was demands on their time or agitation on the drug that had led to their dropout. A number of

patients who had clearly got worse on Prozac were deemed to be treatment non-responders rather than sufferers from side effects of the drug. This pattern had begun from the very first trials, with patients who became severely agitated, suicidal and psychotic being classified as treatment non-responders. Yet when Lilly was approached by investigators wondering how to handle emerging side effects, one of the options suggested was to reduce the dose of Prozac—an option that concedes a causal link to Prozac.

Today the statistical analysis of clinical trials would be done according to a plan put in place before the trials began, but this didn't happen with Prozac. Investigators in many cases were allowed to break the blind and put patients who had done well on Prozac onto maintenance treatment with it, or switch those who had done poorly on, for instance, imipramine to maintenance treatment with Prozac. Maintaining a group of patients in this way on Prozac makes it possible then to claim that when the company controlled for length of exposure on the drug there wasn't a hazard. In this case what is happening is that patients with the early onset side effects linked by Teicher and Cole to Prozac are diluted by the addition of a selected group of favourable responders to Prozac. There may have been nothing deliberate about this kind of selection, just simple inexperience or incompetence on the part of the company personnel running the trial.

Lord brought out an equal and opposite problem: which happened when patients did poorly on Prozac. The pattern was that after a certain number of weeks off Prozac, all possible drug-induced difficulties were coded under whatever other drug the patient might then be on. On the surface this might seem reasonable. After all, if a patient has been some months off Prozac and is having difficulties, should these be put down to previous Prozac? But in fact it is far from reasonable. The rate of suicidal acts on placebo or other antidepressants in Prozac trials is less than 5 per 1,000. The rate on Prozac is 10 per 1000 patients. But if the records of 1,000 patients are tracked after they go off Prozac, only those who have problems are recorded, and 5 of these have a suicidal act and are added to the non-Prozac group, this instantly pushes up the non-Prozac rate to approaching 10 in 1005 — a rate

identical to the Prozac rate.^{xxiv} The sicker the patients are or the more likely they are to have drug-induced side effects, the more likely they are to stay in contact with the services and be recorded this way.

It was difficult to know what impact Lord's devastating but highly technical testimony might have had on a jury. It was relatively easy for Lilly to appeal to the fact that the FDA had approved this drug, with the implication that FDA officials must have considered all these points and were nevertheless content to approve Prozac. Smith and Zettler couldn't expect a jury of lay people to find the FDA guilty, but Lord's testimony did a great deal to set up the key event of the Wesbecker case.

Judge Potter had ruled that evidence on Lilly's drug Oraflex was inadmissible, as this was not the drug on trial. Oraflex was the U.S. brand name for benoxaprofen (Opren in Britain), a new painkiller which had been released in mid-1982 in the US after being on the market in Britain and elsewhere for some years. It was an expensive Aspirin that produced adverse effects which Aspirin didn't. Direct sunlight caused a rash and made fingernails separate from their nail beds. Despite these ominous signs, the drug got approval and was released in a wave of hype which stressed that it was particularly safe. There was a rapid increase in sales until it turned out that in the pre-launch investigation of Oraflex, a large number of older people developed a range of seriously disabling liver and kidney problems along with their rashes and peeling fingernails. A number of deaths occurred.

Lilly denied the drug could be causing these side effects. The issue was settled when an independent laboratory demonstrated a dangerous accumulation of the drug in older people. Oraflex was withdrawn and Lilly prosecuted for failing to report to the FDA the full details of its clinical trials program and reports of toxicity abroad. In the UK, over 100 deaths were attributed to Oraflex, and over 4,000 individuals suffered serious side effects. In the US, 49 deaths were attributed to it, and a jury awarded one plaintiff \$6 million. When Lilly finally settled in the UK years later, claimants got \$3,000 on average.

Lilly had another disaster with diethylstilbestrol (DES), a hormone preparation used in the 1950s and 1960s to prevent miscarriages. In 1971 it was discovered that DES could be connected to the development of vaginal cancer in the daughters of women who had taken it during pregnancy. Legal action on DES was still ongoing in the 1990s.

Zettler and Smith had tried to call to the witness stand Beasley and Max Talbott, the Lilly official in charge of regulatory affairs. Zettler had noted that Beasley, when deposed, was perspiring through his suit in what was a cool room. Talbott had cried off his first deposition date and spent long periods of time in the restroom before and during the second date. Lilly argued that the Court could not require the attendance of these witnesses, who lived and worked outside a 500-mile radius from Louisville, and refused to send them. Instead Lilly sent Leigh Thompson, who had been in charge of coordinating the company's responses on the suicide issue.

Thompson praised Lilly's methods of collecting clinical trial data as the model for the field. Other witnesses followed this line, despite the testimony of Nancy Lord. When one of Lilly's experts, Robert Granacher, stated that he would have confidence in any drug approved by the FDA, Smith finally intervened. Lilly, he argued, had opened itself up to detailed questioning on its standards for conducting clinical trials—as, for example, in its trials with Oraflex. Despite his earlier ruling, Potter agreed. It seemed the gloves were about to come off. But Smith suddenly asked for time in adjournment and then declared that the case for the plaintiffs was closing. A surprised Potter asked both set of lawyers if money had changed hands. They denied that it had. One of the jurors later notified the judge that she thought she had heard talk suggestive of a settlement. Asked by Potter to comment on how this juror might possibly have come to this point of view, neither set of lawyers appeared to have any idea.

The jury recessed and came back with a 9:3 verdict in favour of Lilly, the barest minimum Lilly could get by with. They did so after hearing the judge

sum up in a manner that left some of them convinced he had “instructed us to find Wesbecker at fault, so that Prozac had nothing to do with it.”^{xxv} Potter had instructed the jury that they could find Lilly at fault if Prozac was a substantial factor in causing Joseph Wesbecker’s actions. But then he had gone on to instruct them to find Wesbecker at fault.^{xxvi} Had Potter’s summary stressed that all parties agreed Wesbecker carried out the actions, but the question was how much Prozac might have contributed, he would have conveyed a different impression. This was so clearly the case that after the trial, Potter offered Zettler the possibility of a retrial.^{xxvii}

The press wrote up the outcome as a vindication of Lilly and Prozac. Chief Executive Randall Tobias was reported as saying, “The members of the jury, after hearing the scientific and medical facts... came to the only logical conclusion—that Prozac had nothing to do with Joseph Wesbecker’s actions.”^{xxviii} Lilly’s public relations officer, Ed West, indicated how the verdict would be seen: “If it becomes apparent it’s very difficult to win big money in Prozac suits, this probably sends out a message.” West added a statement from Tobias that “The verdict demonstrates the futility of blaming medications for harmful and criminal acts.”^{xxix}

Why did the jury vote this way? The trial transcripts suggest that if there was a single factor that led to Lilly getting out of the case intact, it was the destruction of Wesbecker’s character. They scored no hits on the science of depression or suicide or for their clinical trial procedures, which had so nearly been their undoing. But the jurors were left with the impression that Wesbecker was a bad man and that he had a choice as to his behaviour.

It turned out the Wesbecker case had indeed been settled *before* the jury’s verdict. Rather than face evidence on Oraflex, Lilly had offered what was later described as an “astonishing” sum of money. Pre-trial estimates were that Lilly stood to be hit for anything between \$150 and \$500 million if they lost. Added to that would be the incalculable consequences of a guilty verdict. The settlement terms offered a high-low split, so that whatever the jury verdict, the plaintiffs got substantial sums of money—a large amount if the plaintiffs won

and a lesser but still significant amount if the defense won. Smith's share made him a wealthy man.^{xxx} An angry Potter filed a motion to have the not-guilty verdict quashed and replaced with "dismissed with prejudice as settled." The case went to the Kentucky Supreme Court, which found that "there may have been deception, bad faith conduct, abuse of the judicial process or perhaps even fraud."^{xxxi}

As Potter later put it, "In my opinion, it was not proper because I do not think you should secretly pay money to the other side to have them pull their punches. In basketball it's called shaving points, in boxing it's called pulling your punches... I think the public has the right to expect that a trial is a *bona fide* contest and not some sort of show that one side puts on with the consent of the other to influence public opinion. It was done to discourage other plaintiffs and to help settle the pending lawsuits for less money than they might have been settled for otherwise. Between these two parties they got what they wanted but I think a bigger issue is whether the system was somehow corrupted a little bit and I believe it was."^{xxxii}

Meanwhile

I was unaware of legal developments in the US when in 1994 I was approached to write a review for a new journal, *CNS Drugs*, on "The Fluoxetine and Suicide Controversy."^{xxxiii} I sent my draft for comment to some of my contacts in Lilly, took note of the comments that came back, and sent the review off. It was an innocent review, even stating ironically that of course "these data from several thousand patients, and the evidence that fluoxetine reduces suicidal ideation, must on any scientific scale outweigh the dubious evidence of a handful of case reports." Notwithstanding this piece of irony—which was to cost me dearly—the article came down firmly on the side of saying that Prozac did cause suicide. But the problem, as I saw it, was one that could be managed with the proper warnings.

I was forwarded a copy of a formal response from Joanna Nakielny of Lilly.^{xxxiv}

Did I want to reply? I assumed at the time that this letter would not have come simply from Joanna, but I was unaware of the levels of medical and legal scrutiny my article had been subject to and the care that had gone into crafting a reply. It later became evident that the article had crossed the Atlantic and that there had been inputs from high up in the medical division of the company. A standard response must have been drawn up at some point, because several years later when Alyson Bond from the Institute of Psychiatry wrote a further review on some of the complications of SSRIs, Charles Beasley responded almost immediately to her article, and his response covered almost identical ground to Nakielny.^{xxxv}

The Lilly messages claimed there was no evidence that Prozac caused akathisia, no evidence that akathisia led to suicide, and no evidence that Prozac led to suicide. In its response to both Bond's article and my own, the company contrasted the handful of anecdotal reports with the weight of scientific evidence from its own meta-analysis. Beasley referred to the 1991 study by Fava and Rosenbaum as well as a 1996 study by Warshaw and Keller that I was to meet again. Alyson Bond was surprised at the weight of the reply from Lilly.^{xxxvi} Her article had not been aimed at re-igniting the Prozac and suicide story.

At the end of 1994, after he had recovered from illness and surgery, I interviewed Jonathan Cole at an American College of Neuropsychopharmacology meeting as part of ongoing research on the history of psychopharmacology. Cole had been present from the establishment of the field and coordinated the early investigations of psychotropic drugs.^{xxxvii} Our interview was about the evolution of the field during the 1950s and 1960s, not about Prozac, but I did ask if he regretted co-authorship of the Teicher paper. He did not know I had anything to do with the matter and said he didn't regret his role, concluding that Prozac still caused serious side effects^{xxxviii} and that he would be happy to testify anywhere to that effect.

Should Prozac be accompanied by a warning? He supposed most clinicians

would warn patients to take appropriate steps to minimize the risk. Against this background, the need for a warning seemed to him unconvincing.

I was not convinced. Bostonians may have known about Prozac's disadvantages, but elsewhere...? Neither Cole nor I knew about the Wesbecker verdict two days before our conversation.

Two weeks before the Wesbecker trial started—several months after my review article on Prozac and suicide—I had an invitation to meet with Joanna Nakielny and Gordon Coutts from Lilly along with Tim Cassady, a company attorney from the US handling European affairs. The invitation was to advise them on medico-legal issues. Despite having just published the review for *CNS Drugs* that year, I felt no animus toward Lilly. The side effects as I saw them were ones that could be handled with appropriate warnings. I had no idea the corporation might be fighting for its life on just these issues.

We met on September 12th in London. The Lilly group outlined possible clinical scenarios, none of which seemed likely to have been caused by Prozac. If this was the kind of action they were facing, they had my support. They were interested in my views; I gave them. I suggested comparing akathisia to the irritable or snappy state that anyone might get into after one cup of black coffee too many. I could recognize in myself that I might shout at my children and regret it after an extra cup of black coffee. But should someone get off a criminal charge because they'd had too much black coffee? There seemed no way a jury would ever excuse someone on this basis.

They were interested in my views on Peter Breggin. I gave fairly standard psychiatric views. When Breggin's *Toxic Psychiatry* came out in 1991, I arranged for it to be reviewed by the *British Association of Psychopharmacology Newsletter*. The most succinct review by David King from Belfast— "Too toxic to read"—was unprintable. Debbie Harrison of Lilly had in fact written the most favourable review.

The Jick Study

The key event of 1995 was a publication in the *British Medical Journal* right at the start of the year (which meant the article was in press during the Wesbecker trial). This was an epidemiological study by Hershel Jick and colleagues.^{xxxix} There was drama in the figures, the choice of words, and in what one might read between the lines. Based in Boston, Jick and colleagues had investigated the computerized databases of British primary care physicians. They had been able to assemble information on over 172,000 patients prescribed a range of antidepressants including Prozac. The figures for suicides on Prozac were substantially higher than the figures for any other antidepressants—2.1 times higher than those for the reference antidepressant dothiepin. Dothiepin was vehemently denounced by the makers of the SSRIs as the archetypal tricyclic antidepressant, lethal in overdose. Despite this, in 1995 it was still the best-selling antidepressant in Britain.

Because dothiepin was prescribed far more than all the other antidepressants, the figures for suicide associated with its use became the reference figure against which the figures for Prozac and other antidepressants were compared. Dothiepin came out midway among the antidepressants. Compared with other antidepressants supposedly safe in overdose, such as mianserin, trazodone, flupenthixol and Prozac,^{xi}—all of which might have been given to patients who were more suicidal—dothiepin seemed much less dangerous. Were the figures high for Prozac and these other drugs because they were being given to riskier groups? When efforts were made to control for this bias, the figures for mianserin, flupenthixol and trazodone all fell, suggesting that these drugs were in fact being given to patients at greater risk. The figures for Prozac, however, remained the same.

A number of other drugs came out as even safer than dothiepin. One was lofepramine, a tricyclic antidepressant safe in overdose. The figures in the Jick study for lofepramine were mapped onto the figures in a large Swedish study authored by Göran Isacson.^{xii} In this study, lofepramine, which acts

exclusively on the norepinephrine system, came out as the safest antidepressant when, according to 1980s thinking, this should have made it an activating drug and more likely to lead to suicide.

Thinking on antidepressants and suicide in the 1980s was dominated by the ideas of Paul Kielholz which had led to the synthesis of the SSRIs.^{xlii} Kielholz had conducted the first big trial with imipramine, involving approximately 100 patients, in the course of which there were two suicides. Before imipramine, the traditional wisdom had been that people on their way into or out of a depression were most at risk of suicide. This led Kielholz to the idea that any antidepressant might therefore increase the risk of suicide simply by increasing the number of exits from and subsequent re-entries into depression. He later moved on to the idea that activating antidepressants might be riskier than other antidepressants and it was this idea that dominated the field before Prozac. The Jick and Isacson data on lofepramine blew a hole in that.

When Jick and colleagues looked at rates at which people committed suicide in the month after being prescribed a new drug, the figures for Prozac increased even further. This fit exactly with the Teicher profile that Prozac led to suicide by causing agitation during the first few weeks of treatment.

But you can only cut a piece of cloth so far. Older age is known to make suicide more likely. Men are more likely than women to commit suicide. And one of the most robust findings is that previous suicide attempts predict later suicides. All these things need to be controlled for. When the Jick study controlled for all these factors at the same time, the results for Prozac were still 2.1 times greater than the rates of suicide on dothiepin. But this doubling of the suicide rate was no longer statistically significant. No one could say that the Jick study had proven beyond all doubt in all circumstances that Prozac caused people to commit suicide. But the paper unquestionably gave a sufficiently strong signal that Prozac could trigger suicide to warrant at least a follow-up study. Perhaps the most interesting feature of the Jick study is that it could easily have been repeated, but nothing happened.

Homegrown Akathisia

A major part of my research around 1995 involved investigating the cognitive effects of psychotropic drugs to see whether different drugs have different effects on memory or attention. A tranquilizer such as Valium gives a completely different experience to an antidepressant like Prozac; no one who had either of these blind could confuse them with each other or with a placebo. Astonishingly, however, when it comes to giving computer-delivered cognitive tests it may be impossible to detect which drug a person is on or even to confirm that they are not on a placebo. Alternative explanations for these findings are either that inside the brain these different drugs all act the same way, or that our psychological tests are useless. The challenge was to find some test that could discriminate between drugs so obviously dissimilar.^{xliii}

In 1993 Steve Tipper, the world's leading expert on tests to demonstrate negative priming, had moved to Wales. There was good reason to believe that the differences between the drugs should be detectable on his test, a much more subtle one than many conventionally used for this kind of work. We organized to recruit 60 volunteers from the medical and nursing staff of the psychiatric unit as well as clinical psychologists, psychology students, and others. They would be randomized single-blind to a once-off dose of 5 mg of droperidol, an antipsychotic; 1 mg of lorazepam, a benzodiazepine tranquilizer; or a placebo. These drugs were chosen primarily because they came in liquid form and could be concealed in orange juice. Doses were low enough to leave us worried that some people might show no effect.

A steady stream of subjects came through my office, took their orange juice, and sat down in front of the computer screen to do a set of very boring tests. They then had to hang around for three hours before repeating the tests. In the final analysis, the negative priming test did show differences between the drugs. But the results were to remain lying in a drawer not written up, because

something else right in front of my eyes took priority.^{xiv} The volunteers getting droperidol were having difficulties^{xiv}.

I watched fascinated. Drinking their juice in the morning, they looked normal and healthy, but an hour or so after the drug they looked pallid and somehow shrunken. In some cases, they looked like they'd just got the flu, an impression reinforced by running noses. In most cases, they looked restless. This was not akathisia with obviously restless feet, a restlessness whose sufferers might opt to move around without being fully able to explain why. Unlike foot-tapping restlessness, which can sometimes happen without the person being upset by it, these volunteers were uncomfortable. During the three-hour period between the tests, they moved regularly around the unit or to and from their car. They went for walks to "clear my head." But when I asked them how they were feeling the invariable response was "fine."

We later convened a focus group for those who had been on droperidol to get a better idea of what had happened to them. To a person they had felt dysphoric, unsettled, and disturbed even while telling me they felt fine. They found it difficult to put their unexpected experiences into words. It was not like anything that had happened to them before. Some had said nothing because they didn't want to make fools of themselves, assuming they might be on the placebo and worried that complaints might simply demonstrate their suggestibility. Others felt awful but couldn't believe the drug was causing this.. They had begun to think about some of the worst moments in their life. Highly personal memories of previous unhappy times—broken relationships or loneliness—seemed to be flooding back. And if they previously held themselves responsible for these unhappy times, they seemed to hold themselves responsible for feeling the way they did now as well. This happened to Richard Bentall, one of the world's leading experts on what leads people to attribute events that happen them to themselves rather than to the situation they are in. Richard seemed powerless to apply to the situation what on one level he scientifically knew to be true. His heart overwhelmed his head. He was reduced to tears within an hour.

Phil Thomas, a senior university colleague, became irritable and belligerent. Gwen Jones Edwards, a consultant psychiatrist, became restless and unsettled. The drug transformed her skin and posture so that she looked like a “schizophrenic.” She felt everything was an effort one minute and then experienced waves of restlessness the next. One minute she would be okay doing something and the next minute she was paralyzed. And it kept on going. A week after taking just one pill, she was still feeling strange, and at several points during the week she became suicidal.

Gwen later described her experiences on the national radio program “All in the Mind,” and wrote an article for a patient magazine describing the experience very vividly.^{xlvi} She sent the first version of this article to the journal *Human Psychopharmacology*, but the reviewer dismissed this subject as neurotic, arguing that reactions this long after a single dose were not possible. However, I had correspondence from Merton Sandler, a professor of chemical pathology and one of the early psychopharmacology pioneers, who in the late 1950s had suffered adverse effects from a single dose of reserpine for four weeks. It made him paranoid and belligerent.^{xlvii} So Gwen’s reactions were not unusual. What was interesting was how the field had forgotten that reactions like this, lasting as long as this, could indeed happen after psychotropic drugs.

This study changed my approach to the hazards of Prozac. Dotted around the literature are reports from psychiatrists who themselves became dysphoric or suicidal after taking antipsychotics.^{xlviii} Comparing drug-induced agitation or turmoil to the effects of too much coffee no longer seemed right. Other researchers working with healthy volunteers had seen similar effects in their colleagues but had not emphasized the point for fear of jeopardizing all healthy volunteer work.^{xlix} In the course of developing antipsychotics from the 1950s through to the 1970s, it had been common practice for clinicians and scientists working with pharmaceutical companies to try these drugs themselves. They knew all about drug-induced akathisia and dysphoria and how awful it could be. A changing ethical climate in the 1970s made it difficult to conduct scientific experiments on vulnerable populations such as prisoners, the mentally handicapped, or others whose consent could not be freely given.

Students and company employees were also thought to be vulnerable as it could be argued they might feel forced to take the drug.^{xlix} As a result of these changes, company personnel in the 1990s had much less first-hand knowledge of their drug.

Nevertheless, there is a solid literature on antipsychotics making patients suicidal or homicidal. No one denies that this can happen. Indeed, Lilly and other companies from 1997 were to sell their new atypical antipsychotics on the basis that they caused less akathisia and were therefore less likely to make patients suicidal than older antipsychotics. Given that Prozac had been noted right from the start to cause dysphoria and agitation, it was hard to see how Lilly or anyone else could deny it might also lead to suicide or homicide.

On the Brink of Engagement

In the mid-1990s the British media paid much attention to the increasing use of Ritalin for children. In my last year as secretary of the British Association for Psychopharmacology, I put forward the idea of a consensus conference to establish the basis on which it would be legitimate to prescribe psychoactive drugs to children. This took place in January 1997, and involved American, British, Canadian, and European academic clinicians in child psychiatry and learning disabilities along with Paul Leber and Barbara van Zwieten, senior regulators from North America and Europe. In contrast to Ritalin, where all trials showed the drug worked, none of the trials with antidepressants in children published by 1997 seemed to show they were helpful.

An intriguing feature of the meeting was that North American psychiatrists were happy to prescribe large amounts of psychotropic drugs to children, including antidepressants, whereas in Britain the majority of child psychiatrists still boasted that they had rarely if ever prescribed Ritalin or an antidepressant. This didn't seem to be a matter of clinical trial evidence. If everyone had been following the evidence, both countries would have been using Ritalin but neither would have been giving antidepressants. This was a

cultural matter.

As the convener of the meeting, I had to negotiate a path that would work for the advocates of Ritalin and Prozac and for the psychologists in attendance who were hostile to drug therapies for children. The acceptable answer all around was to put the interests of the child first and to monitor whatever treatment was offered, whether pharmacotherapy or psychotherapy. All options should be genuinely on the table and if children were not responding to one approach, there should be a genuine review of their cases to make possible switches from pharmacotherapy to psychotherapy and vice versa.ⁱ

Somewhere around this time I got round to reading John Cornwell's *The Power to Harm*, a gripping inside account of the Wesbecker case published the year before. It took several more years before I knew of dramas Cornwell had missed.

For instance, shortly before the Wesbecker trial began in 1994, Marilyn Tobias, the wife of Lilly's new chief executive, committed suicide. She had been taking Prozac shortly beforehand. Leigh Thompson, the up-and-coming Lilly golden boy who was aiming at a place on the board and who had done more than anyone to save Prozac, vanished after the trial. As the Halcion story suggests, when company personnel become a liability, they move on.ⁱⁱ

Cornwell left unanswered the question of why the Wesbecker case was the first Prozac case to be tried. It turned out that Paul Smith, the lawyer who had wrestled a corporate giant to the floor on the worst possible of cases, had settled the Biffle case in September of 1993, but this case was not cited anywhere as settled until after the Wesbecker trial—some 16 months later. Not knowing about the Biffle settlement had inhibited anyone else from pushing forward any of several other clear cases to trial in the interim. Was it circumstance or design that led to the Wesbecker case's being the first—and very nearly the only—case to actually end up in court?

Smith's depositions in the case appear brilliant to the historian or sociologist

trying to understand how the pharmaceutical industry worked in the 1980s and early 1990s. But not all lawyers would see them this way. For all the revelations he extracted, he let Lilly provide justifications for what had happened that would seriously compromise the ability of other lawyers to tackle the issues. Many lawyers would have cut to the chase, as Nancy Zettler was more inclined to do. Finally, the terms of the Wesbecker settlement required Smith to win or lose: a verdict of 8-4 and a mistrial would have given him nothing. Against this background, consider neutrals' comments that his performance in summing up for the plaintiffs was very weak. These observations scream out for an explanation.^{lii}

Immediately after the Wesbecker case, Paul Smith brokered settlements in a series of outstanding cases—for instance, 14 of the 15 Kannanack, Murgatroyd, Baum and Hedlund cases. These deals made Smith wealthy but later led to legal actions from colleagues.^{liii}

Nancy Zettler had an outstanding Chicago case involving “Corky” Berman. She was perhaps the only person who knew enough after Wesbecker to construct a case to take to the Department of Justice. But nothing happened: she was burnt out after Wesbecker, and her case remained unsettled. Until it went to trial or settlement, this case would inhibit her from taking any action to the Justice Department in case an adverse ruling compromised her clients. The Berman case remained pending until October 2002.

For me, finding out these things lay in the future. In the meantime, notwithstanding the Jick study and our healthy volunteer study, by 1995 the Prozac fire had died back to its embers. I accepted an invitation from Lilly to attend the April 1996 American Psychiatric Association meeting in New York. I had been asked to give a view on a murder case in Britain involving Prozac and had argued that there was no cause to implicate the drug. Other cases had come my way, but none that had led me to implicate Prozac. After one case I had not been able to support, I was contacted by the lawyer involved, Graham Ross, complaining that if he had seen the statement on the bottom of my 1994 article on fluoxetine and suicide that I was a consultant to Lilly, he

would never have referred the case to me. The clear implication was that I was biased against plaintiffs. Despite this statement of my links to Lilly, a set of lawyers who knew all about these links were about to send me a case quite different to anything I had seen before.

* 4. Events in Kentucky

- i. Cornwell J. *The Power to Harm. Mind, Medicine and Murder on Trial*. New York, Viking, 1996.
- ii. Coleman L. Deposition in *Fentress Vs Eli Lilly*, September 9th 1993 .
- iii. Camp Brenda. Trial testimony in *Fentress v Eli Lilly*. 10/31/1994.
- iv. Wesbecker James. Trial testimony in *Fentress v Eli Lilly*. 11/18/1994.
- v. Glenmullen J. *Prozac Backlash*. New York, Simon & Shuster, 2000.
- vi. Letter of Paul Smith, April 27th 1983, to other plaintiffs' counsel on file as exhibit in *Winkler Vs Eli Lilly MDL 1997*, Indianapolis.
- vii. By convention, the case is named after the first plaintiff, listed alphabetically.
- viii. This section depends heavily on an interview with Nancy Zettler, who has subsequently reviewed the section for accuracy.
- ix. There is also a set of documents from the Halcion cases and the trial of Ian Oswald .Ssee Abraham J, Sheppard J. *The Therapeutic Nightmare*. London, Earthscan Publications, 1999.
- x. The depositions included Max Talbott on June 4th 1992 & 13th January 1994; David Wheadon June 9th & 10th 1992; Catherine Mesner Aug 17th & Oct 15th 1993; David Wong on January 12th & April 13th 1994; Paul Stark March 5th, 29th & 30th 1994; John Heiligenstein April 27th, 28th & 29th 1994; Richard Wood 12th May 1994; Robert Zerbe on May 13th & Aug 9th 1994; Charles Beasley May 17th & 18th 1994; Dorothy Dobbs July 11th 1994; Leigh Thompson July 20th, 21st & 22nd 1994; Hans Weber on September 10th 1994; Nick Schulze-Solce on September 16th 1994
- xi. Mesner C. Deposition in *Fentress Vs Eli Lilly*, August 17th (1993)
- xii. Heiligenstein J. Deposition in *Fentress Vs Eli Lilly*, April 27th & 28th (1994)
- xiii. Mesner C. Deposition in *Fentress Vs Eli Lilly*, August 17th (1993)
- xiv. Teicher and Zettler agree on his discomfort with taking the lines through the regulatory and company documents the attorneys wanted him to consider. Zettler portrays him as a frightened man when Smith and herself met him in 1994.
- xv. Breggin P. *Toxic Psychiatry. Why therapy, empathy and love must replace the drugs, electroshock and biochemical theories of the "new psychiatry."* New York, St Martin's Press, 1991.
- xvi. Breggin P. *Talking Back to Prozac. What Doctors aren't telling you about today's most controversial drug*. New York, St Martin's Press, 1994.
- xvii. Cornwell J. *The Power to Harm. Mind, Medicine and Murder on Trial*. New York, Viking, 1996. Kurschner D. "Interview with Randall Tobias." *Business Ethics* 9, 1995, 31–4; Stodghill R II. "Lilly Rides a Mood Elevator." *Business Week* Nov 11th 1996, 63–4.
- xviii. The details here come from Cornwell J, *The Power to Harm* and the trial transcript in *Fentress et al Vs Eli Lilly*.
- xix. *Fentress Vs Eli Lilly* Trial Transcript.
- xx. Trial testimony from Nancy Lord in *Fentress Vs Eli Lilly*, October 24th (1994)
- xxi. *Ibid.*, page 49 (1994).
- xxii. *Ibid.*, page 54 (1994).
- xxiii. *Ibid.*, page 52 (1994).
- xxiv. Schulz-Solce N. Trial testimony in *Fentress Vs Eli Lilly* by video from deposition, page 185 (1994). See also chapter 11 for relevant figures on suicidal acts.
- xxv. In Cornwell J p. 284.
- xxvi. In *Fentress Vs Eli Lilly*, Jury Instructions Friday Dec 9th 1994.
- xxvii. From interview with Nancy Zettler May 15th 2000.
- xxviii. In Cornwell J p. 286.
- xxix. Both quotes in Cornwell J pp. 286 & 287.

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- xxx. John Cornwell later suggested to me that the settlement figure was of the order of \$500 million; my other contacts suggest no more than \$20 million.
- xxxi. In Cornwell J p. 299.
- xxxii. John Potter on BBC's *File on Four* Tuesday 30th May 2000.
- xxxiii. Healy D. "The fluoxetine and suicide controversy." *CNS Drugs* 1, 1994, 223–31.
- xxxiv. Nakielny J with reply from Healy D. "The fluoxetine and suicide controversy." *CNS Drugs*, 2, 1994, 252–4.
- xxxv. Bond AJ. "Drug induced behavioural disinhibition: incidence, mechanisms and therapeutic implications." *CNS Drugs* 9, 1998: 41–57; Beasley CM. "Suicidality with fluoxetine." *CNS Drugs* 9, 1998: 513–14.
- xxxvi. Comments from Alyson Bond.
- xxxvii. Cole JO. The evaluation of psychotropic drugs. In Healy D, *The Psychopharmacologists Vol 1*, London, Arnold, 239–64, 1996.
- xxxviii. I later found out in March 2000 that he had no awareness of my involvement with Prozac and suicide cases.
- xxxix. Jick S, Dean AD, Jick H. "Antidepressants and suicide." *British Medical Journal* 310, 1995: 215–18.
- xl. Mianserin and Flupenthixol were not available in the USA.
- xli. Isacson G, Holmgren P, Wasserman D, Bergman U. "Use of antidepressants among people committing suicide in Sweden." *British Medical Journal* 308, 1994, 506–9.
- xlii. Healy D, Langmaak C, Savage M. "Suicide in the Course of the Treatment of Depression." *Journal of Psychopharmacology* 13, 1999, 94-99.
- xliii. For an example of this kind of work see Harborne G C, Watson F L, Healy D, Groves L. "The effects of sub-anaesthetic doses of ketamine on memory, cognitive performance and subjective experience in healthy volunteers." *Journal of Psychopharmacology* 10, 1996, 134-140.
- xliv. The results were however presented at the 1998 annual general meeting of the British Association for Psychopharmacology.
- xlv. Healy D, Farquhar G. "The immediate effects of droperidol." *Human Psychopharmacology* 13, 1998, 113-120.
- xlvi. Jones-Edwards G. *OpenMind* (1998)
- xlvii. Merton Sandler. Personal Communication. Some of this was also presented at a European College of Neuropsychopharmacology meeting and published in Healy D. "The case for an individual approach to the treatment of depression." *J Clinical Psychiatry* 61, 2000, suppl 6, 24-28.
- xlviii. Kendler KS. "A medical student's experience with akathisia." *American Journal of Psychiatry* 133, 454-455.
- King DJ, Burke M, Lucas RA. "Antipsychotic drug-induced dysphoria." *British Journal of Psychiatry* 167, 1995, 480-482; See Lynch G, Green JF, King DJ " Antipsychotic drug induced dysphoria." *British Journal of Psychiatry* 169, 1996, 524.
- xlix. See Pedersen V, Bøgesø K. Drug Hunting. In Healy D, *The Psychopharmacologists, vol 2*, London, Arnold, pp. 561-580, 1998.
- l. Healy D, Nutt D. "British Association for Psychopharmacology Consensus on Childhood and Learning Disabilities Psychopharmacology." *Journal of Psychopharmacology* 11, 1997, 291-294. The principles at the heart of this statement were drawn from the lessons of the Osheroff Case—See Healy D. *The Antidepressant Era*, Cambridge, Harvard University Press, , chapter 7, 1997.
- li. Abraham J, Sheppard J. *The Therapeutic Nightmare*. London , Earthscan, 2000.
- lii. Cornwell J. *The Power to Harm*, New York, Viking Press, 1986.
- liii. Grinfeld MJ, Baseman G. "Protecting Prozac. Eli Lilly's defense strategy had kept plaintiffs' attorneys at bay—until now." *California Lawyer* Dec 1998, 36-40 and page 79.