## 8. Kafka's Castle[x]

When the Prozac controversy first took shape, Lilly responded by meta-analyzing its clinical trials database—or so it seemed. Lilly brought this evidence to the FDA hearing that "cleared" Prozac in 1991, and confronted Martin Teicher with it at an ACNP meeting in Puerto Rico in December of 1991. Finally, this was the evidence published in the *British Medical Journal,* with Charles Beasley as first author, in September of 1991, coincidentally a week before the FDA hearing was due to take place.[i] Perhaps more than anything else, this article influenced events. For many, the science was on Lilly's side.

Lilly had consulted widely with senior figures in psychopharmacology in the US and Europe. When the article was published, it would have influential support. It was first submitted to the *New England Journal of Medicine*, which sent it back stating that its readers would not be interested.[ii] It was then sent to the *British Medical Journal*. The *BMJ* agonized over pubication: the document had an entirely company authorship line.

The Beasley article represented itself as a meta-analysis of randomized controlled trials undertaken by the company with 3,067 patients. It was claimed that: "Data from these trials do not show that fluoxetine is associated with an increased risk of suicidal acts or emergence of substantial suicidal thoughts among depressed patients." Reading between the lines, the message was: This was science; the anecdotes produced by Teicher and others were simply that—anecdotes. Which was a good scientist to believe, the meta-analysis or the Teicher anecdotes? Which was a journalist going to believe?

I wrote to the *BMJ* to point out that the Beasley article's dependence on Item 3 of the Hamilton Scale was unjustified, and that these trials had not been designed to investigate the emergence of suicidality. Internal documents showed Lilly agreed with me, although the company took issue with these same points in their reply. What I missed at the time—obvious in retrospect—

is that the analysis omitted patients who dropped out because of anxiety and agitation,[iii] which amounted for up to 5% of all subjects in the trials analyzed—about 85 of the approximately 1,700 patients out of the 3,065 who went on Prozac. These patients, at the heart of the debate, were eliminated at the stroke of a pen.

What I couldn't have known at the time was that the Lilly studies involved patients co-administered benzodiazepines in order to suppress manifestations of exactly what was at stake.[iv] Further, the meta-analysis contained seventeen sets of patients. A Dr. Cohn had enrolled six sets; others involved Louis Fabre. When Lilly filed for registration of fluoxetine in 1985, the FDA suggested work by Dr. Cohn be left out of the frame.[v]

Still more pertinently, John Heiligenstein and Charles Beasley, both physicians with Lilly, had re-analyzed the trial data. Their brief was to investigate suicide attempts or suicidal ideation reported in trials and to categorize events as completed suicides, suicide attempts, or "suicide gestures." The latter category was effectively invented for the purpose; the paper reported on suicides and suicide attempts but not suicidal gestures. Catherine Mesner testified that similar data had been forwarded from clinical trials in Europe to Beasley and Heiligenstein to assess and categorize, and that those analyzing the trials managed to re-classify nine out of ten suicide-related events as non-significant.[vi]

While Beasley and Heiligenstein's reclassifications may have been correct in some cases, their approach was entirely inappropriate scientifically. The correct approach is to leave the matter to the statistics to sort out. If suicidal events were happening on Prozac but not caused by it, similar events should be happening on placebo or other antidepressants. The assessment process was therefore neither independent nor conducted with any clinical sophistication. Indeed, Charles Beasley had never practiced clinically, and Heiligenstein had prescribed Prozac once in his life—to a child. Heiligenstein's testimony in his Wesbecker deposition was as follows:

A. Suicidal ideation is not an adverse event.
Q. Why not?
A. It's a component of the illness.
Q. Doctor, is it your testimony that nobody has ever become suicidal because of the use of fluoxetine?
A. In my estimation, to the best of my knowledge, no.[vii]

And Beasley's testimony in the same trial was:

Q. Have you seen an instance where you in your medical judgement have believed that ideation was caused by ingestion of Prozac?
A. No.[viii]

This was not an analysis that might show Prozac to be *less likely* to be associated with suicidality than other antidepressants or placebo, but one in which Prozac could not *in principle* be associated with a single case of suicidality. You couldn't go on Prozac in these studies if you weren't depressed. If you became suicidal, it couldn't be because of Prozac, because only depression causes suicidality. You could have insomnia, a feature of depression, caused by Prozac, or sexual dysfunction, another feature of depression, caused by Prozac, or fatigue, also a feature of depression, caused by Prozac. But never suicidality.

At his deposition in the Wesbecker case, Leigh Thompson faced a December 7th memo, from Richard Huddleston to Hans Weber, inquiring about a German patient who committed suicide. This patient had been on no other medications, and his physician had explicitly connected the suicide to a surge in serotonin. The Indianapolis monitor "judged the report to be not related."[ix]

A similar mindset is demonstrated in the Miller case several years later in the deposition of Wilma Harrison of Pfizer by Andy Vickery:

Q: An eight-year-old boy who was on Zoloft for 36 days and here's what it says about him. "Patient was hospitalized for a suicide gesture, and

dropped from the study. The patient mutilated himself by cutting his feet with a razor blade and tying a tie around his neck. There was no previous history of self-mutilation or suicidality, although family history was significant for affective disorder (mother, maternal uncle) and suicide (maternal uncle). The event was attributed to study drug by the investigator.

What does that last sentence mean to you?

A: I would like to see the report

Q: The question is: What does the last sentence mean to you?

A: I can only answer that in context. This is a patient who was in a study because the patient had major depression, and the patient has a strong family history of both depression and suicide, so this is a patient that's at very high risk for developing suicidal ideation or behavior.

The patient was in the study, and the time in the study was probably not sufficient to completely treat the symptoms of depression, so the fact that this patient made a suicide gesture while being treated says that the patient probably was still depressed and feeling suicidal at the time that the patient committed the suicidal gesture.

Now, in order to attribute it to the study drug, I don't see how anybody could attribute it to the study drug. While it's a possibility that you could say that it could be attributed to the study drug, the illness itself is associated with suicidal ideation and behavior, so it is more likely that this patient had made a suicidal gesture because of the underlying depression that was not yet treated.

Q: That's not what your investigator concluded, is it?

A: I'm a psychiatrist, and I have to assess each case on the basis of facts given to me.

Q: You're not going to tell me that you know the eight-year-old boy, are you?

A: I know about treating patients with depression, and, in my clinical judgment, I would not have attributed this to the drug under study. I would have attributed it to the illness under study.

Q: Do you know anything about this eight- year-old boy?

A: It is not necessary for me to know about this specific eight-year-old boy. You have given me the history of a family history of affective disorder, a child only eight years old who has a serious enough depression to warrant treatment, and a family history of suicidality. That's very strong risk factors for suicidal behavior.

Q: What did Pfizer's clinical investigator conclude with respect to the cause of this boy's suicidal attempt?

A: The investigator attributed it to the study drug.[x]

Part of the fascination of this deposition is that Vickery had already inquired whether Pfizer had confidence in their clinical investigators and been told the company did. Put aside the fact this study was conducted when some American clinical investigators' practices were about to lead to jail terms; this eight-year-old boy, far from being in a study for the treatment of severe depression, was listed as having an obsessional rather than a depressive disorder, and was in a tolerability study that meant pushing his dose of Zoloft to 200mg.

Lilly had conducted a similar analysis of its depression analysis on its database to review aggressive events, and this too, not surprisingly, cleared Prozac. Beasley and Heiligenstein managed to reduce 1,115 adverse events to just 11 that called for further analysis. Let's examine Heiligenstein's testimony in the Wesbecker case again:

Q: And is it fair to say that some of these adverse events listed in and of themselves would indicate risk factors for somebody becoming more violent, aggressive?

A: They may.

Q: And that wasn't taken into consideration…?

A: Depression itself is a risk factor and that was taken into consideration, yes.[xi]

There were further grounds for concern. Reading the Beasley paper in 1991, I had the impression that Lilly had analyzed all the relevant clinical trials from

their database, even though the article clearly stated that the company had only analyzed American studies. But in fact not even all American studies were analyzed. A sample of 3,067 patients had been analyzed out of a total of more than 26,000 patients enrolled in trials. About 23,000 patients simply vanished.[xii]

After all this, the figures presented in the Beasley paper point to "an excess risk with fluoxetine."[xiii] This led one reviewer to recommend a change of title from the original "Fluoxetine and Suicidality: absence of an association in controlled depression trials"[xiv] to the more neutral "Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression." Far from setting the matter to rest, then, the Beasley article raises yet more questions—making it less possible to write off the whole episode as just incompetence, given the steps taken by Lilly, and raising the issue of the failure of the field to notice what had transpired.

The Beasley article was only one element in the equation. In the course of the Forsyth trial, Andy See raised a Daubert challenge against Ron Shlensky, claiming Shlensky

> had no data to satisfy the standard that he himself ought to apply what is generally accepted in the scientific community… In this case to the contrary we have many epidemiology studies, all going the same way… The Fava, if you read what the authors did... shows nothing adverse about Prozac. The Jick study, if you hold to looking at statistically significant conclusions.. supports the conclusion that there's no difference between Prozac and other antidepressants. The Leon study that I talked to Dr Healy about, the Wirshing study, that I talked to Dr Healy about, as well as the Beasley study.. all of those come to exactly the same conclusion. The Beasley study is. ... a very big group of controlled clinical trials but the rest of them are in the nature of epidemiology studies. There were how many lawsuits regarding Bendectin and, in fact, there was no evidence that it caused birth defects, it is almost like that. Every one of these epidemiology studies came to the same conclusion.[xv]

Lilly tried hard to persuade Judge Kay that the epidemiology was on Lilly's side. Why? Because we were in an era when epidemiology and clinical trials talked in the courts. This stab at winning by default should shock any reader, academic or lay. Where the Fava and Rosenbaum study was concerned, See was correct if, as he suggested, one only "read what the authors did." If you read what anyone else made of the same figures, you saw they concluded these figures suggested that suicidality was three times more likely on Prozac than on other antidepressants. Besides, this was not an epidemiological study: it was a post-marketing surveillance study.[xvi]

The Wirshing study, which See had raised with me in the trial, was the study by Warshaw and Keller involving 654 patients of whom 191 had been on Prozac.[xvii] This study appeared to demonstrate the opposite to what Lilly claimed it proved. More to the point, it could not even remotely be described as an epidemiological study.

Warshaw and Keller, along with personnel from Lilly, were authors of another study put forward by Lilly —the Leon study, conceived almost 20 years before Prozac was launched and begun 10 years before Prozac's launch.[xviii] This involved 643 patients of whom 185 had gone on Prozac at some point. To imply this study was in any way designed to test for the possibility that Prozac might be associated with suicidality was ridiculous. Besides which, the numbers of patients involved would almost certainly have made any characterization of this as an epidemiological study in breach of a trade description act, if there were such a thing for epidemiological studies. The puzzling aspect was why the *American Journal of Psychiatry* published the Leon study.

Following the litigation on breast implants, epidemiology had become one of the weapons in the "Tort Wars." Lilly was trying to portray Fava, Warshaw and Keller, and Leon as epidemiological studies. But an epidemiological study by definition requires a study of populations. It is rare to get good epidemiological studies with less than tens of thousands of subjects in their sample, and even then these studies specify steps taken to make these huge samples

representative of the population at large—all but apologizing for the fact that the entire population has not been studied. These Lilly papers, in contrast, were dealing with 500 and 600 patients of whom only between 100 to 200 were taking Prozac, and no effort was made to show what steps had been taken to produce a sample representative of the larger population. To call this epidemiology was at best misleading, if not an effort by force of money to commandeer the current legal high ground. Randomized controlled trials and epidemiological studies had become accepted in court as appropriately scientific methods. However, it takes a great deal of money to run RCTs or epidemiological studies of the kind being proposed. It also requires the cooperation of the psychiatric profession. This is not something that could be undertaken by plaintiffs or their lawyers.

## An Issue Fit for the *British Medical Journal*

There was an issue here any decent scientist could support, even if she thought that Prozac did more good than harm. I drafted an article on the power of the pharmaceutical industry to "buy" the scientific agenda, questioning how it had become possible to claim that randomized trials and epidemiology were the *only* way to prove cause and effect in cases of drug-induced injury, and how the industry had ended up in a position where companies were the only ones able to conduct such studies. Wealth and power often win in legal cases, but it was getting to the point where companies could ensure that cases didn't even get to court.

Graham Dukes, editor of *International Journal of Risk and Safety in Medicine and* author of the standard textbook on drug-induced injury, had responded to my first attempt in this area, before the Forsyth case:

> It seems to me your approach is original and fair.... I had not seen the issues of litigation, regulation and patents juxtaposed in this way before but… I agree entirely from my own experience with many of your comments; there are some striking examples of companies tenaciously hanging onto a profitable and patented drug despite the evidence that it is

> doing more harm than good. Their motives are a mixture of opportunism and genuine belief that the product is being wrongly accused. I also agree with your remarks about the failure of the present overall research approach to elicit a reliable picture of adverse effects and the sometimes unrealistic defenses put up by industry when their products are the subject of injury litigation.[xix]

This article got put on the back burner during the months leading up to the Forsyth trial, but I revisited it while awaiting the outcome. The verdict in favour of Lilly had implications for prescribers. In any future action the prescriber might well be put in the dock along with the company. Had it been possible for the jury to acquit Lilly on the basis that the prescriber should shoulder some of the blame, one legal option for plaintiffs would be to adopt a Cutthroat. This involves putting prescribers in the dock as well, forcing them to sink with the company or swim by testifying they had never been at any educational meeting of any sort which raised the issue of Prozac-induced agitation and suicidality. These options it seemed had been in Lilly's mind when the controversy blew up, because the company offered to indemnify any American doctors who ended up in a legal action because of Prozac.[xx]

There was another flesh and blood reason for doing something. After returning from Hawaii, I met Dave Wilkinson, then secretary of the child psychiatry section of the Royal College of Psychiatrists, who told me that he and colleagues had been using much more SSRIs in the past year than before and were noticing problems. He described the case of a 15-year-old boy who experienced a personality change on Prozac. A normally quiet lad, within days of going on Prozac he became involved in fights. This moved on to burglary and risked escalating further. Dave stopped the drug. A few days later the lad said he was back to normal. Dave asked if the boy would do any of those things now? Definitely not. He'd be too scared. While on the drug it was as if his adrenaline had been turned off.[xxi] The realization that I had authored a consensus statement that might be used to promote increased prescribing to teenagers worried me.

I decided to call into the offices of the *British Medical Journal* to explain the situation to the editor, Richard Smith. Since the *BMJ* had carried the Beasley article, he might be interested to learn about the background to this article. Smith could hardly be faced with a better offer, in the sense of a newsworthy issue from someone who had been the secretary for a national association dealing with an issue of current concern.

Medical journals are essentially journalism, even if a rarefied kind. What determines entry into the *BMJ* or the *American Journal of Psychiatry* is the same as what determines entry into the *Boston Globe* or the *Wall Street Journal*. Knowing the editor or the editor's friends helps. Toeing the party line helps. Defensibility of the story line helps. Something that might hit advertising revenues will be a consideration for most journals. Quality of research is further down the list of priorities.

When I called into the *BMJ* offices. Richard Smith wasn't there, but the deputy editor, Jane Smith, was. I filled her in on the story. We agreed that I would follow up the visit with a formal submission. I sent in the article with a four-page letter explaining the background and acknowledging the issues as very tricky and complex. I stated that I would be happy to discuss matters further if the *BMJ* felt that the piece was of interest, and to modify my submission in the light of any editorial suggestions on how the issues might better be handled.

Richard Smith wrote back:

> I think a version of your paper could well be suitable for publication in the *BMJ* if you can shorten it to not more than 2000 words… I think the Prozac story is especially interesting, and it clearly would make sense for something to be published in the *BMJ* when we have played such a crucial part in the story. I remember clearly the meta-analysis that we published, and I remember something about the debate around the paper at the time. Some people said we shouldn't publish the paper because it would inevitably be biased, making the point, I remember, that if the study had proved the link between Prozac and suicide then they undoubtedly wouldn't have sent the paper to us. Others said that we couldn't reject a paper

> simply because it came from a pharmaceutical company and that we didn't see many major scientific problems with the study. In retrospect, there is clearly a problem with the fact that the study suffers heavily from publication bias,[xxii] but I think it's true to say that we were all much less conscious of publication bias in 1990 than we are in 1999. …. I hope you will have a go at revising the papers, but if you decide to publish them elsewhere then perhaps you could send us copies. We would then pick up on them in the *BMJ*.[xxiii]

The *BMJ*'s Education and Debate Section, toward which I was led to believe this piece was being steered, took 2,000-word pieces. I spent a weekend reducing everything to this length. By Monday I had an article called "A Failure to Warn," which I put in the mail with a further letter emphasizing that should the *BMJ* take the piece I would be open to revising and rephrasing in line with any constructive editorial comments.

The piece was sent to John Geddes, a senior lecturer in Oxford, to review. I have no idea what the covering letter said. At this stage, as I saw it, given the statements and internal documents from Lilly that the company had assigned "probably related" to a number of the case reports of suicidality and suicides on Prozac, it was difficult to see how any further evidence was needed. There was a particularly interesting situation in the light of the fact that Lilly had chosen not to publish conventional clinical trial evidence that confirmed that Prozac could induce suicidality. Smith had been campaigning on the issue of company failures to publish data during the previous year, one more reason to think he might be interested.[xxiv] I left synopses of the Lilly documents in the *BMJ* offices.

Geddes, of course, didn't have this evidence. The next letter from Richard Smith stated: "I'm afraid we don't think it suitable for publication in the *BMJ* in its present form." The Geddes' review was the review of a person considering whether this piece proved whether or not Prozac caused suicidality. But as it stood, the greatly abbreviated piece focussed on the bioethical issues, and wasn't intended to prove this. Geddes' review raised the issue of how certain

we need to be that a risk exists, and how great that risk must be, before we must warn patients and doctors. But this was not a matter for Smith or Geddes to agonize about. FDA statutes *require* companies to warn if there is an association, even if cause has not been proven.

I wrote back immediately, spelling out that the issues we were dealing with were comparable to the issue of informed consent first raised by Henry Beecher in 1966. Beecher's article detailed 22 pieces of research where explicit informed consent had not been sought from the research subjects. Beecher criticized no one and called no one guilty, but no reader could fail to recognize that at least some of the patients in some of these studies had to have entered the research not knowing what was being done to them and might have suffered an injury they would not have chosen to risk. It seemed to me that we were in a very similar position. Even if the *BMJ* or its readers thought Lilly was not guilty, if clinical studies were generally happening in this way, then it was certain that at some point in the proceedings wrong was being done.

Two letters were exchanged, then Richard Smith phoned me. When I protested that data hadn't been provided because he had asked for an educational and debate article, he brushed me aside. When I assured him that data could be provided, he replied to the effect that no matter what I wrote, the article would not be accepted. Things had evolved rapidly and surprisingly.

The *BMJ* in 1991 faced a dilemma. As far as I can make out, the Beasley paper was the first major article to appear in a major journal with a company-only authorship line. Its acceptance by the *BMJ* probably facilitated the appearance of a great number of other articles with predominantly company authorship lines in major journals—the Leon paper may be a good example. At a 1998 meeting on new antipsychotic drugs at the American College of Neuropsychopharmacology annual meeting, delegates bewailed the fact that published clinical trials now invariably supported the compound of the sponsor of the study. They complained that some of these company-only authored

articles on new drugs contained data that simply didn't add up: efforts to re-analyze the data independently indicated the data had been massaged beyond acceptable limits.

## Beyond the BMJ

What could happen next? I'd made contact with Sarah Boseley from the *Guardian Newspaper*, the leading liberal broadsheet newspaper in Britain.[xxv] I gave her a draft of the "Failure to Warn" piece, letting her know there was a good chance it would appear in the *BMJ*. She was geared to picking up on it when it did, and running with the story from there. John Geddes later offered the view that a *Guardian* article would have much greater impact than anything in the *BMJ*. Would it? What kind of impact?

Following the rebuff from Richard Smith, I arranged to meet Sarah. After she left, the phone rang in my office. It was the *Sunday Times* and another Sarah. I ended up spending nearly two hours on the phone with Sarah Tonge, who had gotten hold of the Forsyth documents and details of the case through the Internet and then made contact with Baum, Hedlund. She wanted to know more.

What could I tell her? I wanted the story done thoroughly. Boseley seemed to be offering a 4,000-word piece in the review section of the *Guardian*. Tonge was offering a much shorter piece in the *Sunday Times*. I contacted Boseley, who was alarmed and began work on a shorter first piece which the *Guardian* published on the Saturday before the proposed *Sunday Times* piece. This outlined in brief the details of the Forsyth case and the fact that not all the relevant information had come out. Nothing appeared in the *Sunday Times* the following day. Some months later a pro-Prozac story ran in the *Times,*[xxvi] mentioning "the booming anti-Prozac lobby, with its strident pieces in the middle-market tabloids, its raucous sites on the World Wide Web, its best-selling books."

The main *Guardian* piece came out the 30th of October, Hallowe'en weekend. The review section sported a lurid black Halloweenish cover with the title "Prozac: Can It Make You Kill?" Inside was a five-page article detailing the Forsyth case.[xxvii] It went through the documents indicating that Lilly knew there were hazards from early in the development of the drug. Gripping stuff.

Four days later the *Daily Telegraph* carried an article detailing the death of Robert Woods.[xxviii] The coroner in Carmarthen in South Wales, a Mr. Owen, had noted the fact that Mr .Woods, a farmer who shot himself through the forehead, had been on Prozac for the previous two weeks. Mr. Owen apparently wondered whether Prozac should carry warnings. How many cases like this were coroners seeing?

After the first *Guardian* article, two people approached me, the woman described in the introduction and Jenny Clark. Neither wished to take legal action. But Jenny did want to know more about Prozac. Shortly after Christmas two years before, her 23-year-old son Craig had been put on Prozac by his GP, unbeknownst to his family. Craig did not appear depressed or different to them. But his GP had noted that he had been flat and apathetic since the break-up of a relationship, that he seemed to be moving from job to job, and that he was drinking more than was good for him.

Over the New Year period, Craig did seem different to his family: more agitated and less able to settle,. doing things out of character, getting involved in fights. None of them had any idea why. Craig returned to his GP after a week to ask for counseling. This was fixed up for the following week. But the day before that was due to happen, two weeks after he had gone on Prozac, Craig Clark hanged himself in his apartment. At the inquest a few months later, Jenny raised the possibility that the Prozac her son had been on—that she had not known he'd been on—might have played a part. The coroner dismissed her concerns. The inquest lasted a matter of minutes. She felt that Craig had been written off as unimportant. Jenny thought her GP was excellent. She didn't blame him. Maybe one of the reasons there were so few

legal actions was that people didn't want to take action against doctors they saw as good.[xxix]

A man named John Marshall was referred to me with a request from his lawyers for a report on whether an action could be taken against the psychiatrist who prescribed the Prozac that had made him suicidal. A guild instinct came into play: I "knew" this young man was just manipulative, but agreed to see him. It turned out that his story pointed to a Prozac-induced agitation. Communication had broken down between him and his psychiatrist, who hadn't fingered Prozac in a deteriorating relationship. A psychiatric pharmacist had written a report saying the entire world knew that Prozac could cause difficulties like this and therefore there was a case against the doctor. But was there? It still seemed to me that the coin wouldn't have dropped for many clinicians, given the constant reassurances from Lilly and the appeals to science. Who was going to be unscientific in this era of evidence-biased medicine and blame Prozac? While I was pretty sure about John Marshall's Prozac, I found it difficult to support this action against his psychiatrist. How many other patients had cases that went nowhere because experts like me felt that even if the drug did cause suicidality, it was difficult to hold the clinician responsible?

Jenny Clark's case suggested coroners might be a way forward. I wrote to all 146 coroners in England and Wales; 30 replied. Some said they hadn't noticed anything but would keep an eye out in future. Others said they had noticed something and would keep a closer eye out in the future. Reginald Browning, Craig Clark's coroner, didn't reply. I wrote to him several times without reply. I then wrote and specifically asked him about Craig Clark. Mr. Browning finally replied, stating that he had known nothing about Prozac and that even if he had, it was not his place to do anything other than record a verdict.

I wrote to the British Secretary of State for Health, Alan Milburn, and got back a reply that would have brought a smile to the face of Franz Kafka. It seemed, writing from Wales, I should address the Welsh National Assembly. I wrote

back and apologized for not doing so, but I suggested this was not simply a Welsh issue but was of significance to the rest of the United Kingdom. Nevertheless, I was informed, by phone, that if I had written from France the Department of Health would have considered the issue, but because I was writing from Wales they couldn't. This had to go through Cardiff. Cardiff referred me back to Whitehall—to the Medicines Control Agency.

I had already written to the Medicines Control Agency. Several months later I got a reply: a bland rehash of old statements. They'd considered things in 1990 and decided nothing had been proven. Lilly did include a warning on Prozac, I was told—that there was a suicide risk inherent in all cases of depression and prescribers should therefore take care. I had also asked the MCA to consider the possibility that, because of the way side effects were not being recorded, all patients participating in clinical trials in Britain and elsewhere were putting themselves and others in legal jeopardy. The MCA gave no answer. I wrote back mentioning this. Their subsequent reply made it clear they didn't understand the point.

There were other people to write to. I got a friendly letter back from John Cox, the president of the Royal College of Psychiatrists, who noted my concerns and said that he'd hand my letter on to the psychopharmacology committee. A year later, even after a follow up letter, I was still waiting. Two years after that I was still waiting, despite further overtures from me. Denis Pereira Gray, from the Royal College of General Practitioners, noted my concerns and said that he would liaise with Cox on this issue.

Several TV companies made contact, interested by the possibilities the story offered. However, when they submitted program proposals to the Central Authorities, the reply tended to be that the Prozac story was an old one. Unless something new turned up, all any program could do was repeat what had already appeared in the *Guardian*, and this wasn't sufficient. A later *Guardian* editorial suggested the British media had turned against exposing corporations.[xxx] It was hard to know where things were going at this stage. On

the basis that there is no such thing as bad publicity, maybe all I'd done was to increase sales of Prozac.

In hopes of getting ideas about how to move things forward, I sent documents to friends within companies. Longstanding friends replied asking me not to send anything else like this to them again, especially to a company address. Others have not been in touch since. Several senior contacts drew my attention to the pharmaceutical industry Code of Conduct according to which companies are not supposed to denigrate another company. This prohibited them from even discussing things with me. Others listened at greater length. They agreed, as many other senior clinicians have done, that Prozac could trigger a suicide, but that it was probably a rare event. One executive told me he was horrified and had put the documents in the company safe to make sure than no one else saw them. He had no suggestions about what I might do. It was so messy when these things got into the media.

To try and get a take on whether I was seeing this right or not, I took the documents and the case to key senior company people who had been through the messiness of drug stories in the media. The view that came back was that marketing was marketing and had to be vigorous, but that there was a line and it seemed from the documents that Lilly might have crossed it. What should I do about it? "Write an article to the *BMJ*" was the suggestion. Offers to talk on the issue on company platforms were not taken up. I wrote to the Association of the British Pharmaceutical Industry. The letter wasn't acknowledged.

I presented the material in a series of UK and Irish settings, including Bristol, London, Oxford, Leceister, and Cardiff—although this involved me smuggling the issue in rather than following an invitation to address just this issue. The response from audiences was almost completely supportive. None of the points made here were contested. But my employer, the University of Wales College of Medicine, insisted I make it explicit that I was speaking in my own capacity. Everyone, it seems, was scared of being sued by Lilly. At the Institute of Psychiatry at London, I gave the talk at a "Suicide Club" whose

program was ordinarily sponsored by Lilly. Lilly withdrew the funding for my talk.

I wrote an article for the special March 2000 Prozac issue of the *Hastings Centre Reports* to accompany pieces written by Carl Elliott, a professor of bioethics in the University of Minnesota, and Peter Kramer from Brown University. Lilly, who had been the biggest private sponsor of the Hastings Centre, withdrew its support.[xxxi] Bob Michels, the Dean of Medicine at Cornell and a member of the editorial board of the *Hastings Centre Reports*, persuaded the centre to have my article re-reviewed, on the basis of which they would either apologize to Lilly or make it clear if called upon that they stood behind the piece. It was sent out to three reviewers, one of whom was Max Fink from New York. Fink's review made it clear that the only shortcoming with my piece was that it didn't go far enough.

But while Max Fink and others stood publicly behind me, I was introduced to a new definition of friendship—your friends are the ones who will tell you they can't be seen talking to you. A string of colleagues from Japan through Europe to the US called me or emailed me to tell me that they had been told to have no contact with me—that I was trouble, and about to be *in* trouble.

There was also some good news. After the difficulties with the *BMJ*, I sent "A Failure to Warn" back to Graham Dukes at the *International Journal of Risk and Safety in Medicine,* who accepted it. "We were unforgivably slow in dealing with your excellent paper… It was approved by our reviewers.. no modifications were proposed. I am wondering whether you would agree to our printing it as a guest editorial. I prefer that papers which we are anxious to emphasize get this status."[xxxii]

## Back to the BMJ

It was time to try a second piece in the *BMJ*, an editorial on the question I had raised with the MCA about clinical trials and legal jeopardy. For me this was

beginning to be an even bigger issue than the issue of whether Prozac causes suicidality.

Both the Wesbecker and Forsyth trials, as well as the *Guardian* article and every talk I gave on the issue included the stunning memo from the chief executive in the German branch of Lilly, Claude Bouchy, in which he stated: "Hans had medical problems with these directions and I have great concerns about it. I do not think I could explain to the BGA, to a judge, to a reporter or even to my family why we do this especially on the sensitive issue of suicide and suicidal ideation."[xxxiii] Another memo followed stating: "I personally wonder whether we are really helping the credibility of an excellent ADE system by calling overdose what a physician reports as suicide attempt and by calling depression what a physician is reporting as suicide ideation."[xxxiv]

Lilly countered this in the Forsyth trial by reading the reply to Bouchy from Leigh Thompson, who noted this "good and important point… I would like very much to emphasize again that we never diminish information content in a report by DELETING any words of the reporter—NEVER EVER."[xxxv]
Reading the whole correspondence made it clear this was not a matter of a drug company fiddling results to get itself out of tight situation, but rather a systematic bias affecting all companies and trials. When new things went wrong on a drug, there might be no box in which to code the new problem. You didn't have to delete any reporter's words if the boxes the FDA would analyze didn't mention suicidal ideation. All the events might be present, but if they were coded depression, where was the problem?

The real issue was not what this said about Lilly and Prozac but what it said about all companies and all drugs. The FDA would never analyze side effects happening to patients in clinical trials if a box corresponding to the side effect didn't exist. This might be tolerable if the data from these clinical trials were just used for marketing purposes. But if the lack of data was being used by companies to argue that clinical trials had proven that these side effects didn't happen, then patient participation in trials was putting everyone else in legal

jeopardy. This held whether one believed that Prozac induced suicidality or not. I knew a number of companies unhappy with the situation.

Surely this was the sort of point even Richard Smith couldn't argue with. A 580-word editorial maybe was something he could commit to. Shorn of references, it went as follows:

> In the clinical studies, prior to its launch in 1988, Prozac had been associated with akathisia and agitation, occurring with sufficient frequency and intensity to lead to recommendations that benzodiazepines be co-prescribed with it in clinical trials. A post-launch randomized trial recorded a 25% akathisia rate on Prozac. Leading textbooks on the clinical profile of psychotropic agents mention Prozac's well-known propensity to cause akathisia. Akathisia has been implicated as a mechanism whereby Prozac may in certain circumstances lead to violence and suicide. The physiological mechanisms by which this happens are relatively well understood. Yet Lilly's presentation of the side effects of Prozac from their clinical trials database contains no mention of akathisia.
>
> Emotional flatness or blunting is a not infrequent side effect of treatment reported by patients on Prozac. Arguably this effect is all but intrinsic to the mode of action of the drug, which generally reduces emotional reactivity. It has been reported in observational studies, where it has been linked to other potentially harmful behaviours. But nothing resembling emotional blunting appears in the clinical trials side-effect database for Prozac.
>
> There is published and unpublished randomized controlled trial evidence that SSRI use is associated with a higher rate of suicidal ideation early in the course of treatment than other antidepressants, strongly suggesting that treatment may induce suicidality in some. Whether or not the reader believes that an antidepressant could induce suicidal ideation, as a matter of fact treatment-emergent suicidal ideation is not recognised by any code in current clinical trial systems. It is not recorded as a side effect of Prozac in the Lilly database.
>
> There are a number of problems with the side-effect data from clinical trials. One is the failure of systems to cope with "new" problems. Another is

> a current dependence on self-reporting methods for side-effect collection. In the case of the SSRIs it would seem that these methods only detect one in six of the side effects detected by systematic checklist methods.
>
> If the side-effect profile of a drug drawn from clinical trials were used just for marketing purposes, there might be little problem with this state of affairs. These profiles have, however, also been used in academic debate and for legal purposes to deny that claimed adverse effects are happening. Against this background, it would seem that patients entering clinical trials where side-effect data is collected by spontaneous reporting methods are putting anyone who may suffer a drug induced adverse event into a state of potential legal jeopardy. The consequences for prescriber liability are also uncertain.
>
> This is a problem that could be readily remedied. If UK ethical committees were to insist that consent forms for trials included a statement that side effects collected by current methods could be used for marketing but for no other purposes, the present poor arrangements could continue without posing a threat of legal jeopardy to all of us. Alternatively ethical committees could request better side-effect collection methods, which would both enhance the scientific information provided by clinical trials and minimize the risks of jeopardy. As many important trials are now multinational and must adhere to the same protocols, these simple maneuvers would have an immediate international effect.
>
> Ethical committees came into existence because the process of recruitment of patients to clinical studies was not transparent. Beecher's review of practices in 1966 indicated a situation where it was likely that some abuses were happening or could happen. The same situation applies today to the use of data emerging from clinical trials.

It was no surprise this editorial was rejected. Rather, the reasons were surprising:

> The main reason for this is that we find the editorial very far from clear. We think few BMJ readers would make it to the end, and those that did would, we think, be very unclear about the exact message. I can understand that you must be worrying that we keep rejecting your paper

> because we are covering up a mistake. Perhaps unconsciously we are, but I obviously don't think that is the case. I think that we are rejecting your papers because they are too long, too unfocussed and insufficiently clear.[xxxvi]

It was impossible not to reply: "It's difficult to see how this could be too long." I suggested we could get blind raters to rate for focus. I told Richard Smith I was due to lecture on the issues at the Institute of Psychiatry, not far from the *BMJ* offices, two weeks later, and he would be welcome to attend there or in Oxford some weeks later. In the meantime, he might be interested to know we had completed a new study in which healthy volunteers had, astonishingly, become suicidal on SSRIs.

"I'm sure you will agree that very few people in my position with another article on these issues would approach the *BMJ* but believing that the playing field is indeed level I would be happy to do so. I accept that any paper will need to be peer reviewed and your response will depend on the reply from your reviewers but I also know that publication in any journal is not a simple matter of scientific merit... Would you advise me to send the manuscript to you or would you advise me to go elsewhere?"[xxxvii]

I had a quick reply: "To be honest I cannot see how a study like that you propose would help answer the very important question of whether fluoxetine increases the risk of suicide. It seems to me that this is a question that can only be answered by the methods of clinical epidemiology."[xxxviii] So the playing field *wasn't* level.

I went elsewhere. In the UK at least, if all ethics committees (IRBs) were to act together, companies would have little option but to play ball. But the omens for IRBs weren't promising. I presented my talk at an enhancement technologies workshop attended by a group of North American ethicists. Their reaction was that ethicists on one committee blocking an industry protocol would simply find industry going down the road to another committee at another university. There was no North American forum through which

ethicists could act in concert. Further to my astonishment, I learnt that review boards were being rapidly privatized and run by the organizations that run clinical trials for the pharmaceutical companies.[xxxix]

The situation might be easier in the UK, which had a much smaller number of ethics committees. Richard Nicholson, editor of the *Bulletin of Medical Ethics*, said he was prepared to take an article on this issue. Several months later, while waiting for this article on "Clinical Trials and Legal Jeopardy" to appear[xl], I had a surprise. Max Fink, a New York contact, e-mailed to say he had just been given a copy of my article and that he agreed with what I was saying. He said Jonathan Cole had given him a copy. I had sent nothing to either of them.

## How Many Deaths?

By the time my relationship with Richard Smith went into decline, it had become evident that there was even more data of the kind that he would like than I had suspected. In 1986, a document had been sent to Lilly headquarters in Indianapolis from Hans Weber, Lilly's medical director in Germany, and Barbara von Keitz; this gave figures from clinical trials to that date which indicated a greatly increased frequency of suicide attempts on Prozac compared with other antidepressants.[xli]

On Prozac there appeared to be 54 or 56 suicide attempts in 5,427 patients, a rate of roughly 10 per 1,000 patients. In the patients randomized to imipramine, amitriptyline, doxepin, or mianserin, there were 3 suicide attempts in 1,981 patients, a rate of 1.5 to 1,000 patients. On placebo, there were 7, 5, or 1, depending on how one read the data, from 1,169 patients. This could give rates of 6, 4.3 or 1 per 1,000 patients.

Why the variability in the placebo rate? Lilly had included at least several patients who made a suicide attempt in the placebo washout period of clinical trials in their placebo group. This was highly inappropriate. There were two ways to respond: one was to count only five suicide attempts in the placebo group, giving a 4.3 per thousand suicide attempt rate. The other was to count

all patients who went into clinical trials as placebo cases also, giving a 1.0 per thousand suicide attempt rate. At the very least Prozac was, overall, three times more likely to lead to a suicide attempt than all other treatments combined, and the true figure could be four or five times as high.

In September 1999, I spoke for the French pharmaceutical company Pierre Fabre at a European College of Neuropsychopharmacology meeting in London, in a symposium on their dual serotonergic and norepinephrine reuptake inhibiting antidepressant, milnacipran. Stuart Montgomery, one of the other speakers, presented the results of a meta-analysis of the company's clinical trial database looking at suicide attempts on SSRIs, on tricyclic antidepressants, and on milnacipran. The data had been published two years previously in a review article.[xlii] This again showed an approximately threefold greater rate of suicide attempts on SSRIs than on milnacipran or tricyclics.

At the same meeting, David Baldwin spoke on recurrent brief depression. In mid-presentation he flashed up data on suicide attempts in patients being treated with either Paxil or placebo. Suicide attempts were three times higher on Paxil. The data had not been published, but this presentation put it in the public domain.[xliii]

Ross Baldessarini from Harvard was also working on suicide attempts in clinical trials on both old and new antidepressants. Data from early analyses gave higher figures for suicide attempts on SSRIs than placebo and up to five times higher than on older antidepressants.[xliv] Shortly afterwards, in April 2000, an article appeared in the *Archives of Psychiatry*[xlv] looking at rates of suicide attempts on newer antidepressants compared to placebo. Again the rates on SSRIs were higher than for placebo.

These clinical trial figures made it possible to estimate how many people had made suicide attempts because of Prozac. If ten per thousand make an attempt on Prozac and five per thousand or less do so on placebo or other antidepressants, and if (as is conventionally estimated) 40 million people worldwide have had Prozac, then there will have been 200,000 more suicide

attempts on Prozac than had Prozac not been used. Conventional wisdom is that there is one suicide for every ten attempts. These would give 20,000 suicides over and above the number who would have committed suicide if they had been left untreated or been treated with older agents.

At this point, I had accessed the FDA's Adverse Event Database to look at suicides reported on Prozac.[xlvi] As of October 1999, there were over 2,000. The FDA estimated their database picked up only between one and ten per cent of serious adverse events. This gives a spread between 20,000 and 200,000 suicides on Prozac. Over a quarter of the accompanying descriptions of the patients' mental state prior to suicide gave clear indicators of akathisia. There was one extraordinary feature to the figures. Ordinarily, four men kill themselves for every one woman; in the Prozac database, the sex ratios were equal. Either there was a strange reporting bias here or some abnormal factor was cutting across natural responses.

Then there were the figures from the Jick study of primary care depression: 189 suicides per 100,000 patient years on Prozac. These needed to be set against the only available figures for suicides in primary care depression—approximately 30 suicides per 100,000 patient years (see chapter 5). This would give a total number of 40,000 or more suicides for the 40 million people who have apparently gone on Prozac since its launch.

These figures from three different sources converge on a similar number of suicides. While extrapolations are involved, we must remember the FDA database records several thousand actually dead people. Applying these figures to countries like Canada or the United Kingdom, where there have been up to 20 million scripts for Prozac during the 1990s,[xlvii] would give a minimum of one million people put on Prozac, and as a result at least 500 deaths per country over the decade—one for every week of the '90s, and 10 attempted suicides per week. Applying the figures to the United States leads to estimates of one suicide per day there.

Could something like this be missed? As I now knew, British coroners could easily miss something happening at this rate. There were 150 coroners, and this suicide rate of would give them on average less than one suicide per year each.

But what about Britain's post-marketing surveillance systems, supposedly superior to the FDA's adverse events system? Here another surprise waited. Enquiring in Emergency Departments, I found that a standard exchange went as follows:

Q: Do you guys recognise that among the suicide attempts you get, there is a group of people who come in after a first overdose or suicide attempt, who simply aren't chronic parasuicides?
A:Yes.
Q: Do you have any sense that these patients are much more likely to have recently been put on an SSRI than any other kind of antidepressant?
A: Yes.
Q: What do you do about their antidepressant?
A: We send them home and tell them that this shows the drug is working. It's kicking in.[xlviii]

This disastrous advice explained why surveillance schemes weren't picking up a warning signal: there wasn't much point in reporting that the drug was working. Lilly played some part in this. It had been telling primary care practitioners for some time about something called serotonin pickup syndrome[xlix]—a new term to me. But the point behind telling primary care physicians about this was that if they didn't warn the patients, the patient might stop treatment. Lilly was warning people not in order to minimize hazards but to keep patients from going off Prozac.

In the case of the South Wales farmer Richard Wood, the coroner had publicly wondered about warnings: "Perhaps Eli Lilly should re-examine the literature they supply to doctors as well as their patients." Contacted by the press, Lilly's response was that the care of patients was the responsibility of doctors: "We

provide a patient information leaflet with Prozac and provide clinicians with the best advice."

They did provide a patient information booklet in the United Kingdom called "Day By Day." The advice included:

Day 5

Keep going! No matter how bad you are feeling now, you should feel better in a few weeks.

Day 6

Keep going! The success of treatment is up to you—don't give up on your treatment now.

Day 11

Did you know? Anxiety and nervousness are often troublesome in depression but they usually respond well to treatment in a few weeks.

Day 12

Keep going! Don't give up now—it may take a little longer to feel better but it's well worth it in the end.

Day 13

Keep going! Don't worry if you are still feeling bad, you remain on the road to recovery as long as you carry on with your medicine.

Day 17

Did you know? The more severe the illness, the more likely that antidepressants will help.

Day 20

About your treatment. Any side-effects of treatment are usually nothing to worry about and go away after the first few weeks.[I]

It was hard to know whether the pills or the "advice" was more poisonous.

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i. Beasley CM, Dornseif BE, Bosomworth JC, Sayler ME, Rampey AH, Heiligenstein JH *et al.* Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. *British Medical Journal* 303: 685–92 (1991).
ii. Deposition of Charles Beasley in *Fentress Vs Eli Lilly*, May 17th & 18th (1994).
iii. *Physician Desk Reference*. Entry on Prozac (1991).

iv. See chapter 7 and testimony of Nancy Lord in *Fentress Vs Eli Lilly*.
v. Food and Drug Administration, Psychopharmacologic Drugs Advisory Committee 28th Meeting, Thursday October 10th 1985.
vi. Deposition of Catherine Mesner in *Fentress Vs Eli Lilly*, August 17th 1993.
vii. Deposition of John Heiligenstein in *Fentress Vs Eli Lilly*, April 27th & 28th 1994.
viii. Deposition of Charles Beasley in *Fentress Vs Eli Lilly*, May 17th & 18th 1994.
ix. *Fentress Vs Eli Lilly*, Memorandum from Richard Huddleston December 7th 1990.
x. Deposition of Wilma Harrison in *Miller Vs Pfizer*, 3/14/2000.
xi. Deposition of John Heiligenstein in *Fentress Vs Eli Lilly*, April 27th & 28th 1994.
xii. Deposition of Charles Beasley in *Fentress Vs Eli Lilly*, May 17th & 18th 1994.
xiii. Quote from anonymous *BMJ* referee for the Beasley paper, Exhibit 3 in Deposition of Greg Enas in *Fentress Vs Eli Lilly* (1994).
xiv. Further quote from *BMJ* reviewer. Exhibit 3 in Deposition of Greg Enas in *Fentress Vs Eli Lilly* (1994).
xv. Forsyth trial Transcript 3/12/199.
xvi. Fava M, Rosenbaum JF. Suicidality and fluoxetine: is there a relationship? *Journal of Clinical Psychiatry* 52: 108–11 (1991). See Healy D. Guest Editorial: A Failure to Warn. *International Journal of Risk & Safety in Medicine* 12, 151–6 (1999).
xvii. Warshaw MG, Keller MB. The relationship between fluoxetine use and suicidal behavior in 654 subjects with anxiety disorders. *Journal of Clinical Psychiatry* 57: 158–66 (1996).
xviii. Leon AC, Keller MB, Warshaw MG, Mueller TI, Solomon DA, Coryell W *et al.* Prospective study of fluoxetine treatment and suicidal behavior in affectively ill subjects. *American Journal of Psychiatry* 156: 195–201 (1999).
xix. Letter from Graham Dukes October 13th 1998.
xx. Rosenbaum J. Eli Lilly and Company, personal communication, June 12th 1991. Cited in Clinical Trial by MediA:The Prozac Story, Schwartz HI (Ed) *Psychiatric Practice under Fire*, American Psychiatric Press, Washington DC, pp. 3-28 (1994).
xxi. See Wilkinson D. Loss of anxiety and increased aggression in a 15-year old boy taking fluoxetine. *Journal of Psychopharmacology* 13, 420 (1999) Reply by Healy D. *Journal of Psychopharmacology* 13, 421 (1999).
xxii. Given that none of the studies in the Beasley paper were designed to answer the question, it is debatable whether publication bias has anything to do with what happened to this article. The sheer embarrassment of recognizing this may have played a part in Richard Smith's inability to accept any papers drawing attention to the issue.
xxiii. Correspondence from Richard Smith, date April 12th for first sentence and April 19th for the rest. This correspondence from Richard Smith is included here because as will be clear from the rest of the book, Richard Smith and the *BMJ* are on the side of the angels. Their 'failures' in the Prozac case therefore serve doubly to illustrate the extent of confusions in the field, and the problems with bringing hazards to light. The full correspondence is on *www.SSRIsuicides.com.*
xxiv. Smith R. An amnesty for unpublished trials (see also Doctor's information: excessive, crummy and bent). *British Medical Journal* 315, 622 (1997).
xxv. Starting from the 1960s, the *Guardian* had risen to become Britain's leading liberal broadsheet. While the *Times* and *Sunday Times* were better known internationally, they had been replaced as the leading papers for investigative journalism, certainly for issues like this.
xxvi. Diamond J. In praise of Prozac. *Times*, Monday June 5th (2000).
xxvii. Boseley S. Prozac. Can it make you kill? *Guardian* October 30th Weekend Section (1999).
xxviii. O'Neill S. Coroner calls for warning note on Prozac packets. *Daily Telegraph* November 3rd (1999).
xxix. Details of this case were confirmed by Craig Clark's doctor.
xxx. Monbiot G. Getting your Science from Charlatans. In *Guardian* Comment & Analysis Section, March 16th page 24 (2000). For support for this view from the opposite side of political divide See Bate R. *What Risk? Science, Politics and Public Health*. Butterworth-Heinemann, London (1997).
xxxi. As I understand it, Lilly gave the Hastings Centre $25,000 per annum. See contributions from Elliott C, Healy D, Kramer P, Edwards J, DeGrazia D. *Hastings Centre Report* volume 30, March issue (2000)

xxxii. Healy D. Guest Editorial: A Failure to Warn. *International Journal of Risk & Safety in Medicine* 12, 151–6 (1999). Quote from letter from Graham Dukes, January 8th 2000.
xxxiii. Memo from Bouchy C to L Thompson Re: Adverse Drug Event Reporting—Suicide Fluoxetine. November 13th 1990. Exhibit 117 in *Forsyth Vs Eli Lilly*.
xxxiv. Memo from Claude Bouchy to Leigh Thompson. November 14th 1990, Exhibit 118 in *Forsyth Vs Eli Lilly*.
xxxv. Memo from L Thompson to C Bouchy November 14th 1990. Exhibit 118 in *Forsyth Vs Eli Lilly*.
xxxvi. Letter from Richard Smith December 20th 1999.
xxxvii. Letter to Richard Smith January 6th 2000.
xxxviii. Letter from Richard Smith January 14th 2000.
xxxix. Lemmens T, Freedman B (2000). Ethics review for sale? Conflict of interest and commercial research review boards. *The Milbank Quarterly* 78, 547–84.
xl. Healy D. Clinical trials and legal jeopardy. *Bulletin of Medical Ethics* 153, 13–18 (1999).
xli. Memo from B von Keitz and H Weber to J Wernicke: Fluoxetine suicides and suicide attempts, October 1986, Exhibit 19 in the deposition of Joachim Wernicke in *Fentress Vs Eli Lilly*.
xlii. Kasper S. The place of milnacipran in the treatment of depression. *Human Psychopharmacology* 12, S135–41 (1997).
xliii. Baldwin D. The treatment of recurrent brief depression. European College of Neuropsychopharmacology Meeting London, Sept 24th (1999). There is, however, another study—Verkes RJ, *et al.* Reduction by paroxetine of suicidal behavior in patients with repeated suicide attempts but not major depression. *American Journal of Psychiatry* 155, 543–7 (1998). This appears to show a reduction in suicide attempts on paroxetine compared to placebo; but with 45 patients on paroxetine of whom 35 drop out and 45 on placebo of whom 37 drop out, it is difficult to know what the results mean.
xliv. Communication from R Baldessarini.
xlv. Khan A, Warner HA, Brown WA. Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: analysis of the FDA database. Archives of General Psychiatry 57, 311–17 (2000).
xlvi. FDA adverse events database.
xlvii. UK Prozac sales figures, source Dinlink Compufile Ltd.
xlviii. After the book was finished a study appeared that directly supported these observations: Donovan S, Clayton A, Beeharry M, Jones S, Kirk C, Waters K, Gardner D, Faulding J, Madely R (2000). Deliberate self-harm and antidepressant drugs. Investigation of a possible link. *British Journal of Psychiatry* 177, 551–6.
xlix. Statement from local Lilly representative in my office in November 1999, witnessed by Drs Tony Roberts and Dave Wilkinson.
l. *Day by Day. A guide to your first 3 weeks of treatment*. Distributed by Eli Lilly representatives in the UK.