

Profiles in Medical Courage: Peter Wilmshurst, the Physician Fugitive

"Nothing defines human beings better than their willingness to do irrational things in the pursuit of phenomenally unlikely payoffs."-Scott Adams, US humorist, in *The Dilbert Principle* (1996)

Peter Wilmshurst, a cardiologist in the UK, has taken on medical companies over their honesty not once, but twice. His exciting story illustrates how far companies will go to protect their quest for big bucks and the potential financial risk incurred by honest physicians who do clinical research.

A movie entitled "The Fugitive", based on the popular 1960's television series, was released in 1993. The movie and television series both tell the story of Dr. Richard Kimble wrongly accused of murdering his wife and Kimble's search for the real killer, a one-armed man. In the movie version, Harrison Ford plays Kimble and discovers that the one-armed man, Frederick Sykes, is employed by a pharmaceutical company that is working on a new drug. Kimble had investigated the drug and discovered that it caused liver damage. He also discovers that his friend and associate, Dr. Charles Nichols, who is leading the drug's development, arranged a cover-up, and ordered Sykes to kill Kimble, with Kimble's wife's death being incidental. This is exciting stuff worthy of a movie. Although the plot was plausible, most of us in medical research thought only barely plausible. Little did we realize that the extent some pharmaceutical companies would go to protect their patented products. After all, we are talking about big bucks here.

Amrinone



Peter Wilmshurst

In 1986, seven years before the release of "The Fugitive", Dr. Peter Wilmshurst, a cardiologist in the United Kingdom, went to the Guardian Newspaper with a fantastic story regarding the development of a new drug. Wilmshurst's research was on heart failure. In the 1980's there were few treatments to improve symptoms of heart failure patients and none to improve survival. Wilmshurst was offered the opportunity to do research on a promising new drug, amrinone, patented by Sterling-Winthrop. Research showed that the drug increased the strength of heart contraction in animals. To assess its

effects in man, a group from Peter Bent Brigham Hospital and Harvard Medical School published in the New England Journal of Medicine the results on the hemodynamic responses to amrinone in 8 patients with heart failure immediately after amrinone infusion (1). Amrinone increased cardiac index and left ventricular end-diastolic pressure fell. No toxicity was observed. To those physicians who care for heart failure patients, this new therapy is exciting stuff. The New England Journal is probably the most influential medical journal in the world. The article came from the cardiology department at Harvard and one of the authors was Eugene Braunwald, the most well known cardiologist in the world at the time and head of medicine at Harvard. However, Wilmshurst research disagreed on the effects of amrinone with Braunwald's findings. In a large series of experiments Wilmshurst group showed that amrinone did not affect contractility in patients with heart failure. Furthermore, life threatening side effects were frequent (2,3).

Wilmshurst reported his findings to Sterling-Winthrop. According to Wilmshurst, Sterling-Winthrop employees asked him to exclude the patients with a downward trend in contractility. When Wilmshurst refused he was threatened with litigation (4). Wilmshurst proceeded with publication of his results in abstracts and meeting presentations but his on-going research studies on amrinone ended when Sterling-Winthrop employees removed the drug stocks from the pharmacy (4).

A number of incidents occurred apparently to prevent presentation or discredit Wilmshurst's research. One strange incident involved one of Wilmshurst's colleagues, Alex Crowther, who was due to present Wilmshurst's and his work on amrinone on the second day of a meeting in Luxembourg (4). When Crowther arrived he discovered that his talk had been rescheduled for the previous day. The organizers had received a forged letter that appeared to be from him asking for his talk to be brought forward a day.

When Wilmshurst presented his findings on side effects at another meeting, a Sterling-Winthrop employee stood up and said that he had made up the findings (4). At other meetings, three professors of cardiology, each of who was a paid consultant to Sterling-Winthrop, made public statements that they had tried to replicate Wilmshurst's findings and failed (4). At one point, Wilmshurst was asked to meet with representatives from Sterling-Winthrop and a different professor of cardiology. They assured Wilmshurst he was mistaken about the drug. The cardiologist said that he was aware of findings by other investigators and that these entirely refuted Wilmshurst's data. He advised that Wilmshurst should not publish any more of his findings. He said that we would be found to be wrong and his reputation would be adversely affected.

The Netherlands Committee for the Evaluation of Medicines reviewed Wilmshurst's paper on the side effects of amrinone (6). There were major discrepancies when compared with the clinical record cards submitted to the evaluation committee by Sterling-Winthrop compared to the findings published by Wilmshurst. Wilmshurst showed that Sterling-Winthrop had sent the Netherlands

Committee falsified clinical records on his patients with the information on adverse events deleted.

Because of these discrepancies, Wilmshurst contacted the UK Committee on Safety of Medicines (CSM) and discovered that Sterling-Winthrop had also failed to notify CSM of the side effects observed in his patients (4). Furthermore, Sterling-Winthrop had not obtained a Clinical Trials Certificate for oral amrinone, though they had for the amrinone injection (4). When Wilmshurst raised this with the Sterling-Winthrop, he was told that Sterling-Winthrop executives had told the UK Government that if the company was prosecuted it would close its large manufacturing plant in the UK. Wilmshurst also contacted the Association of the British Pharmaceutical Industry, the Faculty of Pharmaceutical Medicine of the Royal College of Physicians and the General Medical Council, none of whom were interested (4). Wilmshurst spoke to editors of medical journals, including BMJ, Lancet and Nature. Although none disputed the facts, all were afraid to take on a multinational pharmaceutical company with comparatively unlimited financial and legal resources.

While this was going on, Sterling-Winthrop told a hearing of the USA's Food and Drugs Administration that there had been over 1400 serious adverse events in 1200 patients given amrinone in trials and they would cease trials and applications for product licenses worldwide. Yet Sterling-Winthrop continued to market the drug in several third world countries (4). It was at this time Wilmshurst contacted James Erlichman, a Guardian reporter. Erlichman's paper covered the story on the front, back and the whole of an inside page of one issue and in follow-up stories in other issues (4). Sterling-Winthrop withdrew the oral version of the drug world wide in 1986 (4). This is exciting stuff and could have been the plot for a movie. For his efforts Wilmshurst was awarded the HealthWatch Award in 2003 (7).

MIST Trial

Wilmshurst's experience may have served him well in knowing the lengths commercial companies will go to protect their patented products. In 2000 he published an interesting observation suggesting a relationship between the repair of patent foramen ovale (PFO) and the cure or reduction of migraines (8). PFO is a flap-like opening in the atrial septum of the heart, is the most common cause of a right to left shunt, and associated with an increased risk of migraine. As many as one person in four has a PFO (9). The research interested NMT Medical, a small, start-up medical device company based in Boston which manufactured a percutaneously inserted PFO closure device called STARFlex. NMT was planning a trial to see if their device would relief migraine in those with a PFO. The trial, eventually named the Migraine Intervention with STARFlex Technology (MIST) and Wilmshurst seemed the perfect partner for NMT. He had published in the area and was known as an ethical physician who had won the HealthWatch award (10). NMT estimated that a target population of 3.8 million migraine

sufferers and the financial opportunity to be in excess of \$15 billion (11). NMT was riding high with a stock price approaching \$25/share. We are talking big bucks here and this must have been exciting stuff to NMT executives.

The trial ran from during 2005. However, who should conduct the final, post-procedure transthoracic echocardiograms, the implanting cardiologists or echocardiography specialists, was unclear. The echocardiograms would ensure that the STARFlex device had closed the shunts. Wilmshurst, who was not one of the trial's implanting cardiologists, says he had argued from the outset for a central echocardiography core laboratory, however, NMT proceeded with having the implanting cardiologists read the echocardiograms. A compromise was reached. Wilmshurst would review the final echocardiograms. In contrast to the implanting cardiologists who interpreted the echos to indicate that only four of 65 patients had moderate or large residual shunts, Wilmshurst reported that more than a third had a significant residual shunt.

Wilmshurst's results were potentially devastating to NMT with the efficacy of their device being called into question. NMT organized a second review which also identified over a third of the patients with residual shunt although most were classified as pulmonary rather than atrial shunts (10). When the paper was published in 2008, an accompanying editorial in *Circulation* stated "The lack of an established independent core laboratory for echocardiographic data analysis must haunt the trial investigators." (13).

The results of the MIST trial were announced at the American College of Cardiology meeting in March, 2006. Although the study found "an approximate 37% reduction in migraine burden in those patients who received a STARFlex implant and a 17% reduction in those who received the sham procedure," it had failed to reach a significant difference in its primary end point, eliminating migraines (12). Based on previous observational studies, including Wilmshurst's, researchers had expected migraine to have stopped in 40% of the treatment group at six months compared with 15% in the control group (13).

Publication Dispute

Matters came to a head when Wilmshurst attended the Transcatheter Cardiovascular Therapeutics Conference in Washington, October 25-27, 2007. According to Wilmshurst, it had been agreed that he would make presentations about the trial at cardiac meetings and Andrew Dowson, the other PI on the MIST trial, would present the data at neurology meetings. However, Wilmshurst was surprised when he discovered Dowson was scheduled to present the MIST trial data at the cardiology meeting. In the course of giving a separate talk on patent foramen ovale and migraine at the same meeting, Wilmshurst mentioned the MIST trial. At the session was Shelley Wood, a writer for *TheHeart.org*, who realized there was disagreement about the rate of residual shunts and interviewed Wilmshurst. Her article published October 26 during the meeting

quotes Wilmshurst as alleging that NMT lied about whether echocardiograms from the MIST patients have been independently reviewed, and massaged the data to portray its STARFlex device in the best possible light (15). The article also quotes an NMT spokesperson, who says Wilmshurst was "on a warpath" and was never really the co-principal investigator for MIST. Furthermore, the NMT spokesman claimed Wilmshurst had been dropped from the trial for committing protocol violations. Wilmshurst claims he committed no protocol violations. This must have been exciting stuff to those who relish a controversy in medicine.

Libel Suit

Less than two weeks after returning from Washington, Wilmshurst received a letter from UK solicitors acting for NMT, accusing him of having made "seriously defamatory allegations" in the interview he had given to TheHeart.org (10). According to the solicitors, NMT "has a reputation in this jurisdiction which it cannot permit to be tarnished by [Wilmshurst's] serious and unjustified libels upon it." NMT sued Dr. Wilmshurst for libel in the UK during December 2007. Subsequently, three more suits were filed over the next few years.

NMT did not sue TheHeart.org or Shelley Wood who reported Wilmshurst's comments. This may be because the suit would need to be filed in the US and American courts are highly protective of free speech rights under the US Constitution. However, the UK libel laws differ in several aspects from the US and have several provisions that favor the plaintiff (16):

1. The onus of proof is on the defendant.
2. Legal fees are usually considerably greater than the damages that might be awarded. In other words, even if the defendant wins he may have a considerable financial loss.
3. Lawyers fees are often not contingent on winning in the UK.
4. Trials are long often placing considerable financial hardship on the defendant.
5. There is no compensation for personal cost, such as time wasted and earnings lost by spending time dealing with the case.
6. "Libel tourism" is permitted, so that wealthy foreign individuals or corporations are allowed to sue in the UK but are themselves immune to actions brought against them in the UK.

Wilmshurst's libel case created some attention in the UK. Wilmshurst was asked to appear on BBC 4's morning radio program (for which he was sued again by NMT) and even called to the office of the UK Minister of Justice to discuss his case. Several medical journals picked up on the case, most notably the British Medical Journal which published a 4 page review in January, 2010 (10). The perception was that an American corporation was using the UK courts to suppress a UK physician from telling the truth resulted in a call for libel reform in the UK (17). This is exciting stuff.

Circulation Correction

Over a year after publication of the MIST trial in August, 2009 *Circulation* published a 700 word correction (18). The correction notes that Dr. Peter Wilmshurst did not sign the Copyright Transfer Agreement because of an internal disagreement about the conduct of study. According to Wilmshurst the correction contains information regarding device embolization which had not been disclosed in the original paper, but there is no mention of several of Wilmshurst's other concerns, including the alleged conflicts of interest of some authors of the paper and the two echocardiogram reviews (16).

CLOSURE I Trial

In January 2008, NMT announced it was closing its follow-up MIST trial in the US. Although the company denied that failure of the first trial was the reason for cancellation, they did note that the trial had become "an expensive endeavor with little likelihood of being completed in a reasonable timeframe." (10). Costs of the trial were estimated at \$14 million and instead NMT decided to focus its resources on a trial designed to evaluate the effectiveness of PFO closure by STARFlex as a treatment for stroke compared with existing medical therapy, the CLOSURE I trial. However, like the MIST trial the results of the CLOSURE trial were disappointing (19). The rates of stroke or TIA were no different between those who had the STARFlex device inserted and anticoagulant therapy.

Financial Fallout

The results of the CLOSURE I were obviously distressing financial news for NMT. NMT's stock which had been as high as \$25/share had decreased to \$0.25/share after announcement of the CLOSURE I trial.

Apparently legal trials move as slowly in the UK as in the US. In the three years that had elapsed since filing of the initial the suit and the announcement of the CLOSURE I results, no legal action was taken, although legal expenses continued to accumulate (16). Wilmshurst had accrued over \$150,000 in out of pocket expenses and was in danger of losing his house. The anticipated trial costs were estimated at over \$5 million for each side and would have required Wilmshurst to be in court for about 6 months. Obviously this would be both financially and professionally ruinous to Wilmshurst. Predictably, NMT filed for bankruptcy in April, 2011 but not before filing the fourth libel action against Wilmshurst in March. The bankruptcy filing ended the legal actions against Wilmshurst.

Wilmshurst's Account

After the bankruptcy filing, Wilmshurst published a summary of his experience in *Radical Statistics* (16). In this article Wilmshurst points out that while the data supporting the STARFlex device was unfavorable, NMT's website and annual report did not reflect the data. On a rotating banner on the website and in the annual report were the names and photographs of the three patients who had a STARFlex implant and who were free of migraine. Wilmshurst points out that an important question is how NMT came to make contact with the three patients.

Wilmshurst said "My experience suggests that corporations can use the English defamation laws to misrepresent the results of clinical research. A corporation can propagate a misleading version and can use the defamation laws to bully those who object into remaining silent." (16). He goes on to say "The law courts are not the best way to determine scientific truth. Few judges and even fewer juries have the training to weigh scientific evidence. An adversarial system is not the appropriate way, particularly when it pits an ordinary individual with limited financial resources against expensive barristers employed by corporations with more money. Truth should not be decided by those with greatest wealth using bullying and threats to make a scientist retract what he or she knows is true."

We should remember Peter Wilmshurst for his courage in standing up for the truth, not once but twice. However, given our system and the comparatively large financial resources of corporations, physicians do so at their own professional and financial peril. Some such as the UK not for profit group, Libel Reform, seek to change the UK libel laws to prevent incidents such as Wilmshurst's. Many physicians both in the UK and US likely agree that the exciting stuff experienced by Wilmshurst do not need to happen when a physician stands up for the truth. However, this is doubtful in the absence of real legal reform. After all, we are talking about big bucks here.

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