Mr. Silverless and the story of two eye drugs

Mr. Cosmo Silverless was an active 80-year-old Australian at the time his central vision began to fail in July 2005. He not only enjoyed travelling but was also researching local coal mining history with a few colleagues. He reports:

This has involved field visits, interviewing older people, research at Wollongong Library and the University, reading many books and writing. It is imperative that I retain at least partial eyesight to continue with this work.

He suffers from chronic kidney disease and is on dialysis and exchange bags four times daily:

This condition has put a stop to major activities such as flying and travelling long distances by bus or train. Holidays are therefore curtailed.

Finally, he has severe arthritis in both knees which makes walking difficult:

Life would be made far more difficult if I could no longer drive.

Unfortunately Mr Silverless is one of the thousands of elderly Australians who live with the effects of an eye disease called Age-related Macular Degeneration (AMD). The macular of the eye is responsible for central vision. This small area of the retina enables the eye to see detail required for reading and driving. Mr Silverless is already legally blind in his right eye due to damage to its macula. He needs monthly injections into his left eyeball to keep his left macular area healthy and keep him from losing his remaining central vision.

Avastin (with the generic name bevacizumab) and Lucentis (generic name ranibizumab) are potent forms of a drug that blocks blood vessel growth factors. They were the product of an attempt to cure cancer by restricting the blood supply to growing tumours (Hess 2006). Both of these drugs were developed by the pharmaceutical company Genentech.

Avastin eventually received FDA approval for treatment of some forms of cancer and is quite expensive at many thousands of dollars per treatment (Hurwitz and Kabbinavar 2005). But Avastin was found to also be effective at controlling wet AMD when given in very small doses allotted from the larger cancer treatment dose which made it very cheap (Rosenfeld, et al. 2005).

Lucentis was designed to be exclusively used in the treatment of wet AMD and underwent extensive clinical trials in order to demonstrate its safely and efficacy and was delivered to the market in single dose form for the treatment of wet AMD (Steinbrook 2006). Unlike Avastin which was very cheap, Lucentis was very expensive per treatment dose. This unprecedented scenario led to increased costs in some countries such as Australia which supported and subsidised the use of Lucentis (O’Shea 2010). In many countries the Avastin-
versus-Lucentis debate has brought about a systematic challenge to the status quo of the way pharmaceuticals are researched and delivered, such as in the US where research challenging the position of Lucentis as the standard treatment of wet AMD is continuing (CATT Research group 2011).

In Australia the case of Mr Silverless highlights the challenges of meeting best practice clinical standards and conforming to a complex medical system. Mr Silverless first lost the central vision of the right eye in July 2005. When Avastin became available in Australia in April 2006 Mr Silverless was given an injection into his right eye and it reduced the swelling of the retina but the damage was already too great to have any improvement in vision and so no further drug treatment was given to the right eye. As soon as the left eye showed signs of vision blur and wet AMD blood vessel growth in June 2007 the eye was treated with an injection of Avastin and the central vision returned to normal. At the time the similar drug Lucentis was not used because it was not yet subsidised by the Australian government and at $2000 per injection was too expensive (Avastin was only $100 per injection). Mr Silverless received a number of monthly injections of Avastin but then his treatment drug was changed to Lucentis when it became fully subsidised by the Australian Government. This treatment of wet AMD with injections into the eye of both Avastin and Lucentis is invasive and risky as the treatment is designed to improve the central vision but, for example, there is a risk that the vision in the whole eye can be lost due to potential side effects of the injection (Wijngaarden and Qureshi 2008).

Despite the risks and the ongoing expense the ability to maintain Mr Silverless’ central vision is vital to ensuring his quality of life. Lucentis treatment is heavily subsidised by the Australian Government for the treatment of wet AMD. Over $18,000 per year is required to treat Mr Silverless’ left eye with monthly Lucentis injections. In 2009 over $150 million was spent on Lucentis through the Australian Government’s Pharmaceutical Benefits Scheme. This excessive cost has been noted in the literature:

An ophthalmologist undertaking 30 injections on their morning list would spend just $535.77 of public money on pharmaceuticals with Avastin. By contrast, if they used Lucentis they would spend $59, 460 (O’Shea 2011: 12).

So although Avastin costs less than one tenth of the price of Lucentis, the Australian Government’s own policies and the apparent lack of scientific testing of Avastin means that it will be some time before cheaper drug treatments are widely available through the Australian health system despite the objections of the treating clinicians (Taylor, et al. 2007).

There is little incentive for the pharmaceutical and biotechnology companies to conduct this costly research on the cheaper drug (Mitchell, et al. 2011). Health systems across the developed world have faced various barriers to conducting their own clinical trials on the cheaper drug such as Genentech’s attempts to restrict the use of Avastin (Goldstein and Chase 2007). This dilemma, in which the lack of research on Avastin has held back the reform of drug treatments for wet AMD, is an example of what is known as the problem of undone science. Medical retinal diagnosis and treatment has become more effective since 2005 but AMD is such a huge problem for people in the community that much more needs to be done to be able to mitigate the impact of this blinding disease.

It has long been recognised that some research priorities gain precedence over others for political and economic rather than clinically derived reasons (Richards 1991). More specifically David Hess describes science that is left incomplete or under-resourced for political and economic reasons as “the problem of undone science”. According to Hess this undone science can be the result of a systemic effort by elites who put structures in place that keep research from being completed (Hess 2007).

The concept of undone science has emerged from the sociology of science as a useful tool for highlighting the politics of research priorities where alternatives that are less profitable can be readily marginalized (Frickel, et al. 2009). The undone science of wet Age-related Macular Degeneration treatment research can be used to illustrate broader themes related to the production and direction of biomedical sciences.

The key to understanding the power of the undone science of wet AMD treatment is to see the research that is deliberately left under resourced as a way of maximising short term profit of pharmaceutical companies from the patent system. The drugs Lucentis and Avastin can slow and often reverse this loss of vision (Mitchell 2011).
two drugs are very similar and mainly differ in the way that the much cheaper drug *Avastin* has struggled to attract funding for large scale clinical trials research (Harvey, et al. 2011). In fact these drugs were derived from the same humanised mouse antibody and this was seen as an early threat to potential profits of *Lucentis* (Goldstein and Chase 2007). The *Avastin* research that has been left to one side is part of a broader group of visual problems that have been given a lower priority by market forces guiding much of the research funding (Wright, et al. 2007).

This paper seeks to investigate how the undone science of medical retinal drug treatments came to influence the options available to treat someone like Mr Silverless, and, more broadly, how the problem of undone science came to increase the financial and treatment burden of Age-related Macular Degeneration on the Australian community.

The role of social theory in the reshaping of health care

Health professionals take pride in the ongoing search for best practice. Often evidence based studies are performed that demand the practitioner rethink their approach to an area of expertise (DeMets 2005). Much of the time these studies come from an area of scientifically recognised research, but social theory can also influence the way a health practitioner can think and the way a health system can function. Each clinical encounter is an opportunity to apply and adapt best practice both within the clinic and in the society at large. A clinical encounter is mediated by communication occurring in an essentially social space which is one of the ways the tools provided by social theory can find immediate application (Leder 1990). Social reconstruction is a process offered by recent theorists that in some ways invites a rethink of the way technoscientific practices are justified. It is a process that involves critical analysis of recent historical cases and has been used in such diverse areas as the greening of industries, non-weapon based defence and alternative medicine (Woodhouse, et al. 2002). Reconstruction of a social practice, especially a technoscientific social practice prone to technocratic absolutism such as evidence based medicine, is an idea that can be important to achieving significant reform. Recent political and economic crises underline that the lack of reform and the unsustainable expense of current health systems represents a fundamental challenge to civil society.

At certain stages during the period 2005–2010, the main problem with *Avastin* use was the lack of comprehensive clinical trials research, hence creating a problem of undone science for those who may have wished to justify its use as a treatment for wet AMD. As Guymet points out in the March 2007 *Medical Journal of Australia* (just three months before Mr Silverless’ left eye was affected by AMD):

> No prospective randomised studies comparing ranibizumab (*Lucentis*) and bevacizumab (*Avastin*) have taken place, although there are plans for such a trial through the US National Eye Institute. Until the results of such a comparative trial are forthcoming, government and the community face a dilemma of whether to approve and subsidise the well studied but expensive drug ranibizumab or delay that decision and therefore condone the off-label use of a drug (*Avastin*) that has not been submitted to the rigours of a randomised clinical trial nor studies to the extent that we expect before a new drug is introduced (Guymet 2007: 276).

Despite the recognition that wet AMD is an extraordinary economic burden to the community and that it has an enormous impact on quality of life, many studies simply use economic and epidemiological data to argue for the relative benefits of funding research, and subsidising treatment and diagnosis of wet AMD. This may be due to ongoing controversy surrounding the commercialisation of this area of medicine. Studies that focus on using preventive techniques to reduce the social impact of AMD and research in low vision and rehabilitation of visual function in those people affected by AMD have an important role to play in addressing this disabling condition (Smith, et al. 2001).

This case study of Anti-VEGF treatment research gave an opportunity to apply David Hess’ interpretation of undone science. In Hess’ (2006) chapter “Antiangiogenesis Research and the Dynamics of Scientific Fields” he identifies certain factors as important to the study of undone science: denaturalization of the material world,
universalization of values, expansion of scale and differentiation of institutions. Hess’ work examines how certain societal aspects of conducting research can create a process of uneven development.

Denaturalization of the material world means that science and technology can tend to become more distanced from living entities over time. The idea of denaturalization leads to an understanding of the importance of identifying patentable substances, as opposed to substances and preventive techniques that may be effective but are deemed too natural to be patented and therefore more difficult to be converted into a successful drug treatment. In the case of Lucentis, which was produced specifically for the treatment of retinal blood vessels, the question of patent was uncomplicated and the ease of predicting an economic return meant that research could be funded.

On the other hand Avastin was already available as a treatment of bowel cancer when it began to be used to treat retinal blood vessel growth. This meant that any research that was conducted on Avastin as a wet AMD treatment would need to be performed without the expectation of the same economic returns as Lucentis. Also, because successful Avastin research would hurt the profitability of Lucentis, it is not surprising that the company conducting Lucentis research would not support the funding of Avastin research. By denaturalizing the material world and creating patentable substances we can see in this case how the priority can quickly become conducting research in the most economically productive areas of a scientific field and allowing the silence of undone science to marginalize the less profitable alternatives (Nickisch, et al. 2009).

Hess also describes the universalization of values, a tendency for fields of science to develop formal methodologies of dispute resolution such as the use of Randomised Controlled Trials (RCTs) in the area of clinical medicine. RCTs are recognized as the gold standard for evaluating treatment but also impose large costs and scale requirements on the required research. This makes the imperative to use the most economically viable substance more important when looking to make a profit on investment in drug treatment options. Phase I, II and III drug trials can cost many millions of dollars and are seen as important to ensure that new drug treatments are safe and effective.

These experiments are conducted in a way that attempts to minimise certain forms of bias. But the social factors at play in undone science are rarely taken into account when addressing the case for and against using particular drug treatments. Because comprehensive research has not been conducted on Avastin as a treatment for wet AMD, the clinician who wishes to justify using this drug may point out that the potential bias of the observer is not the only relevant bias when evaluating the literature. The societal factors at play also need to be addressed in the way they shape the research available to the clinician.

Expansion of scale is also identified by Hess as shaping the contours of research, where the cost and scale of laboratory sciences have expanded faster than the ability of public institutions to fund research. As the cost and scale out pace the public purse, many more organizations seek to bring new science to the public, some of which are only involved in order to realize a financial return on their investment. Thus the way these organizations go about their business can further shape the contours of scientific progress. This can be demonstrated in the case of the privately funded Lucentis and the public funding of Avastin wet AMD treatment research. The expansion of scale of science means that it is not always possible to conduct research in areas that are for the common good without a deliberate effort to coordinate public knowledge resources and work to limit the exploitative profiteering of engineered ignorance.

So in scientific fields there can be lots of organizations, both public and private, and large amounts of money at stake. Hess shows the importance of the differentiation of these institutions in shaping science. Hess points out that conflicts regarding roles and organizational goals increasingly arise within and between various fields of action of science. In the case study of Lucentis and Avastin this differentiation of institutions has been identified as a challenge and an opportunity for bringing about organizational and political change that can help institutions evolve to serve the changing needs of the community. For example, public institutions such as hospitals and professional organisations can bring about reform of a scientific field by cooperating in ways that address the lack of research in an area where there is little hope of a financial return but huge cost savings for the
community (O'Shea 2011). Avastin may not be as profitable a treatment of wet AMD as Lucentis but there are potential benefits for institutions to cooperate in order to fund and conduct the relevant research and work together to incorporate the findings of this research into the health system (O'Shea 2011).

Conclusion

Overall an awareness of societal and historical aspects of technoscientific practices has been shown in recent literature to be important in the progress of science and the modernization of society (Kleinman 2005). The incorporation into social studies of science of cases that demonstrate the extraordinary effect on the direction of scientific fields exerted by simply controlling the resources available to conduct research has been important to understanding science as a social practice (Proctor 2008). Hess’ study of undone science, when applied to the treatment of wet AMD, is a robust example of how societal factors can be the key consideration for people, both patients and practitioners, in their everyday encounter with clinical best practice.

An understanding of the implications of denaturalization of the material in the current era of patent for profit is important for those seeking reform. When trying to find ways to resolve disputes, also essential is finding ways to break down the problems of institutional differentiation, expansion of scale and universalization of values. Civil society should learn to be less tolerant of convenient blind spots in scientific knowledge that exist only to advantage those willing to compromise society’s best interest for short term profit. Thus an ongoing examination of the way that progress in biosciences can be interpreted in terms of social theory such as that of undone science is important for the global community.

References


Received: October 25, 2011
Approved: October 29, 2011
Conflicts of interests: none