The Dr Hadwen Trust for Humane Research: 39 years of *Replacement* Science

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Summary — The year 2009 will not be remembered mainly because it is the Chinese year of the ox, but probably, for many, because it is Charles Darwin's bicentenary, the 150th anniversary of the publication of his masterpiece, *The Origin of Species*, the 50th anniversary of the publication by Russell and Burch of *The Principles of Humane Experimental Technique*, where they introduced the concept of Three Rs, and also the 40th anniversary of the foundation of the Fund for the Replacement of Animals in Medical Experiments (FRAME). FRAME will always remain our senior, since the Dr Hadwen Trust for Humane Research is only celebrating its 39th anniversary this year! After four decades of learning, challenging, contesting, creating, promoting and advancing the Three Rs concept, the idea of the replacement of the use of animals in research has itself become a science, giving the old sterile debate between pro- and anti-vivisectionists a new dimension. Although scientific progress has been the main reason for such changes, it is important to remember that, without the people and organisations whose aim has been devoted to this cause, these changes might never have happened. Still, as illustrated by the 2008 statistics on animal procedures, many more changes will have to be made, and it is by considering the progress achieved during the last 40 years that we can find the strength and motivation to pursue our goal of scientific research and testing that no longer relies on animal-based techniques.

Key words: *animal experimentation, Dr Hadwen Trust, ethics, FRAME, replacement, Three Rs.*

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Dr Hadwen: Pioneer of Non-animal Science

Whilst we are celebrating the golden (50th) anniversary of the publication of *The Principles of Humane Experimental Technique* by Russell and Burch (1), and the ruby (40th) anniversary of FRAME, the Dr Hadwen Trust for Humane Research will have to content itself with coral for one more year before it is entitled to its own ruby celebrations! But while we are celebrating these anniversaries, what is the story of the last four decades, and what achievements have we witnessed in the replacement of animal use in scientific research?

The Dr Hadwen Trust for Humane Research was officially launched on 27 April 1970, as a foundation dedicated to the champion of the anti-vivisection cause, Dr Walter Hadwen. But who was Dr Hadwen JP, MD, LSA, MRCS, LRCP (2)?

Walter Robert Hadwen, the elder of two boys, was born in Woolwich on 3 August 1854. In 1872, at the age of eighteen, he moved to London, where he had obtained a post in charge of a pharmacy, but still found time for studying. He graduated at the Pharmaceutical College in London in 1876 and it was at that time that he became a vegetarian, following a bet with a fellow student that he could not live six months without meat. Not only did he win the bet, but he took the matter to heart. At the age of 22, he wrote to a friend: "*For my part I am quite satisfied with my trial of Vegetarianism, and it would take more than mortal power to persuade me once again to make my stomach a graveyard for the purpose of burying dead bodies in!*"

Pursuing his scientific path, he gained entry to the Medical School at Bristol University in 1888. He later took his degrees in Surgery at St Bartholomew's Hospital in London and in Midwifery at Queen Charlotte's Hospital. A man of many qualifications, he was also awarded numerous trophies, including that of First Prizeman in Physiology, Operative Surgery, Pathology and Forensic Medicine, and also that of Suple Prizeman and double Gold Medallist in Surgery and Medicine.

He obtained his MD at St. Andrew's University in 1893, before moving to Gloucester in 1896, where he came to be known as Dr Hadwen of Gloucester. An invitation to speak at a meeting of the British Union for the Abolition of Vivisection (BUAV) in 1898, from its founder, Frances Power Cobbe, who knew of his exhaustive research into the history of medicine in relation to experiments on animals, led him into the anti-vivisection movement. Their common view on animal testing led him to become the BUAV President following the death of Miss Cobbe in 1904. For 36 years, Dr

Hadwen had the reputation of being not only a skilled physician but also a general practitioner who was always aware of the human needs of his patients. In 1932, when still in active practice at the age of 78, he had a severe heart attack and died peacefully within a few hours.

With such advanced and considerate views, what better choice could there have been for naming the Dr Hadwen Trust? He challenged, a century ago, the preconceived idea that support for medical science and for anti-vivisection causes cannot go hand-in-hand. He truly was ahead of his time, but four decades later the general opinion had barely moved on.

Animal Testing: An Ethical Scientific Issue

The original idea of the Dr Hadwen Trust was first conceived in 1968. It was the brainchild of Sidney Hicks, then General Secretary of the BUAV, during an interview with a journalist, who had asked him how the BUAV intended to honour the memory of Dr Hadwen. Since the only memorial so far was the Dr Hadwen room, *"a rather shabby room at the back of the shop at 47 Whitehall"* (3), Sidney Hicks replied on an impulse, no doubt motivated by slight embarrassment, that the BUAV was considering building a laboratory where non-animal techniques could be developed, a place worthy of so great a man. Such an announcement made a good media piece for the journalist, who duly published the news. For the BUAV, as for most anti-vivisection organisations in 1968, the issue was often mainly an ethical one, so that the creation of a laboratory dedicated to the development of non-animal methods was a definite change in its stance. Ultimately, the project of a research laboratory was converted to the more affordable creation of a funding organisation that would support scientists in laboratories that were already equipped to carry out *replacement* research, and in 1970, the Dr Hadwen Trust for Humane Research was established.

The year 1970 saw the first Earth Day celebrated in the USA, and the publication of the first volume of *Studies in Animal and Human Behaviour* by Konrad Lorenz (who won a Nobel Prize in medicine without ever using invasive techniques and brought ethology to the attention of the general public), yet the number of animals used for experimentation in Britain was then at a peak of 5,580,876! However, together with other charities such as FRAME, which had been established a year earlier, the Dr Hadwen Trust was one of the earliest organisations to challenge the validity of animal testing in medical research, not only on ethical grounds, but also for scientific reasons.

In 1971, the Dr Hadwen Trust awarded its first grant towards the replacement of animal use in medical research, by giving a modest sum to Dr John Garvican for a study on cancer at King's College London. This first participation in *replacement* research marked the beginning of an ever-increasing contribution to the development of more-relevant and more-reliable research to benefit humans and laboratory animals. In 1972, always at the forefront of *replacement* techniques, the Dr Hadwen Trust funded the first Tissue Culture Symposium to be held in the UK, which brought together experts from all over the country. Only three years later, in 1975, the Dr Hadwen Trust launched the first ever cell culture study of eye irritancy as an alternative to tests in rabbits, although we have had to wait until 2009 for the international acceptance of non-animal methods to replace the Draize rabbit test for severe eye irritancy (4).

A New Hope

The road that led to the Dr Hadwen Trust becoming one of the leading medical research charities that funds and promotes *replacement*, was not an easy ride. In 1981, only a year after the approval by World Health Organisation of a cell culture alternative to polio vaccine tests in monkeys, major changes at the BUAV resulted in this organisation withdrawing its financial support to the Dr Hadwen Trust. Although such a decision could have led to the termination of a very promising venture, Dr Gill Langley, then Science Adviser at the BUAV, felt that the Dr Hadwen Trust should continue its vital work in promoting the development of alternative techniques, and saw the opportunity for the Dr Hadwen Trust to become independent. From her own home, and with a very restricted budget, she re-launched the Dr Hadwen Trust as an independent medical research charity.

This rebirth turned out to be very beneficial to the trust, which from then on could focus on its scientific aims as an ethical scientific charity, denuded of political constraints. The launch of *Alternative News*, the Dr Hadwen Trust's quarterly newsletter, quickly followed, and subscriptions to it allowed supporters of the Dr Hadwen Trust to contribute to the Charity's survival. By 1982, two further research projects had received grants from the Dr Hadwen Trust. One of these was an investigation by Dr Muir of Leicester Polytechnic of *in vitro* methods for studying eye irritancy as replacements for the Draize eye test. Dr Muir developed the opacitometer, which provided the essential groundwork and inspiration for the Bovine Corneal Opacity and Permeability (BCOP) test, one of the methods adopted by the OECD (Organisation for Economic Cooperation and Development) last September for the replace-

ment of the Draize eye test for certain purposes.

Over the following decade, the Dr Hadwen Trust continued its *replacement* quest through an increasing number of diverse projects, such as the formation and survival of oligodendrocytes in brain cell cultures (Sheffield University, 1985–1986), the regulation of insulin release (Aston University, 1985) and the evaluation of cultured renal proximal tubular cells (Surrey University, 1984–1987), all of them evidence of the changes taking place in medical disciplines. During the 1980s and 1990s, the successes of *replacement* techniques such as those used in these projects, increasingly became seen as valid alternatives to animal use in research. Nevertheless, these changes only became truly noticeable at the end of the 20th century, and it is the last decade that has offered an increasing number of clues reflecting changes in the antiquated debate between pro- and anti-vivisectionists.

A New Debate for an Old Issue

The origin of animal testing can be traced back to Greek antiquity, when Aristotle performed dissections that revealed internal differences among animals, and later to the Romans, with the physician, Galen, in 200 BC, who is recognised as the 'father of vivisection'. Progress in medicine and science was very slow during the Middle Ages, and although the Renaissance and Enlightenment witnessed definite developments, it was not until the 19th century that the use of animals in experimentation became more common and more accepted, mainly due to the development of experimental science as a whole.

With the increased use of animals in science came the debate between pro- and anti-vivisectionists. At that time, the debate was mainly on ethical grounds, questioning whether humans have the right to use an animal in the name of science to improve human welfare. The debate was heightened in 1859, when *The Origin of Species* was published by Charles Darwin, in which he proposed an evolutionary link between humankind and animals. This 'link' can, of course, be used by both camps: for pro-vivisectionists, the similarities between species makes a good case for animals as models of humans, whereas for anti-vivisectionists, humanising animals makes the use of animals even less acceptable! Even today, this remains a frequently evoked element of the debate. However, whereas in the past, the limitations of the available scientific methods were a reason for the lack of alternatives to animal testing, the scientific advances of recent decades have dramatically changed this situation. The old argument between "the reasonable scientists" and "the over-sensitive animal supporters" has been replaced by a more sophisticated debate, in which the scientific validity of animal models is questioned and their replacement proposed through the use of more-advanced and more-ethical methods. This new debate represents a major step forward, since it does not involve only emotional considerations, but includes the new components of the weaknesses and inadequacies of animal models, plus the implementation of existing *replacement* techniques and the possible development of new ones that can equal and, in many instances, surpass the animal models.

During the last few decades, the incredible progress of technology has allowed us to consider the future of science in a different way. A 2006 report by the USA Food and Drug Administration (5) calls for a new generation of product development tools to improve upon the present 20-year low in the number of new medical therapies. The same report states that 92% of compounds that pass animal tests subsequently fail in phase I clinical trials. Whereas such numbers would be set in stone, if the same methods were to remain in use, the development of new non-animal techniques, which are more advanced and more human-specific, can now provide the possibility of a better science whilst diminishing reliance on the use of animals.

The Science can Change the Policy, and the Policy will Change the Science

Fortunately, the science scene has not been the only area where changes have taken place over the recent decades, and in 1986, a major policy event concerning animal testing took place: the long-awaited *Animals (Scientific Procedures) Act* became law and replaced the 110-year-old *Cruelty to Animals Act 1876*. Although the *Animals (Scientific Procedures) Act 1986* is now 23 years old and should perhaps be updated, as is currently being attempted in Brussels with its EU counterpart, *Directive 86/609/EEC*, the long overdue replacement of the Victorian law denoted the begining of a major change in political attitudes in the UK, reflecting the increase in public concern.

Four decades later, with increasing public awareness and greater understanding of scientific matters, the need for more-ethical science is now widely shared by the public. In a recent survey by the European Commission, 93% of the European citizens questioned believed that more needs to be done to improve the level of welfare and protection of animals used in experiments, and 79% believed there is not enough public funding at the European level for the development and validation of alternative methods to replace animal experiments (6). The public also demands a greater participation in the issue of

animal testing, with 92% of the respondents wanting the EU to play a leadership role in promoting a greater awareness of animal welfare internationally, particularly with regard to animal experimentation. Clearly, the public's view and preferred choice for a more ethical science is motivated and justified, not only by advances in methodology, such as in analytical biochemistry, cell culture, molecular biology, bioinformatics and imaging, to name but a few, but also by the new multidisciplinary approaches that the intelligent combination of these different techniques can offer. The debate has now changed, because it can change.

Although scientific progress had major effects on changes in attitudes toward animal experimentation, it would be unfair to see organisations such as the Dr Hadwen Trust and FRAME as charities that have passively benefited from scientific progress. Indeed, one has to acknowledge the active role of these organisations in promoting and funding changes in scientific research. For example, as early as 1979, FRAME set up an expert Toxicity Committee, to review current toxicity testing procedures to assess the potential of alternative non-animal systems for testing the safety of chemicals. For the Dr Hadwen Trust, which has always concentrated more on the replacement of animal use in medical research, numerous examples can illustrate its active role in bringing *replacement* techniques to the fore, even when their novel and innovative aspects made it difficult for them to be accepted by the traditional authorities. A good example is a technique called Transcranial Magnetic Stimulation (TMS), a non- invasive method used in neurosciences to study brain activity. Over 10 years ago, the Dr Hadwen Trust was one of the first organisations to provide support for this advanced technology, which is now used internationally in neuroscience research and in psychiatry, and has wide-reaching applications in the replacement of studies involving the use of non-human primates.

These examples illustrate how, over the last four decades, the role of charities such as the Dr Hadwen Trust, FRAME, the Humane Research Trust and the Lord Dowding Trust for Humane Research, has changed. Whereas their original role was often limited to expressing the voices of their members and their discontent, the new role of such scientific organisations has become more complex. These charities still have, first and foremost, a duty to represent their members without whom they would not exist, but they now have the responsibility as experts to inform and enlighten both their members and the general public. Given its expertise in *replacement*, the Dr Hadwen Trust also sees its role as to raise awareness among the scientific community and encourage initiatives in implementing and developing new non-animal methods. Finally, this role is not confined to scientists, but includes advising politicians about the science that will lead to changes in laws and regulations. As a whole, the activities of these charities have provided a platform from where the debate between anti- and pro-vivisectionists can move on.

What's Next?

Whilst the Dr Hadwen Trust is continuing to fund advanced *replacement* research projects in areas as diverse as cystic fibrosis, Huntington's disease, brain cancer and brain infection, amongst others, the Three Rs concept is now increasingly accepted by scientific organisations and integrated as parts of their policies. A good example is the creation by the UK government of the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) in 2004, which reveals a will to bring together experts from a range of disciplines to explore the Three Rs potential of new technologies in research and to stimulate changes in practice. On the international scene, the 50th anniversary of the birth of the Three Rs concept was marked by leading experts from across the globe at the recent *7th World Congress on Alternatives and Animal Use in the Life Sciences* in Rome, who endorsed a Resolution calling for a fundamental paradigm shift in the science of toxicology that will result in entirely animal-free and human-relevant testing (7). The signatories included *replacement* experts, industry representatives, policy makers and research scientists from around the world, including the Dr Hadwen Trust and FRAME teams.

However, despite much progress made in alternatives to animals in research over the last 50 years, millions of animals are still used in experiments around the world each year (8). In the UK, the number of animal procedures is at a 22-year high, as 3.6 million animals were used in 2008 (9). In Europe, *Directive 86/609/EEC* is being revised, and major decisions are being taken as this article is being written (10). In the USA, the National Research Council published a report in 2007, entitled *Toxicity Testing in the Twenty-first Century: A Vision and a Strategy*, which provides a vision for the future of toxicity testing, with a shift away from testing chemicals by using traditional animal methods, toward non-animal solutions that rely on advanced methods more relevant to human biology. As shown by the statistics, a lot more remains to be done, but scientific progress, together with national and international Three Rs initiatives, encourages the Dr Hadwen Trust to believe that much more can be achieved, and that there will be a great deal more to celebrate on its own 40th anniversary in 2010.

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