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Personal Reflections on Russell and Burch, FRAME, and The HSUS

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Summary — The coincidence of anniversaries associated with the publication of William Russell and Rex Burch's *The Principles of Humane Experimental Technique*, the founding of the Fund for the Replacement of Animals in Medical Experiments (FRAME), and the establishment of the collaboration between FRAME and the University of Nottingham, provides an opportunity to reflect on Russell and Burch's legacy and how it was carried forward by FRAME. *The Principles*, published in 1959, was the pioneering work in what later became the alternatives or Three Rs field of replacement, reduction, and refinement of animal use. Such was the book's initial and undeserved obscurity, however, that FRAME, following its founding in 1969, pioneered a similar approach independently of Russell and Burch's work. The Humane Society of the United States (HSUS) was also an early champion of the alternatives framework, and through the establishment of the Russell and Burch Award, helped unite Russell and Burch with what had emerged as the alternatives community. Thanks largely to FRAME, Russell and Burch were able to participate in Three Rs activity before their deaths. They lived long enough to see their ideas take hold, but not long enough to see the emerging revolution currently under way in toxicity testing, toward the use of non-animal methods.

Key words: *alternatives, Burch, FRAME, HSUS, principles, Russell, Three Rs, UFAW.*

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The year 2009 holds special significance in the history of the "Three Rs", or "alternatives", community, which is dedicated to replacing, reducing, and refining the use of animals in biomedical research. It marks the 50th anniversary of the publication of William Russell and Rex Burch's *The Principles of Humane Experimental Technique* (hereinafter called *The Principles*), which proposed the Three Rs framework as a means of advancing animal welfare and scientific progress (1). This year also marks the 40th anniversary of the founding of the Fund for the Replacement of Animals in Medical Experiments (FRAME), the British charity that has done much to promote the Three Rs, especially replacement. And finally, it is also the 30th anniversary of the beginning of FRAME's collaboration with the University of Nottingham.

These anniversaries provide an opportunity to reflect on the histories of Russell and Burch and FRAME. I will also take the opportunity to draw connections among Russell and Burch, FRAME, and the organisation where I have worked for the past 24 years, The Humane Society of the United States (HSUS).

The broad outlines of Russell and Burch's contributions to science and animal welfare are well-known (2). In 1954, at the behest of the Universities Federation for Animal Welfare (UFAW), these young British scientists undertook a multi-year study of humane experimental tech-

nique. *The Principles*, published in 1959, was the product of that effort. The authors then each moved on to other endeavours in their careers, leaving it to others to take up the challenge of replacing, reducing, and refining animal use. Decades later, in 1990, they learned that their report had spawned the Three Rs or alternatives field. Both of them eventually became active participants in this field again, at least intermittently, until their deaths in 1996 (Burch) and 2006 (Russell). Indeed, Russell gave *tour-de-force* presentations at various conferences, notably at the *3rd World Congress on Alternatives and Animal Use in the Life Sciences*, held in Bologna, Italy, in 1999, before several hundred conferees (3).

Few scientists have the vision to lay the foundation for a new field of inquiry. What is particularly remarkable in Russell and Burch's case is that they did so in only a few years (1954–1958), and, moreover, they were not on the scene to champion their cause during the formative decades of the Three Rs movement, namely, the 1970s and 1980s.

Little notice was taken of *The Principles* following its publication in 1959, despite the cogency of both its analysis of the historical progress of humane technique and its proposed framework for moving forward (4). Enter FRAME in 1969. With this new organisation blazing the trail, the alternatives approach started to reach a certain critical mass during the 1970s. Without FRAME, the rise

of the alternatives approach might have been delayed for another decade.

What is truly amazing is that FRAME carried out its early work whilst apparently unaware of Russell and Burch and *The Principles* (2). FRAME's founder, Dorothy Hegarty, her advisors, and subsequent officials of the organisation, independently devised a similar approach, especially with respect to *replacement*.

The initial ascendancy of Three Rs approach during 1970s and 1980s coincided roughly with the rise of the modern animal rights movement and the concomitant intensification in the controversy over the use of animals in testing and research. The Three Rs framework was thus available to be deployed — however inadequately, at first — as a practical approach to addressing the vivisection issue.

Thanks largely to FRAME, the Three Rs approach eventually went from obscurity to acceptance. But during this transition, it was greeted with scepticism in some quarters, especially by defenders of animal experimentation, who felt it implied that something was wrong with vivisection, that the Three Rs approach oversold its potential to effect change, or that it was somehow being foisted on the scientific community by the newly emboldened animal rightists (5). In this regard, it is important to note that the Three Rs approach is firmly rooted in the scientific tradition. Both Russell and Burch were practising scientists. Their 1950s project for UFAW was carried out in consultation with a UFAW committee chaired by one of the most prominent British scientists of the 20th century, Peter Medawar (6), who went on to win the Nobel Prize for Physiology and Medicine.

FRAME, too, followed in the Russell and Burch tradition of science in the service of humaneness (or “humanity”, as they called it). Up to the present day, many FRAME staff are scientists, not animal welfare campaigners *per se*, and the organisation supports an active alternatives laboratory.

Russell and Burch's work broke new ground in applying scientific principles to animal welfare, in that it went beyond the traditional scope of concerns about the welfare of research animals, namely, their care, housing, husbandry, and handling. They addressed the more highly charged area of experimental technique (6), broadening the application of what would now be called refinement. But perhaps more importantly, they were willing to consider biological and statistical means of reducing animal numbers or even replacing an animal-based experiment altogether.

This approach was unusual for its time. Consider that, when the *Animal Welfare Act* was enacted in the USA in 1966, regulating animal experimentation, it included an explicit provision that “Nothing in this Act shall be construed as authorising the Secretary [of Agriculture] to prom-

ulgate rules, regulations, or orders for the handling, care, treatment, or inspection of animals *during actual research or experimentation* by a research facility as determined by such research facility” (7; emphasis added). This exclusion was precisely the scope of Russell and Burch's analysis.

HSUS Connections

Before 1990, Russell and Burch were historical figures in the blossoming Three Rs community. Their names were invoked, principally in reference to their 1959 book, which by 1990 had long been out of print. As far as I am aware, the alternatives literature did not include a single photograph of them; neither man attended — or apparently was even aware of — Three Rs conferences. All this was about to change.

In 1990, The HSUS decided to establish an award to honour scientists who advanced the Three Rs. We wanted to name it after Russell and Burch, but first needed permission to use their names. At the time, my contacts did not know if they were still alive. Eventually, I approached UFAW, who contacted them on my behalf. Bill and Rex graciously agreed to have their names associated with the award, so long as it recognised all the Three Rs, not just *reduction* and *replacement*, as we had originally proposed (8).

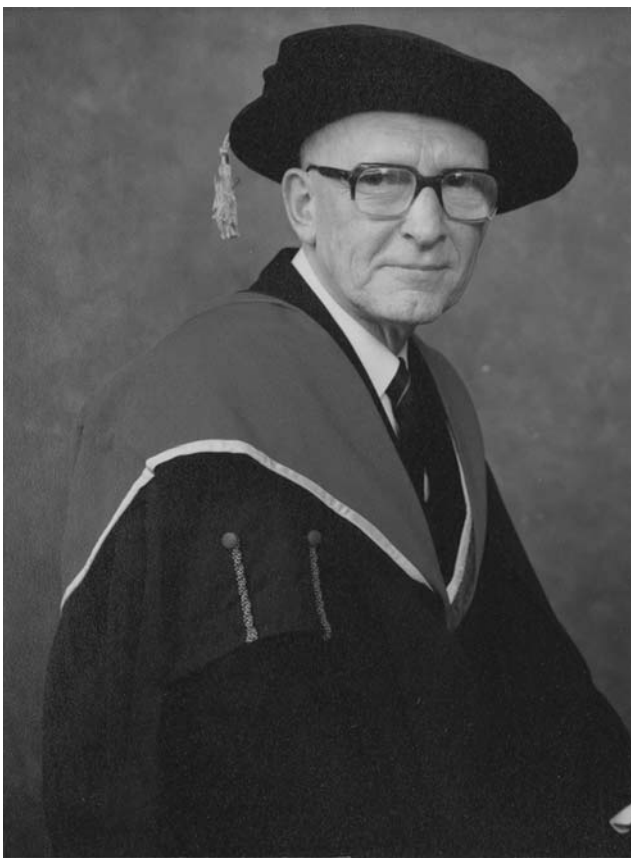
In 1991, following our initial correspondence, Rex sent me a framed photograph of himself with an inscription to The HSUS, “wishing you every success in your endeavours.” I include the photo here, as there are very few photos of Rex in the alternatives literature (Figure 1).

In 1992, citing the inauguration of The HSUS's Russell and Burch Award, UFAW reissued *The Principles* as a “long overdue tribute to Bill Russell and Rex Burch”, as well as a memorial to Charles Hume, the founder of UFAW, who had hired Bill and Rex to carry out the study of humane experimental technique (6).

In 1993, I visited Rex and Bill in England, with the assistance of UFAW. I met Bill and his wife, Claire, at their house in Reading, and we drove to Sheringham to spend the day with Rex. Bill and Rex had not seen each other since their work together in the 1950s, and they greeted each other warmly. We gathered in the Town Hall, where Bill and Rex, and UFAW's Roger Ewbank, presented me with a copy of the new edition of *The Principles*, signed by the authors. Rex showed us his microbiological testing laboratory, located in the same building (8).

I saw Bill and Rex again at the same Town Hall in 1995, at the opening ceremony of a Three Rs workshop in Sheringham (9). Sadly, this proved to be the one and only time that Bill and Rex participated in a Three Rs conference together, as well as

Figure 1: Rex Leonard Burch in a photograph he sent to the author in 1991



being the last time that I saw Rex. He died less than a year later.

In the early days of the Russell and Burch Award, Bill and Rex autographed copies of the special edition of *The Principles*, which UFAW embossed with the name of the winner and forwarded to me for the award ceremony. Bill helped bestow these awards at the first, second, and third *World Congress on Alternatives and Animal Use in the Life Sciences* (in 1993, 1996, and 1999). Rex was not up to the rigours of international travel in his later years, but he recorded an audio message that was played at the award ceremony at the first World Congress.

Bill and Rex's pioneering work had a profound effect on my career and activities. When I joined the staff of The HSUS in 1985, my first assignments included preparing a lengthy layperson's guide to the Three Rs (10), followed by an analysis of the contributions of replacement methods to Nobel Prize-winning research (11). These and later projects reflected The HSUS's long-standing commitment to, and promotion of, alternative methods.

In fact, historian Bernard Unti uncovered evidence, from personal correspondence and testimonials from contemporaries, that Fred Myers, HSUS President from 1954 through 1963, was

familiar with and supportive of the Three Rs approach (Bernard Unti, personal communication to the author, 29 May 2009). Thus, *The Principles* did not fall into complete obscurity during the decade following its publication in 1959; a few animal protection organisations, in particular, took notice.

Though FRAME may have operated in its early years without knowledge of Russell and Burch and *The Principles*, it has done more in recent decades to honour the legacy of these men than any other organisation. In 1995, Michael Balls, then Head of the European Centre for the Validation of Alternative Methods (ECVAM), took the lead in organising the Three Rs workshop mentioned above, which featured Bill and Rex. It was held in Sheringham, so that Rex could participate (2). FRAME also named its new headquarters Russell and Burch House (in 1995), arranged for the University of Nottingham (home of the FRAME Alternatives Laboratory) to be the repository of Bill's papers (in 2009), and, most recently, published an abridged version of *The Principles* (in 2009; 12).

The early years of the Three Rs era can be depicted as a straight line, beginning with Russell and Burch and the publication of *The Principles* (1959), and going directly to the founding of FRAME (1969). In later decades, that history looks more like a branching tree than a line, but I'd like to think that The HSUS is an important part of the story. And that story reveals the many connections between The HSUS and Russell and Burch, UFAW, and FRAME. In addition to the examples mentioned above, The HSUS hired FRAME's Scientific Director, Andrew Rowan, in 1978; The HSUS bestowed the Russell and Burch Award on FRAME's Chairman, Michael Balls, in 1994; and The HSUS and FRAME are working together to promote alternatives to the LD50 testing of *Botulinum* neurotoxin (13).

The Present and Beyond

It was fortunate that Russell and Burch lived long enough to see the Three Rs approach translated into national and international law and policies, numerous alternatives centres, awards, conferences, publications, and more (4). Alternative approaches have radically changed the nature of biomedical education and training (14). Uptake in biomedical research has been more limited, but has still been appreciable, especially in the area of *refinement* (15). But the most dramatic advances in the Three Rs have come in the area of toxicity testing.

The replacement, reduction, and refinement of animal use in toxicity testing has benefited substantially from the good work over the years of

FRAME and related organisations, such as ECVAM, ZEBET (the German alternatives center), the Center for Alternatives to Animal Testing (CAAT), the Institute for In Vitro Sciences (IIVS), and many others. But we are now poised for a more profound change.

In 2007, the US National Academy of Sciences (NAS) proposed a vision and strategy for a complete paradigm shift in toxicity testing (16). Its report, *Toxicity Testing in the 21st Century*, calls for a transformation away from assessing pathological signs in exposed animals and toward an assessment of perturbations in biological pathways modelled in cells and tissues, principally of human origin. If successful, the new approach would supplant the current *ad hoc* efforts at one-to-one replacement. New methods would not necessarily be mapped onto the old animal-based methods, an approach that has meant that the new methods were assessed on the basis of how well they predicted the dubious results of high-dose animal studies. The outcome of the new paradigm would not be so much a series of replacements as a wholly new approach. The US Government moved quickly to embrace key elements of the new approach (17, 18).

In as little as one generation, say by the 75th anniversary of *The Principles*, with the proper investment in research and development, the Three Rs approach may well have reached its ultimate goal in toxicity testing — *full replacement*.

The NAS Committee that devised this vision for toxicity testing in the 21st century, had been asked to consider a number of issues, including the scale of animal use and suffering in the current paradigm. However, the Committee's overriding charge was to come up with the best vision from a scientific and public health standpoint. The goal was not to replace animal use, but rather to fix a toxicity testing system on the brink of collapse (19). However, the approach settled upon turned out to be a milestone in the evolution of the Three Rs, once again demonstrating Russell and Burch's theme that good welfare goes hand-in-hand with the best science.

One of the proudest activities in my career was to serve on the Committee that prepared the NAS report. Although its realisation will take many years to be completed, it is a shame that Russell and Burch did not live to see its initial stages.

A similar quest for full replacement of animal use in biomedical education within a generation, also seems achievable, whereas that time frame seems more quixotic and far-off in the field of biomedical research, where the bulk of animals are used. Yet this is the challenge that Medawar put before us several years after his involvement with Russell and Burch's project. He speculated that scientific progress, including knowledge gained through animal experimentation, might one day

enable science to dispense with animal use altogether (20) — the ultimate goal of *replacement*.

If (when?) this idealistic vision is realised, there will no longer be a need for the Three Rs, FRAME, the Russell and Burch award, etc. Three Rs scientists could then focus exclusively on good science. Campaigners could work on other animal protection issues. I'd like to think that Bill Russell, Rex Burch, Peter Medawar, Dorothy Hegarty, and many others would be smiling.

Acknowledgements

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