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Professor W.M.S. Russell (1925–2006): Doyen of the Three Rs

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Abstract
The rich and varied life of W.M.S. Russell — academic, author, classicist, composer, correspondent, musician, philosopher, raconteur, scientist and soldier — is reviewed. Particular emphasis is placed on his work with Rex Burch, which led to the publication of *The Principles of Humane Experimental Technique* in 1959. Comments are made on some of the key messages conveyed, not only in *The Principles*, but also in some of his more-recent works, notably his memorable contributions to the first four World Congresses, and in his last major review, *The Three Rs: Past, Present and Future*, published in November 2005. The impact of *The Principles* over the last 50 years is reviewed, along with an evaluation of how the opportunities provided by the Three Rs are, or are not, being seized today. Finally, news is given of a plan to establish a *W.M.S. and Claire Russell Archive* at the University of Nottingham.

Keywords: animal experimentation, alternatives, 3Rs

Introduction

William Moy Stratten Russell preferred to be known, officially, as W.M.S. Russell, and more informally, as Bill. The only child of Sir Frederick Straten Russell, Director of the Plymouth Marine Laboratory, he was born in Plymouth, England on 26 March 1925. He was educated at Marlborough College, and was awarded a Scholarship in Classics at New College, Oxford, in 1942.

After service as a rifleman in the King's Royal Rifle Corps from 1943 to 1945, he took up his scholarship at Oxford, but changed his subject from Classics to Zoology. He graduated with First Class Honours in 1948, then undertook postgraduate research on animal behaviour, leading to the award of a DPhil in 1952 (Figure 1).

He was an Agricultural Research Council Fellow at Oxford University from 1951 to 1954, whereupon he worked on humane experimental technique for the Universities Federation for Animal Welfare (UFAW) until 1959, the outcome of which will be the main focus of this tribute.

He was in private practice as a psychotherapist between 1959 and 1964, when he became Scientific Information Office at the Commonwealth Bureau of Pastures and Field Crops, London, as a result of which he learned Japanese. Then he became a founder member of the new Department of Sociology at the University of Reading, where he progressed from Lecturer (1966) to Reader (1976), Professor (1986) and Emeritus Professor (1990).

Perhaps due to his non-traditional career path, Bill's scientific contributions were not recognised by the Royal Society, and his many other achievements did not lead to his inclusion in any national honours list. Nevertheless, when he died in Reading on 27 July 2006, at the age of 81, he left behind a host of friends and admirers, throughout the world.

W.M.S. Russell as a polymath

Polymath, from the Greek, polymathēs, "having learned much", is a term used to describe a person who is very well educated, or who excels in a wide variety of subjects or fields — one who has a broad, encyclopaedic knowledge.

Polymaths are seekers of enlightenment, driven by curiosity and interest, who integrate feelings and sensibilities with thought. Comparable terms are *Renaissance man* and *Homo universalis*, which, like polymath, are reserved for very special people.

Well-known polymaths include: Hildegard of Bingen (1098–1179), Leonardo da Vinci (1452–1519), Galileo Galilei (1564–1642), Isaac Newton (1643–1727), Benjamin Franklin (1706–1790) and Thomas Jefferson (1743–1826).

W.M.S. Russell richly deserves to be listed along with these greats and other unique individuals. He was an author, classicist, composer, entertainer, linguist, philosopher, pianist, psychologist, psychotherapist, raconteur, singer, sociologist, and soldier (Paskal, 2006).

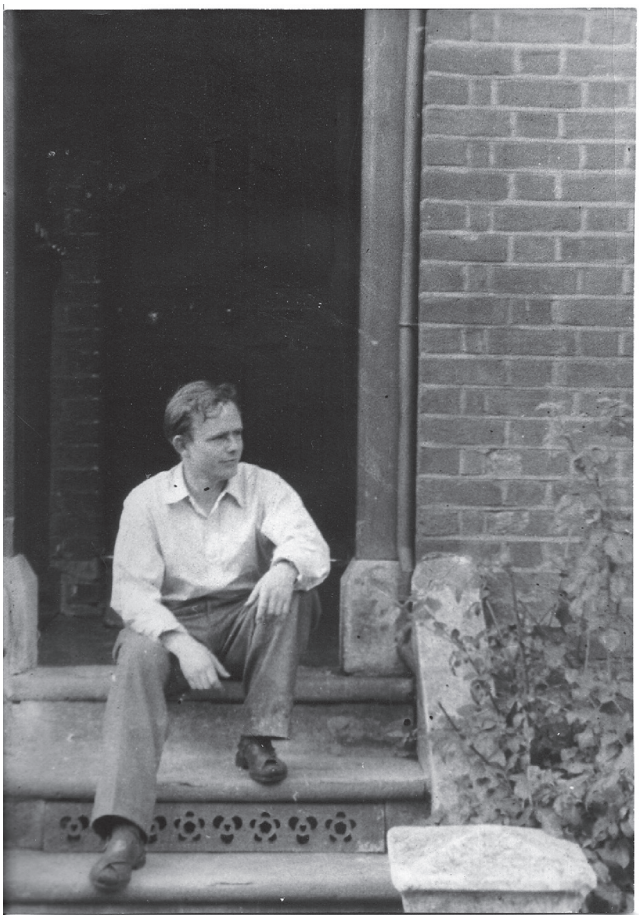

Fig. 1: Bill Russell as a young man.

His research and publications covered animal behaviour, comparative sociology, demography, ecology, ethology, evolution, folklore, genetics, geography, history, human behaviour, mythology, primate sociology, science fiction, statistics, population control, and zoology (Figure 2).

Bill Russell and the Three Rs

The title of this tribute names Bill Russell as the *doyen* of the Three Rs (Figure 3). *Doyen* is one of many French words which cannot satisfactorily be translated into English, other examples being *ennui*, *fait accompli* and *joie de vivre*. It describes a man who is the eldest or most senior of a group. It is derived from the Old French, *deien*, which was, in turn, related to the Latin, *decanus*, or the Greek, *dekanos*, chief of ten, which is also the root of *dean*, a senior administrator of a college or similar organisation.

Bill Russell and his partner, Rex Burch, developed the Three Rs concept, which embraces *reduction* as a means of lowering "the number of animals used to obtain information of a given amount and precision", *refinement* as any development leading to a "decrease in the incidence or severity of… procedures applied to those animals which have to be used", and *replacement* as "any scientific method employing non-sentient material which… may replace methods

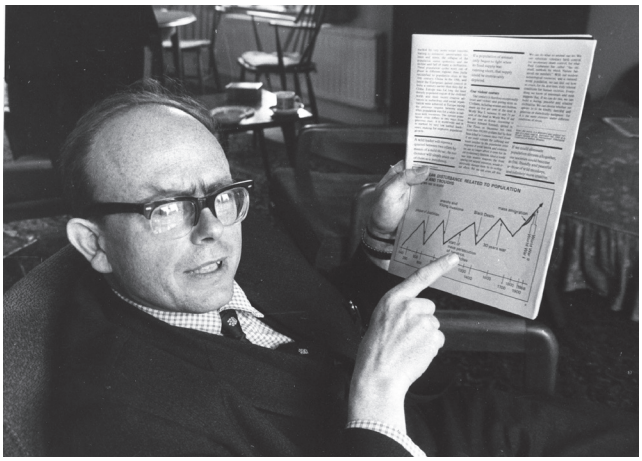

Fig. 2: Bill Russell, the scientific data analyst.

which use conscious living vertebrates" (Russell and Burch, 1959).

Nearly 20 years after the publication of *The Principles of Humane Experimental Technique*, David Smyth gave us a Three Rs definition of *alternatives* to animal experimentation, to include "all procedures which can completely replace the need for animal experiments, reduce the number of animals required, or diminish the amount of pain or distress suffered by animals in meeting the essential needs of man and other animals" (Smyth, 1978).

Nevertheless, it was not until the mid-1980s that new national and international laws were passed, which were built on the Three Rs concept, and not until 1993, with the first *World Congress on Alternatives and Animal Use in the Life Sciences* that a worldwide movement based on the Three Rs, really began (Balls, 1997).

The ECVAM/CAAT workshop on *The Three Rs: The Way Forward*, held in Sheringham, England, in May–June 1995 was a truly remarkable occasion for all who were privileged to be there (Balls et al., 1995). This was the only scientific meeting Bill and Rex attended together after the publication of *The Principles* (Figures 4, 5). Sadly, Rex died in March 1996, and, since there is a danger that the part he played in defining the Three Rs concept, might not receive the credit it undoubtedly deserves, I am very pleased that he recorded his own view of the progress of human experimental technique since 1959, in an article published in *ATLA* (Burch, 1995).

Bill attended the first three Congresses, at which he gave characteristic and memorable performances, which included singing and dancing (Figure 6). All concerned were particularly delighted that he was with us at the *3rd World Congress* in Bologna, Italy, when *The Three Rs Declaration of Bologna* was made, with acclamation, on 31 August 1999, in the Aula Magna of the University of Bologna, Europe's oldest university (Anon., 2000). The Declaration includes the following statement:

Fig. 3: W.M.S. Russell, Doyen of the Three Rs, at the NC3Rs, London, in January 2006.

Humane science is a prerequisite for good science, and is best achieved in relation to laboratory animal procedures by the vigorous promotion and application of the Three Rs. The Three Rs should serve as a unifying concept, a challenge, and an opportunity for reaping benefits of every kind — scientific, economic and humanitarian.

The question of inhumanity

The Principles of Humane Experimental Technique is not an easy book to read, especially for those whose first language is not English. For example, in discussing their "concept of inhumanity", Russell and Burch were careful not to "imply ethical criticism or even psychological description of persons practising any given procedure". Rather, they saw the examination of "the concept of humanity (or inhumanity) as an objective assessment of the effects of any procedure on the animal subject".

What emerges from a profound and complicated discussion is a very useful distinction between two main types of inhumanity:

1. *Direct inhumanity:* the infliction of distress as an unavoidable consequence of the procedure applied. Russell and Burch discussed it in terms of *incidence* (e.g. in control and experimental groups), *severity* (e.g. the severity of a procedure in those animals that are affected), and *special character* (e.g. post-operative pain and distress, effects of particular pathogens, or death due to various types of toxic chemical).

Fig. 4: Rex Burch and Bill Russell during the Sheringham workshop (1995).

2. *Contingent inhumanity:* the infliction of distress as an incidental and inadvertent by-product of the use of a procedure. Russell and Burch saw the avoidance of contingent inhumanity as mainly a matter of good husbandry, diligent care and common sense.

The problem and the solution

The central problem inherent in laboratory animal use is determining what is and is not humane, and what can be done about it, bearing in mind the need to promote humanity without prejudice to justifiable scientific and medical aims. Russell and Burch's solution was to encourage the diminution or removal of inhumanity through the application of the Three Rs.

The defined *reduction* as "reduction in the numbers of animals used to obtain information of given amount and precision", *replacement* as "any scientific method employing non-sentient material, which may in the history of experimentation replace methods which use conscious living vertebrates", and *refinement* as decreasing "the incidence or severity of inhumane procedures applied to those animals which still have to be used", when *replacement* is not (yet) possible, and every device of theory and practice to *reduce* the number of animals to a minimum has been employed.

The progress

Russell and Burch concluded their book with the following words: "In this book we have sought to limn [i.e. *sketch*] the barest of outlines; it will remain for many others to fill in the interior. We hope the book may stimulate some experimentalists

Fig. 5: Rex Burch, Claire Russell and Bill Russell, with the participants in the Sheringham workshop.

Fig. 6: A song and dance in the Aula Magna of the University of Bologna (1999).

to devote special attention to the subject, and many others to work in full awareness of its existence and possibilities. Above all, we hope it will present to those beginning work a unified image of some of the most important aspects of their studies. If it does any of these things, this book will amply have served its purpose."

Given that the first announcement of the Three Rs concept had been made in 1957 (Russell, 1957), what progress has been made in the intervening 50 years?

Reduction

Despite the valiant efforts of a few scientists with a sufficient understanding of both biology and statistics, the undoubted scientific and ethical benefits of reduction still remain to be achieved, and many research scientists are still unaware that "better design and analysis would improve the scientific validity of their work and reduce the numbers of animals needed to obtain a given level of scientific information" (Festing, 2004). Indeed, there continues to be great concern about the misuse of statistics in papers published in medical journals, which goes back more than 70 years (Altman, 2004), as was evident at a FRAME Reduction Committee Symposium, held in 2002 (Balls et al., 2004).

Refinement

Russell and Burch said in *The Principles* that "… the freedom of choice of the experimenter is often much wider than it at first appears. The full use of this freedom is the mark… of humane and successful experimentation.… there is perhaps no limit in animal experimentation to the progress of *refinement*." The experimenter's choice involves species, procedure,

and the careful and appropriate use of anaesthesia, analgesia and euthanasia.

In fact, while it is often claimed that *refinement* is the poor relation among the Three Rs, it is arguably the one where most progress has been made. This is largely due to positive developments in the roles played by animal laboratory technicians and laboratory animal veterinarians, together with a recognition of the truth promoted by Russell and Burch, that the best cared for and best treated animals provide the best results.

Replacement

Replacement is the most difficult of the Three Rs to achieve, not least because of our lack of fundamental understanding of the physiological processes, pharmacotoxicological processes and diseases about which we would like to obtain information of greater reliability and relevance than that provided by animal procedures.

Russell and Burch distinguished between *absolute replacement*, where sentient vertebrates are not required at any stage, and *relative replacement*, which includes non-recovery experiments on intact, living, but completely anaesthetised animals, and the painless killing of animals to provide cells and tissues.

Nowadays, attention tends to be focused on *replacement alternative methods*, which include the use of lower organisms, the early embryonic stages of vertebrates, isolated *in vitro* sub-cellular, cell and tissue preparations, and cell, tissue and organ cultures, computer based (*in silico*) models, and even the ethical use of human volunteers.

It is also useful to distinguish between *direct replacement*, in which a method provides more or less the same information as would have been provided by an animal experiment, and *indirect replacement*, in which the information provided is different in kind, but can be employed for a purpose similar to that for which animal data would have been used.

Fidelity and discrimination

By their very nature, models must differ from what is being modelled, and the importance and consequences of this difference depend on two major factors, *fidelity* and *discrimination*. As Russell and Burch put it: "Fidelity means overall proportionate difference, and high fidelity means that *all properties are equally badly reproduced*. Discrimination, on the other hand, means the extent to which the model reproduces *one particular property of the original*."

It has long been common practice in biomedical research and testing to rely on laboratory animals as high fidelity models of humans, partly because of a lack of the knowledge necessary to identify the features which would be required in high discrimination models.

However, there is another reason — a failure to take sufficient account of what Russell and Burch called the *high fidelity fallacy*. Paraphrased, their description of the fallacy runs like this. Man is a placental mammal, so members of other mammalian species are more likely to be useful as models of man than would be birds or, still more markedly, microbes. The general physiological properties and pharmacological responses of other mammals are more likely to be similar to our own than are those of other organisms. Therefore, mammals are always the best models to use in fundamental biomedical research, drug development and toxicity testing.

The relative importance of replacement

Russell and Burch said that, "in general, refinement is never enough, and we should always seek further reduction, and if possible replacement. Still more generally, replacement is always a satisfactory answer, but reduction and refinement should, wherever possible, be used in combination. This principle should be borne in mind… [throughout the succeeding chapters of *The Principles*]".

However, when I recently emphasises this point (Balls, 2006), Bill Russell responded in the following words (Russell, 2006): "But to say that refinement is insufficient is certainly not to say that it is unnecessary, especially while laboratory animals are waiting for particular replacements to be developed, validated and accepted by the scientific community and the regulators. Therefore, refinement remains of the utmost importance for animal welfare and medical science."

A comment on toxicity testing

Russell and Burch said that: "It is a prerequisite for the progress of humane technique that the law in this area should be kept fully rational and fully up to date. Experimental biologists should be constantly reassessing policy in advance, in order to make the necessary recommendations without undue loss of time. All this is especially important in toxicity testing, and such phenomena as the high fidelity fallacy may be more prevalent and influential at the legal than the laboratory level."

These truths appear to continue to escape many of those involved in toxicology and toxicity testing, as the following two examples will illustrate.

Firstly, in an ECVAM workshop report on *in vitro* tests for detecting chemicals affecting the embryo implantation process, Bremer et al. (2007) said, "It appears that humans and animal (rodent or non-rodent) models have some differences in the process of implantation, in addition to the well-known variabilities with regard to the uptake and metabolism of drugs and chemicals. These data suggest that there is a high uncertainty with regard to the correctness

of a risk assessment based on reliance only on animal studies. Therefore, new *in vitro* models based on human tissues (cell and tissue culture, uterus perfusion, etc.) can provide mechanistic information to address the problem of inter-species variation, and such information can facilitate reliable predictions which are relevant for human hazard identification."

Secondly, in an *ATLA* editorial on the need for EU REACH testing requirements *not* to be driven by reproductive toxicity testing in animals, Spielmann and Vogel (2006) said: "The advocates of the continuation of animal testing have a simplistic view of the current situation. They claim, for example, that *in vitro* embryotoxicity testing is useless, even if the tests have successfully been validated as capable of distinguishing between chemicals which are/are not likely to be embryotoxic, since the results will always trigger further testing *in vivo*, for the following reasons: if the results are positive, they have to be confirmed by an *in vivo* animal study, and if the results are negative, they must be confirmed *in vivo*, in order to confirm the safety of the chemical."

The Russell legacy and archive

Claire Russell, a distinguished psychotherapist, author and poet, died in January 1999, and, as reported above, Bill Russell died in July 2006.

They left their possessions, and the rights to all their publications, to Cleo Paskal, with whom they had protracted discussions about how they should be handled. Their house in Reading contained about 25,000 books and at least 1000 box files, as well as a wide variety of Bill's personal mementos, dating back as far as the 1930s. The files included details of Claire's psychotherapy sessions with her patients, which must be kept secure for decades to come. However, most of the files contained detailed chronicles and correspondence concerning Bill's enormous breadth of activities. They represent a remarkable record of the life of a remarkable polymath over more than 60 years.

Cleo Paskal has decided to donate Claire and Bill Russell's papers to the University of Nottingham as the basis for a *W.M.S. and Claire Russell Archive*, which is to be established with the cooperation of Dorothy Johnston, the University's Keeper of Manuscripts and Special Collections. At the time of writing, the first selection of files and papers are about to be moved from Reading to Nottingham.

When the archive is established, scholars will be able to research the answers to many intriguing questions, including the following:

How did Bill Russell and Rex Burch work together, and what was the role of Rex Burch in the production of *The Principles*?

What events immediately followed the publication of *The Principles* in 1959?

What did Russell do about humane experimental technique between the early 1960s and the early 1990s?

What contacts were there between Russell and Burch during this period?

Why did a series of governments, Home Office officials and the scientific establishment (*and animal welfare organisations*) do so little to implement the Three Rs in the UK during the 1960s and 1970s?

Some early gleanings

The archive will contain the original outline of *The Principles*, as presented to UFAW, the original typescript, and the proofs of the book, with many comments by Bill Russell.

In 1960, The Humane Society of the United States offered him $10,000, plus $5,000 expenses, to work for a year on proposals reducing pain in higher orders of animals — he refused the offer, because of "too many commitments".

In 1968, Methuen, the publishers of *The Principles*, proposed that the remaining copies should be pulped, as they were not selling. Eventually, Christine Stevens, of the Animal Welfare Institute in Washington DC, bought them all.

Russell, who held the copyright for *The Principles*, allowed UFAW to print a special edition of book in 1992, but he retained the copyright of the original text.

In 1995, Russell and Burch proposed the setting up of a National Animal Welfare Information Centre. This later became a suggestion for a European Animal Welfare Information Centre, but Burch died before the idea could be developed into a real plan.

The archive will contain fascinating records of interactions with all kinds of organisations and individuals over many decades. The correspondence between Russell and Burch, and also with others who took up the Three Rs cause, will be of particular interest.

The humanity criterion

During the last few years of his life, Bill Russell returned to active involvement in the promotion of the Three Rs concept, by writing invited publications, by attending conferences and congresses, and by engaging in correspondence with many of those involved in seeking the reduction, refinement and replacement of animal experimentation.

Some of those with whom he interacted recorded their appreciation in a series of short tributes in ATLA (Balls et al., 2006).

Bill's own last major publication was a personal review of the past, present and future of the Three Rs, which, in its way, is as remarkable as *The Principles* itself (Russell, 2005).

In concluding, I want to take this opportunity to

re-emphasise the central message of *The Principles*, a legacy left to us by Bill Russell and Rex Burch, which will endure for the rest of time:

If we are to use a criterion for choosing experiments to perform, the criterion of humanity is the best we could possible invent. The greatest scientific experiments have always been the most humane and the most aesthetically attractive, conveying that sense of beauty and elegance which is the essence of science at its most successful.

References

Altman, D. G. (2004) Improving design and analysis of research: lessons from clinical research, ATLA 32, suppl. 2, 31-39.

Anon. (2000) The Three Rs Declaration of Bologna, in Progress in the Reduction, Refinement and Replacement of Animal Experimentation, ed. by M. Balls, A-M. van Zeller, and M. E. Halder, pp.15-22, Elsevier, Amsterdam.

Balls, M. (1997) The Three Rs concept of alternatives to animal experimentation, in Animal Alternatives, Welfare and Ethics, ed. L. F. M. van Zutphen and M. Balls, pp.27-41. Elsevier, Amsterdam.

Balls, M. (2006) Animal experimentation: should the Three Rs be abandoned? ATLA 34, 139-141.

Balls, M., Festing, M. F. W., and Vaughan, S, eds. (2004) Reducing the use of experimental animals where no replacement is yet available, ATLA 32, suppl. 2, 1-104.

Balls, M., Goldberg, A. M. et al. (1995) The Three Rs: the way forward, ATLA 23, 838-866.

Balls, M., Paskal, C., Kirkwood, J., Stephen, M. L., Goldberg, A. M., van Zutphen, B., Cervinkova, A., and Cervinka, M. (2006) An appreciation of the life of Professor William Russell (26 March 1925–27 July 2006), ATLA 34, 469-487.

Bremer, S. et al. (2007) *In vitro* tests for detecting chemicals affecting the embryo implantation process, ATLA 35, 421-439.

Burch, R. L. (1995) The progress of humane experimental technique since 1959: a personal view, ATLA 23, 776-783.

Festing, M. F. W. (2004) Preface, ATLA 32, suppl. 2, i-ii.

Paskal, C. (2006) Bill Russell: the singing scientific detective, ATLA, 34, 470-472.

Russell, W. M. S. (1957) The increase of humanity in experimentation: replacement, reduction and refinement, Laboratory Animals Bureau, Collected Papers 6, 23-25.

Russell, W. M. S. (2005) The Three Rs: Past, Present and Future, Animal Welfare 14, 279-286.

Russell, W. M. S. (2006) A note on refinement, ATLA 34, 349.

Russell, W. M. S., and Burch, R. L. (1959) The Principles of Humane Experimental Technique. 238pp, Methuen, London.

Smyth, D. (1978) Alternatives to Animal Experimentation. 218pp, Scolar Press, London.

Spielmann, H., and Vogel, R. (2006) REACH testing requirements must not be driven by reproductive toxicity testing in animals, ATLA 34, 365-366.