

# Comment

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## Animal Experimentation and Alternatives: Time to Say Goodbye to the Three Rs and Hello to Humanity?

**Michael Balls**

*The time has come to plan for a future where the Three Rs will have served their purpose, animal experimentation will have been consigned to history, and humane biomedical science in research, testing and education will have become the norm, for the benefit of humans and animals alike*

I have made many after-dinner speeches, and at least one between the main course and the dessert and one between the starter and the main course. However, I don't think I've ever given one *before* the dinner, with hundreds of hungry guests standing before me, hoping that I'll finish before I've even started!<sup>1</sup> I, too, would like to be sitting at a table with a glass of wonderful Moravian red wine, but I have a duty to perform.

I will try to interest you and entertain you a little, and along the way, I'll have one question for my audience and one challenge. I will deal with three main topics: Prague and the Czech Republic, the Alternatives Congress Trust, and the future of the Three Rs.

### Prague and the Czech Republic

In the 1980s, I had to travel beyond the Iron Curtain, in my capacity as Secretary-General of the European Cell Biology Organisation (ECBO), a federation of national societies of cell biology. The basis of my visits was to convey to societies and governments, the belief of ECBO that there existed a fraternity of cell biologists which transcended all national boundaries and did not recognise national or political differences and divisions. I went to Bucharest, Budapest, Prague and Warsaw, where I was warmly welcomed and listened to. We succeeded in gaining new members for ECBO, but we were able to make no progress with respect to East Germany and Russia.

It was during these visits that I learned the diplomatic skills which were to serve me so well in the European Commission — always to listen

patiently, even in the face of provocation, and never to be too outspoken when I at last had the chance to speak myself.<sup>2</sup> Seriously, though, I considered it a great privilege to pay these visits beyond the Iron Curtain. At that time, these countries were no less beautiful than they are today, their capital cities no less majestic,<sup>3</sup> their people no less courageous, and their scientists no less gifted.

In April 1988, I paid my first visit to Czechoslovakia, as a guest of the Czechoslovak Academy of Sciences in Prague, the Czechoslovak Biological Society, and the Department of Biology, Faculty of Medicine, Purkyně University, Brno,<sup>4</sup> with the support of the British Council.

My host in Prague was Dr Eva Streiblova, a Member of the Academy of Sciences, who, with her young colleagues, showed me all around the fabulous city of Prague.<sup>5</sup> I then took the express bus to Brno, where my hosts were Professor Oldřich Nečas and Dr Augustin Svoboda, with whom I had many great discussions and from whom I received very considerate hospitality. I had many adventures there, though I only have time to tell you about two of them today.

First, I went to the monastery where Gregor Mendel did his work on the breeding of peas, which led to Mendel's first and second laws of heredity and to Mendelian genetics. I had always thought of Mendel as an isolated old monk, who potted around his garden because he had nothing better to do. I found that this was far from the truth. In fact, he was an eminent young physicist, who was a member of a small consortium of leading scientists, also based in the UK and Germany, who set out together to understand the basis of heredity. At

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one stage, the monastery was so full of scientists that the bishop became concerned that they had no time for their religious observances. Mendel eventually became the abbot. I was able to sit in the chair from where he attempted to rule his flock. Unfortunately, he was a disaster as an administrator and as a politician.

In the 1980s, the Czech Government still followed the Soviet Union in rejecting Mendelian genetics and favouring Lysenko's version of Larmarck's heretical belief in the inheritance of acquired characters.<sup>6</sup> As a result, the Director of the Mendel Museum had to be very wary of visitors, until he found that they represented no threat. Realising that I was OK, he took me into the garden for a thorough and open discussion, away from the risk of listening ears or hidden microphones.

My other adventure was in the Department of Biology itself. Good lectures and fruitful discussions were one thing, but the main point about visitors was whether or not they could play table tennis. Professor Nečas was a fanatical player, and, when all but four of us had gone home at the end of the day, we had bread and cheese and wine, then fruit and wine, then just wine, before the game began. The table tennis table was put up in the Department's museum, a smallish room, the walls of which were lined by large glass-fronted display cabinets.

Professor Nečas was my partner, and at one point, in trying to defend us from a smash from the other side, I backed into a cabinet with a 2m by 2m glass front. The broken glass went everywhere, but the next morning, when I arrived for work at 6.30 a.m. (the normal working day was 6.30 a.m. to 3.30 p.m.), the glass front had been replaced and there was no sign of any damage or debris. What had happened the evening before was never mentioned, and I think the rapid repair was done by someone loyal to Professor Nečas, so that he didn't get into serious trouble for allowing government property to be damaged.<sup>7</sup>

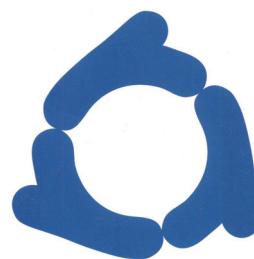
I have made many further memorable visits to what became the Czech Republic, but I must say a few words about TEMPUS project 1485. TEMPUS was the EEC's Trans-European Mobility Programme for University Studies. Our project ran from 1991 to 1994. Its partners were: the Medical Faculty, Charles University, Hradec Králové, The University of Nottingham Medical School, the Medical Faculty of the Free University of Berlin, FRAME (Nottingham), and ZEBET (Berlin). The main collaborators were Miroslav Červinka (Hradec Králové; who, now Dean of the Faculty, welcomed participants to the Prague Congress at the Opening Ceremony on 25 August 2014), Horst Spielmann and Manfred Liebsch (Berlin), and Richard Clothier, Andrew Sparrow and me (Nottingham). We made a complex series of visits among the partners, culminating in a conference at



### Alternativy k pokusům na zvířatech

Sborník příspěvků ze setkání řešitelů  
Společného evropského projektu TEMPUS JEP 1485  
"Alternativy k pokusům na zvířatech ve výuce lékařství",  
které se konalo 24. 5. 1994  
na Lékařské fakultě Univerzity Karlovy  
v Hradci Králové, Česká republika

Editoři:  
Miroslav Červinka a Michael Balls



### Alternatives to Animal Experimentation

Report of the Evaluation Meeting  
of TEMPUS Joint European Project 1485:  
"Alternatives to Experiments with Animals in Medical Education"  
held at Charles University Medical Faculty, Hradec Králové,  
Czech Republic, on 24 May 1994

Edited by  
Miroslav Červinka and Michael Balls



Hradec Králové in 1994, the proceedings of which were published in Czech and in English.<sup>8</sup>

Once again, I am delighted to be in a country I admire, in a city I love, and to have the opportunity to meet so many old friends and colleagues. I particularly want to thank Dagmar Jirová, Horst Spielmann, Guarant, the Hilton hotel, and all those who have played any part in making this Prague Congress such a great success.

## The Alternatives Congress Trust

I have been involved in the organisation of the World Congresses since 1993, when I was invited to partner Bert van Zutphen to organise the 1996 Utrecht Congress. The challenge for us was to match Alan Goldberg's brilliant initiative, in organising the Baltimore Congress in 1993. Then Andrew Rowan joined me to organise the Bologna Congress in 1999, and Horst Spielmann joined Andrew to organise the New Orleans Congress in 2002. Andrew founded the Alternatives Congress Trust, and Horst has played a key role in the organisation of other congresses, in Berlin, Tokyo, Montreal and now, Prague.

The three of us are leaving the Board of the Trust at this Congress, and we have been replaced by Elaine Faustmann, Ellen Fritsche and Gilly Griffin. I must admit that, when wondering what to say about them, I was reminded of the three witches who open Shakespeare's *Macbeth*,<sup>9</sup> saying:

*When shall we three meet again?  
In thunder, lightning, or in rain?  
When the hurlyburly's done  
When the battle's lost and won.*

I hadn't intended to leave that in my speech, but yesterday evening, at a Sponsors' Dinner, Ellen said that she suspected that I had been thinking of the new members of the Board as the three witches in *Macbeth*. That remarkable coincidence was so amazing that I felt justified in including it after all! It would, of course, have been more fitting, had I thought of the Three Graces of Greek mythology, Aglaia (Beauty), Eurphryne (Delight) and Thalia (Abundance), but the truth is, I didn't.

Finally, I want to thank Andrew and Horst most sincerely, for all they have done for the Congresses, and to wish Elaine, Ellen and Gilly every success as they take up the baton from us.

## The Future of the Three Rs

It is important that the 9th Congress should recognise the importance of the Three Rs, given to us by Bill Russell and Rex Burch in *The Principles of Humane Experimental Technique*.<sup>10</sup>

However, as you will see, I think it is time to do more than that.

Rex Burch was a charming and lovable person, but very few people in the Three Rs field ever met him or knew what he thought about *The Principles*. When I was at ECVAM, I gave him a small contract to record his thoughts on what had happened to the Three Rs concept since 1959. This resulted in a wonderful article, published in *ATLA* in 1995.<sup>11</sup> He concluded it with this lovely quotation<sup>12</sup> from Joel in the Old Testament:

*Your sons and your daughters shall prophecy  
Your old men shall dream dreams  
Your young men shall see visions*

I am now one of the old men, and we can have visions, too. I think that we should not be sent off to golf courses, encouraged to go on cruises, or put in care homes, since, freed of administrative responsibilities and released from our former places in hierarchies, we may have something useful to say. In fact, the words from Joel were quoted by Peter in a speech recorded in the Acts of the Apostles,<sup>13</sup> and they tend to be interpreted as indicating that the old and the young should work together, bearing in mind that a *vision* is "the ability to think about or plan the future with imagination or wisdom", while a *dream* "is a cherished aspiration, ambition, or ideal".

Those words also made me think of Bill Russell, and I realise that I seem to have been getting steadily closer to his way of thinking. We both studied zoology at Oxford, where the course dealt with every animal order from the protozoans to the great apes, including *Homo sapiens*. The emphasis was on adaptive radiation, the process whereby animals evolve to fill every available niche and survive in very different environments. The focus was on differences between the animals, not their similarities, and it never occurred to us or our teachers that one group could be models for another.

This led Bill Russell to question the value of models and to warn us of the danger of the high-fidelity fallacy — a warning that has been largely ignored. Today, it continues to be imperative that we think far, far more carefully about the nature and value of animals as models for humans:

1. The development of models is dependent on having sufficient understanding of what is to be modelled: we usually don't.
2. It also requires sufficient understanding of the models to be used: we never have that either. Rodents, dogs and non-human primates have not evolved, or been designed, to be models of *Homo sapiens*.
3. The models should be simple and without uncontrollable variables: they never are.

4. Modifying the models, e.g. by genetic manipulation, will make them even more complicated: the result is more uncontrollable variables and greater uncertainties.
5. The human being to be modelled doesn't actually exist: human genetic polymorphism results in infinite diversity, further complicated by a variety of different lifestyle factors, other diseases, and exposure to many other different factors.
6. The diseases being modelled don't exist either: there is no such thing as Alzheimer's disease or Parkinson's disease: these names refer to symptoms, not single diseases. For example, there are at least 100 forms of dementia: finding relevant and usable animal models for them would be impossible.

As it happens, our recent work, published in *ATLA* by Jarrod Bailey, Michelle Thew and myself, has had the effect of throwing down the gauntlet at the feet of the supporters of routine animal testing.<sup>14</sup> In two scientific articles,<sup>15,16</sup> after an analysis of the most comprehensive database of publicly-available animal and human toxicity studies yet compiled, we have shown that the results from tests on animals (specifically, the dog, rat, mouse and rabbit) "are inconsistent predictors of toxic responses in humans, and are little better than what would result merely by chance — or tossing a coin". As a result, we have concluded that "the preclinical testing of pharmaceuticals in animals cannot currently be justified on scientific or ethical grounds".<sup>16</sup>

Relying on animal models to answer essential questions is rather like trying to complete a jigsaw puzzle without being sure that all the right pieces are there and without having a picture of what is to be created.<sup>17</sup> We must use the new *in silico*, *in vitro* and (safe and ethical) human *in vivo* technologies to give us puzzles with all their parts and with clear pictures of what they are, so that we can conduct studies and set up tests of direct relevance to humans, without the pitfalls of inter-species differences and using models as complex as humans themselves. That will require a re-evaluation of how we think about and apply the Three Rs.

## The Question and the Challenge

My question is this: "Do you think that Russell and Burch's main contribution was giving us the concept of *reduction*, *refinement* and *replacement* — *The Three Rs*?" [A show of hands indicated that many of the guests tended to agree.]

I used to think that, too, but I gradually came to realise that Russell and Burch's *concept of inhumanity* was more fundamental and more long-lasting. They saw the *central problem* as "determining what is and what is not humane, and how

humanity can be promoted without prejudice to scientific and medical aims". They distinguished between *direct inhumanity*, "the infliction of distress as an unavoidable consequence of the procedure employed", and *contingent inhumanity*, "the infliction of distress as an incidental and inadvertent by-product of the use of the procedure, which is not necessary for its success". The Three Rs were put forward as a route of escape from the consequences of inhumanity, through the development, acceptance and use of humane techniques, under the broad headings of *replacement*, *reduction* and *refinement*. Their philosophy was brilliantly summed up in the words of *The Humanity Criterion*: *If we are to use a criterion for choosing experiments, that of humanity is the best we could possibly invent. The greatest scientific experiments have always been the most humane and attractive, conveying that sense of beauty and elegance which is the essence of science at its most successful.*<sup>18</sup>

It has taken 55 years to gain acceptance of the Three Rs concept to the extent that it is accepted today, and the scientific community should be rather ashamed that it has taken so long. More worrying is that the lucrative animal experimentation industry continues to thrive and expand as if nothing has happened. For example, the numbers of transgenic animals produced and used continues to increase, year on year, and we must now face the chilling prospect that the introduction of the CRISPR/Cas-9 technology will make it economically possible to produce transgenic non-human primates.<sup>19</sup> Furthermore, we cannot know what proportion of the commitments made to support the Three Rs are genuine, and which are mere lip-service as a means of diverting criticism while really seeking to maintain the *status quo*. That was Roman Kolar's disturbing conclusion in his excellent plenary lecture at the Prague Congress,<sup>20</sup> where he emphasised the ongoing increase in the use of animals in fundamental research, and the stark contrast between the ideals and the realities of *Directive 2010/63/EU*.

That leads me to the three main points I want to put before you as I come to the end of this speech. Firstly, the Three Rs were never meant to be an end in themselves, as many would seem to want to have us believe — Russell and Burch proposed them as a means to an end. Their goal was *replacement*, which they said, "is always a satisfactory answer", with *reduction* and *refinement* merely being steps along the way. Perhaps an appropriate analogy to a much-loved biblical verse,<sup>21</sup> would be to say, "these three remain: *reduction*, *refinement* and *replacement*; but the greatest of these is *replacement*".

Russell and Burch were concerned that "progress in replacement has been restricted by certain plausible, but untenable, assumptions [*the high-fidelity fallacy*], which have yielded only

gradually and piecemeal to the logic of empirical practice". That concern was justified in 1959, and it is of no less concern in 2014.

Secondly, I want to touch on the concept of *alternatives*, of which I have always been a strong defender. In 1998, Dr Herbert Allgeier, then the new Director General of the Joint Research Centre, founded a new Institute of Health and Consumer Protection, of which he would be the initial Director, and which now included ECVAM (the European Centre for the Validation of Alternative Methods), which he moved from the Environment Institute. He said to me that he didn't like ECVAM's name, and that it should be called the European Centre for the Validation of Advanced Methods. I disagreed with him at the time, but I now recognise, somewhat belatedly, that he was absolutely right.

I have a vision of a future in which non-animal methods, involving *in silico*, *in vitro* and ethically-acceptable and safe *in vivo* procedures involving humans themselves, will have become the routinely-applied norms, i.e. the relevant and humane procedures of choice, albeit, perhaps, with a few animal procedures still in use. These now rarely-employed animal procedures would themselves be regarded as the *alternatives*, temporarily tolerated until the need for them could be done away with altogether.

In order to make this vision become a reality, many biomedical scientists need to be freed from the automatic tendency to resort to animal experiments — that predisposition is like an addiction or an infectious disease, which needs to be treated and cured. Some individuals and organisations in science and industry remain intent on defending the continued use of animal models at almost any cost, whilst seeming to be reluctant to restrict the use of animal procedures to selected, specifically-justifiable circumstances and to make a more-enthusiastic commitment to the development, validation and application of replacement alternative tests and strategies of direct relevance to humans and their diseases.<sup>22–24</sup>

Thirdly, it is not only laboratory animals that stand to benefit from the dynamic and rigorous application of the humanity criterion — human beings also need it to be applied to them. In spite of the vast volume of biomedical research and numerous animal tests, human suffering is on the increase. We are prescribed medicines that don't work, that have unpredicted and unacceptable side-effects, and which interact with each other in ways that are unexpected, while their effects are compromised and complicated by other previous or concurrent diseases, and genetic and lifestyle factors, in ways which were not foreseen.<sup>25</sup> Then there are the ethical, design and logistical issues associated with clinical trials.<sup>22,26,27</sup> There has been a growing recognition that differences among patients can affect, not only the efficacy or safety of

a drug, but even the results of clinical trials (since a sizeable cohort of non-responders or idiosyncratic responders can throw doubt on the efficacy of a drug which is effective for the majority of the individuals in the trial).

In addition, as I know from close and ongoing personal experience, an increasing number of elderly people are suffering from progressive terminal diseases, such as dementia, for which there is no treatment whatsoever, despite the promises of "breakthroughs", about which we read in our newspapers almost every day, but never hear of again.

So my challenge to you is that you join me in preparing to say "Goodbye" to the Three Rs phase of biomedical research, and to say "Hello" to humanity.<sup>28,29</sup> My vision is one of the dominance of humane science, to the benefit of humans and animals alike. This will require the determined pursuit of the fourth R, the *revolution* in philosophy and practice which is long overdue.<sup>30,31</sup> Meanwhile, both animals and humans will continue to suffer unnecessarily — so I appeal to you again, please "Get a move on!"<sup>32,33</sup>

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## References and Notes

- For logistical reasons, what should have been an after-dinner speech had to be given before the dinner. The problem was that the guests had to dine in several small rooms, as no room was big enough to accommodate them all.
- This comment was intended as a joke. I would never claim to have the skills required of a diplomat.
- Deitch, G. (2002). *For the Love of Prague*, 4th edition, 320pp. Prague, Czech Republic: Baset Books. "Prague is still Prague. Regimes come and go. The Castle is still there. I look at a book of photographs of Prague of 100 years ago: the historic streets and palaces, the sky pierced by a hundred towers — our square — and it's all still here to see and feel!"
- Masaryk University, founded in 1919, was renamed Purkyně University in 1960, but reverted to its original name in 1990, following the Velvet Revolution.
- Unfortunately, Eva Streiblova was unwell, and could not accept an invitation to be a special guest at the Gala Dinner.
- Trofim Lysenko (1898–1976) was a soviet biologist and agronomist who rejected Mendelism. He pursued "socialist genetics" and was the favourite scientist of Joseph Stalin. He denounced Mendelian thought as "reactionary and decadent" and Mendelian thinkers as "enemies of the Soviet people". Science textbooks were re-written, his leading position in Soviet science was maintained until the mid-1960s, and his influence persisted long after that.

- 7 Professor Oldřich Nečas (1925–2008) became Head of the Biology Department in 1960. He was frequently in trouble with the Communist regime, and was not allowed to travel abroad for about 20 years. Informers were all around, waiting to catch people out and report them. The Government subsequently appointed a Party member as Head of Department, but Augustin Svoboda was appointed to the position in 1992.
- 8 Cervinka, M. & Balls, M. (ed.) (1995). *Alternatives to Animal Experimentation and Alternativy k pokusům na zvířatech*, 100pp + 100pp. Hradec Králové, Czech Republic: Nucleus HK for TEMPUS JEP 1485, Charles University Medical Faculty.
- 9 Shakespeare, W. (c. 1606). *Macbeth*, Act 1, Scene 1.
- 10 Russell, W.M.S. & Burch, R.L. (1959). *The Principles of Humane Experimental Technique*, 238pp. London, UK: Methuen.
- 11 Burch, R.L. (1995). The progress of human experimental technique since 1959: A personal view. *ATLA* **23**, 776–783. [Reprinted with minor amendments in *ATLA* **37**, 269–275.]
- 12 King James Authorised Version of the Bible (1611). *Joel* **2**: v28.
- 13 King James Authorised Version of the Bible (1611). *Acts* **2**: v16–v18.
- 14 Balls, M. (2014). Openness and animal research: The gauntlet has been thrown down. *ATLA* **42**, 213–214.
- 15 Bailey, J., Thew, M. & Balls, M. (2013). An analysis of the use of dogs in predicting human toxicology and drug safety. *ATLA* **41**, 335–350.
- 16 Bailey, J., Thew, M. & Balls, M. (2014). An analysis of the use of animal models in predicting human toxicology and drug safety. *ATLA* **42**, 181–199.
- 17 Balls, M. (2011). Replacing animal experimentation: On creating the puzzles to be solved. *ATLA* **39**, 1–2. “We must realise that, though we have many pieces to try to fit together, we certainly don’t have all the pieces we need and we don’t know how many pieces are missing. In addition, we must be suspicious that the pieces we do have are not merely the parts of one puzzle, but may be parts of an unknown number of different puzzles. Moreover, we cannot assume that all the pieces are of equal value, as we know that, far from being lifeless equivalents cut from the original picture with a jig-saw to form a conventional jigsaw puzzle, there are, within each piece of information having potential pharmacotoxicological significance, stories and histories, and pluses and minuses, and main streams and blind alleys, and dynamic interactions among them, that are far more profound. Worst of all, we have no picture on a box to guide us — we have to create the eventual picture or pictures ourselves, by using strategies and applying rules which we have to devise and lay down along the way.”
- 18 The use of *humanity* and related words is not without its problems: *humane* can be confused with *human*, and can be a trap for editors and proof-readers; worse — *humanity* can be used to mean “the quality or state of being kind to other people or to animals”, i.e. “the quality or state of being humane”, but it can also be used to refer to “the human race”; *humane* means “marked by compassion, sympathy or consideration for humans and animals”, while *inhuman* and *inhumane* refer to “not being humane” or “lacking compassion, sympathy or consideration”. I have always tried to avoid the use of *cruel*, meaning “wilfully causing pain or suffering to others, or feeling no concern about it”, since *thoughtless* is more likely to apply when laboratory animals are not given sufficient care or consideration. As I was writing this, I came across the headline of an article in my local newspaper, the *Eastern Daily Press*, on 7 October 2014, which read: *Humanity’s rapacious nature is putting entire planet at risk!*
- 19 Combes, R.D. & Balls, M. (2014). Every silver lining has a cloud: The scientific and animal welfare issues surrounding a new approach to the production of transgenic animals. *ATLA* **42**, 137–145.
- 20 Kolar, R. (2014). How long must they suffer? Success and failure of our efforts to end animal tragedy in laboratories. In *Abstracts of the 9th World Congress, Prague, 2014. ALTEX Proceedings* **3**(1/14), 11. There will be no published proceedings related to the Prague Congress, but it is to be hoped that this worrying analysis will nevertheless be published somewhere.
- 21 King James Authorised Version of the Bible (1611). “And now abideth faith, hope, charity, these three; but the greatest of these is charity.” *1 Corinthians* **13**: v13.
- 22 Balls, M. (2012). FRAME and the pharmaceutical industry. *ATLA* **40**, 295–300.
- 23 Bracken, M.B. (2008). *Why animal studies are often poor predictors of human reactions to exposure*, 5pp. Oxford, UK: James Lind Library. Available at: <http://www.jameslindlibrary.org/illustrating/articles/why-animal-studies-are-often-poor-predictors-of-human-reactions> (Accessed 09.10.14).
- 24 Pound, P. & Bracken, M.B. (2014). Is animal research sufficiently evidence based to be a cornerstone of biomedical research? *BMJ* **348**, g3387 [doi: 10.1136/bmj.g3387].
- 25 Balls, M. (2013). The labelling of all medicinal products as *Dependent on Animal Research* would be a minefield to be avoided at all costs. *ATLA* **41**, 325–327. Professor Lord Winston said, “There is a case for having legislation to make it clear that a particular drug has only been possible for human consumption because of animal testing”. This, he said, “Could be stamped on the packet, rather like a [notice on a] cigarette packet”. This made me wonder what manufacturers would need to put on the leaflet inside the drug packet, to explain what the label on the outside of the packet actually meant, and I suggested in an editorial that transparency and total honesty would require something like this: *Testing on animals: Despite the fact that thousands of animals were used in the discovery and development of this product, no guarantee can be offered that it will work or be sufficiently safe in your case. This is because animals and humans are significantly different in terms of their physiology, pathology and responses to drugs, so laboratory animals can usually provide only poor models of human diseases and responses to possible therapies. In addition, the animal tests conducted took little or no account of human genetic variation, of differences in human geographical, societal, occupational or lifestyle factors, of the simultaneous incidence of other diseases, or of the concurrent use of other drugs. It is for these reasons that it must be admitted that there are insuperable uncertainties about the efficacy of the product and the risk of potentially serious side-effects of many kinds.*
- 26 Anon. (2014). Clinical Trials and Medical Research — Ethics Committees. *NHS Choices Information*. London, UK: UK Government. Available at: <http://www.nhs.uk/Conditions/Clinical-trials/Pages/Ethics-committees.aspx> (Accessed 09.10.14).
- 27 Lay, K. (2014). Unethical cancer screening trial has to stop, say experts. *The Times*, 17 September 2014.

- <sup>28</sup> I am delighted that the theme of the 9th Congress was *Humane Science in the 21st Century*, and I hope the co-chairs of the 10th World Congress (September 2017, Seattle, Washington, USA) will consider changing its theme from *The Three Rs in Action* to *Humane Science in Action*.
- <sup>29</sup> My thinking is not out of line with that of two of the most committed and experienced proponents of the Three Rs concept, namely, Horst Spielmann, who provided the theme for the 9th Congress, and Alan Goldberg, who gave an outstanding plenary lecture on *The Principles of Humane Experimental Technique* at the 7th Congress (Rome, 2009; Goldberg, A. [2010]. *The Principles of Humane Experimental Technique: Is it relevant today?* *ALTEX* 27, Special Issue, 25–27).
- <sup>30</sup> In my plenary lecture at the 1996 Utrecht Congress (Balls, M. [1997]. The Three Rs concept of alternatives to animal experimentation. In *Animal Experimentation and Ethics*, ed. L.F.M. Van Zutphen & M. Balls, pp. 27–41. Amsterdam, The Netherlands: Elsevier), I interpreted the “ages” of the Three Rs in terms of the Great Ages of Western Civilisation, as the 1950s: the Age of Renaissance; the 1960s: the Age of Darkness; the 1970s: the Age of Reason; the 1980s: the Age of Reformation; and the 1990s: the Age of Revolution. However, to my great disappointment, the revolution has not happened. All we have is a kind of plodding evolution.
- <sup>31</sup> Balls, M. (2010). *The Principles of Human Experimental Technique: Timeless insights and unheeded warnings*. *ALTEX* 27, Special Issue, 19–23.
- <sup>32</sup> My tie, given to me at the 1999 Bologna Congress by my friend Klaus Cussler (who was also at the 9th Congress) has on it a large number of tortoises, all moving slowly in the same direction. One of them is saying, “Get a move on!”