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Correspondence: Industrial Strategy: important questions to address

Advice to the Prime Minister on important questions the industrial strategy should address and how the government might do so.

Animal research: then and now

Speech by Sir Mark Walport for the 80th Stephen Paget memorial lecture at Understanding Animal Research's Openness Awards.

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Animal research: then and now – Paget Lecture 2016

In doing research in preparation for this lecture, my chronic bibliomania turned out to be rather useful. A few years ago, whilst I was undertaking a review of STEM education for the government of the time, I discussed this with the late, great Lisa Jardine. She told me that I should look at the Cavendish Royal Commission Report on Scientific Instruction from 1870 to 1875. To my delight, shortly afterwards, in the Chatsworth Attic Sale, a copy of the Cavendish Commission reports, all 8 of them, appeared and I duly became the owner of the Duke of Devonshire's personal copy of his Royal Commission reports.

Royal Commission

But Victorian Royal Commission reports are nothing if not deeply specialist; they are neither distinguished by their typography or by their illustrations. So they are of relatively little financial value. This particular lot was padded with a string of other equally esoteric Royal Commission reports, which meant that the transport costs were almost as great as the costs of the books themselves. Amongst the other reports I acquired was the 1876 Royal Commission on Vivisection. I also acquired at the same time the 1849 report on the Application of Iron to Railway Structures; I am looking forward in due course to lecturing on this topic as well. Both of the first 2 of these reports have turned out to be extremely useful, and many of the arguments that they contain are as valid today as they were 140 years ago.

Although references to animal research have existed in popular culture since at least Shakespeare's time, from the 1850s onwards, concomitant with the rise of physiology and also stimulated by the discovery of the anaesthetics, chloroform and ether, there was debate in both the public and specialist press about the propriety of experiments on living animals. The appointments of Professors of Physiology at a small number of British Universities fuelled the debate.

At the meeting of the British Association in Edinburgh in 1871, Sir James Paget, father of the Stephen Paget, whom we commemorate tonight, laid a series of resolutions which were passed. These included the following: Firstly: No experiment that can be performed under the influence of an anaesthetic ought to be done without it; Secondly: No painful experiment is justifiable for the mere purpose of illustrating a law or fact already demonstrated.

So the Royal Commission, initiated on 22 June 1875, purpose was to:

Inquire into the practice of subjecting live animals to experiments for scientific purposes, and to consider and report what measures, if any, it may be desirable to take in respect of any such

practice.

The Royal Commissioners included Thomas Henry Huxley, who was also part of the Commission on Science Instruction. The report itself was issued on 8 January 1876, and commendably is only 15 pages in length, but for those of us that worry about evidence-based reports, it was backed up with 6,551 paragraphs of evidence. It makes fascinating reading.

The list of witnesses is extraordinary. Sir James Paget was joined by some of the founding parents of physiology, including William Sharpey and J Burdon Sanderson. Other luminaries who gave evidence included Joseph Lister, Charles Darwin, Sir William Gull and a panoply of the great and the good of 19th century science and medicine.

A few quotes from the report itself will suffice to indicate its general tenor.

It has been proposed to enact that the object in view shall be some immediate application of some expected discovery to some prophylactic or therapeutic end, and that any experiment made for the mere advancement of science shall be rendered unlawful. But this proposal cannot be sustained by reflection upon the actual course of human affairs.

Knowledge goes before the application of knowledge, and the application of a discovery is seldom foreseen when the discovery is made. 'Who,' says Helmholtz, 'when Galvani touched the legs of frogs with different metals, and noticed their contraction, could have dreamt that ...all Europe would be traversed with wires, flashing intelligence from Madrid to St Petersburg with the speed of lightning...'

Of course that was right then, and it is true now. It is a nice enunciation of the justification and the importance of the conducting of basic research led by curiosity in to answering important scientific questions.

So then as now, in the Commission, the Report and the evidence, examples were given of discoveries important to the advancement of human health. These included the discovery of the circulation of blood, the discovery of the lacteal and lymphatic system of vessels, and Sir Charles Bell's discovery of the compound function of the spinal nerves.

Sir James Paget identified the challenge of discovering an antidote to snake poisons, citing the "many thousands of your Majesty's Indian subjects who perish annually from snake bites." Indeed, less than 20 years later Cesaire Phisalix and Gabriel Bertrand, together with Albert Calmette presented to the French Society of Biology on the 10 of February 1894 their independent work on the development of an anti-venom against Viper venom and Indian Cobra venom respectively. And it was only a few years later that Vital Brazil, head of the Butantan Institute in Sao Paulo, developed the first antisera to South

American poisonous snakes.

Amongst the witnesses was Charles Darwin, and to quote him briefly:

The first thing I would say is that I am fully convinced that physiology can progress only by the aid of experiments on living animals. I cannot think of any one step which has been made in physiology without that aid.

Darwin was then asked:

Now with regard to trying a painful experiment without anaesthetics when the same experiment could be made with anaesthetics or, in short, inflicting any pain that was not absolutely necessary upon any animal, what would be your view on that subject?

And his reply:

It deserves detestation and abhorrence.

But the evidence that probably had the greatest impact of all was that of Dr Emanuel Klein, a physiologist working as an Assistant Professor in the Brown Institute. He appeared completely insensitive to the suffering of animals.

Huxley wrote to Darwin on October 30th, after Klein had provided his evidence:

The Commission is playing the deuce with me. I have felt it my duty to act as counsel for science, and was well satisfied with the way things are going. But on Thursday, when I was absent, (Dr Klein) was examined; and if what I hear is a correct account of the evidence he gave, I may as well throw up my brief. I am told he openly professed the most entire indifference to animal suffering, and he only gave anaesthetics to keep the animals quiet!

I declare to you, I did not believe the man lived, who was such an unmitigated cynical brute as to profess and act upon such principles; and I would willingly agree to any law that would send him to the treadmill.

The impression his evidence made on Cardwell and Foster (two of the other commissioners) is profound; and I am powerless (even if I desire, which I have not), to combat it.

But the Royal Commission report duly, and I think inevitably, concluded that legislation was necessary. And to quote again:

What we would humbly recommend to your Majesty would be the enactment of a law by which experiments upon living animals, whether for original research or for demonstration, should be placed under the control of the Secretary of State, who should have powers to grant licenses to persons and, when satisfied of the propriety of doing so, to withdraw them. No other persons should be permitted to perform experiments. The holders of licences should be bound by conditions, and breach of those conditions should entail the liability to forfeiture of the license, the object of the conditions should be to ensure that suffering should never be inflicted in any case in which it could be avoided, and should be reduced to a minimum where it could not be altogether avoided.

This was the first statement, in a way, of the 3 Rs. The government listened. The result was a Bill placing animal experimentation in Great Britain – akin to the study of human anatomy – under the supervision of the law. This was enacted as the Cruelty to Animals Act on 15 August 1876. Of course this was by no means the end of the history. There was another Royal Commission between 1906 and 1912. And finally in 1986, the 1876 Act was replaced by the Animals (Scientific Procedures) Act. The big change here was that it authorised animal experimenters by means of a personal license, but an additional project license that defined the categories of purpose. That of course is where we are today.

It is an enormous privilege to be asked to give the 80th Paget Lecture this evening. Stephen Paget, in whose memory this series of lectures was instituted in 1927, was a tireless advocate for the value of properly conducted animal research. His work to found the Research Defence Society in 1908, during that Second Royal Commission on Vivisection, was a turning point in the national debate around animal research.

The Research Defence Society was formed to:

...make known the facts as to experiments on animals in this country; the immense importance to the welfare of mankind of such experiments and the great saving of human life and health directly attributable to them.

Stephen Paget would find today's discourse as familiar as we find the arguments of the 1870s.

Science meets values

But this is not a lecture on history. The introduction is intended to show that all of the concerns that continue to rear their head about research using animals have a very long history. And these concerns sit at the interface between the conduct of science, the application of science and the human values held by individuals and societies in different parts of the world.

So what are the core arguments around animal research? In truth they are still the same as those articulated clearly in the 1870s. They are fundamentally utilitarian arguments about one sort of value – the value of scientific research in discovering the secrets of human and animal biology in health and disease. This work brings with it the potential to prevent disease, through vaccination for example, or to treat it, as with the use of insulin in diabetes. That value is balanced against another sort of value, which is our relationship with other species, and the extent to which we are prepared to cause harm to other species to bring benefits to ourselves.

I fear that all too often discussions about science are conflated with arguments about values. So we end up with arguments that are framed as follows: The proponents argue for the necessity of animal research if we are to progress in our understanding of health and disease, and to discover new preventive and therapeutic approaches. Opponents of animal research argue that the research is scientifically invalid, that the results are not transferable from one species to another and that experiments cause unacceptable suffering.

But this is not the real argument. It is an argument that is being conducted at cross purposes. The reality is that there are some who believe that it is simply wrong to experiment on animals, whatever the potential benefit. Equally there are some in the scientific community who do not recognise that, in the face of all of the benefits that they perceive from such research, that it is reasonable that some people oppose the use of animals in research from the perspective of their personal values.

In fact, it is much more complicated than this because many who do not like the idea of animal research express gradations of concern about research on other species. These concerns are based on judgements of a perceived hierarchy. This hierarchy is partly based on perceptions of the capacity of different species to experience pain or suffering. Or on the basis of their evolutionary relationship to humans, so there tends to be less concern about invertebrates – with the exception of cephalopods – and successively more concern moving from fish to mice to rats to rabbits, with cats, dogs and non-human primates the objects of the most concern.

This complexity means that animal research is a topic where the institutions of science meet the institutions of democracy fairly and squarely. It is an area where the arguments will continue and the opposing cases will need to be made and remade. We live in a plural democratic society, where different citizens hold different views based on differing moral precepts. Ultimately it is for democratic governments to decide on the acceptability and conditions under which research on animals is undertaken and how this should be regulated. And this is an area in which the UK is a global leader.

Transparency and communication

My life in science started with experiments on the genetics of the fruit fly in school laboratories in the 1960s, dissection of frogs and extremely smelly formaldehyde-pickled dogfishes, which provided ample confirmation to me, if

it was ever needed, that I was neither going to be an anatomist nor a surgeon.

It was medical school that provided my first insights into research on mammalian species, studying immune responses to mice to chemically induced tumours as part of my Part 2 Pathology course in Cambridge. And participation as a medical elective student at the Karolinska Institute in research on a strain of mice, called C3H/HeJ. This strain of mice shows no response to exposure to lipopolysaccharide, which is a component of many bacterial cell walls that is a cause of the damaging inflammatory response suffered by animals infected with certain bacteria.

My task, as an elective medical student in a couple of months, was to work out the explanation for this failure of responsiveness of the C3H/HeJ mouse to lipopolysaccharide (LPS). I isolated lymphocytes from these and control mice and checked whether they would respond to stimuli other than lipopolysaccharide, which they did. But I did not get anywhere near to uncovering the explanation for how they failed to respond to LPS. Nor, I have to confess, did I understand at the time the importance of these particular mice and why it mattered to discover the explanation for lipopolysaccharide unresponsiveness. So you can imagine my fascination when Dr Bruce Beutler was awarded the Nobel Prize in 2011 for discovering that these mice were genetically deficient in a protein called Toll-like receptor 4.

This is an important part of the innate immune system that confers inherited resistance to bacterial and other infections – and is a member of a group of proteins that have been conserved over a very long period of evolution, with very similar Toll receptors present in those fruit flies that I studied at school. This and related discoveries has opened up a whole new field of research into our immune responses, in both health and disease, and is a good example of how apparently rather basic research enquiries, in this case firstly in flies and then in rodents, turned out to have important utility in understanding the mechanisms of ill health.

So, whilst the arguments about animal research have been conserved through the generations, there is one important respect, in which the landscape for animal research has changed significantly during the last thirty years or so. For a long time, the laws that ensure that animals used in research are treated as humanely as possible have been enforced. However, the laws protecting scientists from illegal harassment by extremists were not. That asymmetry has disappeared in recent years. Scientists can practice their legal experimental work confident that government will support them against extremism. Since the days of a brave few, who were prepared to talk openly about their research on animals, more and more scientists are willing to make the case in public for the research that they do. Animal labs and their host institutions are increasingly open, and the sky has not fallen in. It is worth reflecting on how remarkable that change has been.

Huge progress has been made in opening up animal research to public scrutiny, particularly in the academic community. However, the argument hasn't been won in all parts of the animal research community. We must continue to make the case to our peers for intelligent transparency. Too often the answer is still

to hope that no one asks questions of us, rather than to open the doors and show there's nothing to fear. But importantly, this openness cannot and should not be left to the academic community alone. Industry needs animal research. Industry voices would therefore be a persuasive part of making the public case for why animal research remains necessary.

In 2012, following discussions between the Science Media Centre and the Wellcome Trust, a further series of discussions, in which Geoff Watts played an important role, which led to over 40 organisations working in the biosciences in the UK signing a Declaration on Openness on Animal Research. That included a commitment to developing a Concordat which set out how they would be more open about the ways in which animals are used in scientific, medical and veterinary research in the UK. In 2014 the Concordat was launched and now has 108 signatories.

I think the individuals who have been willing to stand up and to make the case for animal research throughout the years can claim a great deal of the credit for the state that we now find ourselves in. So it is only right that we celebrate their achievements this evening. It is a very good opportunity to thank the successor organisation to the RDS, Understanding Animal Research, for the work that you do. And Fiona Fox and your colleagues at the Science Media Centre – also thanks for your work on encouraging openness. The Concordat has, I believe, been helpful. I would encourage every institution involved in animal research to sign up.

But amidst the fervour for encouraging openness and much more communication, I believe there is occasionally some danger of over-reaction. We want volunteers for communication about animal research, not conscripts. Not everyone is able and willing to communicate effectively. The modern channels for abuse are manifold and a thick skin is needed by those who communicate in some of the more controversial areas of science.

Indeed, enthusiasts for science communication often fail to recognise that it is not a 'singular thing'. Science communication comes in many forms. It is much easier to communicate science discoveries such as the Higgs Boson or to enthuse people about space science, than it is to communicate the role of science in areas where there are conflicting human values. That is not to say that it is easy to explain the Higgs Boson. But here the challenge is not the general public, but actually other particle physicists, who are all too ready to shoot down some hapless colleague who does not fully communicate the arcana correctly.

It reminds me of when I went on the Today programme a few years ago to talk about the potential importance of a new genetically modified potato that was resistant to potato blight. I explained that blight was caused by a fungus that could devastate potato crops. On that occasion it wasn't anti-GMO activists who objected to my interview. It was a letter from a gardening pundit who accused me of extreme ignorance in calling potato blight a fungus. Because it is, in fact, an oomycete, which Wikipedia will tell you is:

A distinct phylogenetic lineage of fungus-like eukaryotic micro-

organisms.

They didn't actually teach me that at medical school, and indeed I don't think it was even known when I was at medical school! But I am not sure that the point of the interview would have been enhanced by this particular element of taxonomic rigour.

The reality is that scientists who participate in public discussions on embryo research, animal research, GMOs, pesticides, climate science and the like will have an utterly different experience from those that talk about science in areas that are not value-laden. And indeed scientists sometimes fail to recognise that how science is used is a topic for all of society, and as scientists, our views do not trump the views of others.

Trust and standards

But please do not think that I am making a case for any kind of 'post-truth' approach to science communication. I am absolutely not. One of the big challenges for science is to become even more rigorous in the way that we conduct research and communicate its results. Indeed I think one of the problems in the way in which science is communicated is the over-emphasis on the reporting of the 'latest paper' on x or y, rather than on what the body of the scientific evidence shows. Frankly, this causes endless problems to those of us that are involved in providing science advice to government. By and large, we are not that interested simply in what the latest paper shows, especially when it's apparently equal and opposite to the paper that was published last week. What we care about is the totality of evidence. What do we know overall, what do we not know and where are the uncertainties?

Where animal research remains necessary, we must clearly and confidently explain why. But we should hold ourselves to the same standard of evidence in communication as we'd expect in our science itself. We mustn't be seduced by our own PR. And here I have a challenge to this audience: To what extent have we as a community, ever subjected our claims about how vital animal research has been to human health to the same level of scrutiny we'd apply to those claiming to have discovered a new cure? And I think if not, we must. A Cochrane-standard review of the contribution of animal research to advances in health and wellbeing over the last 20 years or so would be a valuable contribution. That is a challenge to you as an audience tonight.

Developing and maintaining a supportive environment for research is both more difficult and more necessary in animal research, than it is in less controversial branches of science. People talk a lot about trust so animal research must command public trust. But as Baroness O'Neil is always saying the corollary of trust is trustworthiness. We earn trust by being trustworthy. We cannot be complacent in our maintenance of what we have earned. Therefore the animal research community needs to behave in a fashion that is irrefutably trustworthy.

Set in this context, a robust regulatory environment is not a burden to be borne by those who would do animal research. It is an integral part of the

case we make to the society in the UK. Members of the public can be confident that we are trustworthy precisely because we are so carefully regulated and because we obey those regulations. It follows that we, as a research community, must share responsibility for how we are regulated.

I know my colleagues in the Home Office would welcome more dialogue with the scientific community. However, it would be a mistake for us to interpret that as an invitation to dictate to the Home Office what we want, or for special pleading. As the Chief Inspector in the Home Office, Dr Culverwell in the 1940s, pointed out once to some unfortunate colleagues:

No one ever tells the Home Office what to do.

Rather we should approach discussions with the Home Office in the spirit of partnership, politely suggesting improvements which would better ensure animal welfare and promote the best science.

This brings me to an issue which should be close to the heart of any scientist. We can never be complacent in the pursuit of rigour. As scientists, we must constantly ask ourselves "does this study meet the highest standards of work?" And we must be ruthless in challenging where we see this is not the case: in the work we do ourselves and in the wider research community.

As I'm sure everyone in this audience agrees, there can be no choice between high standards and high volumes of research. It's the standards that trump everything. If we are to make the most of the funding available, the correct approach is to prioritise the best, most reliable work. This is particularly true if animals are involved. It is unethical and wrong to conduct poorly powered studies.

Experiments should always be designed to provide the best chance of generating robust and reliable results. That doesn't of course take away the need for repetition of experiments, to confirm or to refute important findings. But ultimately, we will use the fewest animals in experiments overall if we optimise the experimental designs to give the greatest chance of reliable findings.

With that in mind, the ongoing work to standardise approaches around the world is entirely welcome. We should be proud in the UK, for having some of the highest standards for animal testing in the world. And where other countries' systems meet those standards, we can use their results in our regulatory processes. This is both efficient and good for animal welfare. This is a responsibility for everyone in the scientific endeavour. It's a responsibility for the funders of research, it's a responsibility for the researchers themselves, and it's a responsibility of those that peer review their papers and publish the findings to insist on the highest standards of work, and in doing so drive welfare internationally.

Whilst I don't anticipate a point in my lifetime when animal research will be entirely unnecessary, we must continue to ask ourselves "is there a better

way?" Worldwide, the supply chain of animals for research is fragile. Global public opinion is quite hard to forecast and it may harden against testing. What pharma company would continue the expense and reputational risks of animal tests if they did not have to? What government would not welcome the avoidance of political controversy? What scientist would want to keep using an imperfect animal model if a more accurate alternative existed? The UK should continue to lead the process of finding alternatives. That means that the work of the NC3Rs, the National Centre for Replacement, Refinement and Reduction of Animal Research, is extremely important.

The extraordinary tools of modern biomedical research offer ways to unravel physiology at the level of the cell, the organ and the organism in ways that were inconceivable even a few years ago. In his philosophical poem, *An Essay on Man*, Alexander Pope wrote in 1733:

Know then thyself, presume not God to scan;
The proper study of mankind is man.

Our tools let us study man and woman in the most extraordinary detail and with minimal invasion. But not all of our tools can, or indeed should, be applied in humans. For example, the power of optogenetics to study neural circuitry, or gene editing to create an array of genetic variation, offers opportunities to ask important questions about for example the function and the malfunction of the nervous system in animals, in ways that simply cannot be achieved in humans. And these results are very important for our understanding of humans.

We are in an extraordinary time for science, engineering, technology and social science. The Government Office for Science periodically produces reports on [Technology Innovation Futures](#). Our most recent report concludes that what is happening at the moment is a convergence between technologies. For example, biology meets material science, engineering and 'big data'. So the opportunities and the importance of animal research remains as salient now as it has ever been.

But we should never forget that the pursuit of science requires a 'public license', not least because it is the taxpayer that funds much of our basic research. The return to the taxpayer comes in many forms. Of course, advances in knowledge matter in their own right. But ultimately they are not sufficient on their own. The public expects gains in health and well-being, and gains to the economy from the many billions of pounds that are invested in research and development.

Science, engineering, technology and the social sciences are at the heart of advances in industry and the economy. The UK is a world leader in the biosciences. In that context, animal research is an essential and integral part of the jigsaw of the UK knowledge economy.

Embracing openness

So I will end where I began. The lesson of history is that some things do not change, so we must be resolute in continuing to make the case for animal research. One hundred and eight years after the Research Defence Society was formed, their founding purpose to 'make known the facts' about animal research, needs but one update. We have learned as a community that 'knowing the facts' is not enough. People must be engaged, involved in and ultimately persuaded by the utility of our work.

In 2016, of all years, no one needs reminding of the dangers of assuming the wider public shares the views of experts. But furthermore, the claim of expertise needs careful examination. A true expert should behave with impeccable and dispassionate rigour, properly acknowledging uncertainty where this exists. I am not sure that all self-declared or indeed anointed experts always live up to these standards.

One cannot hope to convince everyone. However, on animal research, it is necessary in a democracy to bring on board the widest possible coalition of the public.

The age old arguments about the pros and cons of animal research have not been resolved, and maybe never will be. They sit at the heart of the debate about our relationship as humans with other species. And they tell us something important about one of the unique attributes of humans. The tiger does not debate whether it is right to bring down and strangle the gazelle with a bite to its neck. Eat or be eaten – nature, red in tooth and claw, but we humans have what appears to be the unique cognitive ability to consider our relationship with other species.

It is the essence of humanity that we care for each other in extraordinary ways and care for other species and our environment, though almost certainly not enough, given the environmental challenges that come with a global population of over 7 billion people. Alexander Pope reminds us of the paradox at the core of humans, even in an era of Enlightenment:

Chaos of Thought and Passion, all confus'd.

It was Hume that noted that the passions often trump reason. Scientists who are human and not, I would suggest, immune from passion, must continue to promote reason. So I think there are a few things I suggest that this mission, to promote reason, requires of the animal research community.

Firstly, keep talking to government about where the regulations could work better to ensure high standards of research and animal welfare, but challenge where you see examples of these standards not being upheld by the community.

Secondly, let us maintain the UK's position as a world leader in the most rigorous animal research, but also in the search for alternatives.

And thirdly, welcome scrutiny for the confidence it provides. Keep talking about what research is undertaken. Keep opening the doors. And let us submit our own arguments for the value of animal research to the same scrutiny we would apply to all of our scientific work.

We cannot fear openness, we must embrace it.

Thank you for your attention.