discovery, because, as Francis Crick pointed out: "now one could ask the right questions".

The next phase of molecular biology, as it was now called, took place in even simpler models – bacteria and the tiny viruses (bacteriophage) that prey on them. Their simplicity and rapid growth allowed breeding experiments to be conducted at great speed, and in a few years the central machinery of biological information flow was laid out.

My own entry into this excitement came when Sydney Brenner invited me to join his group working on a tiny roundworm just 1mm long called *Caenorhabditis elegans,* or the worm for short. Sydney had been one of the pioneers in that first surge of discovery, and like many of his contemporaries he now wanted to see how these findings could be translated into knowledge of animals like ourselves. Humans are too complex, and anyway one can't do experiments on them. Even fruit flies are too complex if we want to look in detail at the individual cells, but the little fast growing worm is ideal for that purpose. My own initial role was to follow the cell lineage of the worm from the single cell of the fertilised egg to the roughly 1000 cells of the adult. Unusually for an animal the cell lineage of the worm is very nearly invariant, and over several years I and my colleagues worked it all out.

Among other things we noticed the predictable occurrence of programmed cell deaths, and this in turn allowed us and our successors to discover the genes that control cell death. It turned out that a number of these genes are closely similar to the corresponding genes in humans, and so are important in medical conditions where cell death happens too much (eg neurodegeneration) or too little (eg cancer). Once again the value of a model system becomes apparent.

But I am getting ahead of the story. Back in the early 80s, when the cell lineage was complete, I found myself absorbed by a new problem. The purpose of all our research was to discover the role of genes through classical genetics: just like Mendel, we selected strange looking worms and cross bred them. But now in the age of molecular biology the aim was of course to go further, to peer inside to see what was going wrong, and to isolate and study the very genes involved. This was difficult. By 1980 we had thousands of mutations in hundreds of genes, but it was taking scientists years to find each gene in the haystack of the worm genome (100 million letters long). There had to be a better way, and a few of us (including Alan Coulson in Cambridge and Bob Waterston and his colleagues in the US) set out to map and finally sequence the genome so that everyone could find their chosen genes easily. We were successful enough that the worm led the way in the genomic analysis of higher organisms, and its example, with the evident benefits to research that genome sequencing brought, helped to usher in the international human genome project, which was successfully completed last year. Though in many ways this is actually the beginning, for we are only just starting to understand this 3000 million letter goldmine and shall be looking at it for centuries to come.

Thus the worm became a model in another and unexpected way. Georgina Ferry and I told this story in our book "The Common Thread", partly because it's a good tale, but also because we ran into a spot of bother which is significant in its own right. In the international human genome consortium we released our data to everyone, just as we had always done for the worm; but we were challenged by a corporation that started to sequence the human genome inaccurately and rapidly, in order to keep the data private and sell it to subscribers. It struck me as extraordinary that anyone would do that, given that the human genome is our common heritage, and as even more extraordinary that so many people would approve. Not only would such a practice be unfair to those unable to pay, thus creating even deeper divisions in the world that we have already, but it would be counterproductive for communications even among the cognoscenti. For, if one is the proprietor of a private database, then one must contract with each of one's clients not to redistribute the data. But because the data is so complex and poorly understood, this restriction means that researchers are unable to publish properly the results of their work. Fortunately we won this battle, but only thanks to the funds of the Wellcome Trust. It bothers me that our national policymakers still do not seem to appreciate the importance of freely available fundamental information to the success and integrity of our society.

In this short talk I've tried to illustrate how our biological knowledge and understanding is helped by the unity of life, first propounded by Darwin and now borne out in ever finer detail by our acquisition of the actual codes of life – the genomes – of many different organisms. Biologists can study many organisms (eg virus, bacterium, yeast, roundworm, fruit fly, *Arabidopsis*, rice, fish, chicken, mouse, human), and learn something from each. Each teaches us something different, all give clues as to how life works, and all contribute to medical progress.

In thinking about appropriate ways forward in our use of animals in research, we should bear in mind that life is complex. We do not yet understand even the simplest organism, so calculations cannot replace animal experiments; research must be open ended if we are to advance our understanding and skills in ways that are valuable to both human and veterinary medicine.

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# The Contribution of Animals to Human Health and Wellbeing

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## Introduction

There is not a person alive today who has not benefited from animal research. This is a basic and undeniable fact. In the past 100 years human life expectancy has dramatically increased as a result of better nutrition, better sanitation and discoveries in biological sciences. Yet, despite this fact there are people who believe that somehow animals have rights that place human welfare at risk. As a neurosurgeon and neuroscientist I feel this is an unacceptable stance and it also worries me that 220 MPs have signed up to a motion banning the use of primates in research. This will endanger efforts to alleviate some of the most devastating conditions that affect man. In this briefing I will summarise some major contributions of animal research to science and society based on my experience.

## Parkinson's Disease

Parkinson's disease affects 2% of people over the age of 60. It manifests itself by uncontrollable tremor, rigidity, slowness of movement and imbalance. Until 1969, sufferers had only recourse to often crippling neurosurgical procedures in the belief that inducing a degree of paralysis was preferable to the condition. In 1961 Hornykiewicz demonstrated that the chemical dopamine was depleted in the parkinsonian brain and in 1969 a precursor L-Dopa was used clinically by Cotzias to treat the condition with dramatic reversal of the symptoms. However within 10 years of its introduction it was recognised that after 5 years' therapy, 70% of these patients would suffer crippling side effects from the drug therapy with uncontrollable thrashing of limbs, psychosis, on-off effects etc. In the absence of an animal model of the condition future developments were bleak.

However, in 1979 an unexpected breakthrough occurred. A Californian drug addict who had taken a modified version of the painkiller pethidine (called MPTP) acquired severe parkinsonian symptoms. He responded dramatically to L-Dopa, as did several of his customers who had developed the same effects. Following his death brain studies showed the changes seen in true Parkinson's disease. In 1983 MPTP was reported to induce parkinsonism in the monkey which was drug responsive and so a model for the condition became available.

Primates and indeed higher primates are central to such studies. They are bipedal like man with neural pathways that are identical. Their brains contain neuromelanin that binds MPTP, unlike lower primates, and hence they offer a stable parkinsonian model. Without this model it is hard to conceive how future therapies would be developed.

The next five years showed an explosion of understanding of the condition using the primate model. By 1989 an area deep in the brain, the sub thalamic nucleus (STN), was identified as being overactive and central to driving the symptoms. Prior to these primate studies the STN had never been thought to have a role in the mechanisms of the condition. By 1990, selective destruction of the STN was shown to dramatically reverse parkinsonism in the primate and render them drug free. Given that destroying such a target had major risks to it, an alternative therapy, that of implanting electrodes into the STN to electrically stimulate it till it stopped functioning was shown to have a similar effect. Within two years of these primate

studies. the first clinical study in people was reported with equal effect. Today, as a result of such studies, over 30,000 people have had deep brain stimulators – a sort of pacemaker for the brain – implanted to control their Parkinson's disease. Many such people are able after years of suffering to reduce or stop medications altogether.

That is not the end of the story. Advanced parkinsonian patients do not respond to either drugs or surgery. About one in five people diagnosed as having Parkinson's disease develop resistance to drug therapy and are unable to move, the parkinson-plus syndromes. They are locked in a frozen nightmare.

Recent primate research into parkinsonism has shown that stimulation of another nucleus, the pedunculopontine nucleus (PPN), may well selectively improve the ability to move. The work is so convincing and the need so imperative that clinical studies are imminent. Such surgery alleviates the condition but repair may be a real possibility. Viruses infect cells and selecting a virus that infects nerve cells, taking out most of its genes and replacing them with the genes to produce dopamine is now possible. In the parkinsonian primate, injections of such viruses into the brain has been shown to dramatically improve the condition, rendering them drug free with no obvious side effects. This is also very near clinical trials in people Further studies are needed to make stem cell transplant a possibility in man.

## Alzheimer's Disease

Alzheimer's disease robs people of their minds. Using transgenic mouse models and primates, drugs have been developed that slow the loss of intellect. In Alzheimer's disease protein deposits develop in selective areas of the brain destroying intellect. In a transgenic mouse model of the condition a vaccine against this protein was shown to be effective in treating the condition. The implications were such that without an intermediate primate investigation human trials were started. The study was abandoned because the vaccine induced brain inflammation in man. More recent studies of newer vaccines that do not induce brain inflammation but bind to the protein whilst in circulation show promise. However these will need trialling in primates prior to man.

Higher primates are central to such research again because as they grow old certain species develop dementias with brain deposits identical to the human condition.

Other developments in neurological disease based upon animal research are clot dissolving drugs for strokes, newer drugs for epilepsy, immunotherapy for multiple sclerosis, drug therapy for migraine, drugs to treat brain tumours, nerve growth factor studies to help recovery from brain and spinal cord injury.

Present day medical therapy is inseparable from animal research. No drug, no implants, no surgical procedure can be done today free of this provenance. Present day regulations for animal research in the UK are very rigorous and experiments carefully regulated such that all are done humanely and with respect for the animals. The numbers used have dropped over the last decade and certain species such as chimpanzees and other great apes are banned from research. Animal care also benefits from such work.

Recently, the argument is raised that animal research has harmed people by introducing dangerous drugs into clinical use. In drug development roughly 1000 animals (usually rodents and some dogs) might be used and if there are no contraindications a safety trial is started using perhaps 100 volunteers and if safe, efficacy trials in approximately 3000 patients will be carried out prior to a drug being released. The animal tests can be relied upon to find certain major side effects and, when combined with non-animal tests and intense medical supervision, protect those taking part in clinical trials. However, none of these approaches – animal, non-animal or even human – will identify every possible side effect in every patient. These will emerge with general use on a much larger scale. All drugs can cause side effects even deaths in certain situations. To demand development of a perfectly safe drug to justify animal research is foolhardy.

Suffering is not a part of animal research. The procedures I perform on my monkeys is the same that I do clinically in patients. Regulations dictate standards of animal welfare in all UK laboratories which in turn are monitored by Home Office veterinarians.

In conclusion, reflecting the fact that 220 MPs have signed an Early Day Motion to ban primate research I ask would they also be happy to sign away the rights of others to freedom from Parkinson's disease, Alzheimer's disease and other diseases and conditions that I have been unable to cover. Such Motions and their implications for the future of mankind must be carefully considered.

# Balancing Human and Animal Needs

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The use of animals in research is an ethical issue that arouses strong feelings on both sides of the debate. Numbers are frequently quoted to make a point but these should be treated with caution. Whilst the numbers of animals used in one area of human activity cannot be used to justify the numbers used in another, a comparison can help to put the figures into perspective. Last year, 2.79 million procedures on animals were started under the Animals (Scientific Procedures) Act 1986 that, by definition, may have caused pain, suffering, distress or lasting harm. This number is tiny compared with the numbers of animals used in the food industry, many of which will suffer some welfare compromise in the processes of production and transport. For example, in 2003, 793.4m broiler chicks were used to produce 745.6m broiler birds (Defra Website 2004), and many broiler birds suffer welfare problems such as lameness (eg Weeks et al 2000 Butterworth et al 2002). Secondly, the published statistics on animal procedures are not a particularly good indicator of suffering. According to the Guidance on the Act:

> "The assessment of the severity band for the project as a whole reflects the number of animals used on each protocol and the actual suffering likely to be caused as a result. It is based on the overall level of cumulative suffering to be experienced by each animal, not just the single worst possible case. It takes into account the proportion of animals expected to reach the severity limit of the protocol and the duration of the exposure to that severity limit, the nature and intensity of the adverse effects, and the actions to be taken to relieve the suffering."

Hence, data are not published on the numbers of animals that reach a particular severity limit, but instead projects are assigned an overall severity rating at their outset, and this can distort the perception of the extent of suffering resulting from animal experimentation. A retrospective system needs to be developed to provide an accurate assessment of the harms experienced by animals so that this can be used to refine procedures and inform the public. This is currently the subject of a joint project between the Animal Procedures Committee and Laboratory Animals Science Association.

Whilst there is undoubtedly public concern about animal experimentation, Mori Polls (1999 and 2002) and the recent House of Lords Select Committee report (2002) indicate that it is society's view animal experimentation should continue as long as there are proper controls and no unnecessary animal suffering.

It is here that UFAW has had a great impact. In 1956 The UFAW scholars, Professor William Russell and Rex Burch, published the principles of the 3Rs which have since become the ethical principles underlying the use of animals in experiments worldwide. The 3Rs are defined as follows:

Replacement of animals with non-sentient alternatives,

Reduction of the numbers of animals in the remaining experiments to a minimum, and Refinement to reduce the suffering of the remaining animals used in experiments to a minimum.

Let us begin with Replacement and Reduction. The statistics show that while animal use has shown an overall decrease since 1970, over the last 7 years the numbers have not continued to fall partly because of the development of new techniques, such as genetic research. However, the numbers of animals required per candidate medicine, has declined dramatically over the last 6 years. There are in fact good reasons other than welfare why scientists should seek to use alternatives to animals whenever possible as animals are expensive to keep and difficult to use. While some argue that Replacement should lead to an ongoing drop in numbers, Russell and Burch clearly understood that, for the foreseeable future, new requirements to use animals would arise, and therefore that there would be a continuing need to seek replacements. Just as scientists are likely to wish to use available replacements, they are similarly motivated to reduce the numbers of animals used to a minimum. However, Festing (2002) has drawn attention to the fact that there is considerable room for improvements in experimental design used in studies. More needs to be done to ensure that experimental designs are optimised. To this end The

Alternatives Section of the Laboratory Animals Science Association, of which I am a co-convenor, held a meeting this year.

Refinement has two components: Refinement of procedure, and Refinement of husbandry. These are equally important, and there has been substantial progress in both. Some of the most important developments in procedure refinement have been in the development of routine use of post-operative pain relief, and more recently in the detection of pain. Signs of pain in animals are not always obvious to human eyes, and ethologists are working on the detection and evaluation of non-obvious signs of pain. Refinement by training animals to co-operate in experimental procedures is another way of reducing the stress associated with routine procedures such as weighing or injection and this is an area of research that UFAW is currently supporting.

With respect to refinement of Husbandry it is a legislative requirement under the European Directive EEC 86/609 that any restriction on the extent to which an experimental animal can satisfy its physiological and ethological needs shall be limited to the absolute minimum. Yet, until recently animal housing was often barren, designed to ensure that animals were physically healthy but clearly did not meet the animals' ethological needs. This is an area where there has been improvement in this country. We need to ensure that improved standards of animal husbandry are disseminated to other countries both in the interests of animal welfare and to ensure that research in this country is not disadvantaged to the extent that research moves abroad where in some countries standards may not be as high as in the UK.

The move away from traditional barren housing to more enriched housing has been led by the input of animal welfare scientists such as those supported by UFAW through its Research Fellowship, Pharmaceutical Housing and Husbandry Steering Committee studentships, and its Research Training Scholarships. Latham & Mason (2004) have identified conflicts between the natural behaviour of mice and laboratory housing to highlight potential welfare issues. Studies of laboratory animals have shown that abnormal behaviour may be more common than generally thought (eg Kroehn et al 1999, Hubrecht et al 1992), and such behaviour not only indicates that the housing conditions that result in these deficits is bad for the welfare of the animals but may also harm the science (Garner & Mason 2002). How then can we know what should be provided for animals? Ethologists have developed techniques to ask animals what they want in their environment and by training them to work for access to various features, to estimate how much they want it (eg Sherwin 1998, van der Weerd et al 1998), and there are now numerous studies that demonstrate the beneficial effects of enriching laboratory cages.

Scientists are sometimes reluctant to use enrichment because of concerns that it might interfere with their research. However, so-called standard environments can also have adverse effects on experimental outcomes, and enriched environments can improve validity (Damon et al 1998, Healy & Tovée 1999, Kuhnen 1999). Nonetheless, it is important to consider possible effects of enrichment on experimental outcomes and it may either increase or reduce variation or have no effect (Augustsson et al 2003, Tsai et al 2003).

Enriching the animals' environment can have other benefits, for example, in a recent study (Hockley et al 2002) the authors used a genetically modified strain of mouse as a model for Huntington's disease (a genetic disorder of the central nervous system resulting in progressive loss of motor control). They found that even limited enrichment slowed the progression of the disease and speculated that their results could provide a basis to ameliorate the effects of Huntington's disease in humans.

To conclude, over the last 10 years or so there has been considerable progress in improving standards of laboratory housing in the UK. Before then, laboratory animal housing was designed largely to avoid the spread of disease and for the convenience of research and animal care staff. Today, with greater understanding of the interactions between animals and their environments and the development of animal welfare science, there has been an increasing emphasis on designing housing that meets the needs of the animals and this is exemplified in the draft revisions to Appendix A of The European Convention ETS 123. Nonetheless, we should not assume that all laboratory housing in this country is satisfactory; there is always a balance to be struck between practical issues, scientific requirements, and the needs of the animal. Moreover, more research is needed in this area, and we need to ensure that laboratory animal standards are raised not only in this country but world-wide.

*References are available from the author on request.*

***In discussion the following points were made:***

Drivers for animal testing include a need for the refinement of drugs and dosages for the average patient although all drugs are unsafe in certain circumstances. Primate housing and management requires careful design since behavioural traits might result in disturbance to deep brain implants. We do not understand how life works, hence experimental results are species specific with no easy transfer of data between species and no absolute safety when relating animal data to human use. The suppression of adverse results is unacceptable. Animal rights extremism feeds off scientists and organisations who shelter behind secrecy and anonymity. Hard core extremists are thought to number some 20 or so individuals which is not unmanageable. Other threats to UK animal testing arise from overseas competition. Irrational differences in the public perception of farm versus experimental animals focuses around the need for deliberate experimental intervention on the latter. Both academic and commercial laboratories need greater protection, and openness to society, if they are to continue to operate here.