Mice and Medicine

Animal experiments, medical advances and the MRC

MRC
Medical Research Council

MRC's principles

The MRC only supports scientific studies which are well designed and likely to provide new information on important questions relevant to human health.

All experimental programmes supported by MRC must avoid using animals wherever possible. The researcher must give sound scientific reasons for their use,and explain why there are no realistic alternatives.

Animal experiments must use the simplest possible,or least sentient, species of animal.

MRC expects researchers who use animals to consider the ethical issues associated with:

- keeping animals in captivity;
- killing animals;
- causing animals distress or pain.

Experiments should use the smallest number of animals that can answer the question posed,and take every practical step to avoid distress or suffering.

All staff involved in animal research,and in the breeding, housing and care of animals, must be properly trained and supervised.

By law, all research must be scrutinised by a local ethical review, and by the Home Office Inspectorate before work begins.In addition,MRC's scientific committees have a responsibility to scrutinise scientific plans for animal experiments to ensure they are worthy of support.

MRC actively supports the development and dissemination of techniques that reduce, refine,or replace animal experiments.

Researchers collaborating with laboratories in other countries must ensure that standards there are consistent with standards in the UK.

These principles are drawn from MRC's ethics guidance "Responsibility in the Use of Animals in Medical Research (1993)"

Introduction

The Medical Research Council was set up in 1913 to help discover the causes of serious and sometimes fatal illnesses, and to use this knowledge to work towards treatment,cures, and new ways of preventing disease.

Most of MRC's work involves studies of people,or studies of cells and molecules:animal research is only a small part of what MRC does. 30% of our projects are dependent on some use of animals.

Animal experiments are an integral part of understanding how basic systems of the body work,and what goes wrong with them to cause disease. They are also a necessary, and in some cases legally required, method of testing that proposed treatments are effective and safe.

At MRC every possible step is taken to reduce the number of animals used and to minimise their suffering. Scientific advances have resulted in the use of animals in research halving over the past thirty years. Research in genetics and molecular biology has clarified similarities and differences between species, allowing a higher proportion of research to be done on the mouse and lower organisms such as fruitflies and nematode worms, and a lower proportion on larger animals.MRC researchers have developed non-animal techniques and breeding methods reducing the need for animal use by tens of thousands, and is currently expanding its work on animal welfare.

Opponents argue about the validity of data obtained from animals – but the results speak for themselves.Many of the best known and most useful medical treatments of the last century, including antibiotics, vaccines, heart surgery and kidney transplants, have been discovered or tested through the use of animals.

This type of work continues.It is not a process that can be abandoned because of the advent of cell cultures or genetic decoding. Many of the MRC's current programmes, aimed at countering some of the most life-

threatening or disabling conditions, are moving forward because of data obtained from animal studies.

The MRC is aware of public concern about animal research and acknowledges that people ask "are such experiments really necessary?" Quite apart from Home Office regulations, which are scrupulously observed, it is the culture and philosophy of the MRC that animals are only used where there is no other way of advancing medical knowledge. Every researcher has to provide sound scientific reasons for using animals, explaining why no realistic alternative exists.

For the future, we expect that the rapid pace of change in medical research will continue to change the sorts of animal studies we do. As we turn to genetics more and more for clues to understand disease, the importance of research on mice will continue to grow. At the same time, sophisticated genetic tests, and powerful new medical imaging techniques, can be applied to animals as well as people, allowing us to gather more information from the animals we study, while causing the animals less stress or suffering. MRC aims to remain at the leading edge in developing and applying these approaches.

Some people argue passionately that no animals should ever be used in any research. Others, perhaps the silent majority, accept the process is necessary if the cures and treatments of tomorrow are to be found.

This booklet sets out some of the research the MRC is doing now and explains how animal research contributes to this. It concentrates on mouse research, as this is the largest part of MRC's animal research, and also the fastest changing (See page 24). Statistical information on MRC experiments on animals of all types are on page 26, and further information is available on MRC's Website. On pages 29 to 33 the booklet outlines the regulations and standards that govern this research, and the standards MRC sets for itself.

Why are animals needed in medical research?

We are still a long way from understanding fully how complex living creatures develop correctly, stay healthy, and why disease occurs. Sometimes the only way to learn more is to study living animals.

Campaigners against animal research argue that the differences between species are so great that information from animals cannot be reliably translated in humans.It is true that data from animal work have to be interpreted with caution – but the similarities between species are much greater than the differences.In many senses the mouse – or even the fruitfly – can be the measure of the man.

Studying disease patterns in animals – as well as their reactions to possible treatments – provides powerful clues about what is happening in the human body. Genetic mechanisms that control certain functions in worms, or fruitflies, or fish,or mice, work in exactly the same way in humans.The genes that control the basic functions of human cells are often similar to those in very simple creatures, and in the mouse,there are counterparts for nearly every human gene. However, studies of the most complex aspects of human life,such as our immune system,brain and our reproduction and growth,cannot be based on research into simple organisms only.

It is sometimes asked why living animals have to be used to understand the causes of illness, or to find new medicines, when we have ways of analysing cells and tissues.

But cells and tissue and organs are not complete bodies.A whole body – be it a mouse or a human – is a vastly more complicated biological engine than just a few constituent parts.

For instance,a diseased liver on its own would not reveal how that illness affected the immune system.Sometimes the complete system, not just the parts, has to be studied.

MRC alternatives to using animals

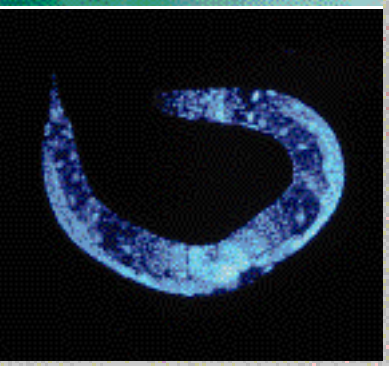
Most MRC research does not involve the use of animals. Where possible cell cultures, tissue cultures, computers and lower organisms such as bacteria or plants are used as alternatives to animal work,usually in the preliminary stages of research.

Cell and tissue cultures

The study of living cells maintained outside the body in a glass or plastic container is known as *in vitro* (in glass) examination. This can allow a detailed examination of specific reactions to a potential drug or other treatment,but it can't provide the whole picture,because the cells are not exposed to all the processes in the body, such as hormones, growth factors and other chemicals that would be naturally circulating.

Tissue cultures, taking thin sections of organs like liver and kidney, or encouraging several types of cells to grow together the way they would in nature,can be used to study the possible effects of drugs on these organs.However, they are difficult to maintain,have a limited life span and cannot give wider information – for example about possible effects in other parts of the body, or how other parts of the body affect the tissues being studied.

These methods are used in almost every area of MRC research, and MRC scientists are constantly developing and adapting these methods to answer new scientific questions.



50% of genes in the fruitfly and 42% of genes in the nematode worm are also found in humans.

Lower organisms

Organisms such as invertebrates, plants, micro-organisms and chicken eggs are used to provide early information on biological systems, and how these respond to potential treatments. Yeast and worms are extensively used by MRC to study the control of cell growth, particularly in cancer research.

Imaging techniques

The advanced brain and body-imaging techniques developed for human studies can be adapted to make animal research less invasive and reduce the numbers needed. An MRC research programme has applied a powerful scanning technique known as Positron Emission Tomography (PET), to study the brains of mice and rats.This is not only providing new information on the activity of chemicals in the living brain,but also means that fewer rats and mice need to be killed.

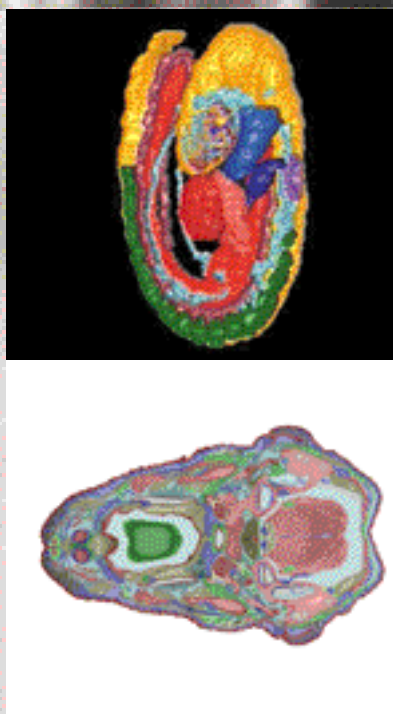
Computers

Computers and mathematical modelling to predict biological activity have revolutionised the process of drug discovery by reducing the need to use animals for the very early "pre-screening" of possibly millions of potential drug candidates. One current MRC project is to create a "mouse atlas"– a 3-D computer model of the genes involved in the development of the mouse embryo. As well as aiding research programmes world-wide by making new data readily accessible,the atlas will also help reduce the numbers of real mice needed, by helping researchers design more focused and efficient experiments.

But all computer techniques depend crucially on what information is fed into the computer, and much about the detailed workings of the body are still not known.

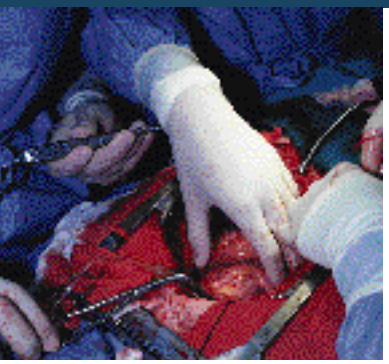
Computers can only make predictions from previous animal, test-tube and human studies – so although we can make better use of the knowledge we still depend on the original data from animals on which to base predictions.

Moreover, computers cannot predict how a medicine might react in a complex living system,or whether unexpected side-effects might show up.



Inside the virtual mouse.
The atlas links gene activity to specific tissue areas.

Past benefits arising from animal work



Every year in the UK more than 30,000 people benefit from heart surgery.

Almost every drug or treatment in current medical use has been developed or validated through animal experiments.

Penicillin,insulin for diabetes, polio vaccines, blood transfusion,heart surgery such as bypass techniques, organ transplantation,antibiotics – including streptomycin,the first effective treatment for tuberculosis (TB) – have all been developed as a result of animal research.

More recent developments including a vaccine against meningitis C, a range of heart drugs, and drugs against cancer, such as the successful breast cancer drug tamoxifen,have all been made possible by animal work. Powerful asthma drugs and effective anti-depressant drugs owe their origins to animal work.

Animals themselves benefit from animal research.In many cases the drugs used on animals and on humans are the same. In other cases specific veterinary medications have been developed. Vaccines against distemper, once a major killer of dogs, and vaccines for cats against feline leukaemia virus, were developed through animal work.

How animal studies have advanced medicine

Animal research has contributed to virtually every area of medical research and most of the best known drug or surgical treatments of the past owe their origins in some way to evidence produced by animal studies.

The effectiveness of **penicillin**, which revolutionised the treatment of bacterial infection, was proved in tests on mice. **Insulin for diabetes**, which affects more than 300,000 people in the UK and millions world-wide,came about because of research on rabbits and dogs in the 1920s.

Polio epidemics, which until the 1950s killed and paralysed millions of children, were consigned to history in most parts of the world by vaccines which resulted directly from work on a range of laboratory animals, including monkeys.

Blood transfusion, without which much major surgery is impossible,became a reality in 1915 after work on dogs. Major **heart surgery** such as bypass techniques and heart transplants were developed in the 1960s through work on dogs and pigs.

Tuberculosis, which used to be a major killer in the UK, was brought under control in the 1940s with the development of the antibiotic streptomycin which resulted from research on guinea pigs, rats and mice. The **BCG vaccine** used to prevent TB was developed through research on animals, mainly rats and mice.

A strain of **meningitis** called Hib used to be common but is now almost unknown in the UK because of a vaccine developed through work on mice and rabbits.

Kidney dialysis, which sustains the life of thousands of people if they are unable to receive kidney transplants, came about through work on rabbits and dogs. **The drug heparin**, to stop blood clotting during kidney dialysis and after surgery, was discovered in dogs and is still obtained from the liver and lungs of cows.

A range of modern treatments from immunosuppressant drugs for organ transplants to **heart drugs** such as beta-blockers and ACE inhibitors were developed through work on animals.

Cancer drugs, pain killing drugs, asthma treatments, anti-depressants, and treatments against HIV and AIDS have been developed using animals.

Future treatments for **multiple sclerosis, cystic fibrosis, spinal cord injury, Alzheimer's disease** and a range of other conditions are being investigated with the help of animal studies.

Animal research is as vital to the development of tomorrow's treatments as it was to those of the past.

Research on animals plays a part in MRC's fight against diseases such as heart disease and cancer, TB, cystic fibrosis, malaria,deafness, raised blood pressure and depression.The questions being tackled,and the methods being used,are very different from those used 30 years ago. Some of the MRC studies described below have given results that are now being used, experimentally, on patients and healthy volunteers; other examples represent longer term investment in understanding the basic causes of illness.

Cystic fibrosis and the mouse

Deafness and shaker mouse

Improving treatments for depression

DNA vaccine against TB in mice

Malaria vaccine – mice clues to parasites

Preventing cancer

Monoclonals and mice

Cystic fibrosis and the mouse

Children with cystic fibrosis need regular physiotherapy to clear their lungs.

Cystic fibrosis (CF) affects one in every 2,500 Caucasian children: only 50% of sufferers live to 30 years. It is now known that CF is caused by a small genetic defect in a protein, called CFTR,which acts as a kind of "valve" to allow the normal passage of salts and water in and out of cells. Children with CF have chronic lung disease and infections, and sometimes digestive problems.

However, there is still much that is not known about how the disease develops from this defect, or what can be done to reverse the process. Nor is it well understood why the disease develops in different ways in different patients.

By changing the mouse version of CFTR at the embryo stage, MRC researchers have developed a mouse version of CF. This has allowed detailed study of what actually goes wrong in the lungs to cause the disease. We now know this includes a failure to clear two important lung germs, known as *Staphylococcus aureus* and *Burkholderia (Pseudomonas)*.

These cause the mucus retention and lung disease seen in children with CF. Comparing CF mice and non-CF mice which were exposed to these common germs, or protected from them, showed the effect these have on the lungs.

Knowing the disease develops in response to bacterial infection in the mouse gives us an opportunity to look at ways of countering this, using drugs or genetic methods.

The mouse model has also provided important clues about the effectiveness of gene therapy in reversing the disease, and has contributed vital information to allow early clinical trials for potential gene therapy on humans to start in the UK.

A number of approaches are being tried to use healthy genes to correct the CF defect, using either viruses or fatty globules as the transport system to get inside the lungs' cells. The CF mice are the testing ground for these approaches.

For example,MRC scientists have found that it is probably only necessary for a small proportion of the 'good version' of the gene to be produced to have significant health benefits. This knowledge will be important in guiding work on treatments, and could not have been obtained without the CF mouse.

Summarising their work they say that even a modest uptake of the gene may have a significant clinical impact. This knowledge would not have been possible without the mouse.

Yet other researchers have found one of the basic genetic causes of a severe intestinal blockage seen in around 20% of CF patients at birth.Having detected the defect in CF mice, the researchers were able to use their knowledge of mouse genetics to narrow down the search for the gene responsible for this complication in CF patients.Identifying this gene will open the way for treatments for this debilitating aspect of CF.

A litter of research mice. The mouse in the middle carries two copies of the modified CF gene.

Deafness and shaker mouse

A shaker mouse.

A natural genetic defect noticed in some strains of mice,which makes them unstable on their feet and also cause deafness, is proving valuable in MRC's work to understand why some children are born with hearing loss, and why some adults become deaf in later life.

Various genes have recently been identified which contribute to hearing impairment,but one in particular, known as GJB2, has interested researchers because it may be responsible for up to half of the genetic cases of childhood deafness.

Another gene that has been the focus of much attention is one known as MYO7A, which can cause sporadic cases of deafness and also the condition called Usher syndrome. This is a hereditary condition which affects hearing, balance and sight.

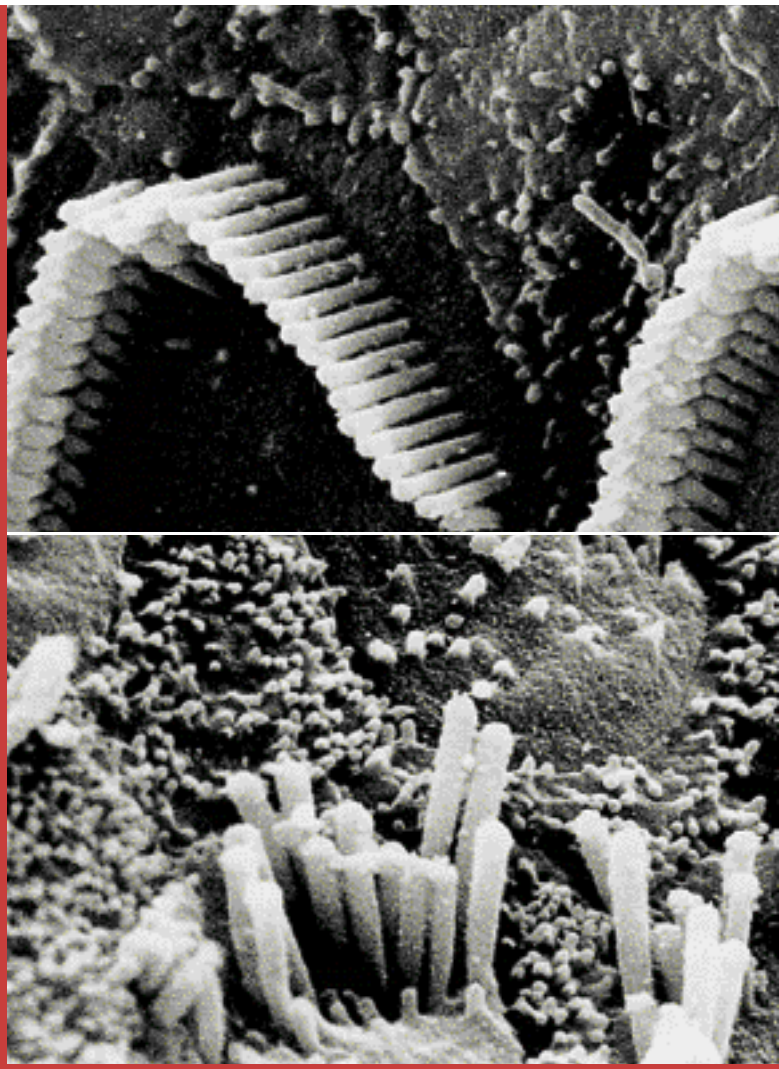
MRC scientists have been examining how such genetic defects affect the function of hair cells in the cochlea,which play a vital role in hearing.

To do this they have been looking at the shaker mouse. This naturally-occurring mouse strain was first discovered by mouse breeders in the 1920s, and shows a shaking movement of the head because of balance problems due to inner ear defects, as well as deafness.

The researchers found, by studying the mice,that the gene Myo7a is altered,affecting the production of a particular type of protein called myosin.This, in turn,affects the development of the sensory hair cells in the inner ear. Each hair cell normally grows around 100 finger-like projections (hairs) called stereocilia on its upper surface, and in the shaker mouse, these stereocilia were very disorganised,affecting the ability of the hair cell to detect the tiny vibrations in sound.

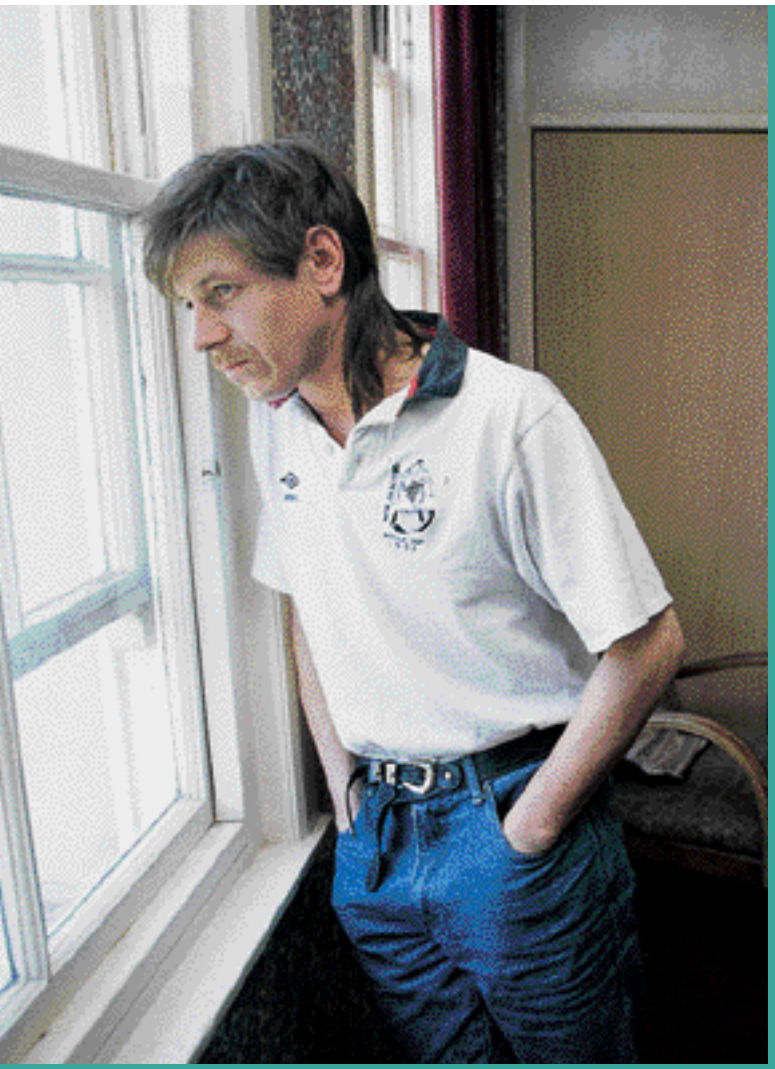
Knowledge of this area is at a very early stage,but it is laying foundations for work on childhood deafness in the future. The researchers reported recently: "Our findings suggest that MYO7A not only has a role

in hair cell function,but also is essential for organising the developing stereocilia bundle." The work would not have been possible without the shaker mouse.



Normal (top) and abnormal (bottom) stereocilia in the inner ears of healthy and shaker mice.

Improving treatments for depression



MRC scientists are working on the biological, psychological and social aspects of depression.

Depression is one of the biggest causes of ill health. Severe depression is one of the main reasons why people take their own lives. Drugs known as SSRIs (eg Prozac), which affect levels of messenger chemicals in the brain,have led to major improvements in the treatment of depression,but the drugs are not perfect. All need to be taken for several weeks before the full benefits become apparent,and even then up to a third of patients do not respond.

Alternative treatments are needed, because if patients do not respond there is an increased risk of sufferers harming themselves or committing suicide.

Pre-clinical (i.e. before human studies) work in animals by MRC scientists has suggested that combining SSRIs with drugs called 5 HT receptor antagonists can improve the speed of onset and the effectiveness of the

treatment. Clinical trials based on this rationale are already well underway in MRC research centres and elsewhere.

Other researchers are looking at whether the food we eat can affect the production of some of the brain transmitter chemicals which are involved in mood and cognition.

One essential amino acid is called tyrosine. This is related to production of a chemical in the brain, called dopamine, that has been implicated in severe psychiatric disorders such as schizophrenia and mania, as well as drug abuse.

In animal studies MRC staff showed that a reduction in tyrosine produced a fall in the production and release of dopamine in the brain.

MRC clinical staff have now started trials in human volunteers, with one study investigating whether reducing tyrosine might be beneficial in patients with manic depression,where too much dopamine is thought to be produced.

DNA vaccine against TB in mice

The hairless mouse is a naturally occurring variation which is now bred for use in research into vaccines.

Collaborative work between MRC scientists and researchers in Brazil is offering hope for a new weapon to fight the global problem of Tuberculosis. Across the world TB causes around three million deaths and some nine million new cases each year. Some two billion people across the world carry the bacterium which causes the illness, and around 10% of carriers will go on to develop the disease.

Eventually this joint research could mean shorter treatment times, fewer bouts of re-infection and the more efficient eradication of the Tuberculosis bacterium in both humans and animals.

A DNA vaccine,jointly developed by the team,has been found not only to offer protection against mice becoming infected,but also to work as a treatment by stimulating the immune system.

Mice infected with TB and then treated with the vaccine recovered from infection more effectively than untreated mice. In a number of cases, mice treated with conventional drugs and then the vaccine were found to be completely clear of residual bacteria.Importantly, the vaccine also works well against one form of drug resistant bacteria.

One of the research team explained: "Being able to kick-start the body's natural defences to work alongside conventional drugs gives us the opportunity to use a potentially powerful and novel approach to fighting this highly infectious disease, which is already becoming resistant to our existing treatments."

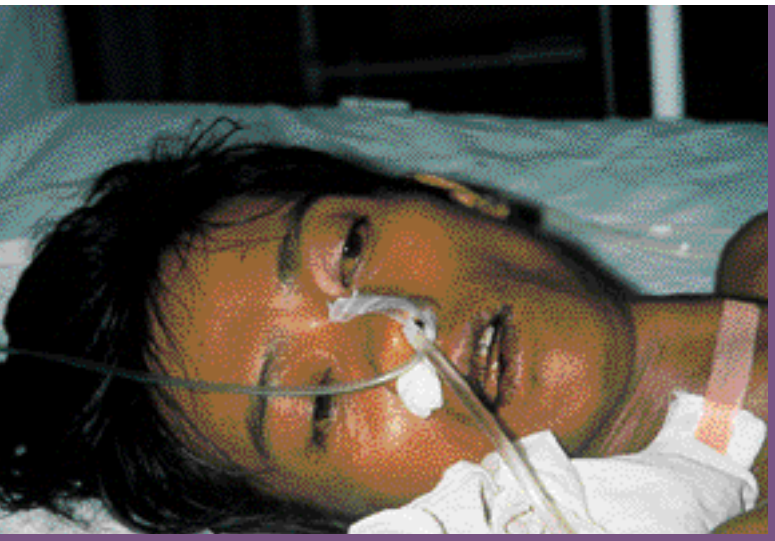
Aside from the deaths and illness it causes, another problem with TB is that drug resistant strains are emerging, and current treatments depend on persuading patients to take

medication consistently for six months, which is often difficult. New approaches are therefore urgently needed.

It is also hoped that the promising research in mice could be applied in fighting the disease in other susceptible animals, such as cattle and badgers.

The DNA vaccines may be valuable in preventing transmission of TB from badgers to cattle.

Malaria vaccine – mice clues to parasites



The most serious malaria attacks can involve brain damage as well as fever and other complications.

Malaria is one of the largest causes of ill health and death across the globe, with more than 300 million cases, and a million deaths each year.

Although malaria is spread by mosquitoes, the damage is caused by a parasite infecting red blood cells. The parasite has a complex life cycle and changes rapidly, making it difficult to develop a reliable vaccine.

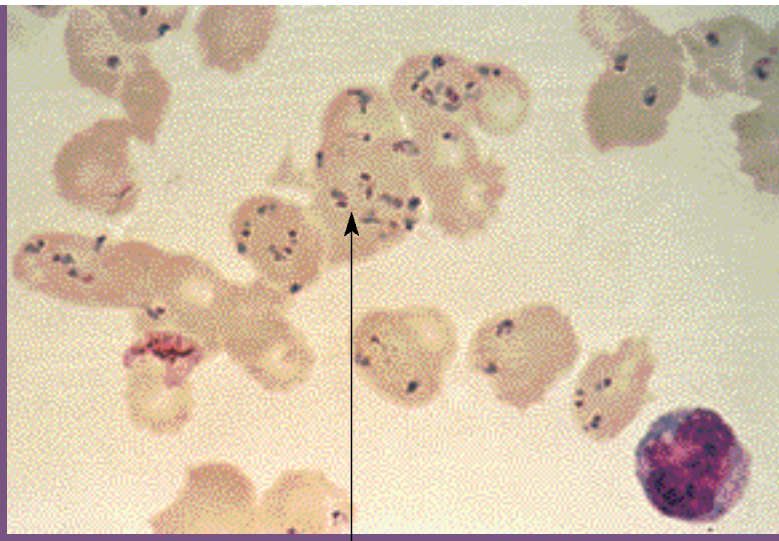
MRC scientists are using mice infected with malaria to learn more about how the immune system deals with the invader, and to find out the parasite's weaknesses which can then be targeted. Malaria parasites not only infect humans but also a number of other animals, including some rodents.

In the laboratory it has been found that mice infected with the parasites can respond by making an immune response that kills the parasites. By

analysing this process researchers hope to find out which particular parts – proteins – of the parasite are attacked by the mouse immune system, and why this is effective despite the constant changes in the parasite.

It will then be possible to see if a vaccine based on these proteins could produce similar immune responses in people who have suffered malaria.

These are the first steps in developing a new vaccine for human trials.



Malaria parasite.

Preventing cancer

The protective effects of curcumin are being investigated.

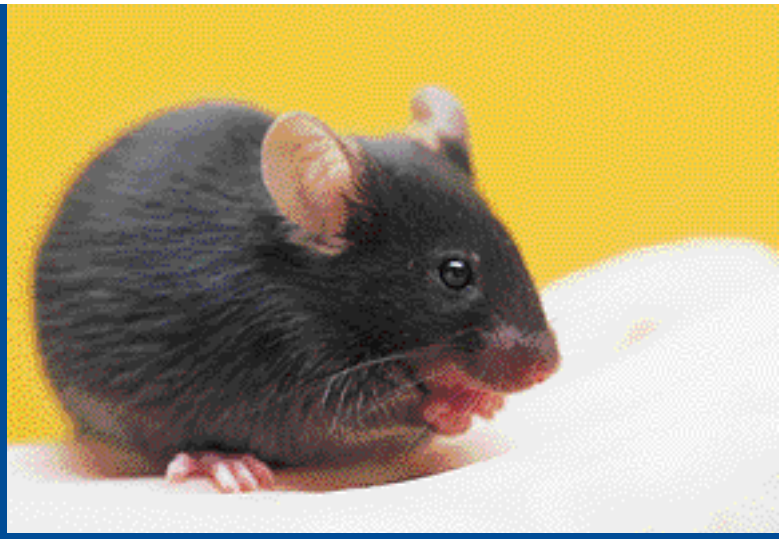
As well as being a social way to round off a trip to the pub, curry is providing clues to new ways in which to prevent cancer.

Alongside much world-wide research into the effects of food as both a treatment and a protection against illness, MRC scientists are investigating the role of a constituent of turmeric, widely used in Indian food, called curcumin.

Mice are playing a crucial role in testing the theory that the chemical can be protective against bowel cancer, and in ensuring that the dose of curcumin is safe before trials in humans start.

Mice that are genetically susceptible to bowel cancer are being given varying concentrations of curcumin and compared with a similar group of mice receiving a normal diet. In studies so far the mice given curcumin have fewer of the early cancers.

The mouse work is helping scientists assess the most effective dose of curcumin to prevent the cancer, without causing side-effects, and trials in human volunteers have recently started.



Monoclonals and mice

The structure of an antibody molecule: research into how the protein molecule is made means fewer mice can be used.

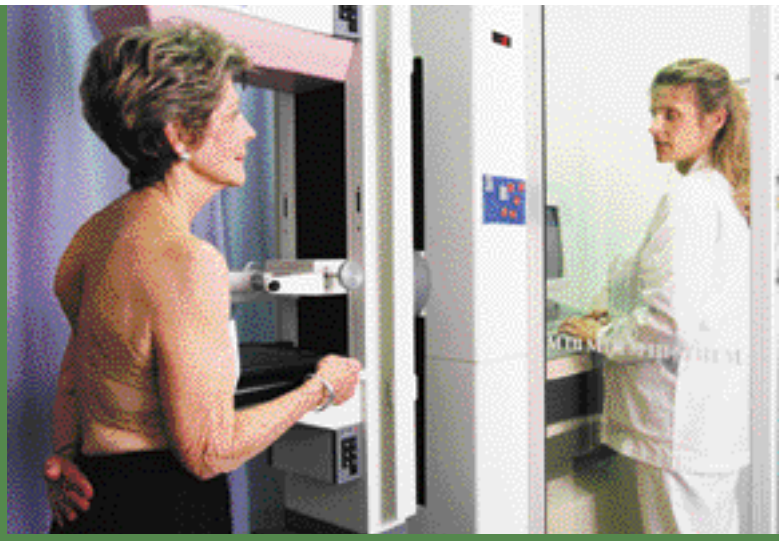
MRC's discovery of monoclonal antibodies – the biological "homing missiles" that can exactly target and lock onto disease cells – have made a huge impact on the diagnosis and treatment of illness, and now a multi-million pound industry exists to make and distribute medical diagnostics and treatments based on antibodies.

The technology illustrates the importance of basic research into how healthy animals function – and also how alternatives to animals can be developed once initial knowledge has been obtained.

Originally monoclonal antibodies had to be made by immunising animals. But in the early 1990s an important new approach was developed by MRC scientists which reduced the need for animals. Antibodies for some uses can now be prepared from a sample of mouse DNA, without having to use live animals. Advances in cell culture methods have also helped reduce animal use.

Current MRC research into how the body makes final modifications to antibodies to get the best possible match to disease cells, may in future help reduce further the need to immunise animals.

MRC research involving monoclonal antibodies to attack disease directly has been licensed to a number of biotechnology and pharmaceutical companies, and new treatments against breast cancer, infections in premature babies, arthritis, and leukaemia have been launched in the last few years.



Monoclonal antibodies are now being used in breast cancer treatment.

The Human Genome Project is unravelling the genetic code for the 80,000 genes that define how our bodies function in health and disease. Most of these genes are new to medical science, and working out the functions they control is the key to designing new drugs, and to detecting illness early, or preventing illness.MRC plans to fill in the gaps in our knowledge in two ways – by looking for possible links between particular genes and ill health in surveys of healthy and ill people,and by looking in detail at what the genes do in laboratory studies of individual cells, simple organisms, and mice.

Virtually all human genes have mouse equivalents, and studying how the genes work in mice is often the most effective way of discovering the genes' role in human health and disease. MRC is investing over £6 million in sequencing mouse genes to accelerate this work.

MRC researchers use natural and man-made genetic changes in mice to study almost every field of illness, including cancer, heart disease,diabetes, obesity, birth defects, cystic fibrosis, muscular dystrophy, vision and blindness, hearing, epilepsy, brain injury and stroke,and Alzheimer's disease.

In some research animals are bred carrying human diseases. Having a living model for a human disease is a powerful tool in understanding how to treat or prevent the illness.Mice have been produced which are susceptible to some human cancers, and more recently the creation of a "cystic fibrosis" mouse has allowed invaluable work into this fatal illness.

Inserting DNA into a fertilised egg.

A more common approach in medical research is to change one,or a few, genes, not to create the human disease in the mouse,but to understand the role that the genes play in the disease. Problems such as inflammation in arthritis involve many separate processes acting together. Treatments that affect only one process may help, but will seldom give a complete cure. Changing single genes can allow the disease processes to be switched off one at a time, to develop a clearer

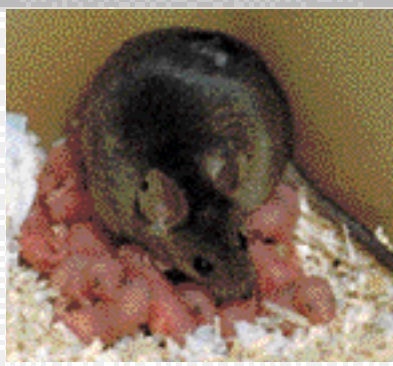
picture of the disease, and how each aspect of the disease might be tackled.

Some people have argued that creating transgenic animals is "unnatural"or represents a new form of cruelty to animals. But others point out that in most cases changing a single gene out of 80,000 will produce only mild effects on the animals'health,and that when breeding animals with certain traits or defects, this can be an advance in animal welfare compared with trying to create such illnesses with drugs or surgery. The effects of genetic modification are closely monitored,against the same standards that apply in every other area of research.

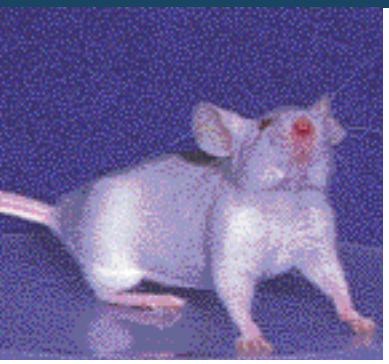
Other concerns have been raised that the process of creating transgenic strains is wasteful,as much breeding has to be done to produce relatively small numbers of altered animals. However, care is taken to try to produce only the numbers of animals that are needed.As better ways of introducing new genes are developed,the process will become more precise.

MRC has helped pioneer the use of IVF and embryo freezing for mice,so that special breeds of mice can be kept without maintaining a large stock of live animals. In some MRC programmes, this has reduced the numbers of mice needed by 20%,and we are now widening its use. This method is particularly valuable if the genetic variation affects the animals'health: reducing the stocks of these mice is a priority.

Genetic modification is an effective research method that can give clear answers more quickly than older research techniques using animals.This does mean that this area of medical research is the only one where the use of animals is increasing. The numbers of animals with man-made genetic variations increased to around half a million in the UK in 1998, while the number of procedures carried out on normal animals fell by 94,000. But this is a necessary development because of the unique opportunities to understand the roles genes play in human illness.



Mouse litter bred using IVF.



Procedures in UK

Figures from the Home Office – which controls animal experiments – show that in 1998 there were some 2.6 million scientific procedures carried out on living animals in the UK,in universities, public and charitable research centres, and industry. Most of these procedures were in applied medical research or basic biological research,but the figures also include veterinary research (7%).About half a million of the procedures are safety tests required by law on new medicines, veterinary products, and other new products.

It is important to note that "procedures"are not the same as "experiments". Many research procedures do not involve significant animal suffering:some are simple tests such as taking blood for analysis. Home Office licences have a severity banding, reflecting the maximum amount of distress or suffering that might be involved, taking account of anaesthesia and pain relief, duration, and the number of animals affected.Around 94% of the licences allow only procedures graded as mild or moderate:less than 2% are substantial.

Moreover, although the total of 2.6 million procedures each year might sound a lot,it pales into insignificance compared to the numbers of animals consumed for food,or destroyed as vermin.

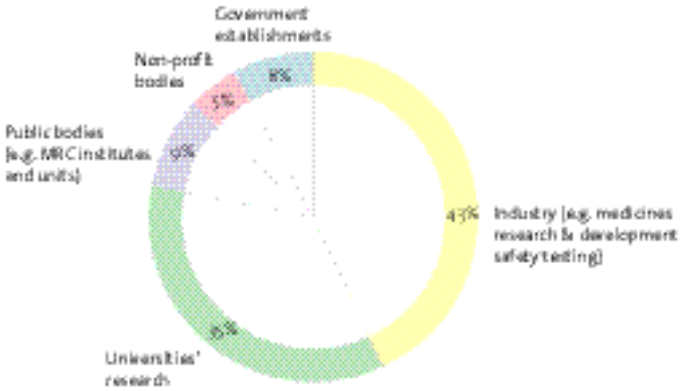
Nationally, mice, rats and other rodents were used in the majority of procedures – 85% of the total.

The majority of the procedures – 73% – involved ordinary breeds of animal.The rest involved mice or other animals with either a natural or a man-made genetic variation.

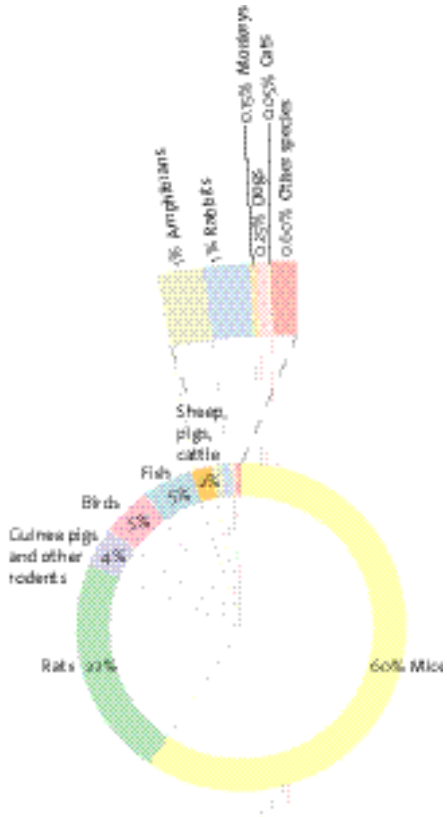
Dogs, cats, horses and non-human primates, which are accorded special protection, were collectively used in less than half of 1% of procedures in UK.

In around a third of procedures – 35% – anaesthesia was used.But animal studies rarely involve surgery, and animals are not anaesthetised for experiments involving injections, blood samples, and other minor procedures.

The main types of organisation conducting animal experiments in 1998



Percentage of procedures carried out on each species in 1998



What happens in MRC

Experiments using animals in MRC research institutes and units account for 161,000 procedures each year. We support roughly the same amount of research again through grants to universities and hospitals.

The figures below are estimates of annual numbers of procedures in MRC institutes and units, based on data from 1998 and 1999.

Species	Procedures
Mouse	152,000
Rat	6,000
Toad,frog or other amphibian	2,500
Fish	300
Rabbit	150
Pig	100
Guinea Pig	100
Sheep	60
Marmoset(new world monkeys)	60
Macaque (old world monkeys)	40
Hamster	30
Poultry	20
Ferret	20
Total	**161,000**

Zebra fish are the most commonly used fish in genetics research.

Since the early 1990s MRC's use of **mice** and **fish** has increased significantly: procedures on mice grew from about 100,000 a year to 152,000 a year. The numbers of mouse procedures are higher, because studies on mice are one of the main ways of understanding the genetics of human disease. In counting procedures, we include every mouse bred simply to keep special genetic strains going – where there is any risk that the genetic variation in the mice might cause illness or disability – as well as mice used in experiments. For this reason the numbers of mice linked to genetic research are higher than in other areas of research.

Over the same period the use of cats, dogs and baboons in MRC establishments (small in the early 90s) has declined to zero. Procedures on other primates, rabbits, rats guinea pigs, hamsters, gerbils and sheep have all declined.

What the law says

Strict controls on the use of animals in medical research are laid down by the law and enforced by the Home Office. Alongside these statutory controls, researchers and scientists are striving to promote animal welfare through a culture of care. The aims are to cut the numbers of animals needed in tests, and where animals must be used, to ensure that distress is kept to a minimum.

Legal controls on the use of animals in experiments have existed in Great Britain since 1876.Britain was the first country in the world to have such a law. These controls were significantly revised and extended with the Animals (Scientific Procedures) Act 1986.

Setting standards

The Act requires that before a researcher can use animals he or she must have a series of special licences.

Such licences are only granted if: the potential results of the research are important enough to justify the use of animals;the research cannot be done using non-animal methods;and the minimum number of animals will be used.

The law also says that dogs, cats and primates are only to be used when smaller, less advanced,animals could not provide the information. Discomfort or pain should be minimised by the appropriate use of anaesthetics or painkillers, although in most cases the majority of procedures are too minor to require this.

It is further laid down that the researchers must have the necessary skill, training and experience with laboratory animals, and the research laboratory has the necessary facilities to care for the animals properly.

Three different licences must be granted by the Government,and these are legally binding documents.

The first licence is called the Certificate of Designation.This is given to a laboratory or research institute which has a properly built and run animal house. This mustmeet Home Office criteria in matters such as staffing, veterinary care,properly trained animal technicians, the size of the animal rooms, the cages, lighting, ventilation and temperature control etc. The certificate holder has responsibility for making sure there are systems and procedures to manage standards and training of staff.

The second licence is the Personal Licence. To obtain this, the researchers must go on a training course to familiarise themselves with the law and ethics of animal research,the basics of caring for animals and handling them in experiments, and ways of recognising symptoms of illness or suffering.

The licence specifies which procedures the person has sufficient knowledge and experience to conduct on which types of animals. A scientist cannot conduct experiments which are not on the personal licence.

The third licence is the Project Licence. This is extremely detailed and may run into scores of pages.It contains a complete description of the research programme explaining why the animals are needed,what experiments will be done,why the information could not be obtained through other means, why the research is important and what steps have been taken to reduce numbers and care for animals.When new results lead to a significant change of plan,scientists must request an official modification to their licence before doing more experiments.

The law says that animals must be examined every day, and a vet must be on call at all times.Any animal judged to be in pain which cannot be relieved must be immediately given pain relief or painlessly killed, regardless of whether or not the purpose of the research has been achieved.

Policing the Act

To oversee the Act, the Home Office employs a team of inspectors who have to be qualified vets or doctors.These advise on whether licences should be granted,and also carry out spot checks on laboratories. Inspectors carry out about 2,500 visits a year and can turn up at any time,unannounced.

In more difficult licence applications, the inspectors can refer to external experts in a particular field, or to the Animal Procedures Committee (APC).

The APC is an independent body set up to advise the Home Secretary about matters to do with the Act. There are 12 members, at least two-thirds of whom must be doctors or veterinary surgeons.Animal welfare groups are represented,and at least half the members will be people who have not done animal experiments, or have not done so for six years.

Compliance with regulations is not enough:MRC expects scientists to have a positive commitment to animal welfare. Most scientists care about animals and work to longstanding principles of care generally known as the 3Rs.This stands for Replacement, Reduction and Refinement. The approach was first outlined in 1959 by researchers William Russell and Rex Burch.MRC fully supports these principles and emphasises that animals should be given due respect and care by all who look after, handle or perform experiments upon them.

The 3Rs call for the **replacement** of animals by non-animal methods where possible;the **reduction** of numbers to the minimum necessary to obtain valid results where replacement is not possible, and **refinement** of all procedures to minimise adverse effects.

Refinement means modifying procedures to minimise stress, boredom or suffering experienced by an animal,and enhance its well-being. Improving bedding, cage space and providing more varied food and making environments more interesting could come under this heading. In other cases the use of more sophisticated diagnostic tests can be employed to detect a disease early, to allow an experiment to end before an animal suffers.

Where larger animals are used,stimulation and exercise are provided. Where procedures are likely to be painful, anaesthetics or pain relief is provided.A high proportion of MRC experiments are mild,where no anaesthetic is needed.Where animals have to be killed,they are killed humanely, following strict regulations and standards.

The MRC insists that when collaborating with outside bodies in the UK or abroad its researchers must ensure that animal facilities at those institutions are of a similar high standards to MRC facilities.

Reduction covers any strategy that will result in fewer animals being used to obtain the same information.In some cases, for instance,

experiments can be designed so that a smaller batch of mice, intensively studied,can answer a wider range of questions.

The vets and animal technicians who work at MRC institutions take their responsibilities extremely seriously and are conscientious in ensuring that both the letter of the law and the spirit of the culture of care are kept constantly in mind.

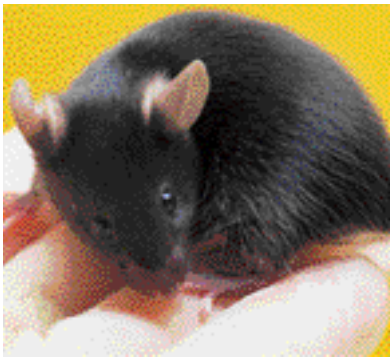
As well as the law, and the voluntary 3Rs approach,the Government recently laid down that from April 1999 a local ethical review process is required in all establishments using animals.

The aim is to strengthen the Home Office's assessment of proposed experiments with a separate, formal, consideration of the justification for using animals, and the scope to replace, reduce or refine use. The MRC fully supported the introduction of this extra safeguard.

A continuing commitment to change

MRC has made major contributions to the development of alternative methods, to more refined and humane research techniques, and to better ways of breeding and housing animals, and will continue to support improvements in animal use.

MRC scientists are also expected to help spread good practice in animal welfare. For instance any new procedure which reduces the numbers of animals needed,or the severity of procedures, should be communicated to other researchers. Published papers should include information which would be likely to help others conducting similar experiments.



The Animals (Scientific Procedures) Act of 1986 makes it a legal requirement to have a named veterinary surgeon (NVS) where animal research is carried out, to be responsible for the health and welfare of the animals in each institution.

Some large institutions have full-time vets and smaller ones use local vets with a contract. Some NVSs also have research and managerial responsibilities, wearing two hats.The responsibilities can be wide – one MRC institute has 65,000 rats and mice,1,500 frogs and 15,000 fish.

David, a vet with a contract with the MRC, explained:"This sector of the veterinary profession is massively misunderstood in lots of different ways.Some people can't understand why vets are involved with lab animals.

"People equate us with cat and dog vets, but working with rats and mice I am in many ways more like a cattle or sheep practitioner. We are interested in the well-being of individual animals, and if they get sick we do something about it,but we also have to be concerned for the well-being of the whole herd or colony.

"We come into this job to make a contribution to animal welfare – to look at the science and say 'does it have to be done this way or could it be done in a way which minimises pain suffering and lasting harm?'

"The work we do is necessary. You look at what is being done and weigh whether the benefit for mankind outweighs the cost to the animals.

"The big problem with science is by its very nature it is experimental and things do not always work as you expect them to. Sometimes things don't work as you hoped – equally you get astonishing discoveries when you least expect.

David points to work involving genes called *HOX* genes, involved in segmentation of the nervous system.It has now been found that these work in every stage of development of the embryo. "If you are looking at the development of the embryo, you have to look at an embryo. You can't replicate that with a cell line. You need the entire biological system.

"Where possible we use non-sentient material,but unfortunately there comes a point where computer simulations won't work.They work if you know everything about the system,and we don't. Cell lines and organ baths are tremendous, but there comes a point where you need to put this information in a living system to see how it works."

David acknowledges that species difference is something that science has to be aware of. But he points out that the similarities with human conditions in some animals are very close.

"For instance, the way the ferret responds to the flu virus is immunologically identical to the way the human immune system responds.There are differences, but there are striking similarities. Just like us guinea pigs can't make vitamin C and need a dietary intake. If you don't feed them vitamin C they develop scurvy, which is a human condition.

"There is a great deal of physiological similarity between mammalian species, and even between non-mammalian species.A lot of work on the *HOX* gene for instance is done on the *drosophila*, the little fruitfly. You can do a lot of work in insects but there comes a time when you need to bring it into a mammalian system."

David argues that the wider perspectives involving the use of animals in this country need to be kept in mind when people raise doubts about the value of animal research.

"Something like three million animals are used in scientific procedures – but each year in the UK we consume 800 million chickens for food.The RSPCA and other charities kill more abandoned unwanted dogs and cats than are used in laboratories. 85% per cent of research animals in the UK are rats and mice. Million of rats and mice are killed each year as vermin."

He is adamant that the law and the in-house culture of care add up to a rigorous system of protection and welfare for the animals.

"Home Office inspectors make unannounced visits most months and sometimes every three weeks.It is a vigorously policed piece of legislation.

"Our animal technicians take their duties very seriously – and are genuine animal lovers.I could take anyone to any part of our animal facilities with every confidence."

David is certain the work with animals is necessary, and also that it is carried out as humanely as possible.

"We all think about the use of animals – it's not something one blithely goes ahead with.It is necessary for me to be here,legally, morally and ethically. Is it necessary for the animals to be here? Yes, I think it is.

"People want new drugs; they want a cure for AIDS and cancer. Animals are necessary for this, but many people don't want to think about it. It is a regrettable necessity – but we need to do it."

Further information

Further information can be found on MRC website www.mrc.ac.uk

The Boyd Group website www.boyd-group.co.uk provides a useful guide to the wide range of ethical views on animal experiments.

The Boyd Group is a forum for open exchange of views on the use of animals in science. It has a broad membership which aims to recommend practical steps to achieving common goals.

Credits

Pictures:page 10 CF Trust/Camilla Jessel,page 17 (badger) BBC Natural History Unit Picture Library and pages 18-19 Wellcome Photo Library.

Medical Research Council 20 Park Crescent London W1N 4AL
Tel 020 7636 5422 Fax 020 7436 6179 Web www.mrc.ac.uk

Designed by Precise.

July 2000