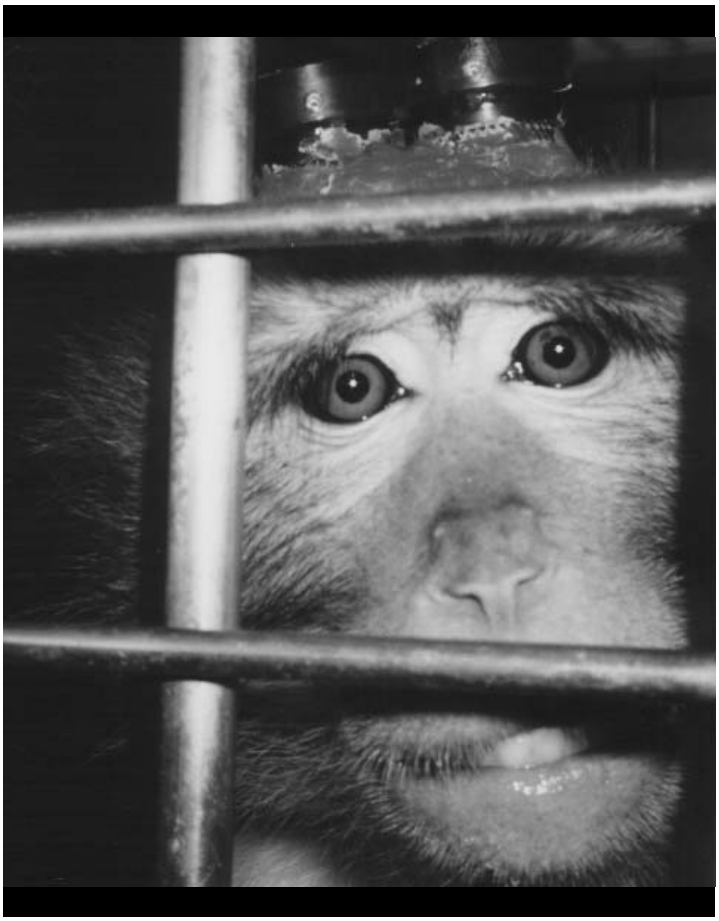

The case for an EU ban on primate experiments

Animal Aid
The Old Chapel, Bradford Street, Tonbridge, TN9 1AW
Tel: 01732 364546 info@animalaid.org.uk
www.animalaid.org.uk

Published by Animal Aid, August 2006
ISBN: 1-905327-20-X

After 20 years, the EU law that governs animal testing across Europe and the UK is being revised. European Directive 86/609 EEC, which applies to animals used for experimental and other scientific purposes, is the legal template on which all EU member states base their national laws. In the UK, the relevant law is the Animals (Scientific Procedures) Act 1986.

One issue arising from this revision is the prospect of a ban on the use of primates. While Animal Aid campaigns for an end to the use of *all* animals in experimentation on both ethical and scientific grounds, it has joined other groups across Europe that are united in calling for a total ban on the use of primates for research and testing.

In Britain, there is already widespread public support for such a ban:

- At a 2002 public inquiry, Cambridge University failed to convince the government-appointed planning inspector of the scientific validity of using primates in research.
- A 2003 NOP poll commissioned by Animal Aid showed a majority of the UK population opposed to primate experiments, with just 40 per cent believing they were acceptable.
- More than 150 MPs signed Early Day Motion (EDM) 1704, tabled in February 2006, which called for a ban on the use of primates.

The ethical case

The use of such highly sentient creatures is morally indefensible. The main reason cited for using primates – their similarity to humans – is also a compelling reason for *not* using them. The pain and stress endured in toxicity tests and in experiments related to brain conditions, including stroke, are appalling to contemplate: retching and vomiting, uncontrollable diarrhoea, tremors and unbearable suffering are inflicted upon these, our near relatives. Monkeys also suffer deprivation of food and water to manipulate their behaviour, are psychologically damaged and made to perform repetitive 'frustration' tasks. They are surgically mutilated and forcibly restrained.

Apart from the physical pain of the experiments themselves, non-human primates suffer fear, loneliness, frustration and stress, simply from being kept in captivity. These intelligent, social animals are typically kept in barren metal cages. Often they are housed alone, sometimes for many years. Some will be killed after a single experiment; others are made to endure procedure after painful procedure in ongoing studies lasting for years.

The scientific case

While there are important similarities between humans and non-human primates, the differences are stark and significant. The human brain is four times larger than that of a chimpanzee, which is four times larger than that of a macaque. There is no equivalent language centre in primates that we are able to recognise, which is especially relevant when studying Alzheimer's and stroke. (1)

The chimpanzee, with whom we share 98% of our DNA, is the closest living relative to humans, in evolutionary terms. And yet that tiny difference has enormous implications when it comes to biomedical research, not least because of crucial differences in the way genes are regulated in humans and chimpanzees. As a consequence, we find that chimpanzees are essentially immune to AIDS, hepatitis B and common malaria – diseases that kill millions of people every year. Primates are commonly used for research into neurological disorders such as Alzheimer's, Parkinson's and stroke but trying to replicate accurately these human diseases in an animal has proved impossible. The animal is usually healthy at the start of the experiment, and so must be made ill by artificial means, in an attempt to reproduce the human symptoms. They are deliberately brain damaged through surgery or by use of toxic chemicals. As soon as the monkeys recover from these preliminary procedures, the experiments

The ethical case
The scientific case

begin. Working with a set of artificially induced symptoms in an animal, however, is not the same as working with a spontaneously arising disease in a human being.

For example, Parkinson's disease becomes progressively worse in human patients, while the chemically induced marmoset version demonstrates gradual recovery. (2) Alzheimer's in humans is characterised by a degrading of the powers of cogent thought and language. How can such phenomena be detected, let alone measured, in non-human primates? Brain-lesioned marmosets used in the study of Huntington's disease do not replicate the pathology or symptoms of Huntington's in humans. (3) Countless treatments for stroke have been developed in primates and other animals – yet all of them have failed or even harmed patients in clinical trials. (4) Thus, whatever is discovered through animal experiments must be 'rediscovered' in the patient because of species differences.

Primates in applied research

Throughout the EU, monkeys are used primarily in applied research. This invariably means the safety and toxicity testing of medicines by the pharmaceutical industry, and is for regulatory approval. Toxicity testing is one of the cruellest of all animal procedures as it involves deliberate poisoning by overdose. Over a period of days, weeks or months, animals are dosed with drugs or chemicals by injection, inhalation or gavage (force feeding). Symptoms of drug poisoning may include vomiting and convulsions. Some of those who survive the experiments will be reused but the majority are killed so that their body tissues can be studied. The total number of monkeys used in this way is approximately 2,500 per year in the UK, with a further 4,500 used throughout the rest of the EU.

Although macaque monkeys are the pharmaceutical industry's primate of choice, there has been an increasing trend over the last few years to use marmosets. These animals are much smaller than macaques, weighing only about 400g, which makes them comparatively cheap to dose with valuable test compounds. Their small size also makes them easy to handle and to incarcerate in small cages or in inhalation chambers.

Applied research examples

These are just a few examples illustrating the scientific and ethical failings of using monkeys in applied research.

- *Isoprenaline* doses (for asthma) were worked out on animals but proved too high for humans. Thousands of people died as a result. Adverse effects suffered by the patients could not be reproduced in monkeys in subsequent experiments. (5)
- *Carbenoxalone* (for the treatment of gastric ulcers) caused people to retain water to the point of heart failure. Again, scientists tested it retrospectively on monkeys but could not reproduce this effect, (6) clearly demonstrating that research on non-human primates would not have predicted the fatal outcome.
- Trials of an important AIDS vaccine were successful in monkeys but when tested on 8,000 human volunteers, it failed to protect them from the HIV virus.
- TGN1412 made headlines in March 2006, when six healthy volunteers who took the monoclonal antibody (mab) showed serious toxic reactions and were admitted to intensive care units. Earlier tests, in which 50 monkeys were given the mab – in some cases in very large doses, and over varying time periods – showed TGN1412 to be quite safe.
- Hormone replacement therapy – given to millions of women following research in monkeys – has recently been found to increase their risk of heart disease, stroke and breast cancer. (7)

Primates in disease research

In neurological disease research, primates are deliberately brain damaged in an attempt to understand more of the nature of the disease in question and to assess the merits of novel drugs and surgical interventions. The following are recent examples of disease research involving monkeys, carried out at UK universities.

Disease research examples

- **Parkinson's disease**
  In 2002, researchers at the Laboratory of Physiology, Oxford University, injected rhesus macaques with a chemical (MPTP) that interferes with normal brain function. The initial dose given to them made it difficult for the monkeys to control their limbs. In the final stages of the experiment, the primates were given a large dose that incapacitated them to the point of rigidity. Parkinson's does not occur naturally in monkeys; in humans it is caused by an as-yet-not-fully-understood death of dopamine-producing cells in the brain that has nothing to do with MPTP. The animals suffered for ten days, during which time they needed intensive nursing to keep them alive. At the end of the experiment, they were killed. (8)

- **Stroke**
  In 2003, five young marmoset monkeys at the University of Cambridge Department of Experimental Psychology were subjected to severe brain damage. This was achieved by permanently blocking the major blood supply to their brains. The marmosets were then subjected to various laboratory tests, three, ten and 20 weeks after the surgery. By the time the animals showed some signs of recovery from the brain damage, the experiment was terminated and the animals killed. (9) Despite 150 years of stroke research based on animal models (10) and clinical trials, only two approaches have shown proven efficacy in acute stroke: aspirin (11) and admission to a stroke unit (12). Neither of these two proven treatments were dependent on animal experiments for their development.

- **Huntington's Disease**
  At Cambridge University in 2000, 12 marmosets each received ten or more separate injections of a seizure-causing chemical directly into two regions of their brains. They were then assessed for dexterity on a battery of tasks over the course of the following nine months, before being killed. Some of the tasks called for them to reach for and retrieve food 'rewards' – sometimes with one hand covered in gauze and immobilised by sticking plaster. The researchers noted that the brain damage caused 'clumsiness' and dropping of food. In other tests, the monkeys' feet were bound in sticky postal labels. The researchers checked how long it took them to bite and tear their way free. Another test involved injecting the marmosets with amphetamine or apomorphine. The second drug caused the brain-damaged animals to spin uncontrollably in their cages – as many as 300 times in a 60 minute session. The researchers acknowledged that they don't know why the spinning happens and that the brain damage they inflicted 'did not... replicate the pathology or the symptoms of Huntington's Disease'. (13)

Primates in fundamental research

Researchers are under no obligation to produce a clear result from fundamental (also known as 'basic') research, but simply to generate new information. While current law makes it difficult to avoid animal testing during the safety evaluation phase of new pharmaceutical products, scientists conducting fundamental research have no legal requirement to use animals. It is left to the individual scientist to judge what is worth studying, and whether or not to use animals.

Fundamental research examples

These are just a few examples illustrating the scientific and ethical failings of using monkeys in fundamental research.

- In 2003, Oxford University researchers removed parts of the brain cortex of three macaque monkeys to see what effect this would have on their memory. The researchers found that one of the monkeys performed worse than the others, as a result of having been unintentionally subjected to more brain damage. In conclusion, researchers saw a link between the deliberately damaged brain regions and the resulting impairment of physical ability, but they could not rule out the possibility that other parts of the brain were responding to the experimental injury and therefore could also have played a role. (14)
- Also in 2003, researchers at Oxford University implanted electrodes into the brains of macaque monkeys in order to determine what part of the brain controls perception of food texture. The monkeys were deprived of food and water and subjected to six-hour testing sessions daily for an undisclosed period of time. The justification for carrying out this study was that 'the texture of food is an important factor that influences the pleasantness of a food and how much is eaten'. By the end of the experiment, the researchers claimed that they had managed to identify some of the nerve cells associated with distinguishing different textures of food. (15)
- In 2004, two adult rhesus monkeys were trained to fixate their vision on a small point for several seconds. Once they had learned this task, they were anaesthetized and had a metal coil implanted near their eye, which was wired up to record eye movements. Part of the brain was exposed and a recording device fitted over it. The monkeys were forcibly restrained and were 'rewarded' with water when they pressed and released a lever. Giving water as a reward indicates that it had previously been withheld. Although the specific aim of this research is not recorded, the authors concluded that different brain cells respond to different patterns seen by the monkeys. (16)

Legal requirements

Although there is no legal requirement to use primates (or any other animal) for the safety testing of medicines, both the pharmaceutical industry and the regulatory authorities continue to use – and are happy to accept – data from animal experiments because it is so readily obtainable.

Animal testing is influenced by both national and EU legislation. The Home Office officially claims that all new drugs are required by law to undergo animal experiments but, on closer examination, this would appear not to be the case. The UK Medicines Act 1968 and other UK regulations do not specifically require animal tests.

The only piece of legislation that specifically refers to animal testing (Annex I of Directive 2001/83/EC) states that toxicity tests 'shall be carried out on two species of mammals one of which must be a non-rodent'. However, this seemingly solid statement is eclipsed by article 7.2 of Directive 86/609/EEC, which states that an animal experiment must not be carried out if a non-animal method could be used to provide the information in question.

It must therefore be concluded that there are essentially no legal obstacles to the replacement of animals in toxicity testing.

Non-animal methods to replace primates

In order to obtain data that is applicable to human health, we need to focus our resources on human-based medicine and research methods. There is a whole range of modern, rapid and accurate tests now on stream. These use, as their raw materials, human cells, tissues and segments of DNA which are processed and assessed through highly sophisticated, rapid screening techniques. Another increasingly important method is so-called 'microdosing', in which tiny amounts of an experimental drug are tracked in the human body by radioactive labelling. This is in addition to the already established methodologies of non-invasive imaging techniques (PET, MRI scans), population studies and post-mortem examinations. The use of anything less than such state-of-the-art, species-specific research methods sells public health short.

There are a number of obstacles to achieving sound, human-based research. They include a self-serving resistance to progress and an unhealthy regard for profits at the expense of animal suffering and human health.

References

1) Buxhoeveden DP, Switala AE, Roy E, Litaker M, Casanova MF. Morphological differences between minicolumns in human and nonhuman primate cortex. *Am J Phys Anthropol.* 2001 Aug;115(4):361-71.

2) Medical Research Modernisation Committee, *Perspectives on Medical Res.* (1991) 3: 35-46

3) AL Kendall et al, *Brain* (2000) 123 (7): 1442-1458

4) Wiebers D et al. Animal models of stroke: are they relevant to human disease? *Stroke* 1990;21,1-3.

5) S Carson et al, *Pharmacologist* (1971) 18: 272

6) CT Eason et al, *Regulatory Toxicology and Pharmacology* (1990) 11: 288-307

7) H D Nelson et al, *Journal of the American Medical Association* (2002) 288: 872-881, Cancer (2003) 97: 1442

8) Reversal of akinesia in experimental parkinsonism by GABA antagonist microinjections in the pedunculopontine nucleus. Nandi D, Aziz T, Giladi N, Winter J, Stein J. *Brain* 2002; 125: 2418-2430.

9) Serial MRI, functional recovery, and long-term infarct maturation in a non-human primate model of stroke. J Marshall, R Ridley, H Baker, L Hall, T Carpenter, N Wood. *Brain Research Bulletin* 61 (2003) 577-585.

10) Wiebers D et al. Animal models of stroke: are they relevant to human disease? *Stroke* 1990;21,1-3.

11) International Stroke Trial Collaborative Group (ISTCG). The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19,435 patients with acute Ischaemic stroke. *Lancet* 1997;349:1569-81.

12) Stroke Unit Trialists' Collaboration (1998). Organised inpatient (stroke unit) care for stroke (Cochrane Review). In: The Cochrane Library, Issue 3, 1999. Oxford: Update Software.

13) The influence of excitotoxic basal ganglia lesions on motor performance in the common marmoset; AL Kendall et al; *Brain* 2000 Vol 123, Part 7, p1442-58

14) The effect of cingulate cortex lesions on task switching and working memory. M Rushworth, K Hadland, D Gaffan, R Passingham. *Journal of Cognitive Neuroscience* 2003,15:3, 338-353.

15) Representations of the texture of food in the primate orbitofrontal cortex: neurons responding to viscosity, grittiness, and capsaicin. E Rolls, J Verhagen, M Kadohisa. *Journal of Neurophysiology* 2003; 90(6): 3711-24.

16) Pattern motion is present in V1 of awake but not anaesthetised monkeys. *European Journal of Neuroscience* 2004, Vol. 19: 1055-1066. Guo K, Benson P, Blakemore C.

A special report by Animal Aid
Published August 2006

Animal Aid exposes and campaigns peacefully against all animal abuse, and promotes a cruelty-free lifestyle

Animal Aid
The Old Chapel, Bradford Street, Tonbridge, TN9 1AW
Tel: 01732 364546 info@animalaid.org.uk
www.animalaid.org.uk