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The Boyd Group

The Boyd Group Papers on

The use of Non-Human Primates in Research and Testing

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Contents

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Preface

The Boyd Group is a forum for dialogue on contentious issues in laboratory animal use.
This collection of papers is the result of a series of wide-ranging discussions between members and observers of the Group, who offer a diversity of perspectives on the use of animals in science generally, and differ in their opinions on the justification for using non-human primates in research and testing.

The broad aims of the Boyd Group discussions on the use of primates (as on other issues addressed by the Group) were to:

(i) clarify key issues of concern identified by members;
(ii) seek points of consensus on these issues;
(iii) explore points of disagreement and the reasons for them; and
(iv) where possible, make recommendations on aspects of common concern within the Group.

In a sense, these papers tell only part of the story of the Boyd Group's work. It is difficult to capture the process of discussion in printed words (a process in which understanding between people who have rather different perspectives and experiences in relation to the issues can be enhanced – even if, at the end of the discussions, disagreements between them still remain).

It is hoped, however, that the collection of papers will give at least the flavour of the Group's discussions and conclusions, and that this might assist others in thinking through the contentious issues surrounding the use of non-human primates in research and testing.

These papers were prepared by a working party of Boyd Group members and advisers with expertise in primatology, animal welfare, biomedical research and regulatory toxicology. The papers were then debated and agreed by the Boyd Group.

Members of the working party were:
Colin Blakemore, Kenneth Boyd (Chairman), Hannah Buchanan-Smith, Richard Byrne, Robert Hubrecht, David Robb, Jane Smith and Les Ward.

Specialist advice was also given to the Boyd Group by:
Tipu Aziz, Krys Bottrill, Stephen Lea, Phyllis Lee, Jonathan Seckl, John Stein, David Whittaker and Sarah Wolfensohn.

The Boyd Group is most grateful to all those who assisted in the preparation of these papers and to The British Psychological Society for publishing them.

The Boyd Group
June 2002

Summary of Discussions and Conclusions

This summary paper reports the Boyd Group's general conclusions and recommendations on the use of non-human primates in research and testing, and includes brief arguments in support of the conclusions. More detailed evidence and argument can be found in the series of background papers following the summary, which were prepared as part of the Group's discussions.

Introduction

Brief background to the discussions

The use of non-human primates in scientific research and testing is highly controversial. Within the EU, standards of housing, care and use of laboratory primates have been the subject of criticism (see for example, Jones, 1996; Ruhdel & Sauer 1998), and there have also been calls for a total ban on their use. More generally, some campaigners are seeking an extension of legal rights to Great Apes, world-wide.

Britain and France are the major users of non-human primates in research and testing in the EU. In 2000, 2951 non-human primates (mainly marmosets and macaques) were used in scientific procedures carried out in British laboratories (Home Office, 2001). Just over three-quarters of these animals were used in toxicological studies, the vast majority of which were carried out for legislative reasons, and all involved substances intended for use in pharmaceuticals. The remaining animals were mainly used for fundamental and applied research, most commonly on the nervous system and special senses, such as vision. See Paper 1 for further information.

Arguments put forward to justify the use of non-human primates usually point to physiological similarities with humans that are not shared by other species, and which, it is argued, make non-human primates the best, or the only suitable animal models for the work. Paper 1 includes three examples of the use of non-human primates in research, to illustrate the kinds of fundamental and more applied benefits that might be sought from such work, and Paper 5 gives some examples of the use of non-human primates in toxicological studies.

In recent years, the use of non-human primates has become more and more tightly regulated in Britain. Under the terms of the Animals (Scientific Procedures) Act 1986, every use of non-human primates requires special justification, in that such work will only be licensed if it can be shown that no other species is suitable, and further restrictions have been imposed since the Act's inception. In particular, the use of Great Apes was formally banned in November 1997 (though in fact there had been no use of these species in Britain since the 1986 Act came into force, and probably not since the late 1960s/early 1970s), and the use of wild-caught primates was also banned, except where exceptionally and specifically justified. Furthermore, a sub-group of the Government's statutory advisory committee on laboratory animal use, the Animal Procedures Committee, is currently considering 'how to minimise, and eventually eliminate, primate use and suffering' (Home Office 1998). See Paper 1 for further details of legislative controls on primate use in Britain.

Specific questions addressed in the Boyd Group's discussions

1. The Boyd Group's discussions focused mainly on the 'moral status' of the non-human primates commonly used in research and testing in the UK and, in particular, on

(a) how far the use of non-human primates in science is a very special case, deserving exceptional justification;

(b) whether the UK's ban on the use of Great Apes in research and testing should be extended to other species of non-human primate; and

(c) if the answer was 'yes' in either case, whether this special status should apply equally to all the various species of non-human primate.

The Group approached these questions by considering physiological, behavioural, psychological and philosophical evidence that could have a bearing on the moral status of non-human primates, paying particular attention to the similarities and differences between Great Apes and monkey species. Two background papers were prepared to support the discussions. The papers explore:

(i) empirical evidence on the moral status of non-human primates (Paper 2,) and

(ii) the possibility that these animals might be regarded as 'persons' (Paper 3).

2. The Group also considered what might count as sufficiently strong reasons for using non-human primates in research and testing (where it was accepted that there might be at least some use of these species). Here, the focus of discussions was on the use of monkeys in fundamental research including consideration of the case studies presented in Paper 1 and in regulatory toxicity testing (Paper 5).

3. Finally, and throughout the discussions about moral status and justification for use, members sought consensus on practical steps that could be taken to safeguard, and where possible improve, the welfare of non-human primates currently used in research and testing. A further background paper was prepared as part of these discussions (Paper 4).

The conclusions from all these discussions, along with brief arguments to support them, are reported below. More detailed evidence and arguments are contained in the collection of papers that follow this summary.

Conclusions from the discussions

1 Moral status of non-human primates

1.1 Moral status of Great Apes (chimpanzees, pygmy chimpanzees, gorillas, orang-utans)

(a) Consideration of a wide range of available evidence shows that Great Apes have complex mental abilities. These are likely to enhance their capacity for suffering to such an extent that it is unethical to confine them in laboratories and use them in research and testing.

(b) For this reason (as well as on grounds of conservation of the species in the wild) the use of Great Apes in research and testing should be prohibited world-wide.

(c) The question whether, further than this, Great Apes have 'rights' is more contentious and remains unresolved.

There is very strong, clear evidence that Great Apes have complex mental abilities similar in some important ways to those of humans. For example, the evidence explored in Paper 2 strongly suggests that the animals have:

- a sense of self, such that they have insight into their own thoughts and feelings;
- a developed sense of time and purpose, so that they can think about the future and reflect on the past;
- an ability to empathise with the thoughts and feelings of other members of their own species; and
- more contentiously, perhaps the capacity to communicate their thoughts and feelings via symbolic, syntactic language.

These abilities are likely to enhance the Great Apes' capacities for suffering to such an extent that it is unethical to confine them in laboratory housing and use them in scientific procedures. A ban on the use of Great Apes in research and testing (as currently in place in the UK) is strongly supported on these grounds, as well as on grounds of conservation of the species in the wild, and should be respected world-wide. There is no evidence to suggest morally relevant differences between the mental capacities of the different Great Apes, and a world-wide ban should apply equally to all species.

Whether Great Apes are 'persons', having rights, to life and liberty for example, are more contentious questions. As already noted, evidence suggests that they have the capacity for self-consciousness, often considered a necessary and sufficient condition for personhood. However, making self-consciousness the touchstone could accord personhood to Great Apes, but not to human neonates, for example. Similarly, rights might be denied both to Great Apes and neonates on the grounds that rights are correlative with responsibilities, which may be too much to expect of apes, as well as neonates. An alternative view, explored in Paper 3, is that the 'capacity for intersubjectivity' is a sufficient condition for personhood (i.e. that persons share a capacity to recognise and have insight into each other's mental states). But the difficulty with this approach is that capacity for intersubjectivity can only be established by the judgement of another person, which, of its nature, is subjective. Nevertheless, the fact that many primatologists and others judge that Great Apes possess a capacity for intersubjectivity is weighty testimony, and arguably puts the onus of proof on those who judge that Great Apes are not persons. Moreover, in spite of unresolved debate about apes' personhood, the evidence on grounds of suffering alone predicates against their use in research and testing.

1.2 Moral status of other non-human primates

(a) *Non-human primates commonly used in research (mainly marmosets and macaques), do not appear to share the most sophisticated mental abilities of Great Apes.*

(b) *Nevertheless, there is strong, though not incontestable, evidence that the general richness of monkeys' social lives and mental abilities means that compromising their way of life by using them in research and testing has the potential to cause them greater social and mental suffering than other laboratory species.*

(c) *Therefore, the Boyd Group is agreed that any use of non-human primates in research and testing requires very strong justification (and the nature of any such justification is explored in Section 2 below). Further than this, some members of the Boyd Group argue that these animals should not be used at all.*

Monkey species commonly used in research (mainly marmosets and macaques) differ from Great Apes in that the weight of evidence suggests they do not share the apes' most sophisticated mental abilities (once thought to be exclusively human); or, at least, that they possess them in more rudimentary form. For example, the evidence presented in Paper 2 suggests that, when compared with Great Apes, monkeys have a less well-developed 'theory of mind' – in that, for example, their insight into their own thoughts and feelings, ability to empathise with others of their kind and/or to imagine a personal future and ponder on the past, are less well developed[1]. Nevertheless, the evidence in Paper 2 (pp.26–27) also shows that monkey species commonly used in research have rich mental abilities related to their complex social lives, which involve rich and highly discriminative social interactions. These abilities appear to be more developed in monkeys than in other non-ape primates (such as lemurs, lorises and bushbabies)[2]. It is clear that compromising a monkey's social life (for example, by confinement in the laboratory) causes suffering. Furthermore, evidence suggesting that at least some monkey species have an ability to think about/reflect on what is happening to them could bring an extra dimension to their capacity for suffering.

The relative moral status of monkeys compared with other laboratory animals is more contentious. To begin with, monkeys comprise a heterogeneous group of species, with a wide range of habitats, social organisation, behaviour and psychological attributes. More generally, it is difficult to find ways of comparing the potential for suffering of any given

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[1] Whilst this conclusion applies at least to the monkey species commonly used in research, it may not be applicable to all other non-human primates. Capuchin monkeys, which are not used in research in the UK at present, show considerable cognitive skills, which could be superior to other monkey species and, in some aspects could be similar to the abilities of Great Apes (see Paper 2).

[2] These animals used to be known as prosimians, but are now classified as strepsirhini (see Paper 2).

species (in this case, say, a marmoset or a macaque) with the potential for suffering of another species (such as a dog, or a rat, for example). Furthermore, the importance for moral status of a potential for what might be called social or mental suffering, as compared with a potential for more physical suffering (feeling pain, for example), is uncertain. It is more difficult for us, as humans, to judge capacities for suffering in species which are evolutionarily more distant from us, and it might be argued that according any species of monkey special moral status reflects human prejudice in favour of species more like ourselves.

Nevertheless, neither lack of *proof* about monkeys' capacities to suffer, nor the possibility of equivalent suffering in other non-primate species, need prevent us from according special moral status to monkeys. There is strong, though not incontestable, evidence (Paper 2) to suggest that the general richness of monkeys' social lives and mental abilities means that compromising their way of life causes them greater suffering than other animals which do not share these capacities. This potential for social and mental suffering implies, at least, a need for very strong justification if these monkeys are to be used in research and testing – and some members of the Boyd Group go further, arguing that these animals ought not to be used at all.

On present knowledge, this is the best consensus that can be achieved within the Boyd Group on the question of moral status of non-human primates. The statement does not preclude arguments in favour of special moral status for other, non-primate, species (but the focus of the present discussions is on evidence about non-human primates). Nor does it preclude future agreement within the Group that the ban on use of apes should be extended to particular monkey species (and perhaps all non-human primates) – should further evidence, judged less contestable, mark any of these species out as closer to Great Apes and/or more strongly different from other species in their potential for suffering.

2 What might be a 'very strong' justification for using monkeys in research and testing?

The conclusion that very strong justification is required if monkeys are to be used in research and testing, requires further qualification. Where it is accepted that there might be *some* use of non-human primates, what could be the nature of such a justification? To attempt to answer this question, the Boyd Group considered two broad areas in which non-human primates are currently used – fundamental research and regulatory toxicity testing.

2.1 General considerations

It is axiomatic that, whatever the reasons for using monkeys, the 3Rs (of replacement, refinement and reduction of animal use) would have to be very rigorously applied. That is:

- the use of monkeys would be the only possible means of addressing the questions, or would offer very significant scientific advantages over all other possible alternative approaches – this judgement being based on an active search for alternatives;
- the minimum possible number of animals would be involved, consistent with the aims of the work, and the experimental design would be very robust;
- every effort would be made to refine all aspects of the use of the monkeys (from birth to death of the animals), and the possibilities for further refinements would be continually reviewed. Thus, the following aspects would all be considered, and monitored throughout the project (see also Boyd Group recommendations in Smaje *et al.* 1998):
  - – source and transport of the animals;
  - – husbandry and environment of the animals;
  - – experimental design and techniques used;

– care of the animals before, during and after each procedure;
– end-points of the procedures; and
– method of killing the animals (or re-use, re-homing, or other fate at the end of the procedures).

Beyond these requirements to minimise the harms caused to monkeys, however, there is uncertainty about what might constitute a sufficiently serious or worthwhile reason for using these animals in research or testing. Thus, there is considerable room for debate about the nature of the special protection that monkeys (and other non-human primates) should receive under UK law.

2.2 Example 1: Use of non-human primates in fundamental research

For example, if the justification required is that monkeys are the best, or only, model for humans in studies of significant problems for human health, where would this leave fundamental research? In 2000, around one-in-six of all the monkeys used in scientific procedures in Great Britain was used for fundamental biological research. That is, in biological studies aimed either 'solely at an increase in knowledge', or 'with a view to providing a practical solution to a medical or veterinary problem once the issues are more clearly defined and understood' (Home Office, 2001, p.5). Can such objectives provide very strong justification for using monkeys?

To explore this question further, the Boyd Group invited scientists using monkeys in fundamental research to describe their work to the Group. Two specialist primatologists also joined the discussions. Summaries of the scientists' presentations are reported in Paper 1. All three of the examples in Paper 1 were described by the scientists as fundamental research, presumably because none of the projects involved *directly* applying the knowledge gained. Nevertheless, the cases varied considerably in how close the work was to a potential medical application.

The first example described work carried out in the USA, but it was also noted that similar work is in progress in the UK. The other two projects (as well as the UK equivalent of the first project) had obtained funding from major UK granting bodies, after fierce competition with other projects for limited funds – and thus, in each case, the science had been subjected to competitive peer review. Moreover, in all three cases it was argued that the use of monkeys was the only possible means of achieving the objectives of the work, and the researchers all said that they had applied the 3Rs as rigorously as they could. However, the question remained whether the potential benefits of the work could be said to be sufficient to warrant use of monkeys.

It is clear from the three case studies that there is considerable blurring of the boundaries between fundamental and applied research. At what point in such a continuum of distance of work from potential application could there be very strong justification for studies involving non-human primates, and at what point should such work no longer even be considered?

There are two possible categorical replies to these questions. As already noted, some members of the Boyd Group argue that there is *no* position in the continuum at which the use of monkeys, or other non-human primates would be justified. At the other end of the spectrum, it can be argued that, provided the science is high quality and there are no alternative ways of achieving the objects of the work, then use of monkeys in pursuit of *any* knowledge relating to human physiology would be worthwhile – since, through serendipity, any knowledge could one day turn out to be useful in addressing a problem of human health. Indeed, there are numerous examples of unforeseen or unintended medical benefits arising from fundamental physiological research.

However, members of the Boyd Group are agreed that the latter argument is not strong enough to justify the use of non-human primates in fundamental research. Such studies ought to have more *specific* aims, in that, at the very least, they should address key questions relating to human (or veterinary) physiology or behaviour, with the strong expectation that better scientific understanding will provide a foundation for future research leading to medical advances – and the science should be impeccable. More than this, the strength of any such justification has to be judged case-by-case (see further comments in Section 3, below).

2.3 Example 2: Use of non-human primates in regulatory toxicology (see Paper 5)
As already noted, three quarters of the non-human primates used in laboratories in the UK are involved in toxicological studies of pharmaceuticals. Almost all of these studies are reported to be performed for legislative reasons – that is, to meet the requirements of UK, EU or foreign regulations intended to ensure that new pharmaceutical products are safe to use, and that any risks to the consumer are minimised (Home Office, 2001). In the UK, non-human primates are only rarely used in testing substances intended for non-medical use. For example, in 1998, 40 marmosets or tamarins were used to test 'substances intended primarily for use in industry' (Home Office, 1999). These substances were probably phthalates, tested because of concern about the safety of using them in toys mouthed by babies.

In practice, toxicologists argue that non-human primates are used only when they are, scientifically, the most appropriate species for the particular study, and no non-animal alternatives are available and/or acceptable to the regulators. The main use of these animals is as 'second' species, after rodents, in routine chronic and acute toxicity tests, when dogs (the more usual non-rodent species) are considered unsuitable (e.g. because dogs are particularly sensitive to the test compound). In addition, non-human primates tend to be used when the test compound is antigenic to other species, or when there are physiological or metabolic similarities between non-human primates and humans that are not found in other species (e.g. similarity of receptors). In some cases, it is possible that toxicologists may regard non-human primates as the *only* scientifically suitable species – for example in testing certain biotechnology-derived pharmaceuticals ('humanised' medicines). See further discussion in Paper 5.

Decisions to use non-human primates in testing can also be influenced by pressures and considerations other than their scientific validity as models for humans. Because non-human primates have been used in testing in the past there is a great deal of historical and background information available from these species, with which to compare the results of new studies. Thus, even though there might be potential to use other species such as mini-pigs and ferrets, continued use of non-human primates can be favoured owing to concern that data will be rejected by regulators if they are from species for which there is relatively little background data. If data prove unacceptable to the regulatory authorities there can be costly delays in bringing the test compound to market – the costs of delays being seen in terms of financial expense and time, (so affecting company profits, share prices and dividends etc), the potential effects on human health of delaying the new medicine, and also the requirement to use more animals in another round of tests. Some members of the Boyd Group argue that previous background data should not be allowed to dictate the continuing use of non-human primates.

Similarly, growing consumer demands for safety of chemical products, coupled with an increasingly litigious consumer climate, can put pressure on companies to test more widely on animals before moving to human studies, and this may involve pressure to use non-human primates because of their similarities with us.

Some members of the Boyd Group believe that non-human primates (and other animals) should not be used in toxicity testing at all. However, whilst non-human primates continue to be used, there is an urgent need for everyone involved critically to evaluate decisions to use these animals in testing, in order to ensure that choices are made strictly on sound scientific grounds, and not as a result of other pressures that could be overcome.

Currently, toxicologists argue that it is difficult to meet the goal of characterising the potential toxic effects of new pharmaceutical substances, in order to provide evidence on which to base decisions about whether to move to human testing, without the use of non-human primates in at least some cases. It might be thought that use of transgenic mice expressing specific human receptors could eventually do away with the need for testing in more than one species altogether. However, this is unlikely because the remainder of the animals' physiology is unaffected by the specific genetic modification, and there remains a need to examine wider systemic effects of drugs – which, presently, requires the use of two different species.

In future, development of better *in vitro* tests, which can be used as pre-screens at least, should help to reduce or eliminate the use of *in vivo* tests, perhaps including use of non-human primates. This approach has resulted in an enormous saving in the use of animals in screening compounds for potential efficacy, and there is a need to develop similar screens to look for toxic effects.

When no non-animal alternatives are suitable, decisions whether or not to use non-human primates in regulatory toxicity tests should take into account the particular benefits of the substances being tested (see 3.4 below), the scientific need to use non-human primates, and all relevant welfare considerations. The judgements involved can be complex, and there is a need for careful consideration of the issues posed in each case – see Paper 5 for further discussion.

Clearly, discussion and negotiation with the relevant range of regulatory authorities is desirable at an early stage in study design. Although, to a large extent, this already goes on, there is sometimes a need for better communication between regulators and scientists. In addition, there is also a need for deeper understanding of the biology of the various species that might be used, so as to ensure that in each case the choice of species is as scientifically informed as possible.

As in fundamental research, there is no straightforward 'formula' for arriving at decisions on whether or not there is justification for using non-human primates in particular regulatory toxicity tests. Once again, the issues need to be considered case-by-case.

3 Ethical review of proposals to use non-human primates in research and testing

From the above discussions, it is clear that there have to be very strong reasons to justify the use of monkeys in fundamental or applied research or in toxicity testing, and that, if these reasons are to command confidence (indeed, if these animals are to be used at all), there is a need for very rigorous ethical review of projects. Because there can be no generally applied formula for such decisions, it is essential that the procedures used to arrive at them are as thorough, effective and transparent as possible.

3.1 Involving appropriate expertise

In Britain, ethical aspects of the use of non-human primates are considered in a variety of different forums. These include reviews carried out by:

- the Home Office inspectorate – in deciding whether or not projects involving animals might be licensed under the terms of the Animals (Scientific Procedures) Act;

- local ethical review processes in each establishment in which animals are used – in advising the establishment's Certificate Holder (who bears ultimate responsibility for the use of animals within the establishment) whether or not to sign project licence applications and forward them to the Home Office; and in considering wider issues arising in the use of animals within the establishment; and
- funding bodies or commercial sponsors – in deciding whether or not to grant funds to support such work.

Each of the different review processes can bring valuable perspectives to bear on the ethical issues arising in the use of non-human primates. It is important that, wherever possible, each process involves appropriate experts in the care and use of non-human primates, who can act as the animals' advocates, and can advise, for example, on:

- whether and how far the use of non-human primates is scientifically justified;
- whether all possible measures have been taken to avoid the use of non-human primates and to minimise the impact of the research on these animals; and
- how far local facilities for husbandry and care of the animals will meet the animals' needs and ensure the highest standards of welfare.

Whilst each of the different review processes should enquire into all these questions, the focus of the reviews will vary, and the questions will be asked from a different perspective in each case. Each process can therefore add value to the overall ethical review. For example, funding bodies have a particular role in enquiring into the scientific justification for the use of non-human primates, and local ethical review processes are vital in ensuring that all possible steps are taken to enhance and safeguard the welfare of the animals *in practice*.

3.2 Explaining the Home Office's approach

The Home Office Inspectorate (HOI), acting on behalf of the Home Secretary, bears the ultimate responsibility for judging whether the use of animals is justifiable under the terms of the Animals (Scientific Procedures) Act 1986 (ASPA) and can be licensed to proceed or not.

It is unclear, however, how the HOI arrives at such judgements. Whilst the Chief Home Office Inspector has provided guidance on the factors that should be taken into account in such ethical review (Home Office 1998), this does not explain how, *in practice*, the different considerations are brought together in arriving at a decision whether or not to licence the project. For example, what weight is given to the standing and experience of the research team involved and its source of funding? How are 'quality of science' issues addressed, and how does the HOI obtain the necessary expertise to question such aspects? How far is the lifetime experience of the animals considered? For, example, what weight is given to adverse effects due to the supply and husbandry of non-human primates? How is the value of different kinds of potential benefit distinguished, including scientific knowledge, so that it can be weighed against the harms caused to the animals?

It would be helpful if the HOI would provide case studies to illustrate its approach, particularly where non-human primates are involved, requiring particularly strong, and, in some cases, exceptional justification. Such illustration and clarification of the Home Office's approach:

- would help to inform the debate on how such ethical review is applied in practice;
- could assist others, such as members of ERPs, in carrying out their reviews; and
- might help to enhance wider confidence in the judgements on use of non-human primates that are made under ASPA.

3.3 Using retrospective review to inform future judgements
Judgements that there is 'very strong' justification for using primates in research or testing have to be made on a balance of probabilities, in particular because it is impossible to predict exactly how useful, in scientific or applied terms, a given project will turn out to be. Moreover, it can take a long time for all the outcomes and benefits of research to become apparent (particularly in the case of fundamental research) and these can show themselves in a variety of ways. For these reasons, periodical retrospective review of the fundamental and/or applied outcomes of projects involving non-human primates can be helpful in informing future judgements.

In Britain, the Animal Procedures Committee (APC) could enhance its role in this regard. The APC is established under the terms of ASPA, and its remit includes reviewing all applications for project licences which involve the use of non-human primates in procedures of substantial severity, and those in which it is proposed to use wild-caught primates. The Committee, by virtue of its wide membership (which includes animal welfare specialists and anti-vivisectionists, as well as scientists, veterinarians, philosophers and others) brings diverse perspectives to bear in its ethical review.

The APC can provide an important forum in which judgements on acceptable practice in laboratory animal use can be tested against a diversity of opinion. The Committee should be encouraged to enquire more deeply into how decisions on the use of non-human primates are actually made. For example, it could extend its review to examine retrospectively *any* application or licence to use non-human primates, with a view to informing future ethical judgements.

3.4 Review of the use of non-human primates in toxicity testing: benefits of substances tested
It has already been argued that decisions to use non-human primates in toxicity testing should take into account the particular benefits of each substance being tested. However, in Britain under ASPA, the benefits of using animals in toxicity testing are viewed in relation to the objective of ensuring that products and ingredients can be manufactured and used safely, rather than in terms of the likely benefits/needs for the substances themselves. On these grounds, project licences may permit the use of animals in testing a wide range of different kinds of substance, defined only in general terms in the licence. Project licence holders have responsibility for justifying species choice in general terms to the Home Office, but are not required to do this in advance for *each* substance tested (although, if asked, they must provide justification retrospectively).

Whilst some practical objections are raised (see discussion in Paper 5, pages 55–56), most members of the Boyd Group are agreed that the following steps should be taken to enhance the assessment of benefit when non-human primates are used in regulatory toxicity tests:

(i) All 'blanket' project licences for the use of non-human primates in regulatory toxicity testing should include an additional condition requiring that the ethical justification for tests be considered by the local ERP on a substance-by-substance basis.

Each time a new substance is brought to, or put forward by, the company for tests involving non-human primates, the case should be referred to the ERP for ethical review that takes into account all pertinent information – including the potential benefits of the substances involved.

In order to enhance the credibility of this process:

- the ERP should include people from outside the organisation concerned, encompassing as wide a diversity of viewpoints as is consistent with reasoned discussion of the issues and client confidentiality, and should preferably have a 'lay' Chair who is not involved with the issues at stake, and

- the relevant HOI should sit in on the discussions as often as possible.

Since relatively few different substances are likely to be tested using non-human primates in a given company, it should not be unreasonable to expect all such cases to be referred to the ERP. This process should enable wider consultation on which uses of non-human primates the company ought to regard as particularly controversial, as well as widening debate on the issues themselves. Practical objections to implementing such reviews might be overcome when it is remembered that the ERP is a *process*, not just a committee, that can be designed to minimise unnecessary delays, whilst at the same time ensuring that all the ethical issues are addressed. For example, each time it is proposed to test a new substance using non-human primates, information about the tests could be circulated to members of the ERP, with members meeting to discuss the proposals whenever one or more of their number raises concerns.

(ii) The ERP's decision, and the reasons for it, should be communicated to the HOI. This would enable the relevant HOI to comment on the decision, and could assist the HO in building up a body of knowledge on the application of the cost-benefit assessment in such circumstances, so that, in future, the HO could recommend and refine criteria for assessing the potential benefits of substances.

(iii) The Home Office inspectorate should regularly 'spot-audit' pharmaceutical and contract testing companies' internal enquiries about proposals to conduct tests involving non-human primates, in order to evaluate whether and how far the enquiries are making a difference in practice.

For further discussion, see paper 5, pages 54-57.

4 Welfare considerations in the use of non-human primates in research and testing.

In spite of the lack of strong agreement on the general moral status issue, and a fundamental difference of opinion on whether or not *any* use of non-human primates should be permitted in future, members of the Boyd Group are agreed that whilst non-human primates continue to be used in research and testing, every effort should be made to minimise the social deprivation, mental suffering, and/or physical harms caused to the animals.

In order to put flesh on the bones of this conclusion, the Group systematically examined and compared the consequences for animal welfare of supply and use of marmosets and macaques (both cynomolgus and rhesus macaques) – that is, the monkeys most commonly involved in research and testing. The results are reported in Paper 4.

Members of the Group are agreed that, whilst non-human primates continue to be used:

4.1 The choice between marmoset (a New World monkey) and macaque species (Old World monkeys) is not always straightforward on welfare grounds, and needs to be considered case-by-case (depending, in particular, on the scientific procedures involved and the objectives of the experiment).

In general, the breeding, supply and laboratory husbandry of macaques involves greater costs to animal welfare than does the breeding, supply and husbandry of marmosets. On these grounds, it might be argued that marmosets should be the species of choice where possible. However, marmosets are difficult to train to accept handling by humans, and do not easily tolerate disruption to, or removal from, their family groups. They also appear to find some routine scientific procedures more stressful than macaques.

4.2 The blanket Home Office distinction between New and Old World primates is not helpful.
Since 1996, the UK Home Office has required that use of Old World as opposed to New World primates must be specifically justified, i.e. that, in practice, special justification is required for the use of macaques rather than marmosets (Home Office 2000, p. 47). However, for the reasons given in 4.1, this requirement is not particularly helpful, since it is not always the case that the use of marmosets involves less cost to animals than the use of macaques. Moreover, both New World and Old World primates are heterogeneous groups, and the distinction between the groups in terms of welfare costs involved in using them breaks down when species other than those commonly used in laboratories (e.g. capuchins) are considered.

4.3 Steps should be taken to improve welfare in the breeding and supply of macaques used in research and testing.
An end to transport of monkeys from source countries should be achieved as soon as possible. In the meantime:

(i) *Welfare conditions in breeding facilities in source countries should be regularly assessed and monitored against standards expected under British legislation, and improvements made where necessary.* It is understood that Home Office visits have taken place, but more frequent assessment will require more personnel. It would be helpful if reports from these visits were made available to local ethical review processes and appropriate licensees, so that more informed choices can be made about animal supply.

(ii) *There should be a long-term strategy to build up captive breeding populations of macaques in source countries, so that there is no longer a need to take animals from the wild.* Currently, many of the captive bred animals supplied for research are actually the first generation bred in captivity, and breeding adults continue to be replenished from the wild.

(iii) *Early weaning of animals should be exceptional and not accepted as routine.* Opinions differ on the most appropriate weaning age for captive-bred infant macaques (see Paper 4 for further details). Weaning is not an abrupt event, but a process lasting over several months. Whilst most infant monkeys can feed themselves at six months, they remain socially dependent on their mothers for at least a year, returning to them when disturbed and to sleep. Unless specifically justified, infants should remain with their mothers until they are no longer dependent on them, and each animal should be considered individually. Possible exceptions arise because, for example, it is preferable to wean harem groups together, and then maintain these animals as a group, in order to avoid disturbing the social relationships between them. Sometimes this can involve a compromise on weaning age, since it likely to be better to wean a younger animal, of say nine months, with its older half siblings, rather than to postpone weaning and introduce it three months later to an unknown group (Wolfensohn *pers. comm*).

(iv) *Whilst non-human primates continue to be used and supplied from abroad, transport to establishments in the UK and Europe should be as direct as possible; and means of avoiding a change of transport from air to road for the final leg of journeys to Britain should be investigated.* At present airlines are unwilling to land primates destined for research in Britain because of animal rights action.

4.4 Further consideration should be given to means of improving welfare in the husbandry of non-human primates, and the actual effects on animal welfare of suggested improvements should be scientifically evaluated. In particular, standards for non-human primate caging require urgent revision, and should be amended and implemented across Europe, since unilateral action by the UK could result simply in work being moved abroad. Individual housing of non-human primates should require exceptional justification, and should never be long-term.

The minimum cage sizes for both marmosets and macaques detailed in Home Office guidance (1989), and in European standards, are inadequate – particularly in respect of vertical dimensions of cages – and do not reflect current best practice (see Paper 4, page 39). Changes to the European Convention and Directive are currently being negotiated. Once these changes are agreed, it is likely that the Home Office will then amend its 1989 guidance to bring it into line with the revised European codes.

4.5 Every effort should be made to train non-human primates to accept routine scientific procedures, and so minimise the stress caused to the animals. On both welfare and scientific grounds, repeated, stressful, capture within the cage and sedation of these animals for routine scientific procedures should be avoided.

Although more difficult for marmosets, such training is usually possible for macaques, and is particularly important for repeated procedures. Telemetric methods for physiological monitoring, and in-cage testing, should be considered and used wherever they would represent a refinement.

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Paper 1: Background information on the use of non-human primates

1 Controls on the use of non-human primates

1.1 Controls on the use of non-human primates in research and testing in Britain

(i) In Section 5(6) of the Animals (Scientific Procedures) Act 1986 (ASPA), which regulates the use of laboratory animals in Britain, special mention is made of the use of non-human primates (as well as cats, dogs and equidae), in that a project licence for use of these species will not be granted unless 'no other species is suitable…or it is not practicable to obtain animals of any other species that are suitable for those purposes'.

(ii) All applications for project licences to use non-human primates in procedures of substantial severity and to use wild-caught primates must come before the Government's statutory, independent, advisory committee on animal experiments, the Animal Procedures Committee (APC).

(iii) During 1996, further measures on the acquisition and use of non-human primates were introduced under the terms of the Animals (Scientific Procedures) Act, such that:

- the use of wild-caught primates is banned, except where it can be exceptionally and specifically justified;
- special justification is needed for the use of Old World rather than New World primates;
- similarly, special justification is needed for the use of Old World primates in toxicological procedures of more than mild severity;
- primates can only be imported from overseas breeding or supplying centres which have been approved by the Home Office;
- transport arrangements for such animals must also be approved by the Home Office.

(iv) In addition, a ban on the use of Great Apes was introduced in November 1997.

(v) A sub-group of the APC, the Primate Sub-Committee, advises the APC on matters relating to the acquisition, housing, care and use of non-human primates in scientific procedures. Recently, the Sub-Committee has taken on a more 'strategic role' and 'will lead on issues such as:

- how to minimise, and eventually, eliminate primate use and suffering;
- acquisition of primates (availability of primates in the UK, the suitability of overseas sources and transport arrangements);
- housing and care;
- the use of wild-caught primates (should this be allowed at all and, if so, what should constitute the specific and exceptional justification needed if such use is to be authorised);
- the use of primates in regulatory toxicology' (Home Office, 1998).

1.2 Specific controls on the use of non-human primates in research and testing in the EU

The EU Directive and Council of Europe Convention for the protection of animals used for scientific purposes include very little specific reference to the use of non-human primates. The Directive contains only two specific references, concerning the identification of non-human primates (along with dogs and cats, they must be individually marked for identification before weaning or as soon as possible after arrival in the establishment) and their origin (they must be specially bred unless special exemption is made). The Convention contains no such references (see Jones, 1996).

2 Scale of use of non-human primates in research and testing

2.1 Use of non-human primates in Britain

In 2000, 2951 non-human primates were used in scientific procedures in Britain, representing 0.11 per cent of the total number of animals used in that year (Home Office, 2001). The primate species involved are shown in Table 1. No Great Apes have been used since ASPA was introduced, and, as noted, the use of Great Apes has been formally banned since November 1997.

Table 1: Number of non-human primates used in scientific procedures in Britain in 2000
Source: Home Office (2001)

	Species	**Number of animals**
New world monkeys:	marmosets, tamarins	1060
	squirrel, spider, owl monkeys	0*
Old world monkeys:	macaques	1891
	baboons	0#
	Total	**2951**

* *In addition, in 2000, 24 squirrel, owl or spider monkeys continued to be used in procedures begun in 1998*
\# *Baboons are used occasionally - most recently in 1998, when four baboons were used in immunology studies*

The reasons for using these animals are shown in Tables 2 and 3. Seventy-six per cent of the non-human primates used in 2000 were involved in toxicological studies on pharmaceutical substances (see details in Table 3), 7 per cent of the animals were used in non-toxicological applied studies in human medicine or dentistry, and 16 per cent were used in fundamental research. The last mainly comprised studies on the nervous system or special senses (49 per cent of the fundamental research procedures), and on the reproductive system (19 per cent).

Table 2: Reasons for using non-human primates in scientific procedures, Britain 2000
Source: Home Office (2001)

	Number of animals used in:				
Species used	Fundamental research	Toxicology	Applied studies in medicine and dentistry (not toxicology)	Direct diagnosis of disease	Total
Marmosets, tamarins	264	616	179	1	**1060**
Macaques	207	1641	37	6	**1891**
Total	**471**	**2257**	**216**	**7**	**2951**

Table 3: Number of non-human primates used in toxicology studies in Britain in 2000
Source: Home Office (2001)

Species used	**Pharmaceuticals**			Testing non-medical substances	Toxicology method development	Other	Total
	Safety tests	Efficacy tests	ADME* and residue tests				
Marmosets, tamarins	548	–	54	–	–	14	616
Macaques	1451	53	129	–	8	–	1641
Total	**1999**	**53**	**183**	**–**	**8**	**14**	**2257**

* absorption, distribution, metabolism and excretion tests.

Paper 1: Background information on the use of non-human primates *(continued)*

It was reported that 99 per cent of the toxicological procedures were carried out in order to meet regulatory authority requirements.

2.2 Use of primates in elsewhere

The UK and France, together with Germany and the Netherlands, are the main users of primates in research and testing in the EU – at least 80 per cent of reported primate use takes place in these countries (Jones 1996, Ruhdel & Sauer 1998, European Commission 1999). The species involved are mostly monkeys (see Table 4), but in 1996 (latest available statistics), both Belgium and Austria reported using apes (species unknown), and the Netherlands reported using 1082 'simians', which could have included apes.

Table 1: Use of non-human primates for scientific purposes in EU countries, 1996.
Source: European Commission (1999)

Country	Total number of non-human primates used in 1996	Of which: Prosimians (lemurs etc)	Monkeys	Apes
UK	3786	0	3786	0
France (1997)	2622	82	2540	0
Germany	1519	155	1364	0
Netherlands	1082	0	1082 'simians'	
Italy	772	0	772	0
Belgium	600	0	569	31
Austria	164	0	116	48
Denmark, Finland, Greece, Spain and Sweden also used non-human primates, <60 each in 1996				

The USA, together with Japan, is the main world user of non-human primates in research and testing, including Great Apes. The United States Department of Agriculture collects annual statistics on the use of laboratory animals, but there is considerable under-reporting. The most recent statistics show that at least 57,000 non-human primates were used in the USA in 1998.

3 Case studies in the use of monkeys in 'fundamental' research

Three examples of the use of non-human primates in research are presented here, in order to illustrate the kinds of fundamental and more applied benefits that might be sought from such work. Paper 5 also gives some examples of the use of non-human primates in toxicological studies.

The case studies are summaries of presentations given by scientists using monkeys in research, who described their work (or the work of colleagues) to the Boyd Group.

Case Study 1

A university physiologist described work carried out mainly in the USA, aimed at understanding how the brain makes perceptual decisions about the movement of visual stimuli. (British researchers collaborated in some of the studies, and similar work is carried out in the UK).

Recordings from single neurones in the middle temporal (MT) area of the cerebral cortex of the brain (a visual area of the brain) of conscious monkeys were made at the same time as the monkeys made decisions about the net direction of motion of patterns of dots displayed on oscilloscope screens. The monkeys were trained to discriminate the directions of motion of the patterns of dots (up vs. down; right vs. left), and to indicate their judgements by making an eye movement to one of two light-emitting detectors, corresponding to the two possible directions of motion in a given trial. When trained, the monkeys performed this task with more than 95 per cent accuracy for strong motion signals. The patterns of dots could be manipulated by the researchers, so that the net direction of the motion was less obvious and the monkeys had to make more considered decisions about the overall direction of the stimulus.

It was already known that more than 90 per cent of the neurones in the MT area are 'directionally selective', responding only when the direction of motion of the visual stimulus is in their 'preferred' direction. Surprisingly, the studies described above showed that individual MT neurones detected the direction of movement with a statistical reliability equivalent to that of the animal's perceptual judgement about the direction of motion. In other words, the way in which only one neurone (or a small group of neurones acting together) responded matched the whole animal's behaviour. Not only this, but the researchers found that stimulating tiny groups of these neurones with extra electrical impulses could bias an animal's judgement. In summary, the work showed that the correlated activity of small pools of neurones in the MT area of the brain accounted for the accuracy of the animals' judgements about the direction of a visual stimulus.

Following from this, questions for consideration included:

(i) where in the brain were these decisions made? – recordings from pathways that link MT to the oculomotor planning centres of the brain could be used to investigate this;

(ii) were the neural structures underlying the decision process different in monkeys trained to indicate their decisions using arm, rather than eye, movements?

Non-invasive brain imaging techniques were not suitable for this work, because they measure differential blood flow in the brain, which is related to the total activity of the neurones in a given area of the brain, and therefore they cannot discriminate responses at the level of individual neurones. The studies described above can be regarded as complementary to brain imaging work, and can help to explain what the results of brain imaging mean at the neuronal level.

Other than this, no direct applications are foreseen for the work, which was primarily curiosity driven and was carried out in order to gain scientific understanding. However, it might be envisaged that better understanding of the neurological mechanisms involved in visual perception could provide a foundation for future advances in treatment of human visual disorders caused by disorders of brain function. This fundamental research was described as 'potentially Nobel prize-winning'.

Most of the work was carried out using three monkeys. Non-human primates were used because of their similarity to humans and their ability to be trained. It was argued that there were no other suitable models for humans at the level of cerebral and cerebellar organisation, and the work was only possible with stump-tailed monkeys and rhesus macaques, because of their abilities to perform the tasks.

It would not have been possible to carry out the experiments on human subjects, because the work involved implanting electrodes into the brain. The animals had to sit in primate chairs for the recording sessions and were required to hold their eyes steady during the presentation of each visual stimulus, so that the pattern of dots was detected by the particular 'receptive field' of the brain neurones from which recordings were being made. To check that this was the case, the monkeys' eye positions were measured using the 'scleral search coil technique', in which tiny magnetic coils were inserted around the corneas of the animals' eyes and the position of the eyes were detected using magnetic coils which surrounded the animals during the experiments.

It was reported that the animals participated eagerly in the experiments, climbing into the primate chairs, helping to set up the recording apparatus on their heads, and starting the electronic tasks they were provided with. However, the monkeys were also deprived of water before each experiment, so that they were thirsty at the start of the recording sessions. They were 'rewarded' for correct choices with sips of water or fruit juice, and incorrect choices resulted in brief 'time out' sessions between trials.

Case Study 2

Two university researchers, one a physiologist, the other a clinician, described their long-standing research programme on how the brain controls movement, which involved the use of rhesus monkeys. Although much of the work could be said to be 'fundamental' research, all of it was carried out with a view towards improving human treatments.

Research areas included:

- work on the motor effects of temporary inactivation of the parietal cortex of the brain, studying (in particular) how visual stimuli are converted to eye movements. (In human patients, damage to the parietal cortex causes patients to cease to attend to visual stimuli). Serendipitously, this work had implications for the study of dyslexia, since the resulting altered eye movements bore striking comparison to the eye movements of dyslexic children;
- recording from and studying the effects of temporary inactivation of regions of the cerebellum. Again, there were potential benefits from this basic research, in that
  – dyslexic children have a mild disorder of the cerebellum (which is innervated from the parietal cortex), and
  – the cerebellum and its in/outputs are frequent sites of lesions in multiple sclerosis, so the work was leading to treatments for patients suffering movement disorders due to MS;
- studying the control of movement by the brain stem, working towards better treatments for Parkinson's disease. MPTP-treated monkeys provided good models of human Parkinsonism, and were being used to develop treatments involving lesioning, cooling or stimulating specific parts of the brain, so as to alleviate motor symptoms without causing cognitive problems.

Non-invasive brain imaging studies were not suitable at present, because the techniques were limited in their spatial and temporal resolution, operating at a scale orders of magnitude larger than that required to examine the single cell responses being investigated. Imaging studies did not allow study of *how* brain processes worked, only *where* the processes occurred in the brain.

Non-human primates were considered to be the best available animal models for this work, because their visual and motor control is very similar to humans'. The rhesus monkeys were trained in the tasks they were required to perform and the researchers reported that a relationship developed between researcher and monkey. Also that, since the monkeys were required to co-operate with the researchers, it was in everyone's interests to reduce any animal suffering as far as possible. MPTP caused periods of discomfort for the monkeys. However, it was reported that only mild symptoms were induced, and any further symptoms were relieved by administration of L-DOPA. Marmosets were considered less suitable for work on Parkinson's disease because they lack neuromelanin in their brains, resulting in unstable disease states. Furthermore, they could not be trained like Old World monkeys. Thus, although marmosets were considered useful in studying acute, pharmacological, interventions, they were not regarded as suitable for this kind of surgical work.

Case study 3

A clinician and academic researcher described his studies on the effects of increased maternal steroids (specifically the 'stress' hormones, glucocorticoids) on later disease in low birth weight babies. Widescale, worldwide, epidemiological studies had shown that lower birth weight babies had increased risk of developing hypertension, diabetes and a whole range of other diseases later in life. Long-term excess of glucocorticoids (Cushing's syndrome) also caused such diseases, and increased maternal glucocorticoids were known to reduce birth weights. Taken together with many other data, these findings suggested (i) that the practice of routine administration of glucocorticoid (specifically, long-acting dexamethasone) to prevent premature delivery in at-risk mothers could lead to later disorders and (ii) that deficiency of the natural enzyme 'barrier' in the placenta to maternal glucocorticoids may explain the link between low birth weight and later disease. *In vivo* experimental work supported this suggestion: when mother rats were given dexamethasone or inhibitors of the placental enzyme barrier they produced low birth weight young, which grew rapidly to catch up with their peers, but *always* remained hypertensive and had high blood glucose levels. (Malnourishment produced the same results and reduced levels of the placental barrier enzyme.) Further studies with rats helped unravel possible molecular mechanisms for this effect.

It was difficult, however, to persuade obstetricians to consider changing their practices, since administration of glucocorticoid saved babies. There was thus a need for further work to confirm and explain the effects in humans, but research involving human subjects was limited to observational studies. Studies of causation, involving sampling during infancy, and interventional studies to examine the mechanisms by which the effects were exerted, would not meet with ethical approval. Furthermore, no controls were possible because steroids (the conventional treatment) *had* to be given when pre-term delivery was threatened; therapeutic manipulations would not be possible without strong animal data.

A wide range of possible animal models was considered for this work, and it was concluded that Old World monkeys were the *only* possible model. These animals had appropriate glucocorticoids, long gestations with single fetuses, and similar relevant behaviour. By contrast, rats and mice, for example, had the 'wrong' glucocorticoid, short gestations producing multiple fetuses, and showed key behavioural differences; sheep had 'odd' glucocorticoid biology and major placental differences; whilst New World primates crucially were glucocorticoid resistant and many produced multiple fetuses.

Against this background, the work in non-human primates was considered justified by the researcher, on the grounds that it was novel and important – a critical issue for human health related to a variety of diseases which affected many people in both developed and developing countries. The studies would provide a rapid means of determining the longer-term safety of an 'established' human therapy.

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Paper 2: Empirical evidence on the moral status of non-human primates

Close behavioural and physiological similarities between non-human primates and humans are frequently cited as the justification for using the animals in research and testing – as the 'best' or 'only' model for human beings in the particular work. Yet these very similarities pose ethical questions about their use. It might be asked, for example:

- *Are the cognitive and psychological abilities of (at least some) non-human primates such that they have the potential to suffer more intensely than other laboratory animals used in the laboratory?*
- *Should these animals therefore be given special moral status compared with other animals, and either not used at all, or used only where there is special or exceptional justification?*
- *If so, should the special status apply, equally, to all the various species of non-human primates used in research and testing?*

As part of discussions on the use of non-human primates in research and testing, the Boyd Group has examined evidence that might have a bearing on the moral status of the different non-human primate species. This working paper sets out physiological, behavioural and psychological criteria identified by the Group, and, for each aspect, reviews some of the available evidence pertaining to Great Apes and monkeys. In addition, Paper 3 examines some relevant philosophical arguments.

1 Evolutionary relationships/genetic similarities with humans

Humans are members of the Super-family of primates known as Hominoidea, or apes. The other members are the chimpanzees, gorillas, orang-utans and gibbons (Table 1, overleaf).

On an evolutionary timescale, humans, chimpanzees and gorillas are closely related: current opinion is that the chimpanzee and human lines separated only around 4.5 million years ago. Orang-utans diverged from the rest of the Great Ape line somewhat earlier (between 12 and16 million years ago), whilst the gibbon and Great Ape lineages separated around 19 to 17 million years ago (see Byrne *pers. comm.* and 1995).

The world's monkeys are divided into two major groups, one of which evolved in South and Central America (the New World monkeys, which comprise two major families – see Table 1) and the other in Asia and Africa (the Old World monkeys, including the macaques and baboons). Apes diverged from the Old World monkeys around 30 million years ago.

Traditionally, humans have been classified separately from the Great Apes, and termed Hominids. However, recent evidence shows that humans are *not* a separate lineage from the apes, and the classification has been revised, to show that humans are apes. As yet, there are no agreed Latin names for the Great Ape and African Great Ape groups (Byrne, 1995; Fleagle, 1999).

Comparison between the structures of a range of a human and chimpanzee proteins shows that the average human protein is around 99 per cent similar to its chimpanzee counterpart (King & Wilson, 1975), and hence that the DNA coding for the proteins is also very similar. These data have been much cited as evidence on the similarity between humans and chimpanzees. However, they do not necessarily demonstrate such close functional similarity. Indeed, King and Wilson note that their data suggest a genetic distance between humans and chimpanzees which seems too small to account for the morphological differences between the species. They argue that the major differences between human and chimpanzee DNA are unlikely to be in sequences coding directly for proteins, but in sequences which control the expression of the different genes, small changes in which could cause major phenotypic differences. King and Wilson conclude that, from the time of their common ancestor, chimpanzees appear to have evolved relatively slowly whereas

Table 1: Main groups in the classification of primates (see Byrne 1995)

PRIMATES

Strepsirhini ('wet nosed' primates). Lemurs, lorises, pottos and bushbabies/galagos.

*Formerly Prosimians, minus a little known group, the tarsiers, which are now classified with the Simians.

Haplorhines ('dry nosed' primates). These are the tarsiers, monkeys and apes:

- **Tarsiers**
- **New World monkeys**
  - Family *Atelidae* (howler, spider monkeys etc.)
  - Family *Cebidae*:
    - Aotines (owl monkeys)
    - Cebines (e.g. squirrel monkeys, capuchins)
    - Callitrichines (e.g. marmosets, tamarins)
- **Old World monkeys**
  - Family *Cercopithecidae*:
    - Cercopithecines (cheek-pouched monkeys, e.g. macaques, baboons)
    - Colobines (leaf-eating monkeys, e.g. langurs)
- ***Apes***
  - Family *Hylobatidae* (gibbons)
  - Family *Hominidae*:
    - Great Apes: orang-utans;
    - African Great Apes: common chimpanzees, pygmy chimpanzees, gorillas, and humans

humans have evolved more rapidly, and that, given the similarity in DNA, the likely explanation is change in control sequences.

This argument does not negate or necessarily diminish the importance of evidence about genetic similarities between humans and chimpanzees or other primates. However, it shows that such evidence can be difficult to interpret clearly, and should not be considered in isolation. It is equally possible, for example, that species which are genetically very different can have significant similarities in behaviour and physiology (as a result of 'convergent evolution', where different lines independently arrive at the same 'solutions' to similar 'problems'). In all such cases there is a need also to examine morphological and functional similarities closely.

2 Brain development

'Intelligence' is not easily defined, but for humans the term implies being able to think 'creatively' – to have one's own thoughts and, in particular, to use these to devise solutions to novel problems, to be able to plan, anticipate and remember, to have a sense of self, and to able to think about those same thoughts. All of these attributes could enhance a capacity for suffering. In humans, such abilities are associated with a relatively much larger brain than any other species (making allowance for body weight), and, in particular, with a greatly expanded frontal region of the cerebral cortex of the brain.

Paper 2: Empirical evidence on the moral status of non-human primates *(continued)*

'Encephalisation quotients' (the amount of brain over and above that expected to be concerned with purely bodily functions, compared with an average mammalian value) have been calculated for a range of mammalian species, including a variety non-human primates (Table 2). The calculations show that primates over a wide range of body sizes have relatively large brains. Within the primates, the relative brain to body size of humans is nearly three times greater than that of chimpanzees, more than three times that of squirrel and rhesus monkeys, and over four times that of marmosets – and it might be concluded that intelligence varies in similar fashion.

However, interpreting these data is not so simple. It is possible that variations in brain size relative to body size may be caused solely by differences in body size due to diet type. Increase in gut size (relatively long guts being required in foliage cf. fruit eating primates) leads to increased body weight and body length, but requires little increase in brain size for maintenance functions. Thus, species with larger guts come out with artificially small encephalisation quotients.

(Interestingly, the data in Table 2 also show that large brains are not the exclusive domain of primates. Dolphins have brain sizes closer to humans' than do chimpanzees, and elephants and whales have relatively larger brains than marmosets.)

Table 2: Encephalisation quotients of a variety of mammals
Source: Macphail 1982 (after Russell, 1979 and Jerison, 1973).

Human	7.44	Dog	1.17
Dolphin	5.31	Wild pig	1.01
Chimpanzee	2.49	Cat	1.00
Squirrel monkey	2.32	Horse	0.86
Rhesus monkey	2.09	Sheep	0.81
Elephant	1.87	Mouse	0.50
Whale	1.76	Rat	0.40
Marmoset	1.71	Rabbit	0.40

Given the difficulties in interpreting information about overall brain sizes, it is probably more helpful to look at the part of the primate brain known to be associated with intelligence – the neo- (or frontal) cortex. In humans, the neocortex is concerned with complex information processing, and is thought to be where 'conscious thinking' arises. In particular, the neocortex seems to be associated with an ability to reflect on one's own thought processes, and to make inferences about other people's thinking. Recent studies of brain function in autistic people who show little understanding of their own mental states or those of others supports this view (see review by Povinelli & Preuss, 1995).

Neocortex size increases across the primates in similar fashion to overall brain size, with human frontal cortex being proportionately larger than in other primates (Deacon, 1990; Rilling & Insell, 1999), and this might suggest concomitant variation in creative thinking. However, as with the genetic data, it is not necessarily the case that anatomical differences imply differences in function or performance, and evidence about brain development needs to be considered alongside information about the animals' behaviour.

3 Behaviour

Evidence about genetic relatedness and brain development, whilst suggestive, sheds little direct light on the possibility that monkeys, apes or other non-human primates have thought processes analogous to those of humans. Of course, attempting to understand whether, what, and how another living creature thinks is not easy: what goes on inside the heads of other individuals is an essentially private business, and one must rely on secondary, outward signs that might indicate the creature's internal thought processes. However, despite the difficulties, careful scrutiny of the behaviour of other creatures (including other human beings) can enable plausible inferences to be drawn about what and how these creatures might be thinking.

A range of painstaking studies of the behaviour of non-human primates, both under natural conditions and in experimental situations, suggests that Great Apes at least, and particularly chimpanzees, have thoughts, feelings and understandings similar in important ways to those of humans. Such evidence (though not always undisputed) may have played an instrumental role in the Home Office's recent decision to ban the use of Great Apes in UK laboratories (Home Office, 1998).

Whether the available evidence suggests similar abilities for monkeys is more open to speculation. As already indicated, they are evolutionary more distant from humans, and may have rather less well developed brains (though the significance of the differences in brain size and structure is uncertain, and the brains of all primate species are amongst the largest in the whole animal kingdom).

Does behavioural evidence suggest that monkeys can think as humans can, and how do monkey's abilities compare with those of Great Apes?

There is no doubt that non-human primates can experience the world in ways similar to humans. They have sensory capacities similar to humans' (e.g. stereoscopy, similar hearing etc) and can suffer in similar ways to humans (and other animals), for example. But, more than this, can the animals think about their experiences in ways that humans can? For example:

- Have they a sense of 'self', such that they can ponder on their own feelings, and understand what it means to be 'me', as distinct from another animal?
- Have they a sense of time and purpose, such that they can plan and anticipate future events and feelings, and reflect on the past?
- Can they empathise with others of their own, or even different species, such that they have insight into the thought processes of other individuals, and can make inferences about what those other individuals might be feeling, wanting or believing? (Creatures that have this ability in its full-blown form are said to possess 'a theory of mind').
- And, can they communicate their thoughts and feelings via symbolic, syntactic language?

Evidence on each of these questions is reviewed below for Great Apes (mainly chimpanzees) and a few monkey species. (Some of this evidence is also considered in the report of a working party of the Institute of Medical Ethics – Smith & Boyd (Eds.), 1991).

Possession of any of the above abilities would suggest important similarities with human thought processes, and such evidence might have implications for the moral status of the various non-human primate species. In particular, as already noted, any or all of the abilities might enhance a capacity for suffering. For example, being able to worry (prospectively or retrospectively) about unpleasant or painful experiences could intensify suffering; and having a rich mental life could intensify the effects of any privation.

3.1 Evidence of self awareness/reflective consciousness

In humans, awareness of 'self' develops gradually in infancy and early childhood, so that children only gain full self awareness towards the end of their second year of life (Kagan, 1981). At this stage, the child becomes able to understand what it means to be 'itself' as distinct from others. Not only does it have feelings, but it develops a capacity to think about those feelings and to reflect on how it is similar to and different from others. The emergence of these capacities seems to be correlated with maturation of the child's developing brain.

The responses of young children to their own reflections in mirrors offers one, rather particular, insight into this development. Children show some inklings of self recognition in a mirror from as young as nine months. However, this ability increases strongly at around 18 to 24 months, when children also begin to use mirrors to attend to and explore their bodies – including pointing out marks painted on them by researchers (Lewis & Brooks-Gunn, 1979). The capacity for self recognition in a mirror thus appears to emerge at the same time as the capacity reflective thought (Kagan, 1981; Lewis *et al.,* 1989).

Similar experiments with non-human primates suggest that Great Apes alone have the ability to recognise themselves in mirrors. Both chimpanzees and orang-utans show 'self' directed behaviour when presented with mirrors – they make faces into the mirrors, use them to groom parts of their bodies which they cannot see directly, and examine marks painted on their faces, for example. Other non-human primates, such as macaques, baboons and gibbons, respond as if their reflections are other members of their species – they behave either aggressively or socially to their reflections, and show no mark-directed behaviours (Gallup, 1977; Povinelli *et al.*, 1997). It seems that the differences in behaviour are not simply because the monkeys do not understand how mirrors work – there is evidence to suggest that they do (Anderson, 1984). However, it is debatable whether the capacity for self recognition in a mirror is in fact necessary for self awareness (and vice versa). See further criticisms of such mirror studies in Heyes (1994), and a robust response from Gallup (1998); also a recent review by De Veer and Von den Bos (1999).

Looking more generally, complex behaviour (particularly the ability to solve novel problems 'creatively') might imply a sense of self and, with this, a capacity for reflective thought (Byrne & Whiten, 1988). However, complex behaviour alone is not necessarily indicative of such capacities, and it is often difficult to discount completely alternative explanations that the animals concerned might be using simple 'rules', rather than reflective, creative thought to solve problems. Indeed, biologists, traditionally, have sought to explain animal behaviour in the simplest possible terms and to avoid using complex explanations when simpler ones will do: the principle of parsimony. (Though this approach, of course, begs the question of what is to count as a 'simple', compared with a 'complex', explanation).

There comes a point, however, when the most parsimonious explanation seems, of necessity, to require invoking self reflective, creative thought. Many of Jane Goodall's, and others' observations of chimpanzee behaviour seem to fall into this category. Goodall (1995), and others, report that chimpanzees, for example,

- display a whole variety of postures and gestures similar to humans in similar situations (e.g. humans and chimpanzees greet one another similarly – kissing and embracing for example – play and reassure each other similarly and show similar signs of aggression);
- have emotional expressions (e.g. anger, sadness, joy) and needs (e.g. for comfort and reassurance as infants) similar to humans';

- can learn simply by observing the behaviour of other chimpanzees;
- not only use, but also *make* tools (modifying grass stems to fish for termites, or using hammer and anvil techniques to crack open nuts or fruits) – techniques which, because of chimpanzees' abilities to learn by observation, imitation and practice, show geographical and perhaps 'cultural' variation;
- show 'cross modal transfer of information' in that they can, for example, recognise by touch alone objects that they have previously only seen;
- can understand and use abstract symbols in their communication (e.g. chimpanzees reared in captivity can be taught to use sign language symbols to represent objects, actions and desires, as well as relations such as 'same as' and 'different from');
- have complex social relationships and can manipulate social situations to achieve their own ends. (See also Goodall, 1971; Premack, 1983; Byrne & Whiten, 1988.)

The last attribute, in particular, has been much cited as an example of behaviour indicative of self reflective thought (see anthologies and discussions in Byrne & Whiten, 1988, and in Whiten & Byrne, 1988). Anecdotal reports of apparently intentional 'tactical deception' are widespread in primatologists' reports of the behaviour of primates in the wild, and some of these records are 'exceptionally difficult' to explain as the products of rapid learning by association, or as mistaken interpretation on the part of observers (Byrne, 1998; Byrne & Whiten, 1992). For example, an observation by Plooij (from the anthology in Whiten and Byrne) shows how chimpanzees can realise that another chimp is deceiving them:

> 'One chimp was alone in the feeding area and was going to be fed bananas. A metal box was opened electrically from a distance. Just at the moment when the box was opened, another chimp approached at the border of the clearing. The first chimp quickly closed the metal box and walked away several metres, sat down and looked around as if nothing had happened. The second chimp left the feeding area again, but as soon as he was out of sight, he hid behind a tree and peered at the individual in the feeding area. As soon as that individual approached and opened the metal box again, the hiding individual approached, replaced the other and ate the bananas. So here a chimpanzee clearly realised the other was deceiving him and, in his turn, deceived the other. It concerned two adult males. At this time, singleton chimps only were fed, on a strict ration; so the second male, although dominant, could not have gained the bananas any other way.'

The most parsimonious explanation for such behaviour, it is argued, is that the deception is an example of intentional behaviour, the result of flexible and creative thinking, indicative of a capacity for self reflection. The argument being that, in order to deceive, the animal concerned must be able to infer the thoughts and feelings of other members of its species and that this ability must be based on an understanding of its own thoughts and feelings (see also, for example, Humphrey, 1986). Along these lines, it has furthermore been suggested that complex, reflective thought is a function of complex social living: in a highly social environment animals must deal with highly changeable situations, which vary with and depend on their own actions and their interactions with others in the group. To flourish in such a setting, it can argued, the animals involved are likely to need to be in tune with both the psychology of their companions, and, by implication, their own psychology as well (Byrne & Whiten, 1988). A similar argument might be advanced in relation to predators' understanding of their prey, and vice versa (see Jolly, 1966).

Monkeys also show complex behaviour. Macaques and other monkeys used in laboratory neurophysiology studies, for example, are generally quick and enthusiastic to learn about and use the computer gadgetry and games involved in the experimental tests. However, broadly speaking, monkeys' intelligence, like that of apes', seems to lie primarily in the social domain – in their understanding of relationships with other members of their social group, rather than of inanimate objects and of the wider environment (Cheney & Seyfarth, 1988a). Relevant observations might include the following (much of which derives from the long-term observations and field experiments of Cheney and Seyfarth, working with wild vervet monkeys in Kenya):

- Like apes, monkeys have a complex social life. Not only do monkeys seem to recognise relationships between particular individuals in their social groups (Cheney and Seyfarth 1988b), but may also form concepts about the relationships between other animals. Field experiments on vervet monkeys (Cheney and Seyfarth 1986; 1988b) and laboratory experiments involving long-tailed macaques (Dasser 1988) suggest that monkeys can recognise that, even when different individuals are involved, some relationships share similar properties. The results of these studies, however, are open to interpretation, and it is possible that, rather than involving reflective thought, they might also be explained as feats of memory, or simple associative learning, respectively. Moreover, other (non-primate) species, such as social small mammals, may have similar capacities.
- Although apparent instances of intentional tactical deception are documented for monkeys, Byrne (1998) concludes that there are few, if any, examples that are not equivocal, in that they can be interpreted as products of associative learning or mistaken interpretation (see also Byrne & Whiten, 1992). The vast majority of cases of intentional tactical deception, he argues, come from Great Apes.
- There is evidence to suggest that monkeys, when compared with Great Apes, show less responsiveness to the emotional states of other individuals of their kind. For example, after a conflict, both macaques and Great Apes (chimpanzees and gorillas) may engage in 'reconciling' behaviour – however, chimps and gorillas, but not macaques, engage in 'consolation', when a participant in a conflict seeks reassurance from, and is comforted by a third party. A possible explanation for the difference is that the Great Apes, but not the monkeys, make inferences about the emotional state of the comforted animal (de Waal & Aureli, 1996).
- Carefully executed field experiments involving vervet monkeys, suggest that the animals can communicate symbolically (Seyfarth, Cheney & Marler, 1980). Vervet monkeys have different alarm calls for different predators (as do some birds, for example) and Cheney and Seyfarth's experiments showed that, when tape recordings of the calls were played to the monkeys in the absence of any real predators, the monkeys exhibited appropriate responses to the calls. (Animals on the ground responded to leopard alarms by running into trees, to eagle alarms by looking up, and to snake alarms by looking down.) Because cues from real predators were absent, the experiments suggest that the calls alone communicated the concept that a particular predator was present. Later playback experiments suggested that the monkeys' softer grunts convey messages about social relationships between the animals (Cheney & Seyfarth, 1982, 1990a).
- Although monkeys show significant social knowledge, they show less well developed skills in their interaction with objects. For example, monkeys seem less inclined than apes to solve problems using objects, and, with the exception of the New World capuchin (*Cebus*) monkeys, there are few examples of tool use by monkeys (Beck, 1980).

Taken together with the evidence about brain development and self recognition in a mirror, one possible interpretation of the broad sweep of these observations might be that, compared with Great Apes, at least some kinds of monkeys have less well developed (or at least different) senses of self and capacities for reflective thought. Such a conclusion, however, requires further evidence, and, even then, is likely to remain tentative (see further discussion in Section 4 below). Moreover, the conclusion may not hold for all the different species of monkey, which differ considerably in size (including brain size) and life-style (varying life histories, social systems and habitats, for example).

In particular, capuchin *(Cebus)* monkeys are highly adaptable, show problem-solving skills akin to those of chimpanzees (Visalberghi, 1997), and both use and make tools – including flaked stones which they use as cutting tools (Westergaard, 1995). What these observations say about the animals' intelligence and insight is controversial. For example, there is debate about whether capuchins' tool use is based on experimentation and insight, or trial-and-error – and the findings of observational studies on this question are contradictory (see, for example, Chevalierskolnikoff, 1991, and Fragaszy, 1991).

3.2 Evidence about anticipation and planning

Much of the evidence about self awareness reviewed in the previous section has a bearing on this, and subsequent, sections.

Byrne (1998) argues that anticipation requires 'imagining a personal future' which, presumably, requires a sense of self. Animals which can anticipate can 'suffer in anticipation' and, Byrne argues, 'to assess their welfare needs properly, the safest course would be to treat them as humans' (p.122).

Reviewing evidence related to self awareness and theory of mind, Byrne concludes that in only a few primate species (he suggests Great Apes alone) is there 'suggestive evidence of an ability to imagine the future'. He draws on observations of wild chimpanzees, who show 'real anticipatory teaching' (e.g. a mother demonstrating to her infant the best way to crack nuts using a hammer stone and anvil), and signs of 'long-term planning' (e.g. chimpanzees have been seen to carry scarce hammer-stones up to a kilometre to sources of nuts). Furthermore, Byrne argues, chimpanzees sometimes take considerable risks for apparently long-term gain (e.g. chimpanzees have been observed to kill leopard cubs, suggesting that they are acting to limit the number of adult leopards in the longer term). There are no similar examples for other non-human primates.

Byrne also notes that Great Apes, but not monkeys, engage in intentional tactical deception, and that, similarly, Great Apes but not monkeys perform well in tasks which require them to understand the goals and intentions of other creatures, which can allow prediction/anticipation of the future needs of others (examples are given in Section 3.3. below).

However, ability to imagine the future might not require these most sophisticated abilities, involving understanding the thoughts of *others*. It has already been argued that monkeys have complex cognitive abilities, related to their elaborate social lives – suggesting that some species at least may have insight into their *own* thoughts. This could well bring with it a capacity to thinking about the future, although perhaps only in the relatively short-term (see review by Lea, 2001).

3.3 Evidence on 'theory of mind'

Humans can empathise with the thoughts, intentions, desires, beliefs, and so on, of others; they can understand others' mental states. Finding such abilities in other animals could suggest that they share important capacities for thought with humans, and might have implications for the animals' moral status (see Boyd Group Paper 3, which explores this issue in more detail).

The possibility that non-human primates, and in particular chimpanzees, have a 'theory of mind' remains the subject of lively debate. Observational evidence of tactical deception suggests that Great Apes understand enough about the thought processes of other creatures to try to manipulate them. A few experimental studies also indicate that chimpanzees can understand the intentions, goals and desires of human beings. For example, Premack and Woodruff, 1978, showed a captive chimp, Sarah, videos of a human actor in a cage experiencing various 'problems' (e.g. trying to reach bananas, just too high overhead). Sarah was then given several photographs depicting various 'solutions' to the problem, only one of which could be considered correct (e.g. in the example given, a picture of the actor standing on a chair). Sarah selected the photographs showing the solutions with a success rate well above chance, suggesting that she understood the intentions and desires of the actor. In the example given, she seemed to appreciated that the actor was not just 'jumping up and down', but 'wanted' the bananas and was trying to get them. Strikingly, three-year-old children failed similar tests (see review by Premack, 1988).

Further experimental work by Povinelli *et al.* suggests that monkeys lack an ability to empathise with others. In separate studies, individual chimpanzees and rhesus macaques were trained to co-operate with human partners to obtain a food reward. One member of the human-primate team could see the food, hidden in a special apparatus, but could not operate the correct handle, from a choice of several, to retrieve it; the other could pull the handle, but could not see the food. The animal or human who could see the food had to point to the correct handle in order for their partner to retrieve the food, which they then shared. Both the chimps and macaques learned to co-operate with their human partners in the task (chimps more readily), but only chimpanzees could immediately adapt to a reversal of roles in the partnership (Povinelli, Parks & Novak, 1992; Povinelli, Nelson & Boysen, 1992). The results, Povinelli *et al.* argue, suggests that in contrast to the chimps, the rhesus macaques had been learning the task by trial and error and had little comprehension of the roles, and thought processes, involved in the partnership. However, the design of these studies can be criticised because, for example: the animals are required to co-operate with humans, and thus the studies could be biased in favour of apes (who, being more closely related to humans than monkeys, might find it easier to relate to humans); and, in each trial, one member of the human-primate team knows where the food is hidden, so a Clever Hans effect could operate.

Other work by Povinelli *et al.* (1990 and 1991) and by Cheney and Seyfarth (1990b) suggests that neither chimpanzees nor other non-human primates such as macaques understand the connection between 'seeing and knowing' in others. For example, the animals do not appear to understand that someone present when food is hidden, but with his head covered, cannot know the location of the food. From a variety of similar experimental observations, the authors suggest that, because the animals cannot understand that the act of seeing creates internal knowledge, they also cannot understand that others have internal 'beliefs' that can be manipulated (see review by Povinelli & Preuss, 1995).

Children appear to acquire the notion of 'belief' at about four years old (before this age children fail the same tasks as the non-human primates). Thus, if the findings of the experimental studies are reliable, it can be argued that both the young children and the non-human primates lack a full-blown 'theory of mind'. However, it is also possible that non-human primates, like children, may be able to 'recognise' beliefs without understanding that the beliefs 'represent internal mental states'. For example, 'the subtle ways in which young children use mental verbs such as 'want', 'hope', and 'wish', suggest strongly that they know that they, along with others, are 'repositories' of unobservable mental states, even if they have not yet grasped how the mind can also serve as a mechanism to copy or represent the state of affairs in the world' (Povinelli & Preuss, 1995; see further discussion in Gomez, 1998, and Paper 3).

3.4 Evidence about symbolic and syntactic language

The famous ape language studies, in which chimpanzees have been taught to use American Sign Language, and experimental studies of wild vervet monkeys already cited, suggest that both apes and monkeys can communicate symbolically. That is, they can use symbols (signs or vocalisations in these cases) to represent both objects and concepts. However, whether these abilities represent a form of 'language' is open to interpretation.

Human language, apparently unlike most animal communication, is marked by its flexibility (symbols can be combined to create myriad new meanings), a quality which analysis of chimp sign language studies carried out by Terrace *et al.* (1979) suggests is lacking in non-human primate communication. Although more recent work claims grammatically-trained apes

(Savage-Rumbaugh *et al.,* 1993 – see Gomez, 1998), there is still widespread scepticism of the possibility that apes, and by implication other non-human primates, can acquire 'true' language.

(Interestingly, Pinker (1994) speculates that calls analogous to vervet grunts might have been the evolutionary forerunners of human language, as they came under control of the cerebral cortex and then began to be produced in relation to more complex events. Pinker also notes that areas in monkey brains have been shown to correspond to human language areas. Although these areas are not associated with the production of sounds, some of them seem to be used to recognise sound sequences and to discriminate the calls of other monkeys from the individual's own calls, whilst in others of these parts 'streams of information from all the senses converge').

4 Interpreting the evidence: some issues and questions

In many places in this brief review it has been noted that 'the evidence is open to interpretation'. Deciding what such empirical evidence tells us about the mental life of non-human primates, and what implications this might have for moral status, is fraught with difficulty. In particular:

- In the first place, it is difficult to decide what is to count as relevant and reliable evidence. Accounts from researchers who have painstakingly observed non-human primates in the wild, and seem really to have 'got to know' the animals, would seem to be the most compelling evidence. Yet, even here, there appear to be difficulties in deciding the significance of the observations, and such studies have sometimes been described as anecdotal. The alternative route – designing experiments (in the laboratory or in the wild) to try to probe the thoughts and feelings of the animals – is also open to criticism. Almost all of the experimental studies cited here admit possible methodological flaws. For instance, it is difficult to decide what are appropriate tests for the species involved, e.g. many of the tasks cited require animals to empathise and co-operate with *humans*, rather than others of their own species; the tasks may focus on features which simply are inappropriate in the wild; mirror experiments may fail because the animals do not understand how mirrors work.

- Furthermore, in deciding what to look for observationally or experimentally, we are constrained by our own particular *human* experience of what it means to be a thinking, feeling being. Other species are likely to 'see the world' in different ways – ways which, trapped inside our own human minds, we have difficulty probing. Dawkins (1993) makes this point in relation to Cheney and Seyfarth's work on vervet grunts. Until Cheney and Seyfarth analysed the composition of the grunts using a sound spectrograph, human observers had not appreciated the subtle differences in the sounds made by the monkeys, nor their role in symbolic communication. We are likely to need to learn more about the subtleties of animal communication via, for example, sounds inaudible or indistinguishable to the human ear, or other senses, such as olfaction, before we can begin to make confident assertions that other animals do not betray signs of 'thinking' analogous to those of humans. (See also discussions in Heffner (1998) and Sommerville & Broom (1998), for example).

- Difficulties in interpreting the evidence are often said to arise because 'rule-based' explanations of observed behaviour cannot be eliminated. The presumption still seems to lie in favour of attributing such rule-based (stimulus-response-type learning) explanations, rather than more mentalistic ones, and the burden of proof tends to lie with those who prefer an explanation which invokes 'creative thinking'. Rule-based explanations are said to be the most parsimonious, and the long-held principle of parsimony dictates that biologists should use such explanations where possible. However, it is not clear:
  (a) Why the principle of parsimony should apply in the first place. Why, particularly for creatures with well-developed brains, should the presumption lie in favour of 'unthinking', learned behaviour, and not with behaviour

as the product of thoughts? In many of the cases cited here, the two explanations appear equally likely.

(b) Whether in fact rule-based explanations are always the most parsimonious. As Byrne (1998) has argued for tactical deception, some kinds of animal behaviour appear so complex that explanations phrased in terms of associative learning become more cumbersome than explanations which invoke creative thinking.

- There are likely to be *degrees* of awareness/thinking ability across the animal kingdom (see, for example, Crook, 1982). As noted, studies of human development show that reflective thinking is not an all-or-none ability, and a number of the studies reviewed here suggest that, in human terms, chimps may have mental abilities at least appropriate to those of a three- or four-year-old child. What, in fact, is the moral significance of animals having thought processes more or less like humans'? As already noted, being able to think and reflect on one's thoughts could enhance a capacity for suffering. But, equally, creatures lacking full self consciousness could potentially suffer more because they are unable to appreciate that the suffering will have an end in the foreseeable future (Sommerville & Broom, 1998). Furthermore, non-human primates might have mental representations different from those of adult humans, but perhaps no less morally significant (Gomez, 1998; see also Paper 3).

- In considering whether the empirical evidence should lead us to afford 'special moral status' to non-human primates there is also a need to make comparison with the cognitive abilities of other creatures. Interpreting similar evidence for different species is likely to be more difficult, as greater leaps of extrapolation are required. However, as animal behaviour is studied with an increasingly open mind on the possibility of mentalistic explanations, the more tantalising the findings become (see, for example, Dawkins, 1993). Dolphins and elephants, for example, have larger brains for their body weight than some non-human primates, and observational and experimental studies suggest that they have capacities for reflective thought (Herzing & White, 1998; Poole, 1998). Birds, in particular have also been shown to have complex cognitive capacities, including abilities to form concepts and to communicate these symbolically. Finding similarities between ourselves and our closest animal relatives, the non-human primates, should not divert attention from the possibility of relevant mental similarities with other, apparently more different, species.

- Finally, it can be argued that all this empirical evidence about mind is something of a red herring, and that other, more philosophical aspects are important in deciding moral status; for example, our capacity to form reciprocal relationships with the animals concerned. For discussion, see Paper 3.

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Paper 3: The moral status of non-human primates: Are apes persons?

1 The moral status of persons

The term 'moral status' refers to what, because something is the kind of thing it is, you may or may not do to it. Because of the kind of thing it is, a pebble on a beach has little or no moral status: there is nothing about pebbles as such, that makes it wrong to throw them into the sea as mere means to your end of amusing yourself. People on a beach are a very different kind of thing. They are the same kind of thing as you are – not mere means but, like you, ends in themselves. Their moral status is that of persons, with a right not to be harmed by you, especially not without their consent.

The difference in moral status between pebbles and people is so obvious, that if anyone asked why they should not throw people into the sea just to amuse themselves, we would doubt their seriousness or their sanity. But what if they wanted to throw people into the sea, not to amuse themselves, but for a good reason such as scientific research which could benefit humanity by saving other lives? Without (at least) the consent of the people concerned, that too would be morally wrong. The example of the hypothermia researchers in Nazi Germany who plunged prisoners into tanks of freezing water illustrates this. While the morality of using the results of that research is debated, the immorality of the research itself is unquestioned.

What this example also illustrates however, is that the moral status of persons has not always been universally recognised and respected. There are countless historical examples of apparently sane people treating other people who were in some respect weaker than them (children, women, slaves and members of other ethnic groups, for example) as if they were not the same kind of thing as themselves. One historical reason for this, no doubt, is scarcity. To regard others as having equal moral status to yourself has demanding implications. It may require you to share your resources with them, or, at least to refrain from treating them in ways which might be to your own or your nearer kin's advantage. But the resources available to anyone are finite; and other people's interests may conflict with your own, sometimes even with your own or your nearer kin's survival. Historically, this was often the case; and since not only material resources, but also people's time and imagination are finite, it is not surprising that some people have regarded others, especially those whose interests may have conflicted with their own, as not having equal moral status to themselves.

Against the background of scarcity, what perhaps is surprising is the emergence of the modern view of the moral and legal status of persons. This view emerged, slowly and patchily, from different strands of religious and philosophical reflection. But only in recent centuries was it formalised, and widely accepted, as the principle that the moral status and human rights of all individual persons should be respected, simply because they are persons, rather than because they are (to others or to God) important persons.

Widespread acceptance of this principle however, has left unsettled the question of who counts as a person and how this is to be determined. The claim that all and only members of the species *Homo sapiens* are persons, simply because they are members of that species, is now too contestable, on mature philosophical reflection (see Tooley, 1998), to settle the matter. This opens up the possibility that some humans may not be persons and that members of some other species, especially primates, may be persons. But how do you determine who or what counts as a person?

Perhaps the most common philosophical way of trying to answer this is by saying that what determines whether members of other species count as persons, is whether they have properties or characteristics which make them sufficiently similar, in morally relevant ways, to humans whose personhood is not in doubt. The characteristics most often cited as morally relevant are intelligence and the capacity to suffer pain or distress. But stated as simply as that, without further qualification, these are characteristics of the members of many non-human species. The moral status of members of these species clearly is much higher than that of pebbles, and probably higher than that of living creatures which (assuming this could be shown) are less intelligent or sensitive to suffering. But to characterise them as persons may be to broaden the meaning of that concept so much that it loses its distinctive content.

2 Apes, metarepresentational capacity, and intersubjectivity

For the concept to have content, further qualification of the characteristics morally relevant to determining personhood seems to be required. The variations on this theme in the literature are many, particularly with reference to consciousness and self-consciousness. But one recent version, by the psychologist Gómez (1998), is particularly interesting for the present purpose, both because it concerns apes, and because it defends a claim to personhood on their (but not necessarily all primates') behalf, against the very stringent criteria for personhood suggested by the philosopher Dennett (1976).

According to Dennett, persons must be not only intentional agents, but capable of reciprocal understanding that other persons are intentional agents. This requires 'metarepresentational ability', the ability to represent, in one's own mind, other persons as having minds and metarepresentational ability of their own. But metarepresentational ability can be developed and detected only by means of language. So creatures that lack language cannot be persons.

Responding to these criteria, Gómez notes that there 'seems to be little controversy that apes... are intentional creatures that follow goals with a diversity of behavioural and instrumental means and who form complex expectations about the world at some representational level'. But do apes 'understand others as intentional agents with their own ability to reciprocate in this understanding'? In terms of Dennett's language requirement, Gómez concedes that, in apes, evidence is still at best ambiguous both of linguistic ability, and of non-linguistic cognitive abilities amounting to a 'theory of mind' (i.e., an understanding that other creatures act 'on the basis of thoughts, wishes, beliefs, intentions, etc'.).

Gómez agrees that the 'ability to reciprocally recognise each other's intentionality' is 'an essential feature of persons'. But he questions Dennett's stipulation that this requires an ability to *recognise explicitly* (in metarepresentations) one another's mental states. 'Would it not be possible', he asks, 'to engage in this mutual recognition without explicitly representing the intentions of others as internal mental states?'

If this mutual recognition, or 'intersubjectivity', is the 'essential feature' of persons, what needs to be shown, is whether apes, as 'subjects (intentional agents in Dennett's terminology) can coordinate their 'subjectivities' (i.e., their mental states) with other creatures' subjectivities (i.e., other creatures' mental states) without having recourse to metarepresentations'. Gómez believes that this can be shown, and illustrates this with observations from his own and and others' research – for example that apes, like humans, but unlike some other non-human primates, use eye-contact and other aspects of face-to-face interaction, not in a 'single, predominantly aggressive/defensive way', but 'as a pivotal component of different kinds of social interactions' in which they attend and respond to the intentionality and emotions of others.

This non-metarepresentational intersubjectivity, Gómez points out, appears to be achieved by human infants in the first year of life, and is characteristic not only of apes, but perhaps also of 'adult humans, who do not seem to understand attention contact in metarepresentational terms either (unless they are cognitive scientists engaging in propositional redescriptions with scientific purposes).' This does not mean that apes are the same as humans, whose 'metarepresentational minds are capable of achieving much more sophisticated versions of consciousness and personhood'. But apes do appear to satisfy the key condition for personhood: they 'act and feel as persons in the most essential sense of the word, which I take to be the ability to recognise others and themselves as individual subjects capable of feeling and behaving intersubjectively.'

Gómez sums up his argument thus: 'I am not a person in so far as I think I am a person; I am not a person in so far as another thinks of me as a person. I am a person in so far as I and another perceive and treat each other as persons.' This formulation amplifies the African proverb that 'a person is a person through other persons'. Gómez' view also is similar in some respects to the primatologist Smuts' (1999) claim (illustrated by her experience not only with baboons but also with her own dog) that 'relating to other beings as persons has nothing to do with whether or not we attribute human characteristics to them. It has to do, instead, with recognising that they are social subjects like us, whose idiosyncratic subjective experience of us plays the same role in their relations with us that our subjective experience of them plays in our relations with them. If they relate to us as individuals, and if we relate to them as individuals, it is possible for us to have a personal relationship'.

3 Two objections

One possible objection to Gómez' argument is this. He argues that 'I am a person in so far as I and another perceive and treat each other as persons'. But for apes to be accepted as persons, he needs not only (like Smuts perhaps) 'intuitive, subjective' experience of a personal relationship with individual animals, but also what he calls 'analytical, objective' scientific evidence 'that can be independently and objectively verified by different people'. For the purposes of his argument therefore, whether or not apes are to be accepted as persons does indeed seem to depend on whether 'another thinks of me as a person'. It depends too on whether 'different people' actually do 'verify' the philosophical criteria and interpretation of the scientific evidence offered by Gómez. Since scientific evidence and interpretation are always vulnerable to reinterpretation and further evidence, and since philosophical theories are essentially contestable, Gómez' arguments about personhood and apes are at best persuasive but not conclusive.

This objection is not necessarily fatal to Gómez' argument, however. Whether or not apes are persons is a question to which there may be no conclusive, but only more or less persuasive answers. What is at issue here therefore may be whether Gómez' intersubjectivity argument is more or less persuasive than Dennett's stipulation that to be a person requires linguistic capacity. In this respect, one problem about Dennett's argument is that, historically, many human persons with the capacity for speech (slaves, or 'lesser breeds' for example) have not been 'heard' as speaking meaningfully, and so have not been treated as persons. If there is any doubt about whether apes are persons who are not being 'heard' in this way, Gómez' claim that 'I am a person in so far as I and another person perceive and treat each other as persons', offers a way of trying to answer the question that at least admits that it is a reasonable question. It does not, that is, foreclose the question in advance with the stipulation that a necessary condition for personhood is a physiological capacity which (probably) only humans possess – a capacity moreover which even when present in some human persons, has not proved sufficient to persuade other human persons of their personhood.

Gómez' argument that 'I am a person in so far as I and another perceive and treat each other as persons' receives some support also from the philosopher Gaita's (1991) view that a person is someone who can 'be seen as one who could be someone's friend', even when not heard or treated as a person by almost everyone else. Gaita, however, is impatient of philosophical arguments which make the recognition of others as persons await confirmation that they possess morally relevant properties. In real life, he argues, recognition of others as persons depends not on intellectual beliefs about their capacities, but upon recognition of another 'I' – in Wittgenstein's terms, not 'on the *opinion* that he has a soul', but on 'an attitude towards a soul'.

Gaita's argument here seems close to Gómez' view that 'I am a person in so far as I and another person perceive and treat each other as persons'. But a second objection to Gómez' claims for apes is raised by a further point made by Gaita about someone who can 'be seen as one could be someone's friend'. Such a person, he argues, 'must be seen as someone who is subject to the demands which are internal to friendship, as someone of whom it is intelligible to require that he rise to those demands, no matter how often he actually fails to do so.' (1991). He doubts that this is possible for non-human animals. 'Only human beings (of the beings we know) have an inner life. That is because only human beings can reflect on what happens to them and take an attitude to what happens to them because of such reflection.
An animal can suffer but it cannot curse the day it was born; an animal can be afraid but it cannot be ashamed of its fear and despise itself; an animal can be happy but it cannot be joyous… The problems of life's meaning cannot arise for an animal and only a being for whom life can be problematic can have a spiritual life, and therefore, have a soul.' (1991).

This second objection, again, is not necessarily fatal to Gómez' argument. While arguing that apes 'act and feel as persons in the most essential sense of the word, which I take to be the ability to recognise others and themselves as individual subjects capable of feeling and behaving intersubjectively', he does not deny that humans' 'metarepresentational minds are capable of achieving much more sophisticated versions of consciousness and personhood.' On the other hand, if personhood is something that admits of different versions, can it still do the work that is required of it as a concept that protects the equal moral status of all persons?

4 Moral agents and moral patients

One response to this difficulty is to argue that while all persons have equal moral status, what that entails for how they ought or ought not to be treated, depends on whether they are moral agents or moral patients. A moral patient – a person who is currently unable to exercise moral agency (in Gaita's terms, to 'rise to... the demands that are internal to friendship', for example) – may have equal moral status to other persons, but nevertheless need be treated differently to a moral agent. This distinction within the category of persons avoids the morally unpalatable conclusion that people who have become demented, for example, are no longer persons. It can also be used to argue that, even if apes cannot 'rise to…the demands that are internal to friendship' for example, generosity suggests that they are still entitled (if Gómez' arguments are accepted) to be regarded as persons.

A possible objection to such generosity, suggested by Gaita (1991), is that if animals are moral patients, they (unlike humans) 'are not as they are through misfortune'. If that is a morally relevant consideration, the case for treating apes as persons who are moral patients may be weakened. But are apes moral patients rather than moral agents? The question of whether at least some animals are or may be moral, is at least debateable. Smuts for example, writes this about her dog Safi: 'because I regard Safi as a person, and she regards me as one, we can be friends. As in any genuine human-to-human friendship, our relationship is predicated on mutual respect and reciprocity. Although she depends on me to provide certain necessities, like food and water, this dependence is contingent, not inherent: if I lived in the world of wild dogs, I would depend on her for food and protection'.

Smuts illustrates these claims with various experiences of her relationship with Safi, and concludes: 'I do not claim that any dog will show such behaviours if treated as an equal. In fact, I believe that Safi is exceptional, that she was born, perhaps, with an unusually sensitive nature. However, I do firmly believe – and my experience with other animals supports this belief – that treating members of other species as persons, as beings with potential far beyond our normal expectations, will bring out the best in them…'

It is difficult to see how such claims for animal morality could be substantiated to the satisfaction of many who would regard what Smuts writes as 'sentimental'. If she did live 'in the world of wild dogs', would Safi actually afford her the necessary 'food and protection'? But to identify what is or is not 'sentimental', or to achieve a 'healthy' critical distance from subjectivity, itself is a matter of judgement, and intersubjective agreement may be the closest we can come to the truth about it.

It may, of course, not be possible to achieve intersubjective agreement on questions like animal morality or whether apes are persons, let alone the much more difficult question of the relative moral status of members of other animal species. But at least to try, is incumbent on members of an animal-using species who claim to be moral animals. A serious effort, clearly, needs to examine, carefully and critically, scientific evidence of the kind offered both by Gómez and by others who interpret their evidence differently. But it also needs to examine, just as carefully and critically, the varieties of 'testimony' offered by those who, like Smuts, have first-hand experience of living and working with the animal species in question.

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Paper 4: Welfare considerations in the use of marmosets and macaques for scientific research and testing: A comparison

	MARMOSETS	MACAQUES
Main species used	Common marmoset *(Callithrix jacchus jacchus)*	Cynomolgus macaque *(Macaca fascicularis)* [also known as crab-eating, or long-tailed, macaque]. Rhesus macaque *(Macaca mulatta)*
Adult weight	c.350–600g	<u>Cynomolgus:</u> *c.*9–12kg for males and 5–8kg for females <u>Rhesus:</u> *c.*5–7kg for males and 3kg for females, but can be considerably heavier
Habitat in wild	South American tropical forests (but animals are also hardy in more temperate conditions).	<u>Cynomolgus:</u> Equatorial forests in SE Asia, Philippines, Malaysia, Indonesia & Mauritius. Warm, humid conditions, with little seasonal variation. <u>Rhesus:</u> Wide variety of habitats across N. Africa and Asia, with widely ranging climates.
Lifestyle in wild	Troop-living; apparently usually monogamous. Troops tend to be family groups (with occasional wider associations), comprising around two to 15 animals. Each social group contains one breeding female, who suppresses the breeding of other females in the family. Members of the group share the care of offspring. Groups vigorously defend their territories, and mature adults are hostile to same sex intruders. Marmosets are highly active, finding security in dense tree foliage and seldom spending time on the ground.	Troop-living; polygynous/promiscuous. Troops are very variable in size, but are often large (as many as 50 to 100 animals). A group of related females forms a stable core in each troop, males frequently migrating between troops. There are strong dominance/sexual hierarchies, and aggression is common within troops. Cynomolgus macaques are arboreal, whereas rhesus macaques are semi-terrestrial.
Diet	Mainly fruit and insects – teeth adapted to eating gum from particular species of gum tree.	Mainly frugivorous, but adapt to a wide variety of diets in the wild. As other primates, much of their time in the wild is spent foraging on the ground.
Home range size	Around 0.04km^2 (4Ha). Defend territories of about 0.018km^2 (1.8Ha) around gum trees.	Cynomolgus macaques: average home range c.0.8km^2, and average daily distance travelled c.1.5km. Rhesus macaques: more variable: home ranges vary from 0.05km^2 in towns, to 16km^2 in sub-Himalayan tropical forest.

	MARMOSETS	MACAQUES
Weaning age and time of dispersal from birth group in the wild *i.e. time when infants stop receiving milk from their mothers*	In the wild, weaning occurs when infants are 9–13 weeks old. From around 10 weeks old, infants are carried by their mothers less than 5 per cent of the time; but the young marmosets stay with their birth groups, apparently tending to disperse only after they are sexually mature - from around 18 months of age (though some may never disperse).	In the wild, weaning usually occurs at around 14 months in cynomolgus macaques. However, macaques remain with their mothers until the next baby is born, which can be for up to two years (inter-birth intervals being between 12 and 24 months for both rhesus and cynomolgus macaques).
Routine laboratory housing and husbandry	The animals' relatively small size, climate tolerance, monogamy and preference for living in small family groups make it comparatively straightforward (and not prohibitively expensive) to provide housing and husbandry that appears to meet the animals' needs, and promotes their well-being.	The animals' larger size, greater natural troop and home range sizes, and social characteristics, including complex dominance relationships and aggressive tendencies, mean that it is more difficult to provide laboratory housing which mimics natural conditions for macaques. This, coupled with the physical and microbiological health hazards the animals can pose to humans (as well as climate requirements of cynomolgus macaques) suggests that husbandry of macaques, along with other Old World primates, is 'one of the major difficulties in providing an acceptable quality of life for them as laboratory animals' (Baskerville, 1999).
	Marmosets are usually housed in family groups of up to eight individuals - though they may also be housed routinely in pairs, or occasionally individually, for some studies.	Macaques are usually housed in single-sex pairs or small groups of peers – though they may also be individually caged for some studies.
	Their housing requirements include: ● cages with a height of *at least* 1.5m and a *minimum* floor area of 2.0m^2 for family groups (Poole *et al.,* 1994). But, in practice, cage size could be smaller according to Home Office guidance (1989) which goes by weight, and EU guidelines allow still smaller cages. Some places prefer to keep marmosets in much larger, walk-in cages;	Their housing needs include: ● cages or pens which are as large as possible, to provide space for climbing, leaping, etc.;

Paper 4: Welfare considerations in the use of marmosets and macaques for scientific research and testing: A comparison *(continued)*

	MARMOSETS	MACAQUES
	● sufficient vertical space to allow the animals to flee upwards, preferably above human eye level, and a hiding place;	● sufficient vertical space to enable the animals to stand erect, sit on a perch without head or tail touching the cage, and preferably climb high enough to look down on humans (Home Office minimum cage sizes standards are based on weight of animals and require little vertical height – 1.0–1.5m for macaques – they need amending – see Poole *et al.*, 1994);
	● rich and complex environments, including opportunities for climbing, foraging (e.g. via puzzle feeders placed high up in the cage), gnawing and gouging, swinging, and social play, as well as places to rest.	● rich and complex environments, including opportunities for foraging (e.g. via small food items scattered in wood chips or sawdust on the floor of the cage – which requires solid rather than grid floors, that are also more comfortable and more like the animals' natural environment), climbing and swinging (e.g. via ropes or hammocks – especially important for young animals – though care must be taken with ropes since they can cause injury); and other objects to stimulate interest – provided their value to the animals is assessed and monitored carefully.
Welfare effects of husbandry	Behavioural abnormalities, including stereotypies, are rare in marmosets housed in groups in enriched environments.	Behavioural abnormalities, including stereotypies, are more common in laboratory housed macaques. (Though it should be noted that the animals' behaviour could also be affected by prior confinement in restricted environments.)
Number used in British laboratories	In 2000, 1060 'marmosets and tamarins' were used in scientific procedures in Great Britain (Home Office, 2001), and a survey by EUPREN (1997) suggests that the majority of these animals were marmosets. Marmoset use declined each year from 1993–1998, but rose again in 1999 (Note 1).	1891 macaques were used in scientific procedures in Britain in 2000 (Home Office 2001). Over the past 10 years, in every year except 1993 use of macaques exceeded use of marmosets, and the ratio of macaques to marmosets and tamarins used was highest in 1998 (see Figure in Note 1). A EUPREN survey (1997) suggests that between 1990 and 1995 use of cynomolgus macaques (cf. rhesus macaques) accounted for around 80 to 90 per cent of total macaque use. An historical trend in use of macaques is difficult to determine from data over the past 10 years (Note 1).

	MARMOSETS	MACAQUES
Main users in UK	Pharmaceutical companies.	Contract testing laboratories.
Breeding and supply	● Marmosets breed readily in captivity in the UK. ● They mature relatively early (they can be bred in the laboratory from around 18 months of age). ● Marmosets have a relatively high rate of reproduction: producing young (usually twins) every 5-7 months.	● Macaques are less easy to breed in captivity in the UK. ● They take longer to reach sexual maturity. Males are only fully mature at four plus years old, and females from about two years of age. ● Macaques have lower rates of reproduction. In common with other primates, they usually bear young only once a year at most, and rarely produce twins.
Source of animals used in scientific procedures in UK	Almost all the marmosets used in UK laboratories are bred in the UK; and animals are only very occasionally imported due to lack of availability in the UK (e.g. captive bred animals from South Africa). In 1994, 78 per cent of marmosets used in the UK were bred in-house, and 19 per cent were bred elsewhere in the UK (EUPREN 1997).	The majority of macaques used in the UK are bred in Home Office accredited (though infrequently inspected) extensive breeding facilities in source countries, such as Mauritius, the Philippines, Israel and China. In 1994, 89 per cent of cynomolgus and *c.*50 per cent of rhesus macaques used in UK laboratories were obtained from breeding centres in source countries. The remaining animals were captive bred in the UK, mainly in universities and research institutes. Contract testing laboratories and pharmaceutical companies obtained almost all their macaques from overseas (EUPREN 1997).
Source of animals to maintain captive breeding colonies	Wild-caught marmosets are not available. Those used in the UK generally come from long-term captive breeding colonies, replenished where necessary from other captive-bred colonies and not with wild-caught animals. Although the stresses are likely to be less severe than for wild-caught animals, the brought-in animals are likely to be removed from their existing social group, put into special boxes for transport, and then, on arrival, quarantined for at least 30 days,	Until relatively recently, macaques used in the UK were almost all taken directly from the wild (see Note 2). Captive breeding in source countries is an improvement, but does not avoid capturing wild macaques, nor other welfare problems. Cynomolgus macaques supplied from source countries to the UK are usually the first (F1) generation bred in captivity, their parents having been taken from the wild. Parents are replaced from wild stock when their breeding

Paper 4: Welfare considerations in the use of marmosets and macaques for scientific research and testing: A comparison *(continued)*

	MARMOSETS	MACAQUES
	before adjusting to new social conditions in the recipient colony.	efficiency declines (Welshman 1999). The stresses on the parent animals of capture from the wild, transport to the breeding centre, quarantine on arrival, and adjustment to new physical and social conditions still remain.
Time of removal from birth groups in laboratory housing	Marmosets usually remain in their birth groups until they are at least 18 months old, though at least one UK commercial supplier removes them at about nine months. Marmosets need to assist in the rearing of two pairs of siblings before they are ready to rear their own young.	Ideally, infants in captive colonies remain with their mothers for at least a year, but they are sometimes removed as early as five months (especially in colonies where B virus transmission is a problem). It has been shown that early removal of infants from mothers improves reproductive performance of the colony, but is very stressful for the infants and can adversely affect adult behaviour. See Note 3 for more detailed discussion of weaning age.
Transport from breeding colony and arrival at place of use	Breeding the majority of animals in-house removes the need for transport from breeding colony to laboratory. Otherwise there is a relatively brief journey, within the UK, from breeding to 'using' establishment, where the animals must then acclimatise to the new conditions. Settling down to 'new neighbours' can be particularly stressful for these highly territorial animals, and acclimatisation has to be carefully managed. *Transport of primates, particularly over long distances, and by indirect routes, is likely to be stressful for the animals. However, there is little peer-reviewed published evidence on the welfare effects on primates of transport, and further research is needed* (Wolfensohn, 1997).	Macaques bred in source countries face long journeys to UK suppliers. They are removed from their troop, put into crates, transported by air to Europe, and then by road to laboratories in Britain. Journey times are at least 30 hours, and from China are 50 hours or more. The change to road for the final leg of the journey adds to the stress of transport, but is necessary because, owing to animal rights action, few airlines are now willing to land primates for research in the UK. Prior to export the animals are usually pair housed in cages, health screened and quarantined (for two to four weeks in Mauritius, and 45 days in the Philippines; Welshman 1999). They remain under rabies quarantine during their time in the UK. Since 1999, when the only UK designated supplying establishment for imported primates closed, the animals are imported directly to the laboratories. Although they tend to be nervous of their new surroundings, they are easier to handle than the wild caught animals used in past times, and young macaques may acclimatise quickly.

	MARMOSETS	MACAQUES
Future options for supply of animals	In theory, all marmosets used in the UK could be bred in the UK, but forbidding any imports could lead to over-production.	A EUPREN Working Party (1997) has suggested several possible means of improving both animal welfare and ease of supply of macaques for UK research. For example: ● *increase macaque breeding in the UK*, though this would be costly, would involve less natural conditions for the animals and is likely to require a switch to use of rhesus macaques owing to the climate requirements for successful breeding of cynomolgus macaques; ● *do scientific work in breeding centres in natural source countries;* ● *co-ordinate importation of macaques,* e.g. by chartering flights into UK, avoiding the road leg of journeys; ● *increase welfare standards in breeding centres in natural source countries* – though this will not ease concerns about transport to the UK. There are also moves within Europe to try to promote more self-sufficient macaque breeding colonies in source countries and thus to avoid taking animals from the wild.
Use in scientific procedures *Handling and restraint*	Marmosets do not like being caught, handled or restrained. They can be trained (by giving food rewards) to accept handling, but this can be difficult, and handling usually continues to appear stressful for the animals. Sometimes handling can be avoided altogether, e.g. by using telemetric methods to gather physiological data, or by in-cage testing (e.g. requiring animals to carry out tests using computer screens fixed to the fronts of their cages in neuropsychological studies). However, telemetry involves surgery to implant recording devices and should only be used where it represents an overall refinement.	Repeated capture and physical restraint is stressful. However, macaques can be relatively easily trained (by giving rewards) to enter, say, individual cages or transport boxes, or to squat in special primate chairs for neurophysiological work. On both welfare and scientific grounds efforts should always be made to train the animals to accept handling and so avoid capture/restraint and/or sedation. Again, telemetric methods and in-cage testing can sometimes be used to avoid needs for restraint altogether, but should be used only where they represent overall refinements (see opposite).

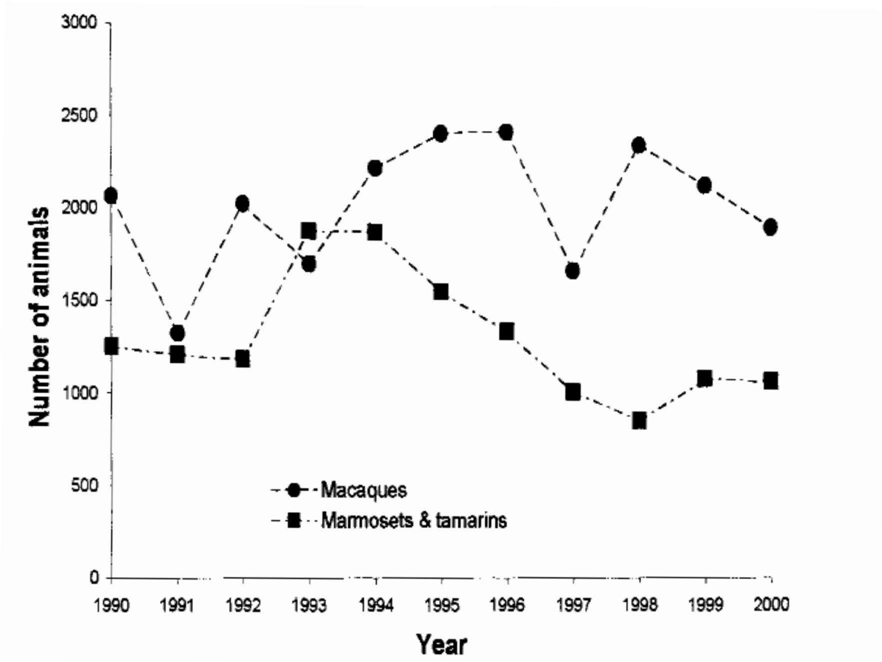
Paper 4: Welfare considerations in the use of marmosets and macaques for scientific research and testing: A comparison *(continued)*

	MARMOSETS	MACAQUES
Separation into peer groups or pairs for test purposes	For toxicity testing, in particular, same-sex peer groups of animals rather than family groups are often used in tests. Taking marmosets from family groups causes great stress, and adjustment to new social conditions can be difficult. Animals in same-sex groups tend to fight, and so are sometimes maintained in individual housing, which is always stressful for them.	Laboratory housed macaques adapt more readily than marmosets to being moved into new groups or into pair housing. The process does not involve the animals being removed from close-knit family groups, and they are likely already to have experienced a variety of social conditions, during breeding and supply. However, such separation may still involve removing animals from a stable group of familiar individuals.
Routine procedures	Once marmosets are restrained, it is relatively easy for experienced staff to take blood samples from the animals, or to give injections. However, marmosets' small size influences the numbers of animals required in some studies. Pharmacokinetic studies require repeated blood sampling, but marmosets are too small to allow a large series of samples to be taken from the same individual. Sequential samples are taken from different groups of animals, thus increasing the number of animals required. Where haematology and clinical chemistry samples are also required, blood volume, in addition to the number of samples, becomes a problem, leading to use of additional animals.	Macaques' larger size makes it easier for licensees to learn to take blood - though macaque blood vessels are more difficult to access than those of dogs. Animals can be trained to present a limb for blood sampling or injections. Otherwise, they must be captured and restrained. Macaques are just of sufficient size to allow serial blood sampling, in pharamacokinetic studies for example. Animals should be trained in studies involving repeated blood sampling or injecting as this can benefit both animal welfare and science (stress and sedation both affect haematological values, for example).
	Marmosets will eat palatable foreign substances concealed in their food. But for other substances, and in many research procedures, accurate oral dosing by gavage is required. This is always stressful for the animals. Often the animals are required to bite on a plastic bar and the gavage tube is passed in over the top of the bar. The technique poses safety hazards for humans, too.	Macaques cannot be relied upon to eat any foreign substance mixed with their food. However, they can be trained to accept oral or nasal gavage without struggle. Without training, more physical restraint is required.

Notes

1. Home Office data showing trends in use of macaques and marmosets (along with closely related tamarins, of which relatively few are likely to have been used in each year) are shown in the graph below:

Use of macaques and marmosets in scientific procedures in Britain, 1990-2000



2. Until relatively recently, the majority of macaques used in UK laboratories were supplied directly from the wild. However,
(i) in the 1970s India banned export of wild-caught rhesus macaques (the major species used in Britain at the time). Some captive rhesus colonies were set up in the UK, but the majority of researchers switched to using wild-caught cynomolgus macaques;
(ii) from the mid 1980s onwards, extensive breeding facilities for cynomolgus macaques were set up in source countries – in response to the increasing conservation threats to wild macaques, and growing awareness of the severe welfare problems posed by use of wild-caught animals; and then
(iii) in 1996, the UK banned the use of wild-caught primates for research and testing, unless exceptionally and specifically justified.

3. Opinions differ on the most appropriate weaning age for captive-bred infant macaques. Sarah Wolfensohn of Oxford University has provided the following analysis of current evidence and advice (Wolfensohn, pers. comm.):

   The Home Office Code of Practice (1989) on housing and care of animals used in scientific procedures requires that young primates 'must not be weaned at less than six months and 1kg in body weight, unless on veterinary advice e.g. mother is unable to rear baby', and 'it is preferable not to wean before 12 months of age.'

Paper 4: Welfare considerations in the use of marmosets and macaques for scientific research and testing: A comparison *(continued)*

The Universities Federation for Animal Welfare's Handbook on Care and Management of Laboratory Animals (Poole (Ed.) 1999) argues that, 'the best compromise is probably to wean most infants at around 6 months, but to leave individuals who are not doing very well with their mothers for a longer period'. However the International Primatological Society guidelines contradict this advice, advising that 'the young monkey should not normally be separated from its mother at an early age (i.e. at three to six months) but should remain in contact for one year to 18 months'.

Interestingly, Goo and Fugate (1984) found that at a year old, infants weaned at twelve months were 200g heavier on average than those weaned at six months, but there were no significant differences in survival to two years among groups weaned at six, eight, ten and twelve months of age.

In light of these contradictory opinions, the important criterion is the monkeys' well being, and in particular that young monkeys are reared with an appropriate social background. If they are not, they will show deficiencies in social behaviours that are indicative of poor welfare. Such indicators include:

- a restricted repertoire of behaviours;
- an abnormal activity budget;
- inadequate social behaviour;
- abnormal behaviours such as self injurious behaviour tendencies.

Lactation in the female has all but drawn to an end by ten to eleven months, so that infants would be fully weaned before the birth of the next baby, and at this stage they do not depend on their mothers for nutrition. Weaning is not an abrupt event but a process lasting over several months. Most infants can feed themselves at six months but remain socially dependent on their mothers and return to them when disturbed and to sleep. After the first year, juvenile animals can become more and more involved in peer groups, especially the males. The National Research Council (1997) points out that although the importance of social stimulation during infancy is well established, considerably less is known about the influence of social contact during juvenile and adolescent stages of development.

In practice, the continual assessment of behaviour and welfare is more important than sticking to rigid temporal criteria. The strategy should be to monitor each animal and if behavioural problems are observed then the management regime, including weaning age, should be reviewed. For example, when animals are weaned in batches it is more important to keep a younger animal of, say, nine months, with its older half siblings of, say, twelve months, with which it has already formed social relationships, than to postpone weaning and introduce it three months later to an unknown group. Of course if that individual was for some reason poorly grown then weaning would be delayed. Each animal has to be considered individually.

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Paper 5: Use of non-human primates in regulatory toxicology

1 Introductory comments

In Britain, almost all use of non-human primates in regulatory toxicology is in testing pharmaceuticals. Non-human primates are rarely used to test substances intended for non-medical use. In 2000, 2257 non-human primates were used in toxicity testing in Britain, 99 per cent of which was for regulatory purposes, and all of which involved pharmaceuticals (Home Office, 2001a). In Britain, non-human primates are rarely used to test substances intended for non-medical use. For example, in 1998 40 marmosets or tamarins were used to test 'substances intended primarily for use in industry' (Home Office, 1999). These substances were probably chemical ingredients called phthalates, tested because of concern about the safety of using them in toys mouthed by babies.

Most routine regulatory testing of pharmaceuticals involves rodent species, or rabbits. However, routine testing also involves use of dogs, non-human primates and other mammalian species such as pigs. Studies can also involve birds or fish (see Table 1).

Table 1: Species used in toxicity testing of pharmaceuticals in Britain, showing numbers of scientific procedures carried out on the different species* (Home Office, 2001a)

Type of test	Number of scientific procedures, involving:						
	Rodents	**Rabbits**	**Dogs**	**Non-human primates**	**Birds**	**Fish**	**Other species**
Acute lethal	47670	–	–	–	–	–	–
Acute & subacute non-lethal	53354	539	1750	1177	519	2202	357
Subchronic & chronic (i.e. longer term) tests	14114	330	1162	594	–	–	–
Carcinogenicity	9662	–	–	–	–	–	–
Mutagenicity	4867	–	–	–	–	–	–
Reproductive toxicity	15727	2641	–	–	–	–	–
Eye and skin tests	2014	268	–	–	–	–	30
Toxicokinetics	14852	144	356	361	–	133	231
Other tests	64611	15037	762	392	11289	4960	2586
TOTAL	226871	18959	4030	2524	11808	7295	3204

**Only a rough guide to the numbers of animals used, because sometimes more than one procedure is carried out on the same animal.*

Regulatory bodies usually require that new substances, including pharmaceuticals, be tested in two species, a rodent and a non-rodent. Tests involving the non-rodent species are used to confirm and clarify the results obtained from rodents – particularly in acute (short-term, non-lethal) and chronic (longer term) oral studies. Dogs are usually the non-rodent species of choice. Non-human primates (usually marmosets or macaques) can be used instead, depending on the circumstances, and, in practice, are used when dogs are considered unsuitable and it is felt that use of non-human primates is the best way to secure regulatory approval.

This background paper explores a range of issues related to the general question of whether, and how far, it might be said to be 'necessary' to use non-human primates in regulatory toxicology.

It is often argued that animals are used in scientific procedures only when strictly 'necessary', but what might 'necessary' mean in the context of the use of non-human primates in regulatory toxicology?

2 Toxicologists' reasons for using non-human primates

Regulatory toxicologists might argue that, as in other aspects of regulatory toxicity study design, the use of non-human primates is not strictly 'necessary', but is regarded as the most 'appropriate' option in a particular set of circumstances. Table 2 gives some examples of the kinds of benefits claimed for toxicological studies involving non-human primates.

Table 2: Examples of benefits claimed for toxicological studies involving non-human primates

Two categories of benefit are claimed for toxicological studies involving non-human primates:

1. where the studies have supported the successful use of the substance in humans; and
2. where the testing has indicated that the risk of transferring the substance for use in or by humans is considerable, and hence the substance is excluded from further development.

Examples include:

- An anti-schizophrenic drug, when assessed in dogs, produced cataracts after sustained dosing. Investigation of the mechanism suggested this might be specific to the dog, and subsequent studies in non-human primates indicated that the risk to humans was low. The pharmaceutical has subsequently been launched for widespread use, and is proving very effective clinically, with fewer side effects than previously available treatments. Reduction in side effects is an important benefit since patient compliance with older treatments is often very poor due to the side effects, with the result that their schizophrenia is not controlled.
- Safety evaluation of a cholesterol-lowering compound in marmosets showed up muscle damage. This resulted in the compound being dropped from development. The marmoset was chosen for this study because it has a lipoprotein profile very similar to that of humans.

In practice, where no validated *in vitro* alternatives are available, species choice by toxicologists is based on the general considerations listed below, each of which requires careful, critical examination (see Smith *et al.*, 2001):

(i) The species chosen should have the highest scientific suitability possible

Home Office guidance requires that 'the most appropriate species for regulatory assessment be chosen on scientific grounds rather than by custom and practice' (2000). Toxicologists might choose to use non-human primates when, for example, the test compound is antigenic to other species, or when there are key physiological or metabolic similarities between non-human primates and humans that are not found in other species (e.g. similarity of receptors). In addition, non-human primates tend be used as second (non-rodent) species when dogs are considered unsuitable, for example, when dogs are particularly sensitive to the test compound (e.g.. a non steroidal anti-inflammatory drug) or the drug vehicle used is incompatible with dogs (e.g. cremaphor, PVP).

In this context, contract testing companies are sometimes asked to use non-human primates when the study is part of a programme in which all other non-rodent work has been conducted in primates and/or because there is extensive background information in primates on the type of material being tested. In such cases, toxicologists would need to make further enquiries, in order to establish that non-human primates could also be regarded as the most appropriate species on scientific grounds.

(ii) Within scientific constraints, the species chosen should experience the lowest welfare costs as a result of experimentation (including transport and handling)

This has to be considered case-by-case, and is not straightforward.

Paper 5: Use of non-human primates in regulatory toxicology *(continued)*

(iii) The choice of species should be practical in terms of availability, transportation, suitability for the particular procedures and techniques involved, housing and husbandry requirements.

In addition:

(iv) The species chosen must also be acceptable to the regulatory authorities.

In practice, these various requirements in species choice can conflict. Balancing them is not easy, and there is likely to be a degree of compromise in most circumstances. The different considerations raise a range of issues related to the 'necessity', or otherwise, of using non-human primates in toxicity testing, and these are explored below.

3 Use of non-human primates compared with other options

3.1 Use of non-human primates cf. use of dogs

In the UK, under the terms of the Animals (Scientific Procedures) Act 1986 (ASPA), 'special justification' is required for use of both dogs and non-human primates. However, the Home Office requires greater depth of argument to be presented in support of use of non-human primates. (A special appendix to section 18 of the licence application form must be completed.)

There appears to be an assumption that use of non-human primates is, morally, 'worse' than the use of dogs in toxicity testing.

- **Are there adequate grounds for such an assumption?**
- **Could it ever be 'better' (in terms of animal welfare) to use a non-human primate rather than a dog?**

There are no clear-cut answers to these questions. In a more general context, the Boyd Group has concluded that monkeys should be afforded special moral status on grounds of their capacities for social and mental suffering. However, the Group also noted that it is more difficult to judge capacities for social and mental suffering in species which are evolutionarily more distant from ourselves. Thus, according monkeys greater moral status than dogs might simply reflect a human prejudice for species physically more like ourselves, and, with this, our lack of understanding of the mental lives of animals that are different from us. It could also be argued, for example, that dogs are 'closer' to humans because of their capacity to form reciprocal relationships with us.

For some members of the Group, use of any animal in toxicity testing is unacceptable. For others, the issues turn on how far the welfare of the different species is compromised when they are used in laboratories. Different non-human primate species have different behavioural and psychological needs, and it may be possible to provide better conditions for some non-human primate species (e.g. marmosets) than for dogs in laboratories (especially because of difficulties in meeting dogs' needs for space and social contact with humans). On the other hand, it can be more difficult to provide for the needs of other non-human primate species (e.g. macaques) than dogs in laboratories – and with regard to the scientific procedures themselves, macaques can be more difficult to handle than dogs.

On welfare grounds, the choice between dogs and non-human primates is, therefore, complex and needs to be considered case-by-case. For example, in circumstances in which animals of either kind are well acclimatised, and living in complex, interesting environments it may be better on welfare grounds to use these animals rather than to import other animals, be they non-human primates or dogs, to a facility to conduct a test.

3.2 Use of second species other than dogs and non-human primates

When dogs are unsuitable, non-human primates are regarded as the automatic default non-rodent species – possibly because data from other potential non-rodent species, such as ferrets and pigs, would not command the confidence of regulators (see further discussion in 3.3, below).

- **Is there potential for use of a wider diversity of second species?**
- **What are the benefits and barriers of using species other than dogs and primates?**

The present tendency to use dogs and non-human primates as second, non-rodent species is partly determined by history. Thirty or so years ago, the moral status of non-human primates was viewed somewhat differently. Baboons, for example, were considered to be a pest species in many quarters – with populations so great that large numbers of animals were shot as pests in their native countries. Thus, the use of these animals in toxicity testing studies did not seem to pose the moral issues it does now. Historically, too, beagle dogs came to be used because they were readily available from hunting packs.

Although, nowadays, both attitudes and practice have changed, use of dogs and non-human primate species in the past means that their continued use is favoured, because there is now a relatively large amount of historical background data on these animals, which can be used to assist interpretation of the results of present studies. As already noted, toxicologists may also regard non-human primates as the most, or only, scientifically suitable species in certain circumstances (on grounds, for example, of metabolic similarities with humans). Some members of the Boyd Group argue that other factors, such as the economic costs involved in moving to the use of different non-rodent species play a large part in determining species choice (see also 4, below).

There is certainly scope for use of other species, and the rationale for the choice of the non-rodent species in the toxicity testing of pharmaceuticals is currently being investigated by the Association of the British Pharmaceutical Industry.

Pigs would be too large to maintain in numbers in the laboratory, but mini-pigs are now widely available, and a physiological/toxicological database is being built up. Supply of suitable ferrets can be difficult, but supply problems are not insurmountable. However, in addition to the need for better background data in these other potential second species, there are other possible disadvantages in their use, including the following (see also Smith *et al.*, 2001, for more detailed points of comparison):

- it is relatively difficult to perform routine tasks in these species (e.g. dosing in ferrets), and this can lead to increased stress or requirements for anaesthesia/sedation;
- it can be difficult to detect drugs in the relatively small blood volumes that can be taken from smaller species such as ferrets;
- other species can be more difficult to train;
- regulatory authorities may regard use of such species in toxicology as a step into the unknown, except in well defined areas – e.g. use of pigs for dermal studies.

Again (and only where it is agreed that animals might be used at all), the welfare costs of using the different species need to be judged case-by-case.

Currently, mini-pigs are increasingly seen as a viable alternative to primates. If non-human primate use was banned in Europe, it is likely that companies would switch to using mini-pigs where possible and export the remaining non-human primate work to the USA and/or China.

3.3 Use of Old World cf. New World primates

Home Office guidance also requires special justification for the use of Old World, as opposed to New World, primates in scientific procedures. In particular, special justification is required for the use of Old World non-human primates in toxicological procedures of more than mild severity, as well as retrospective reporting back of the details of any such procedures.

- **Are there adequate grounds for assuming that it is preferable to use New World, rather than Old World, non-human primates in toxicology?**

On this point, the Boyd Group has concluded that, in general, the choice between marmoset (a New World monkey) and macaque species (Old World monkeys) is not always straightforward on welfare grounds, and needs to be considered case-by-case (depending, in particular, on the source of animals and the scientific procedures involved). See Paper 1, Section 4 and Paper 4. For this reason, the Home Office's blanket distinction between the two groups is not helpful (Home Office, 2000, p.47).

3.4 Other alternatives

- **Can genetically modified rodents or non-animal alternatives eliminate the need to use second species, or animals altogether?**

Mice can now be genetically modified to express specific human receptor proteins and it might be thought that this could do away with the need for testing in more than one species. However, other aspects of the animals' physiology are not 'humanised' by the specific genetic modification, and there remains a need to examine wider systemic effects of drugs, which, presently, involves the use of a second species. Increased use of *in vitro* techniques is more likely to lead to a reduction in animal use than genetic modification. (See also a previous discussion paper by the Boyd Group (1999), on genetic engineering of animals.)

Implementation of better pre-screens (by toxicologists) appears to be the way forward, so as to enable certain *in vivo* tests to be dropped on the grounds that there is already sufficient *in vitro* knowledge of the effects of compounds. This approach has resulted in an enormous saving in the use of animals in screening compounds for potential efficacy, and there is a need to adopt a similar approach in looking for toxic effects.

3.5 Use of non-human primates in testing biotechnology-derived pharmaceuticals

Non-human primates may be the *only* species considered suitable for testing certain biotechnology-derived pharmaceuticals ('humanised' medicines). These medicines are designed to interact with specific human receptors, and such interaction must take place in order for their toxicity to be properly assessed. Thus the species used in testing must express a receptor sufficiently similar to the relevant human receptor, and/or have tissue cross-reactivity similar to that of human tissue. In such cases non-human primates may be regarded as the only suitable species, aside from humans themselves.

- **What are the likely effects on the use of non-human primates of increasing the production of biotechnology-derived pharmaceuticals?**

It is possible that things could go 'either way'. Testing of humanised medicines, and with it the use of non-human primates, is likely to increase as information from the Human Genome Project is increasingly capitalised upon. It appears that macaques are more likely to be involved in these studies than marmosets, because of greater tissue cross-reactivity; and, moreover, it is even thought likely that in some cases only Great Apes would have sufficient cross-reactivity. In contrast, it is also possible that better understanding of the genome could mean better understanding of the mechanisms of action of biotechnology-derived pharmaceuticals, so that testing would be carried out simply to confirm expected results, thus allowing the possibility that fewer animals could be used per test. However, where animals are used in such cases, they would most likely be primates rather than rodents.

4 Effects of regulatory authority requirements

Whilst the choice of species must inspire confidence that data will be accepted by the regulators, *this should not be an end in itself.*

Use of non-human primates in regulatory toxicology is not 'mandatory' under European, US or Japanese guidelines – except where testing biotechnology-derived pharmaceuticals is concerned. Yet, it is a common perception that regulators are driving the use of non-human primates in testing.

- **What pressures, other than scientific, lead to the use of non-human primates in regulatory toxicology?**

Regulatory authorities require those submitting toxicology data to justify that their study designs (including species selection) are suitable. Non-human primates may be selected out of caution of the risk that choosing another species may later prove unacceptable to the regulators, and thus result in costly delays in bringing a new medicine to market. The 'cost' of delays being seen in terms of financial expense and time (so affecting company profits, share prices and dividends, etc), the potential effects on human health of delaying the new medicine, and also the requirement to use more animals in another round of tests.

Predicting the suitability of a species in advance of a study can be difficult, because, for example, different species vary in how they metabolise test compounds. The science involved is not exact, and decisions have to be made on grounds of probabilities. Use of familiar species is likely to be favoured, owing to concern that data will be rejected if it is from untried and unproven species for which there is relatively little background information. Thus, one facet of a decision to use relatively novel second species is likely to be a judgement on whether or not the animal welfare benefits of using the different species will outweigh the probability that the trial will be rejected by the regulators. Clearly, discussion and negotiation with the relevant range of regulatory authorities is desirable at an early stage in study design, and, to a large extent, already goes on – though there is sometimes a need for better communication between regulators and scientists. Recent Home Office guidance on the conduct of regulatory toxicity studies notes that 'timely consultations with relevant regulatory authorities should help to prevent unnecessary or inappropriate tests and help refine and modify tests already in progress' (Home Office, 2001b).

Another difficult judgement is involved in deciding at what point in the testing process there is sufficient information to proceed to clinical trials of new pharmaceuticals. Animal tests are a prelude to limited clinical trials, not widespread release of a new drug. The use of animals helps in gaining confidence that the risks and benefits of the new drug are sufficiently well understood to enable a properly informed choice about whether or not the drug should enter clinical trials. Once again, such a judgement is made on the balance of probabilities, and the question of what should count as sufficient/acceptable data to properly inform the judgement is not easy. Growing consumer concerns about the safety of chemicals, coupled with an increasingly litigious society, provide their own pressures to test more widely in animals before moving to humans; and this may involve pressures to use non-human primates, on grounds of their similarities with us.

Paper 5: Use of non-human primates in regulatory toxicology *(continued)*

There is a need for all involved critically to evaluate decisions to use non-human primates in testing. If these animals are to be used at all, the choice to use them must be made strictly on sound scientific grounds, and not as a result of other pressures that could be overcome.

5 Benefits/necessity of the substances tested

Under ASPA, the justification for using animals (including non-human primates) in regulatory toxicity testing is viewed in terms of 'the need for regulatory authorities to have sufficient information to assess risks to which humans, animals, plants or the environment are exposed when the test substances are produced, transported or used', rather than the utility of the substances themselves (Home Office, 1998, p.56, paragraph 5.24; and Home Office, 2001b, paragraph 1.3). In other words, under ASPA, the benefits of using animals in toxicity testing are assessed solely in relation to the objective of ensuring that products and ingredients can be manufactured and used safely, and there is no requirement to include consideration of the nature and strength of the likely benefits of / needs for the substances themselves.

On these grounds, project licences may permit the use of animals in testing a wide range of different kinds of substance, defined only in general terms in the licence. Whilst project licence holders have responsibility for justifying species choice in general terms to the Home Office, they are not required to do so in advance for *each* substance tested (although, if asked, they must provide justification retrospectively).

In contrast, when animals are used in the *development* of new products and ingredients, 'the utility of the new materials is one of the main determinants of benefit' (Home Office, 1998, p. 56, paragraph 5.22). In some cases, substances undergoing regulatory toxicity testing will have been developed using animal procedures licensed under ASPA and thus their potential benefits will already have been considered under the terms of ASPA. However, in other cases (for example, where foreign clients bring substances to UK contract testing companies), development of the substances will not have involved the use of animals under ASPA and, therefore, the potential benefits of the new materials will not have been considered under the terms of the Act. In such cases, there is no legal requirement that these benefits are included as part of the justification for using animals in testing.

- **Is there a need for intended uses of non-human primates in toxicity tests to be justified in advance to the Home Office and/or local Ethical Review Process (ERP) in terms of the benefits of <u>each</u> substance tested under the licence (bearing in mind that almost all such substances are medicines)?**

Members of the Boyd Group are agreed that it is desirable that the potential benefits of individual substances are considered as part of the justification for using non-human primates in regulatory toxicity testing. However, there is considerable debate about how, in practice, such judgements should be made, and members of the Group suggest a variety of approaches. Consideration of the different options raises a number of general questions, including:

- when, in the whole process of developing and testing new substances using animals, questions about the benefits of the substances should be addressed;
- who should make the judgements – for example, who is competent and how wide a diversity of views should be sought; and
- what factors should be considered in assessing the benefits of substances?

5.1 Review by the Home Office?

Some members of the Group argue that the relevant project licence holder should inform the Home Office of each new substance they intend to test using non-human primates, so that a full 'cost-benefit' assessment can be made in each case – including consideration of the potential benefits of the particular substance. It is suggested that it would not be necessary to submit a new project licence application for each study, but that the conditions of the original licence should require a case-by-case justification. Moreover, it is argued that this would require no more than a telephone call for guidance followed by the submission of one or two pages of typescript for early discussion with a Home Office inspector.

Other members of the Group, however, believe that there would be serious bureaucratic resource implications if the Home Office had to be notified of all such intended uses of non-human primates and that the effect of the resultant delays could well be to drive such work abroad (see also point 7, below). They argue that there are already significant hurdles to be overcome when use of non-human primates is mooted, so that the choice to use these animals is not taken lightly. These hurdles include, for example, obtaining licences – which already require special justification for use of non-human primates – obtaining suitable animals, dealing with health and safety/zoonotic disease issues, providing appropriate housing and husbandry and ensuring suitable expertise. UK industry, it is suggested, effectively self-regulates (see 5.2) and uses non-human primates only when essential. In addition, when pharmaceuticals discovered in the UK require the use of animals in their development, the benefits of the new medicines have already been considered under the terms of ASPA. However, this is not the case for work originating overseas, although it may have been subject to overseas national legislation or assessment.

It is also recognised that questions about the benefits of particular ingredients and products are complex, and that views on the 'need' for new substances depend on the particular stand-points from which questions are asked. Thus, some members of the Group consider that it is inappropriate to expect individual Home Office inspectors to judge the value of different substances, and, as is mainly the case in use of non-human primates, to distinguish the need for different pharmaceuticals. However, others point out that this kind of judgement is already expected of Home Office inspectors when dealing with project licences for development of pharmaceuticals.

5.2 Review by local Ethical Review Process?

Local ERPs have an important role in decisions on whether and how non-human primates are used in regulatory toxicity testing. Review by ERP has the advantage of widening consultation on such issues, usually including lay/external perspectives (which could be said to offer a limited 'societal' view), as well as a range of people who have to 'live with' the decisions that are made (the people who in practice will care for and/or use the animals). ERPs, moreover, make their judgements in the context of sound understanding of local factors that can impact on the use of animals, such as facilities, expertise and management.

Most members of the Boyd Group are agreed that all 'blanket' project licences for the use of non-human primates in regulatory toxicity testing should include an additional condition requiring that tests be approved by the local ERP on a substance-by-substance basis; and that the ERP should carry out a full cost-benefit analysis for each substance tested, taking into account all pertinent information – including the potential benefits of the particular substance.
However, some members and observers of the Group have concerns about the practicality of such local reviews. Since, in Britain, almost all substances tested using non-human primates are pharmaceuticals, questions are again raised about whether, and how, local ERPs could be expected to distinguish the benefits of different pharmaceuticals so that these can be weighed against the costs to animals of the tests. Furthermore, whether ERPs would always be able to obtain

sufficient information about the nature of the substances under test to enable them to carry out such full cost-benefit analyses, since contract testing organisations often obtain and require only limited information about the substances brought to them for testing. Some members and observers from within industry also express concern about the time taken for such reviews which, they argue, might result in lost business for UK contract organisations, yet provide little benefit for animal welfare. They suggest that only issues identified as contentious by project licence holders and/or study directors within the companies should be referred to the local ERP.

Contract research organisations and pharmaceutical companies say that they always enquire about the scientific justification for using primates in particular regulatory tests, whether the study is generated in-house or is commissioned by an external client. These enquiries are aimed at ensuring that the tests provide the best possible information to enable risk assessment, and take account of the Three Rs. However, some members feel that this process is not sufficiently independent or impartial to ease concern over how such primate experiments are regulated. Most members of the Boyd Group support the suggestion made by industry that one way forward would be for the Home Office inspectorate regularly to 'spot-audit' these internal company enquiries.

Despite the practical objections, most members believe that the companies' enquiries ought to be extended to include examination of wider concerns about the value of the test substances themselves, and whether this value can always be viewed as sufficient to allow the use of primates. They argue that proper application of the cost-benefit assessment under ASPA demands that such discussions take place within ERPs. They suggest, moreover, that that there is a need to be proactive in this area, since new developments, such as 'lifestyle drugs', are raising difficult ethical issues, including questions about the justification for using animals in testing.

5.3 A 'societal' judgement?

As noted above, most members of the Boyd Group agree that the local ERP should carry out a full cost-benefit analysis for each substance that is tested using non-human primates, taking into account all pertinent information – and including the potential benefits of the particular substance. Some also argue that the Home Office should carry out such assessments as well, and all are agreed that in each case, the relevant Home Office Inspector should be informed of the ERP's decision and the reasons for it – not least, because such reviews can help to ensure that everyone involved takes personal responsibility for the decisions that are made.

Nevertheless, bearing in mind once again that tests on non-human primates almost always involve pharmaceuticals, some members also argue that reviews by the ERP and/or Home Office come too late in the whole process of development of new medicines. By the time that new pharmaceuticals are put forward for safety testing, a great deal of thought, time, effort, and often use of animals, has gone into their development, and it would be wrong to forfeit all this work at a late stage. Consideration of the need for and value of new pharmaceuticals, it is suggested, raises fundamental questions for society as a whole – including, for example, whether and how far economic benefits (such as employment, contribution to the country's GNP, monies for shareholders) as well as the efficacy of the pharmaceutical product should be considered a legitimate part of the justification for the product and the need to use animals.

Further thought, however, brings this argument full circle – in that one must next consider who should make these kinds of judgements on behalf of society. In practice, such judgements cannot be made by 'society as a whole', but have to be taken by informed representatives of society, who understand the issues and are sensitive to the different perspectives on them. In this case, local ERPs, together with the Home Office inspectorate, could be considered to offer the possibility of a limited societal consensus on such issues. Wider confidence in this limited consensus depends on how far the rest of society trusts these people to make cost-benefit judgements on their behalf. This trust will depend, in part, on whether the ERPs include a sufficient spread of members and encompass as wide a diversity of viewpoints as is consistent with reasoned discussion of the issues.

5.4 Ways forward?

Whilst some practical objections are raised (see 5.2 above), most members of the Boyd Group are agreed that the following steps should be taken in order to enhance the assessment of benefit when non-human primates are used in regulatory toxicity tests:

(i) All 'blanket' project licences for the use of non-human primates in regulatory toxicity testing should include an additional condition requiring that the ethical justification for tests be considered by the local ERP on a substance-by-substance basis.

Each time a new substance is brought to, or put forward by, the company for tests involving non-human primates, the case should be referred to the ERP for ethical review that takes into account all pertinent information – including the potential benefits of the substances involved. In order to enhance the credibility of this process:

- the ERP should include people from outside the organisation concerned, encompassing as wide a diversity of viewpoints as is consistent with reasoned discussion of the issues and client confidentiality, and should preferably have a 'lay' Chair who is not involved with the issues at stake; and
- the relevant Home Office Inspector should sit in on the discussions as often as possible.

Since relatively few different substances are likely to be tested using non-human primates in a given company, it should not be unreasonable to expect all such cases to be referred to the ERP. This process should enable wider consultation on which uses of non-human primates the company ought to regard as particularly controversial, as well as widening debate on the issues themselves. Practical objections to implementing such reviews might be overcome when it is remembered that the ERP is a process, not just a committee, that can be designed to minimise unnecessary delays, whilst at the same time ensuring that all the ethical issues are addressed. For example, each time it is proposed to test a new substance using non-human primates, information about the tests could be circulated to members of the ERP, with members meeting to discuss the proposals whenever one or more of their number raises concerns.

(ii) The ERP's decision, and the reasons for it, should be communicated to the Home Office Inspectorate.
This would enable the relevant Home Office Inspector to comment on the decision, and could assist the Home Office in building up a body of knowledge on the application of the cost-benefit assessment in such circumstances, so that, in future, the Home Office could recommend and refine criteria for assessing the potential benefits of substances.

(iii) The Home Office inspectorate should regularly 'spot-audit' pharmaceutical and contract testing companies' internal enquiries about proposals to conduct tests involving non-human primates, in order to evaluate whether and how far the enquiries are making a difference in practice.

6 Effects of toxicity tests on non-human primates

- **How substantial are the toxic effects caused to non-human primates in regulatory toxicity testing, and what further steps could be taken to minimise such adverse effects?**

Toxicologists argue that it is necessary to demonstrate some toxicity at the highest doses to satisfy both the regulators and, in a contract testing environment, the clients who commission the tests, but that the effects produced usually need only be mild. For example, signs such as a minimal decrease in appetite, changes in blood parameters, decreased growth rates in experimental cf. control animals (not more than 10 per cent difference in weight) can all be used.

Nevertheless, clients commissioning tests vary in the extent of the effects they ask for. This variation can be a result of cultural differences, or simply because less effort is required to interpret the more obvious signs. Moreover, the demands of overseas clients can sometimes pose a challenge to the cost (harms to animals) – benefit assessment required under ASPA. For these reasons, reducing the harms caused to non-human primates (and other animals) in testing can largely be viewed as a matter of educating clients and relevant regulators to understand the predictive power of the milder toxic symptoms. This requires efforts by companies carrying out the tests to negotiate and communicate in each individual case.

- **It has been suggested that no toxicological experiment of more than mild severity should be approved in non-human primates. What would be the effects of any such further restriction on the use of non-human primates in regulatory toxicity testing?**

On the arguments above, most toxicity testing in non-human primates could be restricted to the mild severity band. However, the effects of compounds are sometimes difficult to predict and, moreover, where insufficient toxicity is demonstrated such studies would not be acceptable to the regulators, and further toxicology work would not be conducted in the UK. For example the new CPMP Note for Guidance on Repeated Dose Toxicity studies of new pharmaceuticals (CPMP/SWP/1042/99) states that:

1 The general rule is that two species should be used, one of which must be a non-rodent (referencing the original EC Directive); and
2 Dose levels should include 'a high dose, selected to enable identification of target organ toxicity or other non-specific toxicity, or until limited by dose'.

There are other similar examples within EMEA/CPMP Notes for guidance on other specific subjects, e.g. pre-clinical safety of biotechnology products.

Companies argue that if studies cannot be conducted to meet the regulations, there is no justification to do them at all. On these grounds, they claim that there is usually a need for such project licences to permit work on non-human primates within a moderate severity banding; but every effort should be made to ensure that the effects do not go above mild.

7 Risk of merely exporting work

Some members of the Boyd Group urge caution in unilateral tightening of restrictions on use of non-human primates in research and testing in the Britain. They argue that unless the relevant legislation is equally rigorous within Europe, and preferably world-wide, UK tests involving non-human primates may well be taken abroad, where standards of welfare may be poorer – and with consequent loss of revenue from Britain. If further restrictions are imposed on use of non-human primates in Britain without similar restrictions elsewhere in the world, then, they argue, export of work seems more likely.

Other members of the Group, however, believe that whilst it would be preferable to have world-wide legislation, this argument should not prevent unilateral action by Britain.

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