Response to the statement of the EU Scientific Steering Committee on the use of non-human primates (NHP) in biomedical research
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A briefing paper for Members of the European Parliament

The European Union’s Scientific Steering Committee (SSC) produced a scientific opinion paper in 2002 on the use of non-human primates (NHP) in biomedical research. This paper made a series of statements about scientific research on NHP, and it has informed the EU’s decision-making process on the matter.

In this briefing for MEPs by Animal Defenders International (ADI), the National Anti-Vivisection Society (NAVS) and the Lord Dowding Fund for Humane Research (LDF) addresses each of the statements made by the SSC. We discuss current scientific opinion on the issues raised, and the scientific basis for adopting non-animal alternatives in biomedical research.

The statements made by SSC are given below in blue, followed by the response from ADI/NAVS/LDF.

Our Background:

Animal Defenders International with offices in London, San Francisco and South America, was founded in 1990. ADI represents the NAVS and LDF internationally, and works on a range of animal and conservation issues worldwide.

The National Anti-Vivisection Society (NAVS), founded in 1875, remains in the forefront of public information campaigns on this issue, conducting scientific research and publishing scientific and technical reports.

The Lord Dowding Fund for Humane Research (LDF) (founded 1974) is a department of the NAVS. It funds non-animal scientific and medical research in a wide range of fields in medicine, science and education; our annual research spend is €445,600.

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1. **Scientific Steering Committee ‘Statement’ section**

In its first statement, the SSC considers that the use of NHP will need to be decided on a case-by-case basis, taking into account:

- justification
- the possible existence of alternatives
- ethical considerations
- the problems that could result from not using NHP (i.e. perceived need)
- unnecessary and duplicated or redundant research using nonhuman primates should be avoided at all costs (and for example by a EU-wide coordination between research laboratories),
- that the housing and welfare conditions of the animals should be optimal
- that, for each research proposal, it should be verified that no alternative is available and that it is ethically justified.

However, it considers that for certain experiments there may be no alternatives to the use of non-human primates, for example, drugs and vaccines for diseases such as: AIDS, TSE 1, malaria, influenza.

**ADI Response – justification; species differences; limitations of laboratory animal research:**

There is scientific criticism of the use of animal models of human disease, for example:

- “Animal models cannot determine whether a vaccine will be effective against HIV-1 infection of humans; only phase III trials in humans can do so”\(^1\).

- The outcome of laboratory animal tests can be influenced by many factors including sex, age, diet, genetic strain, health, degree of starvation, method of dosing, temperature, humidity, and even bedding material\(^2\).

- “Animal models can only be validated after successful trials in humans... “It would be risky to extrapolate vaccine success based solely on results of challenge studies in nonhuman primates”\(^3\).

- “Animal models differ from their human counterparts. Conclusions drawn from animal research, when applied to human disease, are likely to delay progress, mislead and do harm to the patient”\(^4\).

- The various elements of the laboratory environment i.e. loud noises, restraint and separation from companions are said to have the same effect as electric shocks in that they hamper the antibody response to bacterial and viral infections, while stresses affect the nervous system, thus increasing circulating hormones and suppressing the immune function\(^5\).
ADI Response – alternatives:

Although the SSC supports the adoption of alternative methods, experience has shown that non-animal alternatives will not be widely introduced without parliamentary action. For example:

- **Hepatitis C:** The SSC states that this virus cannot be cultured and therefore chimpanzees must be used. This is no longer correct. Various authors have published *in vitro* hepatitis C models, including as recently as 2005.  

- **In a recent review of *in vitro* replication models of HCV it was said, “For regulated expression of HCV in vitro, numerous models have been reported, wherein all or part of the HCV genome has been expressed in cell culture.” Some were described as “…representing a major breakthrough…” and that they provide “…a powerful tool for studying the HCV life cycle and developing antiviral strategies against HCV going into the future”. The paper notes, “the limitations in both the variable course of HCV infection in chimpanzees and their endangered status required the development of more practical models for the future studies on HCV replication”.

- **Furthermore, work on establishing a culture method for hepatitis C virus has been ongoing for at least ten years; a 1997 paper reported use of human liver tumour tissues, and that significant progress in the development *in vitro* cell culture systems of HCV had been made in several laboratories.**

- **Malaria:** The SSC justifies the use of primates in malaria research by stating that primate malaria parasites are very closely related to human malaria parasites. However, this approach does not address the problem of the fundamental differences between humans and other primates.

- **Furthermore, it is unnecessary, as many papers have now been published on the use of alternatives to animals in malaria research, for example:** Malaria parasite studies utilizing methods exclusively or in combination with each other *in vitro*; human volunteers; epidemiological studies of the disease in the environment; studies of human and parasite genetic diversity; as well as vast literature reviews.

Increasingly refined methods and human-specific biochemicals are used within drug research, development and testing, which requires the use of sophisticated human-based testing systems, for example:

- human skin models
- QSARs (predict effects of chemicals based on their structural properties)
- dendritic, liver, endocrine and other tissue/cell cultures
- DEREK (knowledge-based toxicity predictor)
- physiologically based biokinetic models
- New technology developed by NASA has been used to create a 3D neurotoxicity testing system using human cells;
• fMRI: This technology enables visualisation of brain cortex function in response to physical tasks, by detecting an increased flow of oxygenated blood in areas of nerve activity;

• Similar advances in the design of functional brain imaging techniques such as Positron Emission Tomography (PET), Electroencephalography (EEG) and magnetoencephalography (MEG) also allow the brains of humans to be studied, without causing harm.

• Synthetic Aperture Magnetometry: a brain imaging technique to non-invasively record nerve cell activity in the human brain without the limitations encountered with previous techniques.

• Human stem cells can be stimulated to grow into any type of tissue. This can be used to cure diseased organs and tissues.

• DNA “chips”, or micro arrays, carry hundreds or thousands of short strands of DNA. These can be used to identify which genes have been damaged when human cells have been exposed to test substances, giving an indication of the degree of toxicity. This technology, called toxicogenomics, could save animal lives, and offer a sensitive test method using human genes in order to avoid the problems associated with species differences.

• Volunteers can be used for pharmacological studies to investigate the uptake of new drugs and their actions upon the body. Properly controlled volunteer studies also play a significant role in psychiatric and psychological research.

The university of California Centre for Animal Alternatives has created a search grid of databases of alternatives to animals, which enables researchers to access information quickly and easily. One of the links in the “toxicity” section leads to a website access to “approximately 360 abstracts about alternatives to irritation and corrosion testing in animals that are currently on-site”.

**ADI Response – duplication, redundant research:**

Whilst so much research and testing is carried out in secret, and much unpublished, duplication or redundant research on non-human primate species is almost inevitable.

• Data sharing by companies developing new products is an ongoing problem. Commercial testing laboratories are obliged to keep results secret, as they are commercially sensitive and the property of the client.

• For chemicals, the REACH regulations provide for mandatory data sharing. This was considered to be critical for avoiding the duplication of animal tests between, often competing, commercial companies. Commissioner Margot Wallström commented: “...several measures are foreseen... to avoid unnecessary tests, to save animal lives and to reduce cost to the Industry. For example, available data will be accepted to avoid performing new tests, and the establishment of consortia for data sharing will be strongly encouraged”.

• At Inveresk contract testing laboratory in Scotland, some animals were used in tests for products that were already in human trials. And in a test for an asthma drug, cynomolgus monkeys suffered effects including, diarrhoea, swelling in the stomach, the males’ testes increased in weight, they suffered
red and swollen penises and scrota and females suffered abdominal and umbilical hernias. The monkeys lost weight and their heart rates fell. Yet the (confidential) report of this study admits that the client was in possession of information from previous experiments on cynomolgus monkeys, “... has indicated that the test compound may affect the cardiac function and produce pericardial effusion in cynomolgus monkeys when given intravenously or via inhalation".11.

- In 2002, 5 rhesus macaques were infected with HIV in order to test the efficacy of vaccines. The animals were given four immunizations at 3-week intervals. The vaccines were already being tested in human clinical trials when the experiment began and no new knowledge was gained12.

- All but one of the findings in a study using chimpanzees to look at the differences between acute and chronic hepatitis, were supported by an equivalent human study13.

- During HIV experiments with newborn macaques, different infants were given infected material by mouth – one animal was fed the blood of another youngster that had developed AIDS. The findings were unclear, but the authors claim a paper from two years previously, confirmed their findings in neonates14.

**ADI Response – laboratory animal housing, transport, ethics, primate supply trade:**

The very act of being in a laboratory is immensely stressful to NHPs. The laboratory is very different to their natural environment in space and complexity, so they suffer from both physical and mental confinement. In addition the nature of transport – the capture, placing in boxes, travel and isolation has significant adverse effects on primates:

- “*Non-human primates endure considerable harms even before they reach the laboratory*”15.

- In one study it was found that international air transport and subsequent re-housing resulted in the animals’ welfare being compromised, thus changing their behaviour, which indicated heightened stress levels; these levels took more than a month to return to the baseline levels16.

- Although captive breeding of marmosets in laboratory facilities has been successful, this has not been the case with macaques, baboons and squirrel monkeys. Consequently between 1994 and 2000, UK animal researchers imported 13,467 monkeys from: USA (207); Guyana (635); Israel (1,365); Philippines (1,841); Indonesia (241); China (1,196); Kenya (139); and Mauritius (7,843)17. In 2003, only 38% of the primates used in British experiments came from within the UK18.
2. **The Scientific Steering Committee position**

“[SSC] ...considers that non-human primates are required in biomedical research for the following reasons:

1. to ensure safety. Many new vaccines or biologicals must be assessed for specificity and safety in a “near-human” immune system before they enter the clinic.
2. to determine the efficacy of non-human primate models for infections for which no other suitable animal models exist. These so-called “proof of principle” studies are critical in catalysing interest and development capital for development and clinical trials.

**ADI Response – safety and efficacy/species differences:**

There have been no systematic reviews of animal research and testing to confirm whether this methodology is providing the assurances of safety that the public expects:

- The Toxicology Working Group of the UK Parliament’s House of Lords Select Committee on Animals in Scientific Procedures reported in 2002, saying “the formulaic use of two species in safety testing is not a scientifically justifiable practice, but rather an acknowledgement of the problem of species differences in extrapolating the results of animal tests to predict effects in humans”, and, “the reliability and relevance of all existing animal tests should be reviewed as a matter of urgency”\(^{19}\).

- A study carried out in 2005 demonstrated that many common drugs and household chemicals have been certified as safe for humans on the basis of animal tests that are accurate, on average, just over half the time\(^{20}\).

Primate experiments cannot guarantee safety, and can be dangerously misleading:

- In 2006, the first human trials of the experimental drug TGN1412 in the UK caused volunteers to suffer serious, and permanent, life-threatening damage. Prior to human trials, the drug was tested on monkeys. The monkeys received 500 times the human dose but did not suffer the side effects experienced with the volunteers\(^{31}\). Several studies, specific to TGN1412, have highlighted the crucial differences between the human and simian immune systems\(^{21}\).

The use of NHP is often justified as the ‘only’ way to conduct research into neurological diseases such as Alzheimer’s and Parkinson’s, which are increasing with the ageing population – people are living longer. It is estimated that the number of people with cognitive impairment in England alone, is likely to rise by 66% between 1998 and 2031\(^{30}\).
However there is now evidence that both behavioural neuroscience and other neurological experiments on animals are fundamentally flawed due to species differences. For example:

- Human brains have a folded cerebral cortex whereas smaller primates, such as the marmoset, have a smooth cerebral cortex. Not only are there anatomical differences between the two brain types, but evidence suggests that there are functional differences, too22.

- Lower and higher primates differ in a number of structural features in their nervous systems and sense organs. Lower primates’ brains are much smaller in relation to body size than those of the higher primates. The areas which govern the transfer of information between the different brain centres, differ in development between brains of higher and lower primates23.

- Animal models of Alzheimer's do not develop the characteristic 'neurofibrillary tangles' or show significant neuro-degeneration as humans do26.

- The drug MPTP is used on non-human primates to attempt to create a ‘model’ of human Parkinson’s disease. However, Parkinson’s disease is unique to humans27 and slowly progressing, whereas MPTP-induced Parkinsonism is rapid in its course. There are differences in nerve degeneration and the transmission of nerve impulses in naturally occurring human Parkinson’s disease and MPTP induced Parkinson’s disease in animals28. There are major differences at both the behavioural and nerve chemistry levels between different monkey species when given MPTP29.

- Drs Palfreyman, Charles and Blander in ‘Drug Discovery World’ observed: “One of the major challenges facing the drug discovery community is the poor predictability of animal-based strategies . . . many drugs have failed in later stages of development because the animal data were poor predictors of efficacy in the human subject . . . . One of the overriding interests of the pharmaceutical and biotechnologies industry is to create alternative development strategies that are less reliant on poor animal predictor models of human disease . . .”32.

- It has been noted that the way drugs break down and are excreted are similar in monkeys and humans, but metabolism rates differ markedly33, and the cynomolgus macaque has been referred to as the most misleading laboratory animal model for the study of toxic effects on the human heart34.

- Evidence is mounting that standard lab conditions cause enough stress to affect the physiology of research animals. The concern is that this change in physiology will swamp the effects of experimental perturbation or drug35.
3. The Scientific Steering Committee's five examples of diseases of concern

The SSC listed diseases of concern:
(a) AIDS
(b) malaria
(c) tuberculosis
(d) hepatitis
(e) immune-based diseases (arthritis, multiple sclerosis, type 1 diabetes etc)

In addition at the end of this section, we have discussed TSE (e.g., BSE, CJD), which was also mentioned by the SSC:

(a) AIDS

SSC: “The etiologic agent HIV-1 is an example of a virus with a very complex interaction with the immune system and a very limited host range. It only readily infects humans and to a lesser extent chimpanzees”.

ADI Response:

• Although HIV can infect chimpanzees it does not induce disease in them. Human beings are the only species to have been found to be susceptible to HIV.

• In America, in 1995, the NCRR (National Center for Research Resources) introduced a moratorium on the breeding of their chimpanzees for research. When the AIDS epidemic began, it was thought that the chimpanzee would be an ideal model of the disease. It was not; the moratorium came shortly after it was established that the chimpanzee model was not helpful in the study of AIDS vaccines, as chimpanzees suffer little harm from HIV. In 2007 the director of NCRR announced that the NCRR had decided to make the moratorium permanent.

• Researchers in Denmark and the USA have highlighted the need to reconsider the use of primates in research. The team compared genes found in humans to their equivalent genes in chimpanzees. They found that the genes which differ the most between humans and chimpanzees are those related to immune defence and cancer development.

• In order to infect primates with HIV, a hybrid HIV-SIV strain was generated in the laboratory, calling it SHIV. SIV is a closely related monkey retrovirus that also induces AIDS in inoculated animals. Non-existent in nature, the SHIV strain infection in monkeys is an extremely rapid and exaggerated model of HIV infection in humans.

• The UK’s scientific ethics body, the Nuffield Council on Bioethics notes that HIV is a virus that has “proved difficult to treat and cure, despite the availability of animal models” and, “…no single animal model perfectly
reproduces the symptoms of HIV-1 infection and development of the disease in the diverse human population”\textsuperscript{42}.

- One scientist stated “more studies are needed not because chimpanzees are good models for human diseases, but rather because they are surprisingly bad models in many instances, for example, HIV infection progressing to AIDS and \textit{P. falciparum} malaria.”\textsuperscript{43}.

\textit{SSC}: “The Rhesus macaque has been well characterized... to allow for the study of vaccine efficacy in an outbred primate species”.

\textbf{ADI Response:} others do not agree–

- One research team commented “Animal models cannot determine whether a vaccine will be effective against HIV-1 infection of humans; only phase III trials in humans can do so.”\textsuperscript{44}.

- Another team, intending to highlight the value of the primate model for AIDS research conceded that, “Animal models can only be validated after successful trials in humans”...we are as yet unable to validate any of the currently used nonhuman primate models for vaccine in research. “It would be risky to extrapolate vaccine success based solely on results of challenge studies in nonhuman primates”\textsuperscript{45}.

\textit{(b) Malaria}

\textit{SSC}: “The relationship between the parasite and the host is quite specific”.

\textbf{ADI Response:}

ADI agrees with the Scientific Steering Committee that the relationship between the parasite that causes malaria, and the host species infected with the disease, is very specific – each parasite has its own host species.

- Differences exist not only between the host species but the strains of malaria \textit{plasmodium} that they contract are also distinct and specific to the host species\textsuperscript{46}:

<table>
<thead>
<tr>
<th>Natural host</th>
<th>Malaria species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>\textit{P. falciparum}, \textit{P. vivax}, \textit{P. malariae}, \textit{P. ovale}</td>
</tr>
<tr>
<td>Chimpanzee</td>
<td>\textit{P. reichenowi}</td>
</tr>
<tr>
<td>Gibbons</td>
<td>\textit{P. hylobati}</td>
</tr>
<tr>
<td>Old world monkeys</td>
<td>\textit{P. cynomolgi}, \textit{P. knowlesi}, \textit{P. simiovale}, \textit{P. gonderi}</td>
</tr>
</tbody>
</table>

This makes research using NHP even more complex, because a different parasite and a different host species are being studied. Furthermore, when success is achieved in infecting a NHP with a human malaria parasite, the differences in response to the parasite, combined with the fundamental differences between human and non-human primates, will affect the outcome of the research.
**ADI Response to EU SSC position paper on primates**

**July 2007**

**SSC:** “[human malaria parasites]...do... infect some non-human primate species...”.

**ADI:** Response: use of primates is unnecessary, as advanced scientific techniques are available; use of primates opens the research to misleading results:

- Although chimpanzees are susceptible to experimental *P. falciparum*, it causes only brief and moderate parasitization and no severe infection⁴⁷.

- Guyanese and Bolivian squirrel monkeys used to test malaria vaccine, differ in their antigens that act as receptors to *Plasmodia* (parasite) antigens, so one sub-species is susceptible and the other is not⁴⁸.

**SSC:** “...the parasite has obligatory intra-hepatic developmental phases that are not amenable to in vitro cultivation”.

**ADI Response:** This is no longer correct.

- A human liver cell culture has been produced recently, which supports two of the human malaria strains and allows the study of the biology of the liver stage parasite which is needed for the development of drugs and vaccines⁴⁹.

**SSC:** “...well-characterised models with similar immune responses to humans (such as macaques) are essential in vaccine development”.

**ADI Response:**

- Human malaria *plasmodium* was mixed with vaccinated macaque blood *in vitro* because of the inability of the monkey to contract the human malaria parasite. In tests to assess safety for humans, and potential to predict likely immune response, it was found that the rhesus immune response was higher than in humans, as well as other species differences⁵⁰.

- As mentioned earlier, in the ‘alternatives’ section, there are many advanced technology systems that replace the use of animals, including *in vitro*; human volunteers; epidemiological studies of the disease in the environment; studies of human and parasite genetic diversity, as well as large scale literature reviews of malaria research.

- Environmental solutions can be found in order to reduce the risk factors involved in malaria infection. Human activities associated with different social groups for example have been seen to have an impact on malaria exposure and consequently immunity⁵¹. The use of insecticide treated nets as a means of reducing the transmission to humans from malaria mosquitoes, has been seen to reduce the deaths of young children by an average of 20%⁵².
(c) **Tuberculosis**

SSC: “A careful analysis of two macaque models (rhesus and cynomologus) has shown the value of these two models and their similarity to the human situation”. “These models are being used to screen and select among new candidate vaccines”.

**ADI Response:**

- Research examining the use of two primate species to test the efficacy of TB vaccine bacillus Calmette-Guerin (BCG), found that they differed greatly in the efficacy of BCG.  
- One study of the early stages of TB in primates stated that “like human studies, the genetic diversity of monkeys results in an inherent degree of animal-to-animal variability and, therefore, heterogeneity of data is seen”.
- A study of the effects of TB on animals showed that they had widely disparate pathogenicities. This led to the conclusion that “the outbred nature of macaques can be viewed as a limitation on performing some studies.”

(d) **Hepatitis**

SSC: “Hepatitis C cannot be cultured”.

**ADI Response:**

- This is no longer correct. A recent paper reported partial progress, which has resulted in some techniques that can be implemented. The paper concluded that “…continued effort is required to provide a complete in vitro HCV model: a reliable, efficient cell culture system supporting HCV infection”.

SSC: “The only other species other than man that can be infected is the chimpanzee”.

- ADI: Yet, there are key species differences. Persistent infection rates differ between chimps and humans, with 30-40% and 85% respectively. Fibrosis and cirrhosis, commonly found in humans, are not present in chimps. Another factor critical to disease progression is the fact that chimpanzees do not drink alcohol. It is deemed unethical to place animals on prolonged high alcohol diets.

SSC: “NHP research is essential to bring a truly effective vaccine to the clinic”.

- ADI: Fialuridine, a Hepatitis B vaccine, killed 5 people and caused serious illness in others even though it was tested on dogs, rats and monkeys. A review found that “…unfortunately, there is nothing to indicate that other laboratory animal studies would have been more appropriate or capable of better prediction of the fatal outcome.”
**e) Immune-based diseases**

SSC: “Non-human primate models...are needed for the development and evaluation of new immunomodulatory/immunosuppressive therapies”.

**ADI Response, Multiple Sclerosis:**

- The key laboratory animal model of multiple sclerosis (MS) is called experimental allergic encephalomyelitis (EAE); a condition caused by the injection of toxic substances which causes the immune system to attack the nervous system.

- However, it differs in that it either kills the animal or leaves it with permanent disability; it does not come and go like MS\(^59\).

- Not a single human has been cured using the EAE approach, which has been used to test virtually all MS treatments\(^58\). EAE is a laboratory-created tool rather than a spontaneous disease with a complex development, and therefore relieving the symptoms of EAE is not predictive of relieving MS. Its various models also make it difficult to use for drug screening\(^60\).

- It has been suggested that the EAE model is misleading and that the best way forward without the EAE model restraining MS research, would be to look at the patients themselves\(^61\). Measuring relapse rate, disability and MRI scanning of lesions in the brain enables the assessment of disease activity in MS\(^62\), which is used to determine individual therapies, necessary because of the diversity of the disease in individual patients\(^63\).

**ADI Response, Diabetes:**

- Unlike many genetic disorders that are due to a single defective gene, with diabetes several genes seem to be responsible. Environmental influences also play a part\(^64\). Clinical research has shown that juvenile onset diabetes occurs more commonly in the autumn, when viral infections are more prevalent\(^65\). There are huge disparities in the prevalence of diabetes in different human populations around the world. The disease is increasing in children under 5 in Finland and the UK, which it has been said points to “Major aetiological factors early in life, such as viral infections and nutritional factors”\(^66\).

- In NHPs diabetes-like symptoms are induced using chemicals because “spontaneous development of type 1 diabetes mellitus has not been reported in non-human primates”. The model has its limitations including the “absence of spontaneous immune-mediated beta cell loss”\(^67\).

- In 1977 an eminent diabetes clinician said of animal models of diabetes “…they do not help us in our understanding of the genetics of human diabetes”\(^68\). Twenty years later, other researchers confirmed that this remained true, “The most reliable way of elucidating the cause of a disease is to study it in the animal species and in the environment in which it naturally occurs”\(^69\).
**SSC:** “There is an increasing need of non-human primates as models for CNS biology and disease”.

**ADI Response, Central Nervous System (CNS) diseases (Alzheimer’s, Parkinson’s, Multiple Sclerosis, etc):**

- There are enormous differences in monkey and human brains. Researchers at the Institute of Neurology in London recently blamed “remarkable species differences” for the failure to apply primate findings to human brains.

- The chimpanzee brain is about one quarter the size of the human brain and the macaque brain is around one quarter the size of the chimpanzee brain. Comparisons between these brains are limited by the greater complexity of the human brain, due to its larger size, and exemplified by its unique capacity for language.

- Often, areas in the brain that appear to have a function in monkeys do not have the same role in humans.

- Researchers at two prestigious institutions, the Salk Institute and the University of California wrote: “What is known about the neuroanatomy of the human brain? Do we have a human cortical map corresponding to that for the macaque? And what does the human equivalent of the connectional map look like? The shameful answer is that we do not have such detailed maps because, for obvious reasons, most of the experimental methods used on the macaque brain cannot be used on humans. For other cortical regions, such as the language areas, we cannot use the macaque brain even as a rough guide as it probably lacks comparable regions.”

**SSC:** “The close genetic, immunological and virological relation with humans makes non-human primates an excellent model of this disease [MS]”.

**ADI:** A recent paper on animal models of MS reported the withdrawal of a drug after one patient died and another became seriously ill. It commented “efficacy tests in animal models do not account for the clinical situation”. The drug had been tested on primates, but no similar condition was observed; the authors stated “Spontaneous cases of MS-like disease rarely occur in common laboratory species ... the disadvantage of these experimental MS models is that none of them reproduces the complete clinical and pathological spectrum of the disease.”
**SSC: problems faced in developing vaccines or therapeutics**

1) *Host-viral/parasite relationship:*

(a) For instance some agents such as HCV and malaria intra-hepatic stages cannot be cultured in vitro or, they are so species specific that they only infect humans or other closely related primates.

**ADI Response:**

- Human liver tissue has been developed to support the progression of the early, pre blood cell, stage of two human strains of malaria. This can now be used for studying the biology of liver stage malaria parasite to aid in developing vaccines that target the parasite before it enters the blood cells of its host.

- Hepatitis C virus (HCV) models have been produced that model the clinical progression of the virus, as well as being able to infect naïve cells. This will allow the study of species specific, human host-virus relationship and will contribute to the development of an HCV vaccine.

- Currently around one third of drug candidates fail in the first human trials. Advanced non-animal techniques allow for larger sample sizes and greater reproducibility.

- As far back as 1985, an editorial in the medical journal *The Lancet* stated, "In recent years, many animal tests for the safety of viral vaccines have been replaced by cell-culture tests, which are more sensitive and reliable".

(b) An infectious agent may only cause disease due to its specific interaction with the affected host. A good example is HIV-1 which causes disease in almost all humans, but very rarely in chimpanzees.

- ADI: The use of chimpanzees and other less closely related NHPs are unreliable as models for human specific diseases such as HIV. The chimpanzee is the only non-human animal that can be infected with HIV, but whereas AIDS destroys human health, chimpanzees infected with HIV manifest, at most, transient swelling of some lymph nodes.

- Washington National Primate Research Centre’s pharmaceuticals department had have said, “...a clear road map for HIV vaccine development has yet to emerge....because of the intrinsic nature of the surrogate model and...because of the improbability of any single model to fully capture the complex interactions of natural HIV infection in humans”. It was also noted “SIV models do not allow direct testing of HIV vaccines. Currently available SHIV models do not adequately represent the spectrum of HIV genotypes and phenotypes.”

- Primates, despite their evolutionary closeness to us, are distinct from us in the way they express genes in the brain ['expression' of a gene is the activity or product that the gene causes to occur in the body]. There are even big...
differences in gene expression between humans and chimps, although gene expression between chimps and other primates is similar.\footnote{81}

- Researchers in Denmark and the USA have highlighted the need to reconsider the use of primates in research. The team compared genes found in humans to their equivalent genes in chimpanzees. They found that the genes which differ the most between humans and chimpanzees are those related to immune defence and cancer development\footnote{82}.

**SSC:**

2) **Specificity of new generation drugs/biologicals.**

New generation therapeutics are often so specific that sometimes a change in a single amino acid can result in the difference between a beneficial or deleterious effect. These positive or negative effects cannot be predicted by computer models nor by testing in rodents. Often these important side effects can only be detected in specific primate model.

**ADI Response:**

- It is an error to believe that the use of primate models guarantees total drug safety when used in humans, and there is evidence to demonstrate this, for example a study of animal and clinical tests reported that all the experiments (over 100, involving 3000 animals) were poorly reported. In one set of experiments to treat strokes, the animal data suggested a benefit, but the clinical trials showed no benefit and worse, possible harm\footnote{83}. Another study correlating animal and human trials concluded that it is “prudent to be critical and cautious about the applicability of animal data to the clinical domain” and “animal models may not adequately mimic human pathophysiology”\footnote{84}.

- A study of adverse drug reactions (ADR) found that only “after drugs leave the trial setting and are used in sicker patients do their true risks become apparent”\footnote{85}. A paper reviewing ADR’s in 2 UK hospitals reported that these conditions totalled 6.5% of all admissions, with an estimated cost of €706M a year to the UK alone\footnote{86}.

- The anti-inflammatory drug Vioxx had unexpected effects on human patients, after laboratory animal tests. It has been reported that from 88-140,000 extra heart attacks may have been caused by Vioxx in the five years since its introduction\footnote{87}.

- The case-fatality rate was put at 44%\footnote{88}, therefore fatalities would range between 38,720 and 61,600. It was found to increase the risk of heart attack by 34% compared to people on similar drugs. Many of the participants in the trials were at lower risk of cardiovascular disease than the elderly population that would use Vioxx, so the risk to the intended recipients may have been even greater – up to eight times greater\footnote{89}. One researcher commented that there was a “misconception amongst doctors and patients that because a drug is new, it must be better than older drugs”\footnote{90}.
SSC:
3) Outbredness and the need to consider genetic resistance & susceptibility

Inbred species of mice and even transgenics cannot predict accurately for how long a drug, biological, or vaccine will work or possibly cause adverse effects in an outbred population. An outbred population with specific characteristics, which resemble the human population, is often the most relevant model. Unfortunately, the numbers of captive bred animals needed to maintain this “outbred quality” are high. Smaller colonies of non-human primates will result in a smaller genetic pool in which the predictable value will be lost, or may even result in selective inbreeding, defeating one of the most important needs of primates for research. Thus large, diverse, well characterised, captive-breeding colonies are needed in Europe to maintain this outbred character.

ADI Response:

Even if the “outbred quality” is achieved by large breeding colonies of NHPs – and the practical problems such a huge venture presents appear to count against it – the fundamental species differences that exist between humans and other primates will still remain. Therefore the lack of predictive value of these models will persist.

Only in humans can the relationship of subjective and discriminative drug effects be assessed at the same time. For example, EAE, the model for MS, has proven ineffectual in pointing researchers toward a meaningful therapy as the model does not reflect the pathology and progressive nature of MS.

The SSC included research on TSE in its introduction, citing research on these diseases of the brain to justify the use of non-human primates in research:

ADI Response: TSE (spongiform encephalopathy, e.g. scrapie, BSE, CJD):

- Infecting animals may be pointless – some scientists have suggested that the apparent increase in CJD may not be due to BSE infection, but since the BSE crisis doctors have increased their vigilance and are detecting a naturally-occurring disease. Before the BSE crisis, doctors missed nearly two-thirds of all classical CJD cases, and some said “there is no epidemiological evidence to support a relationship between sporadic CJD and scrapie (or any other animal TSE).”

Furthermore, the NHP model is a poor representation of the human disease:

- A study to show the effects of feeding infected brain tissue to macaques resulted in one animal becoming infected, which subsequently died, while another was unaffected. It was concluded that the data did “not provide a definitive minimum infective dose for transmission of cattle BSE to primates”. It was furthermore noted that in order to match the level of infective material given to the macaques, a human being would have to consume 1.5kg of infected brain material.
Human studies on the other hand, provide better information on the epidemiology and pathogenesis of the disease:

- All vCJD victims have had a particular combination of prion genes – this is present in 38% of the population.\(^9\)

- It has been stated “Particular combinations of psychiatric and neurological features may allow early diagnosis in an appreciable number of patients”; such signs include numbness, handwriting impairment, “odd sensation” and dizziness. These features cannot be identified in primates, making them a poor model for this research.\(^9\)

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