EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Scientific Opinions
C1 - Follow-up and dissemination of scientific opinions

THE NEED FOR NON-HUMAN PRIMATES IN BIOMEDICAL RESEARCH

STATEMENT OF THE SCIENTIFIC STEERING COMMITTEE ADOPTED AT ITS MEETING OF 4-5 APRIL 2002

STATEMENT

The Scientific Steering Committee (SSC) considers necessary to raise the awareness of the Commission Services about the implications that would result from a complete disappearance of non-human primate research facilities.

Whether or not, eventually, non-human primates are used for research, will need to be decided upon on a case-by-case basis, and following a careful assessment, which takes into account the justification below, the possible existence of alternatives, ethical considerations and the problems that could result from not using the non-human primates. The SSC stresses that unnecessary and duplicated or redundant research using non-human primates should be avoided at all costs (and for example by a EU-wide co-ordination 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 are no alternatives to the use of non-human primates. Such experiments may be needed, for example, during the development of drugs and vaccines for prevention and cure of disease such as AIDS, TSE[1], malaria, and influenza.

The SSC recommends that, in addition to the Commission possibly gaining ethical advice on the issue and to the forthcoming opinion of the Scientific Committee on Animal Health and Animal Welfare (SC-AHAW) on animal welfare aspects, a more comprehensive list be prepared of the research areas where well-maintained non-human primate research facilities are needed. Ideally such a list should be developed and maintained within the overall context of the need for animal experiments in general.

BACKGROUND

For finding new ways of improving the living standards of humans and animals the scientists use a lot of different approaches. Some of them do not involve live animals, including *in vitro* techniques, modelling and epidemiological studies. However experiments on live animals are powerful ways of better understanding the complex biological mechanisms. The community is very aware of the consequences of those experiments on the living conditions of the animals involved in experiments. As a consequence a whole set of regulations have been published to avoid unnecessary suffering during the experiments and to provide optimum

[1] The example of TSEs has recently been addressed in the SSC opinion of 6-7 September 2001 on *The use of Non-human primate models for human TSEs*.

living conditions during their whole lives (in particular D86/609/EEC, Council Decision 1999/575/EC).

In the Council Decision 1999/575/EC, it is stated that "…, accepting nevertheless that man in his quest for knowledge, health and safety has a need to use animals where there is a reasonable expectation that the result will be to extend knowledge or to be the overall benefit of man or animal, just as he uses them for food, clothing and as beasts of burden;". The question remains however to weight the costs on the experimental animals and the benefits for the future of humans or animals.

That type of questions is particularly sensitive when primates are involved in experiments. The reasons for this are said to be related to their high cognitive abilities and complex social life which are more easily disrupted than those of other animals by living conditions in laboratories and more specifically during the experiments.

The Scientific Steering Committee (SSC) believes that there are scientific reasons why primates will be particularly useful in future European research programs. It should allow the scientific European community to contribute better to the future of human health. It should also insure that the experiments are done under good laboratory practice. By contrast, the SSC however does not feel competent to decide whether or not to use primates in research but that it should be better commissioned by the European Group of Ethics of Sciences and New Technologies of the European Commission. If it is accepted that the use of primates in research is ethical, those animals should be housed and treated in a way that fulfils their species-specific requirements and avoids any unnecessary suffering. The scientific committee on "animal health and animal welfare" (SC-AHAW) should contribute in the near future to a definition of those conditions.

The Scientific Steering Committee 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.

   It is important to note that to develop specific vaccines, non-human primate models are often required because of safety risks and the chance of unexpected autoimmune or hyper immune reactions and even enhanced infection and or disease (e.g. Respiratory Syncitial Virus). This problem becomes clear when one examines the very specific interactions that parasites and viruses have with their hosts. For instance they are often able to evade the immune system by mimicking immune molecules or altering the regulation of these immune molecules. In most cases their interactions with their host are so species specific that they can only be studied *in vivo* in hosts very closely related to man.

The following 5 examples, which are far from being exhaustive, illustrate the above:

a) **AIDS:** The epidemic is still rapidly spreading and, with more than 40 million infected, a vaccine is desperately needed. 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. Macaques are an important surrogate model which when infected with SIVsm develop an AIDS-like

disease which is almost indistinguishable from AIDS in humans. The Rhesus macaque has been well characterised with regard to CD markers and especially MHC immunogenetics to allow for the study of vaccine efficacy in an outbred primate species.

b) **Malaria:** This is a major cause of human morbidity and mortality in developing countries that is having more impact on developed countries each year. In sub-Saharan Africa up to 2 million children under 5 years of age die from malaria annually. The relationship between the parasite and the host is quite specific, such that human malaria parasites will not infect rodents. They do however infect some non-human primate species, and other malaria parasites of non-human primates are very closely related to the human parasites. Therefore, using both old world and new world monkey, models the relationship between the parasite and the host can be investigated to identify therapeutic and prophylactic possibilities. Although considerable research can be done *in vitro*, the parasite has obligatory intra-hepatic developmental phases that are not amenable to *in vitro* cultivation. To date primates have been used as pre-clinical screens for a variety of new vaccine candidates, based on recombinant sub-unit approaches and live-vectored approaches. Different malaria vaccines will require different immune responses (humoral or cellular) and well-characterised models with similar immune responses to humans (such as macaques) are essential in vaccine development. New malaria drugs will have to work effectively *in vivo*, and many drugs that are effective *in vitro* fail *in vivo*. Monkey models are vital to evaluate promising new drugs for efficacy. More recently genetically modified parasites of primates have been developed and the modifications are allowing vital insight into the critical areas of interaction between the parasite and the host.

c) **Tuberculosis:** One third of the world's population is estimated to be infected with TB. It is a major killer in its own right, and combination with HIV is proving even more of a problem. The current vaccine, BCG, is highly variable in efficacy (in some trials it is ineffective) and existing drugs require long-term treatment and suffer from problems of increasing resistance. Highly virulent new strains such as the Beijing strain are now spreading within Europe, with potentially serious results. Mouse and guinea pig models are used to screen potential new vaccines and drugs, however their patterns of disease and their immune responses are often markedly different from those seen in humans. Recently a careful analysis of two macaque models (rhesus and cynomolgus) has shown the value of these two models and their similarity to the human situation. These models are now being used to screen and select among new candidate vaccines before embarking on the complex, protracted and expensive clinical phase.

d) **Hepatitis**: Hepatitis C is the major cause of chronic liver disease leading to hepatocelluar carcinoma in humans. More than 200 million people are infected with this virus throughout the world and most of them are unknowing carriers. Hepatitis C cannot be cultured and the only other species other than man that can be infected is the chimpanzee. Early HCV vaccine studies in chimpanzees have begun to show progress but non-human primate research is essential to bring a truly effective vaccine to the clinic. Thanks to studies in chimpanzees which are still alive and healthy today, millions of doses of a very successful Hepatitis B vaccine have been given World-wide. However, Hepatitis B is still transmitted and many new infections occur daily. New less expensive HBV vaccines are required for developing countries to halt and eliminate this chronic human pathogen.

e) Immune-based diseases

Non-human primate models of immune-based clinical disorders, such as rheumatoid arthritis, multiple sclerosis, type I diabetes, allergy/asthma and transplant rejection, are needed for the development and evaluation of new immunomodulatory/ immunosuppressive therapies. This is in particular the case with biological reagents that by their species specificity work insufficiently in rodent models and of which the potential toxicity in humans is insufficiently clear to test them directly in patients.

There is an increasing need of non-human primates as models for CNS biology and disease. Multiple sclerosis is one such disease for which there is no cure. MS is an invalidating neurological disease with an underlying autoimmune etiology affecting one in 1.000 young adults. Many investigators feel that the T- and B-cell autoreactivity towards CNS antigens may be triggered initially in genetically susceptible individuals by a yet unknown viral infection. The close genetic, immunological and virological relation with humans makes non-human primates an excellent model of this disease.

Thus the problems faced in developing vaccines or therapeutics against these modern day plagues can be summarised as follows;

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 is so species specific that they only infect humans or other closely related primates.

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.

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 models.

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.