EUROPEAN COMMISSION
HEALTH and CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Scientific Opinions
C2 - Management of scientific committees; scientific co-operation and networks

The welfare of non-human primates used in research

Report of the Scientific Committee on Animal Health and Animal Welfare

Adopted on 17 December 2002

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1. MANDATE

The EU Commission has asked the Scientific Committee on Animal Health and Animal Welfare to prepare a report on the welfare of non-human primates used for experiments.

The Scientific Committee, taking into account the most recent scientific information should propose how the welfare of these animals can be improved, and identify the most important issues within the EU.

2. BACKGROUND

In 1986 the Council adopted Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes. The Directive seeks to improve the controls on the use of laboratory animals, to set minimum standards for housing and care, and addresses in broad terms the training of personnel handling animals and supervising experiments. It also aims at replacing animals with non-animal methods wherever possible, as well as encouraging the development and validation of such replacement methods. Where animals have to be used, the Directive aims to ensure that it is only the minimum number, and that any animal suffering is the minimum necessary to achieve the scientific objective i.e. avoidable suffering should not be caused.

The Directive contains two Annexes: Annex I listing the species of animals that have to be purpose bred, covered by Article 21 of the Directive, and Annex II containing the guidelines for the housing and care of laboratory animals. These Annexes are of a technical nature, and rely on scientific knowledge of the needs of the animals, including those to show certain behaviours, as well as the influence of the environment on their welfare. The guidelines need periodic updating in line with the latest scientific and technical developments.

The Commission acknowledges the fact that Directive 86/609/EEC requires a full revision. Since the scientific basis of the Directive dates back more than 15 years, some provisions require revision based on more recently available scientific data. Furthermore, the scope of the Council of Europe Convention goes beyond that of Directive 86/609/EEC and covers animals used for the purposes of education and training. The Directive would need to be aligned accordingly. At the same time the Commission could fulfil its commitments to improve the controls and welfare of certain species such as non-human primates, and to revisit some of the definitions and existing provisions.

3. PREAMBLE

The Report is divided into chapters that cover the scale of experimental use of non-human primates in the EU (4), their general biology (5), general welfare assessment (6), current husbandry practices (7), breeding and supply (8), specific welfare problems (9), health issues (10), transport (11), and specific issues relating to their use in science (12). These are followed by conclusions (13), recommendations (14), priorities for future research (15) and an executive summary (16). In this report the term ‘primate’ is used to cover all non-human primates; ‘monkey’ to cover both Old World and New World non-human primates except the prosimians; Great Apes to include bonobos, gorillas, chimpanzees and orang-utans; and ‘man’ to mean ‘human’ rather than inferring a male human being. There are varying views on the ethical considerations regarding the use of primates in research and the members of the Scientific Committee are concerned with the ethical issues regarding the use of primates in research. However, it was not within the Committee’s mandate to review the ethical issues of whether or not primates should be used in research. Rather their mandate was to make recommendations on how the welfare of non-human primates can be improved whenever they are used in research. It should be noted that the Decision of the European Parliament and of the Council establishing the Fifth Framework Programme laid down an ethical framework for Community funded research. It stated that “all research activities conducted pursuant to the Fifth Framework Programme shall be carried out in compliance with fundamental ethical principles, including animal welfare requirements, in conformity with Community Law” (EU, 1999; EC, 2002). Possible socio-economic consequences of modifying the use and management of primates in research have also not been specifically considered within the context of this report. The report focuses primarily on the welfare of primates used in research, although, since poor health will result in poor welfare, brief consideration is also give to some important general animal health issues. It should also be noted that some of the general issues concerning the use of primates in research (e.g. validation of alternatives to their use, ethical considerations etc.) will also apply to other animals used in research. The Scientific Steering Committee has already published a statement regarding the need for non-human primates in biomedical research which stresses that “unnecessary and duplicated or redundant research using non-human primates should be avoided at all costs” (SSC, 2002).

According to the European Union Treaty of Amsterdam, animals that are kept for commercial purposes are considered as living and sentient, in the sense that they are able to experience pleasure and suffering. In order to safeguard welfare as far as possible in experimental conditions, animals should be kept in environments that respect their needs, including their needs to show certain behaviours.

The welfare of an animal depends upon its biological features and the housing and management conditions under which it is kept. The biological features of present day animals are the outcome of the process of evolution that has resulted in animals that are adapted to their natural environment or ‘niche’. Thus the behavioural characteristics displayed by animals are essential to their survival and reproduction in their natural environment. Some elements of this adaptation process are common to all animal species, such as orientation, foraging and feeding, whereas others are specific to a particular environment, such as a forest. Since environmental niches have many features in common, especially in terms of temporal and spatial features, adaptive behaviour is usually sufficiently flexible to allow an animal to adapt to different environmental conditions from the ones in which it has evolved, provided that they bear sufficient similarities to the original environmental niche. Domestication makes use of this flexibility but primates have not been domesticated and are in essence still wild animals (Poole, 1992, 1997).

The welfare of an animal will become poorer if it cannot successfully adapt to the conditions in which it is kept and this can occur in several ways. At the behavioural level, an animal can be prevented from developing some elements of its species-specific behavioural activities because of lack of stimulation, restricted space, or the lack of an appropriate outlet for these activities (Dawkins, 1990). These last two restrictions result in the thwarting of needs to show certain behaviours and will often induce suffering, the extent of which depends on the importance of the activity in the behavioural repertoire of the species in question (Dawkins, 1980, 1990). At the physiological level, excessive constraints upon an animal's adaptive abilities trigger a non-specific neuroendocrine response that is usually referred to as the stress response, especially in unpredictable and uncontrollable situations (Hennessy and Levine, 1979; Dantzer and Mormède, 1983). In all these cases, adaptation failure usually results in a number of altered body functions, of which the visible manifestations can be used to assess welfare. Whether this is accompanied by altered emotional states and feelings depends on the emotional and cognitive abilities of the animal under consideration (Dantzer, 2002).

In line with these very general principles, welfare has been defined as the state of an animal as regards its attempt to cope with its environment (Broom, 1993; Poole, 1998). Welfare therefore varies from good to bad, or more precisely from ease of coping to difficulty coping or some failure to cope. Pleasurable mental states will often accompany good welfare and unpleasant mental states are generally associated with coping failure. For many it is these mental states which are the essence of animal welfare (Dawkins, 1980, 1990; Duncan and Petherick, 1991; Mason and Mendl, 1993; Fraser, 1995). Trying to assess animal welfare may therefore involve making inferences regarding mental states in particular.

It is thought that a balance between environmental novelty and predictability is important for animal welfare. Environmental conditions that significantly depart from an animal's 'niche' can be the source of welfare problems, the extent of which depends on their prevalence, duration and intensity, and on an animal's ability to adjust to them. The extent of such welfare problems can be assessed in the subjected animals by a combination of measures, taking into account their physical health, biological functions and behaviour. In general, minimum premature mortality, low morbidity, minimal risk of body injury, the ability to express valued species-specific activities (including social interactions, good mothering behaviour, grooming, foraging, exploration and play) and a lack of abnormal behaviour and of physiological signs of stress, including alterations in immunity, indicate that there are no major animal welfare problems.

4. EXPERIMENTAL USE OF PRIMATES IN THE EU

Non-human primates are maintained in Europe for a wide variety of purposes ranging from fundamental to highly applied research, and testing for regulatory purposes. Significant advances have been made in recent years in collating information on the use of animals in research across Europe, although there continues to be scope for further harmonisation of data collection. Issues of particular importance, when considering research involving non-human primates, include sources of animals and species selection. The available source of amalgamated EU data (EC, 2003) indicates that non-human primates accounted for less than 0.1% of all the laboratory animals used in 1999. Although this is a relatively small percentage, there are special considerations associated with their use and these have been considered elsewhere in this document.

Table 1 (EC, 2003) summarises the number of non-human primates categorised as prosimians, apes, Old World monkeys (OWM), and New World monkeys (NWM) reported to have been used for scientific purposes in EU Member States in 1999. For the 15 Member States, in 1999 9,097 primates were used out of a total of 9,814,171 animals used in scientific experiments. The data shows that more non-human primates are used in the United Kingdom (UK), France and Germany than elsewhere in the Community, although recently published statistics for both the UK and France (Home Office, 2001; Ministère de la Recherche, 1999) suggested a decrease in the number of primates used. However, care should be taken in the interpretation of these trends since they are liable to considerable fluctuation. Furthermore, there are difficulties in analysing the data since there are varying definitions between countries of what constitutes an 'experiment', and an animal can sometimes be re-used in more than 1 experiment in the same year.

Table 1: Total number of non-human primates used for experimental purposes in EU Member States in 1999

Country	Prosimians	NWM[1]	OWM[2]	Apes	Prosimians+ monkeys+apes Total	Use of primates as a % of total animals used [3]
Austria	0	0	7	0	7	0.01
Belgium	0	21	469	0	490	0.06
Denmark	0	0	0	0	0	0.00
Finland	0	0	9	0	9	0.00
France	455	53	1814	0	2322	0.10
Germany	271	1813[4]		0	2084	0.13
Greece	0	0	0	0	0	0.00
Ireland	0	0	0	0	0	0.00
Italy	0	62	450	0	512	0.05
Luxembourg	0	0	0	0	0	0.00
Netherlands	0	42	272	6	320	0.05
Portugal	0	0	0	0	0	0.00
Spain	0	96	0	0	96	0.02
Sweden	0	6	60	0	66	0.02
United Kingdom	0	1073	2118	0	3191	0.17
Total	**726**	**1353**	**5199**	**6**	**9097**	**0.09 (Mean)**

[1]New World monkeys (*Ceboidea*), [2]Old World monkeys (*Cercopithecoidea*), [3] Prosimians+ monkeys+apes as a % of total animals used for experimental purposes in that Member State, [4] In the case of Germany, a combined figure for both Old and New World monkeys is given and so these animals are not included specifically in either the NWM or OWM totals

Some information is available on the sources of non-human primates used in research, including their importation into Europe from breeding colonies located in a diverse range of countries such as China, Indonesia, The Philippines, Mauritius, Israel and the USA. Primates used within Europe are sourced from either self-sustaining in-house colonies, other Europe-based breeding colonies or breeding and holding establishments outside

Europe. Table 2 (EC, 2003) shows some data on the sources of primates used in scientific experiments within the EU, although data for Germany is not included.

The country of origin where primates are sourced has implications for the quality of animals sourced, the duration of transport the animal endures, the genetic profile of the animals and individual subspecies, animal health issues (diseases endemic in area where sourced), and the practices employed in their breeding and handling in the establishments of origin, with consequent impacts on their welfare. Even if such breeding and supply establishments are located outside the EU, their involvement in accreditation schemes could help to safeguard the welfare of primates held there for eventual use in Europe.

Table 2: Place of origin of primates used for experimental purposes in EU Member States in 1999 (A portion of the totals comprise re-used animals)

Place of Origin	Prosimians	NWM	OWM	Apes
From registered breeding or supplying establishments within the EU	323	1169	2274	6
From elsewhere in the EU	0	46	181	0
From other origins	132	56	2736	0
Number of re-used animals within overall total	0	364	595	1

Table 3 (EC, 2003) shows collated available data on the primary scientific purpose for which primates are used (German data are not included). Bottrill (2000) has published an analysis and commentary on primate use in Europe based largely upon corresponding data for 1996/7.

Table 3: Number of primates used in experiments for specifically identified scientific purposes in EU Member States in 1999

Purpose of experiment	Prosimians	NWM	OWM	Apes	Total Primates
Biological studies of a fundamental nature	455	355	469	0	1279
Research and development of products and devices for human medicine, dentistry and veterinary medicine*	0	410	483	6	899
Production and quality control of products and devices for human medicine and dentistry	0	0	895	0	895
Production and quality control of products and devices for veterinary medicine	0	0	2	0	2
Toxicological and other safety evaluations#	0	568	3119	0	3687
Diagnosis of disease	0	0	22	0	22
Education and training	0	0	4	0	4
Other	0	8	198	0	206
Total	**455**	**1341**	**5192**	**6**	**6994**

*excluding toxicological and other safety evaluations, #including safety evaluation of products and devices for human medicine and dentistry and for veterinary medicine

Although not explicitly categorised in the data gathering for most states, the OWM species used most frequently are macaques and, of these, *Macaca fascicularis* has in recent years become the OWM most commonly used in regulatory investigations. *Macaca mulatta* is the second most frequently used species and relatively small numbers of other macaques are used. Over the last decade *Callithrix jacchus* has replaced *Saimiri sciureus* as the most frequently used NWM species. From the data reviewed, it appears that that there is no current biomedical research involving chimpanzees in Europe. In the two EU countries where chimpanzees have been kept for research purposes, namely Austria and The Netherlands, such experiments are to be ended and the animals are being 'retired'. In The Netherlands a law is in preparation prohibiting the use of chimpanzees in biomedical research.

Current datasets concentrate on the number of animals used in scientific procedures, the primary purpose of conducting those procedures and, for some countries, data on the sources of the primates used are also available. They do not capture data on the number of primates maintained for scientific purposes or on the actual severity of experimental procedures to which the animals are exposed. However, as an example, some figures from The Netherlands are presented on the predicted severity of research involving primates (see Table 4). A more detailed breakdown of the number of individual species of primates used would facilitate the identification of trends regarding their use and allow breeding programmes to be planned accordingly. However, categorisation of what counts as 'experimentation' and the degree of pain, distress, discomfort and suffering, caused can vary. The classification of the adverse effects into a very small number of categories presents obvious difficulties, and interpretation and classification can vary between countries.

Table 4: The predicted degree of discomfort of primates used in research in The Netherlands (Anon., 2001)

Species	Predicted Degree of Discomfort					
	Little	Little/ Moderate	Moderate	Moderate/ Serious	Serious	Very Serious
Prosimians	-	-	-	-	-	-
NWM	1	38	44	21	63	1
OWM	130	101	151	84	107	-
Apes	-	-	9	2	1	-

Factors influencing the selection of a particular species are a central issue and have enormous implications for animal welfare and the quality of animal-based science. In some countries special justification for the use of non-human primates is required as part of the ethical review process and involves considering both the selection of non-human primates in preference to non-primate species or humans, as well as selection of the particular species of non-human primate proposed to be used.

4.1. Reason for use and severity

Currently available data differentiate imperfectly in terms of breakdown of why non-human primates are used, although those animals used for toxicological studies are reported separately from those used in fundamental research. Non-human primates are used in fundamental and applied research and the level of intervention of studies involving primates deserves particular consideration. Such studies can range from wholly non-invasive ethological observations in large enclosure settings to highly invasive studies, for example ranging from toxicological studies involving drug administration and repeated blood sampling, to studies resulting in very poor welfare and possibly the ultimate death of the animal. Data are not routinely collated on the classification of levels of severity of procedures to which individual animals have been subjected. The level of pain and suffering for an animal during its lifetime in a laboratory will depend on several factors including the husbandry conditions, the type of experiment being carried out, the intensity and duration of any pain, distress or lasting harm, and the number of times an animal is re-used in the same or a different procedure.

At present, the level of animal suffering is poorly recorded and often is a matter for prospective evaluation i.e. a prediction of what will happen, and not the degree and duration of suffering that actually occurred. A better system would be to have a retrospective reporting system, with reports by animal welfare officers and veterinarians in an institution being collected and reviewed. Furthermore, any methods to alleviate or avoid such suffering could also be identified, and applied. It is difficult to obtain such information at present because it is not required to be written up as a scientific paper as it does not form part of a 'standard experiment' but rather constitutes good clinical observation data. Nevertheless such a reporting system and database would enable experiences to be shared, potentially to the benefit of the welfare of all animals used in research, which in turn would benefit the science.

4.2. Use of the Great Apes in research

Opinions vary as to whether Great Apes should ever be used in invasive research. One approach would be to restrict their use to where it is likely to be in the best interests of those individual apes to be used, or of the long-term survival of that species. Such an approach would lead to fundamental changes and restrictions in their use in biomedical and biological research. An alternative position would be that the option of their use in biomedical research in the future should remain open, if no alternative research models are available for specific critical research in the future. To deal with such unforeseen requirements, a significant number of primates would need to be held in reserve to serve such scientific purposes if they arose. The necessity of such research and absence of alternative research models would need to be assessed and their use approved by scientific regulatory bodies following an ethical review assessment of the research proposed. There is concern that a prohibition of the use of primates for research in Europe could lead to such research being performed in countries where their welfare could be further impinged upon, if they are used in other countries where the standards of animal care and welfare are lower than in Europe. Special considerations may also apply when evaluating the validity of experiments involving chimpanzees. However, such ethical issues are beyond the mandate of this Committee and scope of this Report.

4.3. *In vitro* studies

Additionally, non-human primates are sometimes humanely killed to obtain tissue for *in vitro* studies. Available databases do not currently provide information on animals culled solely for their tissues. When animals are used in this way, there could be co-ordination, optimisation and refinement of primate usage by establishing tissue banks and data exchange networks.

Although such a system is extant in the USA (Primate Info. Net http://www.primate.wisc.edu/pin/) currently, there are no comprehensive pan-European databanks on the use of non-human primates and non-human primate derived tissues and cells, and such a venture would have considerable potential to optimise the information gained from individual animals.

4.4. Networking

In the USA there is a long-established system of regional primate centres that offers potential for co-ordination of primate related breeding and research activities. In Europe, a number of Primate Centres and other primate-related research centres from France, Germany, Italy, UK and The Netherlands have begun a collaborative programme to address some of the issues regarding primate research on a European basis under the aegis of the European Primate Resources Network (EUPREN) which was founded in 1993. EUPREN networking activities at national and cross-community levels have involved holding scientific meetings and facilitating a survey of primate supply for biomedical research in the UK (EUPREN UK Working Party, 1997). A number of cross-disciplinary workshops were held in the late 1990s which included joint workshops with the European Marmoset Research Group (web page at http://dpz.gwdg.de/emrg/emrgcons.htm), one of a number of European groups with particular involvement in non-human primate research. The European Federation of Primatology (EFP), established in the mid-1990s as an umbrella organisation for various national primate societies and groups, is another important cross-disciplinary group involved in the discussion of issues relating to primates.

When using primates in scientific experiments, inter- as well as intra- laboratory collaboration could allow greater scientific benefits from the physiological/behavioural measures, and from the tissues/samples taken from animals during and after the end of the research. Research facilities could ensure that samples of primates' tissues are widely shared within and also outside an institution and bodies funding research could further encourage such cooperation. By fostering and supporting collaborative research efforts, better use of the animals in a single project can be made, as a greater breadth of analytical measures can be carried out on each animal utilising the available expertise from a broader scientific base. This could help to reduce the overall number of primates required to be used in research.

4.5. Re-use

The classification of what counts as a 'use' of animals varies considerably between countries and covers the spectrum of studies outlined in chapter 4.1. As a result, the term 're-use' is open to a wide range of varying interpretations. The issue of re-use of primates raises particular concerns that need to be addressed. The amount of information obtained from one animal could be maximised by performing more than one experiment at a time where this does not detract from the scientific objective or result in poor animal welfare. This would reduce the overall total number of animals required to be used. However, the objective of maximising the data acquired from individual animals must be judged against minimising any adverse affects on their welfare. The level of severity of the effects of scientific procedures to which animals have been subjected will be an important determinant of the appropriateness of their subsequent re-use, either in further scientific procedures or by their return to captive breeding colonies. In addition, the longer lifespan of non-human primates, compared with some other laboratory animal species used, is an important consideration when managing their use and possible re-use in experiments. Some collated data are available concerning the re-use of primates in research (EC, 2003).

5. GENERAL BIOLOGY OF PRIMATES

5.1. Taxonomy and phylogeny

Man and approximately 200 species of non-human primates are placed together taxonomically in a single order called *Primates*. Today, non-human primates are found naturally in Africa (including Madagascar), South and East Asia, and in South and Central America - there are no naturally-inhabiting primates in Antarctica or Australia. Although a few species can live in more temperate areas, like Nepal and Northern Japan, the vast majority live in areas of tropical or sub-tropical climates with evergreen forests (Oates, 1987; Fleagle, 1999). The primate order encompasses a great variation among species in aspects such as body size (25g to 200 kg), food eaten (ranging from leaves and grass to meat), patterns of locomotion (from arm brachiation in trees to quadrupedic locomotion on the ground) and sizes of naturally occurring social groups (from solitary to large groups with more than 200 individuals in complex social organisations) (Harvey *et al.*, 1987; Burton, 1995).

The order of *Primates* is commonly divided into two major groups, or suborders: *Prosimii* (lemurs, lorises and tarsiers) and *Anthropoidea* (monkeys, apes and humans). Although specialised in many respects, prosimians preserve more primitive features, such as aspects of dentition, skulls and limbs, similar to those found in primate fossils dating back 40-50 million years (Fleagle, 1999). Prosimians are the primates most genetically distant from man. They live in Central Africa, (lorises and galagos), Madagascar (lemurs and lepilemurs for example) and South-East Asia (tarsiers). Except for species from Madagascar, extant prosimians are nocturnal with specialised night vision and good hearing.

The greatest abundance and diversity of prosimians occur on the island of Madagascar. This island not only has a great regional diversity in flora, but it has also been separated from the African mainland for many millions of years and has not been inhabited by either larger carnivores or ungulates, or by any of the more advanced primates (anthropoids). Prosimians on Madagascar have, therefore, evolved into both nocturnal and diurnal species (Richard, 1987; Fleagle, 1999).

The New World monkeys, or platyrrhines (broad-nosed monkeys like marmosets and tamarins, howler monkeys, spider monkeys, squirrel monkeys, owl monkeys and capuchins) have an evolutionary history extending back nearly 30 million years and they have been genetically isolated on South and Central America from the rest of the anthropoid monkeys for many millions of years. Due to this genetic isolation, New World monkeys are also genetically distant from man. In dental and cranial anatomy, platyrrhines still have primitive features, lost in the evolution of Old World monkeys and apes, such as having three premolars (Fleagle, 1999). Due to the great diversity of habitats and the absence of other primates (like prosimians), platyrrhines have also evolved to fill a diverse array of ecological niches and today include both nocturnal and diurnal species and exist in sizes from 100g to over 10kg body weight (Smith and Jungers, 1997).

Anthropoid monkeys and apes of Africa and Asia are all included in the infraorder C*atarrhini* (narrow-nosed primates). The catarrhines are further subdivided into two superfamilies; *Cercopithecoidea* (Old World monkeys such as macaques, baboons, guenons and colobines) and *Hominoidea* (hominoids; Lesser Apes - siamang and gibbons, Great Apes and man). They all have the dental formula of two premolars and a total of 32 teeth, just like man, and are the primates most closely genetically related to man. Even though a great diversity exists in habitats and patterns of adaptation, catarrhines are diurnal, generally larger, and some species are also partly terrestrial (Fleagle, 1999).

5.2. Primate habitats and adaptations

The habitat is the specific environment in which a primate is found within its geographic range of distribution. Primates are found in a variety of habitats, ranging from deserts and open grass savannahs to dense, tropical rainforests. Even though most primate species live in forests of one sort or another, these forests are not uniform, and come in many different forms, with variations in climate, altitude, topography and soil type, as well as in the characteristics of the flora and fauna. Furthermore, great variation exists within a single forest as different primate species are adapted to live in various ecological niches in a given habitat. For example, species can be adapted to live on different types of food in the same forest, to live at different heights in the trees or even on the ground. They can be adapted to different modes of locomotion when travelling in the forest and to qualitatively and quantitatively different types of predation (Oates, 1987). The large range of different habitats to which primates are adapted, combined with a sub-specialisation to occupy different ecological niches within a given habitat, are the basis for the great diversity of adaptations found within the primate order. The most important forms of primate diversity are mentioned below (Fleagle, 1999).

Locomotion:

There are four basic types of primate locomotion. Quadrupedal primates use all four limbs, with palms flat, to walk, as do most primarily ground-dwelling primates. Chimpanzees and gorillas knuckle-walk, a specialised version of quadrupedalism. Some larger primates travel through the trees by hanging below the branches. An exceptional form of such suspensory locomotion is called brachiation and is shown, for example, by gibbons. Vertical clingers and leapers prefer small tree trunks and can jump from one trunk to another. They sometimes have claws instead of nails to facilitate grip, as in marmosets. Some species show occasional bipedalism, but man is the only primate adapted to continuous bipedalism. Even though primates are adapted to chiefly use one of the four major types of locomotion, they may use other types at least some of the time, e.g. when a quadrupedal animal climbs into the trees for the night.

Social organisation:

The social organisation refers to how an individual relates to other members of the same species. Primates are all, in one form or another, social animals but they are adapted to many different forms of social structures depending on the species and the habitat in which they live. They recognise each member in their group and establish different social relationships with each of them. Their social bonds are based on attachment, friendship and kinship. They have the capabilities to learn from conspecifics, compete, cooperate with, and appease each other, prevent conflict escalation and can form coalitions. Their social organisations represent complex networks of relationships that vary according to age, sex, familiarity, kin-relatedness and dominance status of individuals (Smuts *et al*., 1987; Fleagle, 1999; Aureli and de Waal, 2000). The availability of companions of a particular age-sex class and engagement in certain kinds of interactions and social relationships have psychological and physiological consequences for individuals.

As the name implies, solitary foragers often forage alone and the only more stable social group is that between the mother and offspring. Solitary foragers use a home range and often the home range of a male overlaps the home-ranges of several females, as for the orang-utans. Inter-male competition is prominent.

In a one male/one female social organisation, the social group consists of a monogamous pair and their offspring, often in a territory defended against other members of the same species. Gibbons from South-East Asia, and titi-monkeys and the nocturnal owl monkey from South America live in monogamous pairs (Robbins-Leighton, 1987; Robinson *et al*., 1987). Sometimes even sexually mature offspring remain in the territory to help the parents with their young. This is found, for example, in the South American common marmosets (Goldizen, 1987).

One male/multi-female groups represent a common form of social organisation. Two types of these groups can be distinguished. In one, several related or bonded females remain in a group and may defend their resources. An adult male may join the group, mate with the females and defend the females and their offspring against other males. In the other type of group, unrelated females may join a male, as long as he can succesfully defend the females and their offspring. There is a strong sexual selection in males, as the males have to repeatedly fight against other males in order to get access to and defend a harem-group of females. In these species, infanticide by strange or newly arrived males is not uncommon. The males in species adapted to live in a one male/multi-female social organisation are often equipped with very large canines and are substantially larger than the females (by 75-100% in the gorilla for example).

Several types of multi-male/multi-female primate social groups exist. In macaques and in some baboons, related females build up the core of the group, they remain in the same group in which they were born and they inherit their rank from their mothers. The males, even though bigger and dominant to females, leave their natal troops at maturity and emigrate to a new troop to gain access to unrelated fertile females (Melnick and Pearl, 1987). A multi-male/multi-female social organisation with more fluidity is the so-called fission-fusion community, seen for example in South American spider monkeys and the African chimpanzees. Related males forage together and patrol and defend a common territory in which unrelated females forage alone or with their offspring. Occasionally, the whole group can meet and forage together at a rich feeding site (Nishida and Hiraiwa-Hasegawa, 1987) In multi-male/multi-female primate social groups of these types, promiscuous matings often occur and a single female may mate with several males at the time of oestrus, and the males also try to mate with as many females as possible. Males of primates with an evolutionary background of promiscuous mating have evolved larger testicles and short copulation times, and females more often show signalled ovulations (Sillén-Tullberg and Møller, 1993).

The basic foraging and reproductive unit of the hamadryas baboon is a one male/multi-female group, but several such units with related males form a clan. A hamadryas baboon herd, containing up to 400 individuals, consists of several such clans.

An important disadvantage of living in social groups is the increased risk of conflict and aggression, as competition between group members for limited resources, such as food, partners or sleeping sites, will be more pronounced (Kappeler and van Schaik, 1992; Aureli and de Waal, 2000). An important aspect of the social life of primates is therefore various forms of behavioural strategies used to encourage sociality (thereby maintaining group structure) and to reduce tension and conflict within the groups. Apart from a diverse variety of behaviours signalling dominance or submission, social grooming is an important behaviour used to establish and maintain social bonds. In recent years, reconciliatory behaviours, i.e. affiliative behaviours shown in the period directly following a conflict, such as social grooming or body contacts, have been shown to be of great importance in reducing the impact of conflict and aggression in primates (Kappeler and van Schaik, 1992; Aureli and de Waal, 2000).

In general, primates are xenophobic, meaning that primates in groups are very restrictive in accepting and incorporating newcomers from outside into the group. How acceptance of newcomers is undertaken in the wild is not very well understood.

Diet:

What a primate eats is determined by its size, teeth, and the anatomy and physiology of its gastro-intestinal tract (Oates, 1987; Fleagle, 1999). Only primates with a gastro-intestinal tract that, with their gut flora, can digest cellulose can eat leaves, stems and grass, and they are commonly called folivores. Among anthropoids, folivores exist among both New and Old World monkeys. Folivores are less restricted by food availability and can therefore live in more dense populations (Oates, 1987). Primates with an acidic stomach cannot support commensals and cannot digest cellulose, and consequently need to find high energy foods, such as carbohydrate-rich fruits or very young leaves and protein-rich insects. They are commonly called frugivores. Larger frugivores have problems finding food containing adequate amounts of protein, and show many adaptations to overcome this problem, and will also eat birds' eggs, tree-lizards and tree-frogs, and even hunt and kill other mammals as food. Unless larger frugivores can overcome this problem of sourcing food, they are forced to live in smaller social groups or even solitarily, like the orang-utan. Some primates, marmosets and tamarins for example, feed to a large extent on plant exudates, such as exudates from gum trees. They have specialised teeth, with which they regularly gnaw holes in the trees to induce exudate production (Goldizen, 1987; Fleagle, 1999; Ah-King, 2000).

The home range is approximately the amount of land used by an individual or a group throughout the year and in which all necessary food-items for survival and reproduction can be found. Home ranges can overlap between groups but a territory comprises a home range actively defended against other groups or individuals. Home ranges vary from 0.1 ha for some prosimians to up to 1,000 ha for orang-utans (Rowe, 1996).

In very general terms, primate females are exposed to higher energy demands than males, due to giving birth and nursing their offspring for a long time. Depending on the availability and distribution of food and the occurrence of predators, females will distribute themselves so as to maximise food intake and reduce the risk of predation. Males, on the other hand, will distribute themselves to maximise their access to fertile females. Due to these differences, all the various forms of social organisation described above have evolved in the various habitats in which primates live (Wrangham, 1987; Fleagle, 1999).

Life histories:

Every primate species has a characteristic life history, which includes timing of events such as gestation length, age at weaning, age at separation from the mother (NB separation differs from weaning, see also chapter 8.4), sexual maturity and total life span. The age at which the female has its first offspring and time of leaving the natal troop, are included in this concept. A great diversity also exists in life histories for different primate species, for example, weaning occurs from approximately 2 months of age in marmosets, while it usually occurs between 3 and 5 years of age in chimpanzees (Harvey *et al*., 1987; Rowe, 1996). The lifespan of primates in captivity is often longer than their life expectancy in the wild, where they may die from predation, disease, injuries or starvation.

Time budget:

A time or activity budget is a list of proportions of time spent in regular daily activities, such as feeding and foraging, travelling, resting, grooming etc. As an example, rhesus macaques have been shown to occupy 20-35% of their time foraging and an additional 10-25% of their time travelling in search of food. Social contacts are also important and 5-10% of the time is usually spent in social grooming and social play (Chopra *et al*., 1992). There is likely to be considerable inter-species variation in time and activity budgets, especially between species that are either folivores or frugivores, with available data suggesting that time occupied by foraging behaviour can vary between 7 and 65% in different species (Milton, 1980; Strier, 1987; Malik and Southwick, 1988, Marriott, 1988; O' Neill *et al*., 1989).

5.3. Biology of primate species most commonly used in biomedical research within the EU

PROSIMIANS

Lesser mouse lemur:

Lesser, or grey, mouse lemurs (*Microcebus murinus*; average adult body weight 100g) are solitary nocturnal foragers, but individuals sleep together during the day. They are frugivores and eat fruits, flowers, exudates, nectar, and insects. During the breeding season, females live alone or with familiar females on small home ranges (0.1-1 ha) while males compete to overlap one or more female home ranges (Martin, 1972; Rowe, 1996). Seasonal reproduction is regulated by photoperiod and outside the breeding season, testosterone levels decrease in males and the gametogenic activity stops (Perret, 1992). The total life-span is approximately 15 years (Harvey *et al*., 1987; Rowe, 1996).

PLATYRRHINES - NEW WORLD MONKEYS

Owl monkey:

The nocturnal owl monkeys (*Aotus trivirgatus*; average adult body weight 1kg) live in monogamous pairs in which the father is the primary caretaker of the infant. The family defends its territory (about 3 ha) against neighbouring groups and in territorial disputes, males fight with males and females with females (Wright *et al*., 1989). It is a frugivore and eats fruits, insects and animal prey. The life-span is reported to be up to 20 years with the offspring emigrating from the natal group when approximately 3 years old (Harvey *et al*., 1987; Ross, 1991).

Marmoset and Tamarin:

Common marmosets *(Callithrix jacchus)* are small (adult body weight range 250-400g), highly arboreal and diurnal. In the wild, they live in family groups of between 5 and 20 individuals. They exhibit a cooperative breeding system in which individuals remain with their natal groups into adulthood, helping to rear the subsequent offspring of the dominant male and female. Mature offspring rank as subordinate to their parents for as long as they remain in their original family groups (Goldizen, 1987). Reproduction is restricted, by behavioural and hormonal mechanisms, to the dominant parent pair, who actively prevent any pair-bond formation between any other male and female combination in the group (Hearn, 1983; Abbott, 1993). Both polyandric (female mating with several males) and polygynic (male mating with several females) family groups have, on occasion, been found. Marmosets are frugivores, eat insects and are specialised in tree gouging and gum feeding. Their natural home ranges are between 1 and 4 ha. Foraging and feeding occupy up to 50% of their time budget and one fifth of their food can come from gum feeding (Goldizen, 1987; Fleagle, 1999). The life-span ranges from 10 to 15 years. Marmosets in the wild give birth to twins, but in captivity triplets are often born, and the gestation length is 5 months (Harvey *et al*., 1987; Ross, 1991).

Tamarins, for example the cotton-top tamarin *(Saguinus oedipus)* or the saddle-back tamarin *(S. fuscicollis),* are similar to marmosets in many respects, but they are slightly larger (average adult body weight 400-500g) and have larger home-ranges (up to 50-100 ha), related to a more frugivorous diet and less dependence on gum-feeding. They can also live in multi-male/multi-female social groups. Most marmosets and tamarins show reluctance to descend to the ground and they display frequent anogenital scent marking.

Squirrel monkey:

The common squirrel monkey *(Saimiri sciureus)* inhabits tropical rainforests at various altitudes and exists in several subspecies with differences in coat colour and facemasks. Body weight of adults ranges from 600 to 1,100g, with males being heavier than females. They are arboreal and live at different levels in the canopy, depending on the temperature, and seldom visit the ground. In the wild, they live in fairly large mixed multi-male/multi-female social groups composed of 20 to 100 individuals. Females remain in their natal group and have matrilineal hierarchies. Males also keep a strict dominance hierarchy, sometimes forming groups of their own in the periphery of the females (Baldwin, 1985). Squirrel monkeys associate predominantly with members of their own age and sex, and females may carry and care for infants other than their own. Squirrel monkeys engage in mating activities during a brief period each year and, in the wild, males gain weight in the months preceding the breeding season. Circulating gonadal hormones increase and the rate of mixed male-female social interactions increase during the breeding season (Dukelow, 1985). Outside the breeding season, females aggressively expel males at the periphery of the group. Squirrel monkeys are frugivores but apart from fruit they also eat a large proportion of various forms of animal prey. They have a wide range of high frequency vocalisations for communication. Their home ranges vary from 65 to 130 ha and daily foraging trips of 1,500 m are not uncommon. The life-span is up to 20 years (Harvey *et al*., 1987; Ross, 1991).

Capuchin monkey:

The tufted or brown capuchin monkey *(Cebus apella)* is sometimes used for research within the EU, but is more regularly used in other countries, for example in the USA. It has an adult body weight range of 1.5–4.5 kg, with males being considerably heavier than females. It is a frugivore and is found in virtually all types of neotropical forests in South America. It lives in multi-male/multi-female social groups usually consisting of 10 to 35 individuals (Robinson and Janson, 1987; Fleagle, 1999). Capuchin monkeys are opportunistic and use their manipulative abilities to obtain food unavailable to other species. Apart from apes, the capuchin monkey is the only species that has been shown to solve experimental tasks requiring abstract cooperation between individuals (de Waal and Berger, 2000). The capuchins live in large home-ranges (25-40 ha) and, in relation to their body size, have a slow life history schedule with long lactation periods, long interbirth interval, and a long life span of up to 45 years or more (Harvey *et al*., 1987; Ross, 1991).

CATARRHINES - OLD WORLD MONKEYS

Several different species of Old World monkeys are used in biomedical research within the EU. The different species used show some general similarities in biology, but also some important differences and they are therefore described separately.

Macaques:

The four species of macaques most commonly used in biomedical research are all from Asia; the rhesus macaque (*Macaca mulatta*; adult body weight range 4-10 kg), the crab-eating or long-tailed macaque, sometimes also called the cynomolgus monkey (*M. fascicularis*; adult body weight range 2.5-8 kg), the stump-tailed macaque (*M. arctoides*; adult body weight range 7.5-10 kg), and the pig-tailed macaque (*M. nemestrina*; adult body weight range 5–15 kg). With the exception of the stump-tailed macaque, males are considerably heavier than females. The life-span of macaques is 30 to 35 years (Ross, 1991).

All members of these species live in multi-male/multi-female social troops which range from 10 to over 100 individuals under natural conditions (Melnick and Pearl, 1987; Fedigan and Fedigan, 1988; Bercovitch and Huffman, 1999). Females outnumber adult males and they remain for the course of their lives in their natal group, forming kinship subgroups, with strong social bonds within the subgroup. The existence of strong coalitions between the individuals determines the relative ranks of kin subgroups and makes the immigration of strange conspecifics difficult. Males also form hierarchies, competing for access to females, and mating associations between males and females range from a few minutes to several days. In macaques, dominant individuals exert a control role that can decrease rates of aggression by intervening in conflicts. For example in pig-tailed macaques, it was shown that entirely female groups display more aggression than groups containing an adult male (Dazey *et al*., 1977).

Females usually give birth every one or two years and siblings and relatives may care for infants. Males migrate from the group on reaching maturity. In species undergoing seasonal reproduction (e.g. *M. mulatta*), testosterone levels and rates of wounding increase in males during the 2 to 3 month long mating season (Bercovitch and Goy, 1990). All these species are frugivores, although they also feed on insects, bird eggs and animal prey when accessible. Their home ranges are usually large and can range from 200 to 400 ha in size, and troops in the wild have been observed to move several km each day (Harvey *et al*., 1987; Chopra *et al*., 1992; Rowe, 1996).

Some differences between these species also exist. For example, the long-tailed macaque is the most arboreal of the species and lives exclusively in tropical areas. Other species live in areas with more variable temperatures, and often forage and travel on the ground. Rhesus macaques have a more hierarchial and dominance-based social system, whereas stump-tailed macaques have a more egalitarian and flexible social system, which is partly based on an extensive use of post-conflict reconciliation (de Waal and Ren, 1988; Matsumura, 1999).

Vervet monkey:

Vervet monkeys (*Chlorocebus aethiops*; adult body weight range 2-6 kg) are a similar type of African monkey and are sometimes kept in laboratories. They are frugivores with a life span of 35 years (Ross, 1991) and live in multi-male/multi-female social troops with similar social dynamics as the macaques, and their troops comprise from 10 to 50 individuals under natural conditions (Harvey *et al*., 1987; Melnick and Pearl, 1987).

Baboons:

Savannah baboons (*Papio* spp.; adult body weight range 12-25 kg) are frugivores, but they also hunt and eat animal prey. They live in complex multi-male/multi-female social troops, which can contain up to 150 individuals. Their social dynamics resemble that of the macaques (see above) and males form dominance hierarchies and are substantially heavier than females. They are quadrupedal and mostly terrestrial and can also inhabit semi-deserts and open savannahs. They have large home-ranges (examples up to 4,000 ha have been described), and they can move up to 10 km each day in search of food (Melnick and Pearl, 1987; Harvey *et al*., 1987; Rowe, 1996).

The hamadryas baboon (*P. hamadryas*; adult body weight range 10-20 kg, males being considerably heavier than females) is also sometimes used in research within the EU. Social organisation and foraging patterns are quite different compared with savannah baboons and macaques. The hamadryas baboon is terrestrial, lives in arid sub-deserts and savannah woodlands, and the basic social unit is a single male with 1-4 females plus their offspring and the male jealously guards the females. Several such one-male groups, probably led by related males together with bachelor males, associate and form bands or clans. Individual harems forage separately during the day in large home ranges, up to 2,800 ha in size (Rowe, 1996), but several harems and clans aggregate during the night and share a common sleeping site on rocky cliffs. The social group at the sleeping sites can be up to several hundred individuals (Stammbach, 1987; Fleagle, 1999). The life span of baboons is 35-40 years (Ross, 1991).

Table 5 gives an overview of the classification in the primate order of species which have been used in biomedical research in the EU.

Table 5: A classification of the primate order, showing the species that have been used in biomedical research within the EU

Suborder	Infraorder	Species	Common name
Prosiimi	**Lemuriformes**	*Microcebus murinus*	Lesser or grey mouse lemur
Anthropoidea	***Platyrrhini*** **(New World primates)**	*Aotus trivirgatus*	Owl monkey
		Callithrix jacchus	Common marmoset
		Saguinus oedipus	Cotton-top tamarin
		Saguinus fuscicollis	Saddle-back tamarin
		Saimiri sciureus	Common squirrel monkey
		Cebus apella	Tufted or brown capuchin
	Catarrhini **(Old World primates)**		
	Cercopithecoidea **(Old World monkeys)**	*Macaca mulatta*	Rhesus macaque
		Macaca fascicularis	Crab-eating or long-tailed macaque or cynomolgus monkey
		Macaca arctoides	Stump-tailed macaque
		Macaca nemestrina	Pig-tailed macaque
		Chlorocebus aethiops	Vervet or green monkey
		Papio spp.	Savannah baboon
		Papio hamadryas	Hamadryas baboon
	Hominoidea **(Apes)**		
	Lesser Apes	*Hylobatidae*	Gibbons and siamang
	Great Apes	*Pan troglodytes*	Chimpanzee

5.4. Hominoids: Chimpanzees

Of the hominoidea, only the common chimpanzee (*Pan troglodytes*) has been extensively used in biomedical research involving non-human primate species. It has been clearly shown that the chimpanzee, more than other species, possesses mental capacities resembling those of humans (Goodall, 1986) and may even understand the mental states, intentions and emotions of others, as suggested by Premack and Woodruff (1978), Byrne (1997), and Call and Tomasello (1998). The chimpanzee species are also the nearest relatives to humans.

The human and the chimpanzees are both members of the primate superfamily of the *Hominoidea* or the 'Manlike Primates', together with the other Great Apes: the bonobo (pygmy chimpanzee, *Pan paniscus*), the gorilla (*Gorilla gorilla*), the orang-utan (*Pongo* sp.), and the Lesser Apes (*Hylobatidae*): the gibbons and siamang. It has long been accepted in science that there is a close phylogenetic relationship between the Great Apes and the human species. This has been based on the considerable similarities described in comparative morphology and physiology and recently even more convincingly on behaviour and comparative molecular genetic evidence.

The human and the two chimpanzee species (bonobos and chimpanzees) share 98.4% of their genetic substance, DNA. In measures of genetic distance, both chimpanzees and humans are closer to one another (an index of difference of only 1.63%) than each one with the next most closely-related primate species, the gorilla: humans-gorillas 2.37; chimpanzees-gorilla 2.21. Each of these is again more closely related than with the last Great Ape, the orang-utan: humans-orang-utan 3.60; chimpanzees-orang-utan 3.58; gorillas-orang-utan 3.55 (Sibley and Ahlquist, 1987). These data have led to a re-arrangement of the hominoid phylogenetic tree. The African apes and the human species have been placed together in the same family, the *Hominoidae*, and some authors argue that man and chimpanzee should be ordered in the same genus *Homo* (e.g. Goodman *et al*., 1998, 1999). The life-span of the Great Apes is over 50 years (Ross, 1991).

Many of the similarities between chimpanzees, bonobos and humans have long been recognised. Their closeness, especially in physiological and immunological respects, has been an important reason for using the apes in biomedical studies, particularly the chimpanzee. In various countries biomedical companies or primate research institutions have kept colonies for this purpose, sometimes comprising more than a hundred individuals.

In addition to these physical similarities, chimpanzees also resemble humans in their psychology and behaviour. During the last few decades a number of studies have led to discoveries emphasising the striking similarities between the human and the chimpanzee (Wise, 2000). These similarities concern their mental (i.e. emotional and cognitive) capacities, their social sophistication, and their cultural development.

5.4.1. Mental capacities

Chimpanzees and bonobos resemble humans more in their mental capacities than any other species. They possess not only such primary emotions as anger and fear, but also many that have often been regarded as typical for the human species, such as sadness, joy, despair, jealousy, and sympathy (Goodall, 1986). They express these by means of expressive behaviours that are very similar to those of humans, such as their facial displays; for example, they can laugh in similar contexts as humans (van Hooff, 1967, 1989).

Since the 1970s, when the first successful studies were performed in which chimpanzees were taught a language system (Gardner and Gardner, 1971; Premack, 1971; Rumbaugh, 1977; Fouts and Mills, 1997), it has been gradually appreciated that these creatures have elementary symbolic thought. For example, a bonobo who has been living in intimate contact with humans understands some 1,000 words and can use a great many of these in active communication (Savage-Rumbaugh and Lewin, 1994). Similarly chimpanzees can count (Boysen and Berntson, 1989; Boysen and Capaldi 2002; Matsuzawa *et al*., 1991) and they have demonstrated basic cross-modal (i.e. concrete and symbolic) numerical and computational competence (Biro and Matsuzawa, 1999). Unlike monkeys, and many other animals, they are able to recognise themselves in mirror images and video recordings. They show a fascination with their own facial expressions and other features (Gallup, 1970, 1982) and thus they demonstrate an awareness of their own behaviours. This same capacity is undoubtedly at the root of their ability to show true imitation. They may also teach one another (Boesch, 1991), which forms a basis for cultural development.

There is strong evidence that the Great Apes, at least both chimpanzee species, can view a situation from the perceptual perspective of others (Boesch and Boesch-Achermann, 2000; Hare *et al*., 2000, Tomasello *et al*., 1999). However, there is some dispute (Hare *et al*., 2000) as to whether this also means that they can form a mental representation of the mental states of others and thus may know what others know, and also know about the intentions of others, that is they can have a 'theory of mind' (as suggested by Premack and Woodruff, 1978; Byrne, 1997; Heyes, 1998; Call and Tomasello 1998). Such capacities might also enable them to feel forms of empathy, as in behaviours such as social consolation and other forms of altruism (Goodall, 1986; de Waal, 1982, 1996; Nishida, 1994).

These characteristics undoubtedly enable them to develop the complex societies that we see especially in the genus *Pan*. These traits also enable them to negotiate with, to manipulate, and even to deceive others. They display a Machiavellian type of intelligence, involving both loyalty and opportunism, in regulating their social relationships (de Waal, 1982; Nishida, 1983; Byrne and Whiten, 1988). In their politics adult male chimpanzees show tactical negotiation and selective tolerance and permissiveness (e.g. in access to sexual mates) towards coalition partners (de Waal, 1982). Mutual support and the exchange of services and favours take the form of implicit social contracts based on expectations about one another's behaviour and a sense of obligation (de Waal, 1991a,b). These expectations can thus acquire a normative character. Here, it has been said, the roots of morality are encountered (de Waal, 1996).

5.4.2. *Behavioural Flexibility*

In 1963 Jane Goodall reported that chimpanzees in the wild not only use tools, but also manufacture them. Since then, such behaviours have been extensively documented, both in wild chimpanzees, bonobos and orang-utans, and in captive colonies (Beck, 1980; Haanstra *et al*., 1984; McGrew, 1992; Sabater-Pí, 1974; van Schaik *et al*., 1996). The ability to make and use tools is applied in flexible and adaptive ways, especially for the acquisition or modification of foods, but also for weapons and displays of intimidation (Kortlandt, 1980; Goodall, 1986). Instrumental knowledge is shown as well, for instance, when chimpanzees become ill they eat specific herbs or the bitter pith of certain plants. Chemical analyses have shown that these plants contain elements that can kill bacteria (Huffman, 1998). Chimpanzees, bonobos and gorillas also swallow hairy leaves to mechanically evacuate intestinal helminths (Huffman, 2001). Thus, the Great Apes engage in self-medication, making use of experience, which undoubtedly is passed on in the form of cultural habits.

5.4.3. Culture

These examples already emphasise the role of culture in Great Ape societies, a phenomenon which has only just recently come to be fully appreciated (Wrangham *et al*., 1994; Boesch and Tomasello, 1998; de Waal, 1999; Whiten *et al*., 1999). Chimpanzees in different regions of Africa show many behaviours that appear to be specific to these regions and are passed on as acquired traditions (Whiten *et al*., 1999). For example, the technique of nut-cracking using hammer and anvil stones is found only in some parts of West Africa, the use of sticks in digging for termites is known only for the chimpanzees of Central Africa, and fishing for arboreal carpenter ants is limited to two sites in Tanzania. Thus there are many cultural variations in food repertoire and food extraction techniques. In addition chimpanzees also show large local variations in social behaviour patterns, e.g. in courtship gestures, grooming postures, intimidation displays, calling behaviour, parasite removal and water-contact behaviour (Boesch, 1996; Mitani *et al*., 1992; Nakamura *et al*., 2000; Nishida, 1980a, b, 1994; Whiten *et al*., 1999). Such behavioural differences between local populations have also been shown to exist in other Great Apes, especially recently in populations of orang-utans (van Schaik *et al*., 1996).

These advanced characteristics, which they share with humans, have led to a re-appraisal of the ways in which they are dealt with. It has confronted humans with the question whether it is morally acceptable to subject beings at this level of sentience and sapience to the treatments involved in invasive biomedical research (Goodall, 1995; Boyd Group, 2002). Some propose that apes, especially the chimpanzees, should be given a special moral status and in various countries philosophers and law theorists are advocating that this must also have legal implementation (Cavalieri and Singer, 1993; Peterson and Goodall, 1993; Wise 2000). Such proposals are based on the conviction that these beings have advanced conscious personalities (Taylor and Leonard, 1998).

An additional consideration is that during the past few decades their numbers in the wild have dwindled dramatically. Of most ape (sub)species there are only a few tens of thousands left, or – in the case of the chimpanzee – about one hundred thousand individuals (Ape Alliance, 1998). Their habitats are being destroyed by logging, mining and forest conversion and most of the remaining habitats are being partitioned into fragments that are too small to support viable populations. Poaching and the trade in bushmeat are also contributing to bringing the remaining populations to the brink of extinction. The predictions are that the Great Apes will become extinct in the wild in the coming decades unless society takes vigorous action (Marshall *et al*., 2000; Rijksen and Meijaard, 1999). Such action is greatly hindered by the fact that most remaining habitats are in areas of political instability, economic hardship and lacking legal control. A major effort is, therefore, required to boost research of natural populations of Great Apes. Such efforts are also demonstrably effective in protecting natural populations. However, for some species, breeding in captivity has been very successful and such animals may in the future be used to re-populate the wild. The use of non-human primates in science must be carefully assessed with regard to their long-term survival, although animals used in research should be purpose-bred. If Great Apes are kept in captivity they need to be kept in ways that provide for all their needs within the context of the overall scientific objectives (e.g. isolation of animals may be required for certain infectious disease research).

Much fundamental knowledge has also been gained from studies on 'naturally housed' captive colonies, such as the Arnhem Zoo community (de Waal, 1982) or the social colony of Matsuzawa, used for comparative cognition research (Matsuzawa, 1998). It is clear that chimpanzees that are kept in captivity need social representativenes and environmental variation and enrichment (Brent, 2001).

6. GENERAL WELFARE ASSESSMENT.

6.1. Introduction

Working evaluations of welfare are based on measurements of various indicators presumed to be related to the extent of failure to cope, or difficulty in coping, with the environment. Such measures that can be used as indicators of animal welfare have been proposed to include:

i) physical or somatic values such as longevity, growth rate, susceptibility to disease, reproduction and infant care, wound healing, occurrence of gastric ulcers, hair coat and body condition, etc.;

ii) physiological measurements such as heart rate, blood pressure, body temperature, serum levels of various so-called 'stress hormones', such as cortisol and noradrenaline, and immunological functions including rates of lymphocyte proliferation or suppression of their activity, etc.; and

iii) behavioural studies, documenting the behavioural repertoire used by an animal under those specific housing conditions in order to investigate if abnormal behaviours are shown.

Even though a synthesis of all such measures would give the most complete evaluation of welfare, a combination of indicators i) and iii) is used in most laboratories, and assessment of welfare is based on a combination of physiological and ethological methodology.

In order to be able to translate these indicators into welfare, it has to be assumed that some kind of ‘normality’ exists, which can be used as a reference point for good welfare. Deviations from such normality may then be interpreted as poor welfare. In most cases, data collected for each species of primate in the wild is the reference for the standard values of ‘welfare’. Therefore, a good knowledge of the natural biology of primates, with a specific knowledge of each separate species (and taking account of variation between different ages) used in the laboratory, is an essential requirement in order to achieve a high standard of welfare for primates kept in captivity. With knowledge of how different species of primates live in the wild, conditions in captivity can be modified to mimic as closely as possible conditions in the wild. By doing so, the primates kept in captivity can perform a wide repertoire of their species-typical-behaviour, which previous experience has shown to be related to good welfare. The welfare of primates requires consideration in a number of situations: breeding, preparation for scientific use, maintenance in captivity, transport, handling, restraint, capture and use in scientific procedures.

Needs are requirements, which are a consequence of the biology of the animals, to obtain a particular resource or respond to a particular environmental or bodily stimulus. To have a ‘need’ is to have a deficiency that can be remedied by obtaining a specific resource or stimulus (Broom and Johnson, 1993). However, enrichment goes beyond simply meeting an animal’s needs. In establishing guidelines for animal welfare two extremes are possible, poor welfare and good welfare (or as optimal/good as possible) (van Hooff, 1986). The minimum option can be defined as the conditions guaranteeing that an animal is free from avoidable suffering, in the form of pain and distress, and that it can fulfil its necessary vital needs. It is generally recognised that such conditions are necessary to ensure the validity of the scientific research performed (Novak and Petto, 1991). The maximum option is aimed at providing a quality of life that goes beyond these minimum requirements; it might concisely be described as the set of positive conditions which ‘make life worth living’, by providing, for example, satisfaction, joy, and fascination for the animals. These are grand terms, which many still reserve for human experience, however, several behavioural biologists are also using these terms in connection with animals’ experiences.

It is generally acknowledged that good welfare reflects the behavioural and physiological propensities of the particular species under consideration in the wild, and is based upon a thorough understanding of the biology of that species, including physiological functioning. Whilst this provides a reasonable frame of reference, it must be remembered that there are significant knowledge gaps in the understanding of wild populations and scant data on objective measures which can be directly extrapolated to situations in captivity. Furthermore, behavioural and physiological indices are known to be context-specific and while there is relatively little information on short-term baselines for measures, such as metabolic profiles and biochemical/immunological parameters, much less is known about trends in such parameters over months and years. It is unrealistic and unacceptable to await such information being available from wild population studies before taking action to increase the quality of lives of laboratory-based primates. A pragmatic interim measure would be to develop and extend research on such species in semi-natural environments, including zoological collections and safari parks although, clearly, there are limitations on the nature and level of invasiveness of such studies. Significant advances have already been made (Chamove *et al*., 1982) by means of such an approach and there are a number of examples of synergies between zoological and laboratory investigations (Markowitz and Spinelli, 1986; Chamove and Anderson, 1989).

Health status is also one of the measures that has implications for assessing welfare. It encompasses such aspects as growth profiles and maintenance of body mass, a range of biochemical markers, freedom from disease and breeding success. Standard ranges of some biochemical indices for macaques and common marmosets are well-established and accepted as baseline values in regulatory toxicological studies (Taylor Bennett *et al*., 1995; Woolley, 1994; McAnulty, 1997). However, little information is cited on the dietary, housing and husbandry conditions under which these standards have been determined and which would undoubtedly influence baseline values. Furthermore, despite the importance of colony management and outcomes, relatively few data have been published on such issues (Box and Hubrecht, 1987).

Even though the life of primates in the wild is used as the reference for normality, this method is also associated with some problems leading to poor welfare. For example infanticide and vigorous fighting among males for access to females are naturally occurring activities, and hunger, thirst and disease will of course occur naturally. Furthermore, exposure to and attacks from predators is a natural phenomenon. When primates are kept in captivity, such natural circumstances associated with poorer welfare can be avoided and prevented. The exact point at which behaviours and physiological reactions in the wild are included and accepted when dealing with welfare of primates in captivity is still an ongoing discussion.

6.2. Behavioural indices

Abnormal behaviours are generally regarded as indicative of poor welfare and of an inadequate environment. They can be of two types, either quantitative abnormalities or qualitative abnormalities (Poole, 1988). A quantitative behavioural abnormality occurs when a behaviour normally performed by a species is carried out at an abnormal frequency in a single individual. Reference values for the normal occurrence of that behaviour would be deduced from that found in wild populations. An example of this is that when a primate in captivity is only given monkey pellets it will eat all its necessary nutrients in a few minutes, whereas in the wild, foraging can occupy from 7 to 65% of a primate's awake time (Milton, 1980; Herbers, 1981; Strier, 1987; Malik and Southwick, 1988; Marriott, 1988; O' Neill *et al*., 1989). A captive monkey will rest for most of its awake time compared with less than 30% of their time in the wild (Maple and Finlay, 1987a).

On the other hand, qualitative behavioural abnormalities are said to occur when monkeys in captivity are performing behaviours that are not found in wild populations. One of the most characteristic behaviours of this type is a stereotypy, which is a behavioural act that, even if its background can often be found in the animal's normal repertoire, is performed in a repetitive fashion and out of its original context and seems to serve no useful purpose. An example is the repetitive pacing in macaques and cage-circling in marmosets. However, the behaviour may not always be abnormal, it may be normal behaviour merely physically constrained by the physical space of the environment. If primate infants are separated early from their mothers they may show hyperaggression and an inability to take care of their own infants as adults. These are also other examples of qualitative behavioural abnormalities (Poole, 1988). An important aspect of abnormal behaviours is that actual deviations of behaviour can reflect both past and present environments. As mentioned above, it is well-known that restricted social environment during development, and early infant separation from the mother, will cause behavioural abnormalities (Ruppenthal *et al*., 1976; Mineka and Suomi, 1978; Reite *et al*., 1981). Animals that are suffering in some way will be physiologically and behaviourally responding to a 'hostile' environment, and this is likely to be an additional and unwanted variable in any research protocol. It may be possible to promote good welfare in primates by enriching their environment.

Time budgets are frequently used to compare and relate captive populations to those in the wild (Chamove and Anderson, 1989). It is relatively easy to quantify objective measures of activity such as social interaction, feeding and drinking, sleep/wake cycles, and patterns of cage use, using automated, semi-automated and manual techniques of varying degrees of sophistication.

Such observational approaches enable alternative provisions such as altered lighting levels, cage design and strategies for environmental enrichment to be evaluated. It is essential in such circumstances to monitor meaningful indices objectively over long periods of time in order to identify good welfare practices. Of course, good experimental design is always essential to evaluate the benefits or otherwise of environmental manipulations such as cage design or provision of enrichment. A scientific demonstration of the benefits to the animals and to the science, or at least so that neither are compromised by the environmental manipulation, is necessary before alternative practices are accepted in many areas of primate use, especially in regulatory toxicology. Manipulation of environmental complexity to promote good welfare in primates has been reviewed extensively by the US Department of Agriculture (USDA, 1999).

There are numerous examples of providing various species of primates with enclosure furnishings and objects (often referred to as 'playthings') which can be manipulated by the animals. However, it is not always easy to predict the preferences of particular species or indeed of individual animals. It has been reported that squirrel monkeys (Williams *et al*., 1988) and rhesus macaques (Kopecky and Reinhardt, 1991) spend more time on rigid perches than on non-fixed structures such as ropes or swings although such observations should not be used as evidence to limit provision of less predictable furnishings. Novelty is an important element in terms of the use and manipulation of furnishings (Taylor *et al*., 1997; Cardinal and Kent, 1998) and some element of alternation of facilities is generally recommended (NRC/ILAR, 1998).

Unfortunately, many studies to examine the impact of environmental manipulation are relatively short-term and so can offer little unequivocal advice on the long-term welfare implications of their use. Nonetheless, there is clear evidence of altered time budgets and decreases in abnormal behaviour following provision of foraging opportunities and objects to manipulate, and this may be of particular importance for animals who are socially restricted (Boinski *et al.,* 1994; Eaton *et al.,* 1993; Kessel and Brent, 1998). Care must be taken to ensure that devices and cage furniture, if not being used, do not have an adverse effect in terms of minimising the useable cage or enclosure space. This emphasises the importance of rigorous observation.

There are relatively few published studies that describe patterns of cage use. For example, Ely *et al.* (1998) and Scott (1991) showed the benefits of simple modifications such as rigid cage extensions for marmosets, and showed that these animals exhibit significantly different patterns of spontaneous activity when housed in upper compared with lower cages.

Information on feeding and drinking patterns, considered alongside health records, can be invaluable in informing discussions on diet and welfare. There are significant opportunities for altering presentation of food, to provide more species-appropriate feeding systems, for example presenting marmosets with an artificial gum tree (McGrew *et al*., 1986) and providing foraging opportunities (Chamove *et al*., 1982). A balance is required between the provision of a complete nutritional diet and foodstuffs that enable animals to express choice and yet encourage them to spend a greater proportion of their time engaged in food-related activities. In the wild, primates may spend widely varying amounts of the hours during which they are awake searching for and eating food (Clutton-Brock and Harvey, 1978) and the pattern of foraging and feeding varies between species and with time of day.

Although a relatively unsophisticated index of welfare, the avoidance of behavioural abnormalities, such as stereotypies, self-mutilation or coprophagy (Erwin and Deni, 1979) is also an important objective in the captive management of primates. Therefore the avoidance of some specific stereotypies such as stereotypical self-biting can be an indicator of improved welfare. Bayne (1989) remarked that "stereotypic behaviour is considered undesirable in any primate management program, but that does not mean that the absence of stereotypies is *prima facie* evidence of mental or psychological health".

It has long been known that small cages increase the incidence of stereotypies, as well as other types of abnormal behaviour not involving locomotion (Draper and Bernstein, 1963; Paulk *et al*., 1977). Providing environments of greater size and complexity can alleviate these abnormal behaviours. For example, squirrel monkeys, which displayed the species-typical stereotypies described by Hopf *et al.* (1974), showed almost no stereotypies in a larger, more complex enclosure (Salzen, 1989).

Equipment and technical approaches for remote non-invasive or minimally invasive monitoring, which have been designed to refine research involving primates, offer the potential to investigate the impact of scientific procedures and housing and husbandry practices. For example, the use of implanted radio-telemetry devices enabled Line *et al.* (1989) to show that changes in cardiovascular parameters that persisted for many hours were observed following routine husbandry procedures such as cage cleaning, and veterinary checks such as tuberculosis testing. Such transient changes in physiological and electrophysiological measures, which result from human intervention, scientific procedures and even interactions with conspecifics, were not unexpected. Moreover, the biological significance of changes demonstrated also needs to be interpreted. Whilst they might have implications for the interpretation of scientific outcomes, for example certain pharmacological studies, the approach offers potential to provide an improved understanding of the impact of different housing and husbandry practices, and if considered alongside other indices it could aid in the identification of good practices and ensuring good welfare.

Implantable radio-telemetry devices have also been used to facilitate measurement of sleep patterns in common marmosets and in rhesus macaques (Crofts *et al.*, 1999, 2001). These studies have demonstrated that sleep architecture in primate species and humans are similar and that they are disrupted by drugs in similar ways. In man, sleep is recognised as an extremely valuable indicator of welfare, and characteristic patterns of sleep disruption are observed in conditions such as depression. Thus, sleep monitoring in primates offers another potential avenue for assessing the psychological impact of scientific procedures, housing and husbandry practices. Of course there are physiological burdens associated with the surgical implantation of radio-telemetry devices and this severely constrains their usefulness for routine use. Non-invasive monitoring of 24 hr activity profiles represents an alternative opportunity to investigate a key chronobiological indicator that reflects an animal's responses to the laboratory environment. Work in progress on small non-invasive data loggers (Mann *et al.*, 2001) offers an alternative approach to the collection of 24 hr activity profiles and some information on sleep profiles can be inferred from these data. This approach obviates the need for surgery and time-intensive retrospective video analysis and shows that it is possible to collect such data on behaviour over many days from unrestrained animals. The use of radio-telemetry in marmosets (Schnell and Wood, 1993) has re-written the accepted measures of resting cardiovascular parameters and also demonstrated (Schnell, 1997; Schnell and Gerber, 1997) the impact of modified housing and husbandry practices. Overall, there is a growing body of evidence relating changes in biological parameters to the prevailing environmental conditions. The challenge, as ever in such research, is to determine the biological significance of any changes observed. Nevertheless, this approach is starting to determine how the animal perceives and responds to its environment and is important for both animal welfare and interpretation of scientific data.

Work is in progress (Crofts *et al.*, 2001) on a multi-faceted study, including assessment of sleep patterns, performance of a complex cognitive task, muscle function, immunological responsiveness and a range of neuroendocrine and biochemical indices in a group of marmosets over 18 –24 months. This could provide a potentially valuable context for assigning functional significance to changes observed in these measures. This study may also form a basis with which to compare alternative practices in this species and inform discussion on the identification of good practices for the housing and maintenance of marmosets under laboratory conditions. The opportunities to minimise the impact of scientific procedures provided by training non-human primates to co-operate with researchers and technicians should not be underestimated. For example, the work of Jaekel (1989) considers training macaques to co-operate in applied psychopharmacological research in an industrial setting (Bloomsmith *et al.*, 1998; Goodwin, 1997; Kessel-Davenport and Gutierrez, 1994; Klaiber-Schuh and Welker, 1997; Mendoza, 1999; Reinhardt, 1990a; Taff and Dolhinow, 1989; White *et al.*, 2000). Traditionally, pharmacological studies have necessitated housing animals in specially designed individual cages to facilitate urine collection. In the case of marmosets, it is possible to train animals to co-operate with urine collection that obviates the need for prolonged single housing (Anzenberger and Gossweiler, 1993). This technique also overcomes the problems of providing information on neuroendocrine indices without the additional stress of blood sampling.

To obtain a complete picture of the impact of husbandry on primates maintained for experimental purposes, there must be a fuller understanding of the interplay between physiological, psychological, immunological and behavioural factors. Whilst it is possible to extract relevant information on control groups in studies designed for other purposes, tangible benefits would accrue from a more focused and targeted research approach. It is inevitable that a cross-disciplinary approach will be needed to agree on the key questions and research priorities and then to conduct, interpret and disseminate the outcome.

Some progress has been made and further efforts are underway for marmoset and tamarin species, under the auspices of the European Marmoset Research Group (website: http://www.dpz.gwdg.de/emrg/emrgcons.htm) and such an initiative could also be instigated for other groups of primates such as macaques.

6.3. What are the requirements of the animals concerned?

It has long been acknowledged that relying upon breeding success in a colony is an imperfect measure of good welfare, as is freedom from overt illness and disease in laboratory housing. A more generally accepted concept is that of animals being able to exhibit as many aspects of their natural, non-injurious behavioural repertoire as possible. In the laboratory situation this freedom to express natural behaviours can be in conflict with the scientifically and economically determined constraints of the management situation. Despite this it is important to guarantee that the most essential welfare aspects are satisfied. This necessitates a thorough understanding of the biology and natural history of the species under discussion as well as careful routine monitoring of behavioural attributes under laboratory conditions. For most primates, the ability to engage in social interactions is of the utmost importance and should be the accepted norm. It is preferable to avoid prolonged single housing, but when it is deemed to be necessary justification is needed on a case-by-case basis. This could be one of the issues to be considered during the ethical review of the research before permission to proceed is granted.

Overall, there is a considerable deficit of objective information on the optimal conditions for maintenance of primates. This is particularly true for long-term assessments of comparative housing and husbandry practices, for example, how to monitor, and then minimise the impact of husbandry, laboratory maintenance and scientific intervention on the welfare of primates. The enclosure size should allow for sufficient environmental complexity and expression of species-typical behaviours, and a minimum enclosure size exists (Annex II of Council Directive 86/609/EEC). However, socialisation, enclosure structure and complexity and the provision of species-appropriate environmental enrichment are probably more important than the available space (Bayne *et al*., 1992a), provided that minimum space allowances are respected.

7. HOUSING AND CURRENT PRACTICE FOR HUSBANDRY AND CARE OF PRIMATES

The majority of primates used in research are housed in pens or cages, either in groups or occasionally singly, for all of their lives. Consequently, it is important that their husbandry conditions meet their biological and behavioural needs, and provide for good welfare, given any scientific, safety and practical constraints, e.g. unless a specific scientific constraint, approved for example by an ethical review process, precludes this.

The current European legislation (Directive 86/609/EEC) and the Council of Europe Convention (1986) define standards for the maintenance and care of non-human primates used for experimental purposes within Europe. Moreover, national legal bodies and organisations from different countries have issued guidelines and recommendations that have also resulted in improved husbandry conditions for non-human primates (Home Office, 1989, 1995; O' Donoghue, 1994). In 1997, the Multilateral Consultation of the Council of Europe (Council of Europe, 1997) adopted the "Resolution on the accommodation and care of laboratory animals" which gives further emphasis to aspects of laboratory animal welfare such as social interaction, activity-related use of space and appropriate stimuli and materials. With special reference to primates the Resolution indicates, as issues of particular importance, the volume of cages, the environmental enrichment, and the social grouping of compatible animals, taking into account the species diversity in social structure. In addition, the Resolution specifies that single caging should be avoided unless a specific scientific justification is provided.

Under the enforcement of the legal requirements and recommendations, the professional standards of the management and care of non-human primates have evolved considerably since 1990, leading to an improvement in captive primate welfare and refinements in their use (Hubrecht, 1995, 1997). From the available data, it appears that the quality of the animals' environment in terms of noise, temperature, light and relative humidity etc. are within their comfort zones.

7.1. Facilities

Various housing systems are used for non-human primates, from indoor cages to outdoor enclosures. European institutions, maintaining and using non-human primates for scientific purposes, show a great diversity in housing systems and husbandry procedures. The dimensions and design of primary enclosures are extremely variable, differing greatly between and within facilities. They vary mainly depending on national legal requirements and on the purposes for which the non-human primates are being kept - whether for breeding, stock or use, as well as on the nature and length of the experiments performed. Within Europe, a relatively small number of facilities are devoted to the breeding, maintenance and use of non-human primates. Although official data on current husbandry practices in European countries are extremely scarce (Bürge *et al*., 1997; Hubrecht, 1995, 1997), the housing systems most frequently utilised can be summarised as follows.

- Individual housing in a single cage

- Pair and connected cages for two primates or a small group of animals

- Pens for group housing

- Indoor-outdoor enclosures

- Semi-free ranging corrals with an indoor enclosure

The choice of indoor, indoor-outdoor or outdoor facilities will take into account the species of primate, local climatic conditions, pest control, frequency of animal handling and observation, and security considerations (Taylor Bennett *et al*., 1995). If time budgets are used as a measure of welfare, it must be ensured that the primates are presented with as many choices and options as possible within the constraints of the laboratory housing. The growing awareness of the importance of social access, complex housing systems, variety in diet and methods of presentation, and the potential of training animals to co-operate with procedures, has encouraged modifications of housing systems with positive implications for animal welfare and scientific quality. It should also be noted that primates have the capacity to adapt to various environments and it is not necessary to strictly mimic the natural environment. Artificial environmental elements may stimulate the perceptiveness and cognitive potentials of the animals and elicit new adaptive behaviours, while still safeguarding good welfare (Röder and Timmermans, 2002).

Individual housing:

This housing system has been the most commonly used and is still frequently used, particularly for Old World primates, when experimental procedures are performed (Hubrecht, 1995). The dimensions of cages are required to conform to Directive 86/609/EEC but some may comply with national guidelines recommending larger space allowances (Home Office, 1989, 1995). In general, the minimal dimensions of the cages recommended by the current European legislation for one or two primates prevent the expression of a wide behavioural repertoire. It is acknowledged that the single cage, normally constructed of metal with a mesh floor, has some advantages;

- it can be easily and effectively cleaned and sanitised,
- it reduces the risks of transmission of infectious and parasitic diseases between animals,

- it minimises wounding due to aggression and fighting between incompatible subjects and
- in females, the oestrous cycle is easily detected thus enabling timed-matings to be performed.

However, individual housing limits to a great extent the normal activity and behavioural patterns of animals, and it also appears to alter some physiological measures (ILAR, 1998). In situations of prolonged social deprivation (e.g. single caging) and an impoverished physical environment, some animals exhibit abnormal behaviours and atypical activity patterns (Bryant *et al*., 1988; Bayne *et al*., 1995; Bayne and McCully, 1989) (see "The social environment" in Chapter 9). Rearing infants in isolation also has dramatic consequences on their psychological development and renders them unable to display normal social interactions with conspecifics (see "Separation of infants" in Chapter 9, also Bayne *et al*., 2002). Placing cages in double-tiers impairs the natural vertical flight reactions of primates and also contributes to poor illumination of cages (Röder and Timmermans, 2002).

Some facilities have successfully adapted the system whereby single cages are attached to a common exercise-play area where the animals can be grouped when there is no need for confinement or separation. However it must be recognised that a standard, isolated, sparsely equipped laboratory cage, regardless of dimensions, when occupied by a singly housed animal, with a complete diet available *ad libitum* still presents that animal with limited options for interaction. It may meet the animal's physical and physiological needs, but presents no opportunity for social interaction and satisfying various behavioural needs and leads to poor welfare.

Pair housing and connected cages:

Permanently housing non-human primates in compatible pairs or allowing them to spend part of the day in physical contact, by joining adjacent cages, will provide the animals with some social companionship. In most institutions, marmosets are kept in unrelated male-female pairs with one or two sets of offspring (Price and Samson, 1997). For these species, this is close to the natural social situation. These husbandry practices enable the performance of many species-typical behaviours and offer some variation, challenge and control of the environment (see "The social environment" in Chapter 9). Also in other species the formation of a pair of adult animals is often more practicable than the constitution of a group of three individuals where a coalition formed against the subordinate individual might have severe welfare consequences in terms of aggression and fighting. Criteria for compatibility include food-sharing, lack of serious injuries and an absence of signs of depression (Reinhardt *et al*., 1987b, 1989; Reinhardt, 1991, 1994a, b). The connected cage system allows for the temporary separation of animals when dosing, sample collection or experimental procedures are performed.

Pens for group housing:

Pens can be large cages, rooms or corrals enclosed by fences, walls, bars or meshed wire and are generally used for housing groups of animals for stock and breeding. These enclosures are frequently structured, for example with at least a perch or shelf, and are large enough to allow the inclusion of a variety of environmental enrichment devices.

Non-human primates housed in social groups display a wide range of behavioural and activity patterns. Their reproductive capability is enhanced, and parental care ensures a normal psychological development of infants. Once the stability of a social group is established, the incidence of aggression and injuries is generally low (see "Risks of social housing" in Chapter 9). However, changes in hierarchies and relationships can always occur resulting in fights and physical attacks. Group housing increases the risk of disease transmission in colonies where new individuals are continually being introduced. Depending on the system of provisioning used to supply food, the access of food resources to subordinate or marginalised animals can be limited. In addition, access to individual animals may require special capture procedures, or animals being trained to cooperate, when sampling or health monitoring is needed. However, if animals are trained to cooperate during capture, handling of individuals may not be more difficult (Bloomsmith *et al.*, 1998; Goodwin, 1997; Kessel-Davenport and Gutierrez, 1994; Klaiber-Schuh and Welker, 1997; Mendoza, 1999; Reinhardt, 1990 a; Taff and Dolhinow, 1989; White *et al.*, 2000).

Indoor-outdoor enclosures:

An outside area is connected to an indoor heated space, where animals can find protection from inclement weather and hide from threats and attacks. Outdoor enclosures are usually made of metal or solid walls, but other weather-proof materials can be used. The system is mainly utilised for social groups of non-human primates intended for breeding and stock that do not require frequent access or intervention. Various European facilities utilise this kind of enclosure for housing breeding groups of Old World monkeys.

It should be noted that the variety and stimuli perceived from the external environment (e.g. varying weather conditions including temperature changes, contact with trees, grass, insects etc.) may themselves form elements of enrichment for the animals. In addition, the costs of installation and maintenance are low. However, the direct contact with the outside environment increases the risk of disease transmission from vectors (insects, wild rodents and birds, etc.) and consequently appropriate disease-prevention measures need to be taken.

Semi free-ranging corrals with an indoor enclosure:

A large natural area with inside quarters can be used for social groups of animals. In this housing system there are limited possibilities of access to individual primates or human intervention. It is the ideal environment for ethological observations of captive non-human primates in that their behavioural repertoire is more likely to be closer to that observed in the wild. Facilities maintaining primates for biomedical research in Europe do not generally include this type of enclosure as it requires large areas and does not guarantee controlled and standardised conditions with regard to the genealogy, health and care of the animals. However, some institutions do maintain primates for research in a semi-free environment.

7.2. Environmental complexity

Besides social enrichment, which is considered the most important contributor to good welfare in non-human primates, the physical enrichment of the environment stimulates self-initiated activities, cognitive capabilities and allows the animals to display a wide behavioural repertoire (see "The physical environment" in Chapter 9).

Physical enrichment encompasses a variety of techniques that vary according to each species. Although there are very few reports on the procedures employed in Europe to enrich the environment of primate enclosures (Hubrecht, 1995, 1997), the general tendency is towards supplying cages with perches, shelves and swings. The provision of these devices is considered to improve the animals' comfort since they are enabled to assume natural postures and locomotory patterns, such as climbing and jumping (especially young animals), perching and resting at a certain distance from the cage floor. In manipulative species, objects and playthings are beneficial to promote tactile, visual and oral exploration, provided that they do not pose health risks to the animals (see "The physical environment" in Chapter 9). When primary enclosures of non-human primates are equipped with one or more elevated resting surfaces, the height of the enclosure is then determined by such resting surfaces. They must be installed in such a way that an individual can sit on them comfortably without touching the ceiling and move under them comfortably without touching them, and for long-tailed species sit on them without the tail touching the floor. There is unequivocal evidence that all species make substantial use of fixed elevated resting places (Reinhardt *et al*., 1996; Reinhardt and Reinhardt, 1999), although such evidence may not be available for swings installed in standard cages.

Devices and methods to stimulate foraging activities are commonly used and include spreading food in a wood chip substrate, offering puzzle-feeders and foraging boards, placing the food in different locations in the enclosures, and providing a variety of different and novel foods. In non-human primate facilities there are different approaches to the type of environmental enrichment and how it is implemented. In some establishments elements that mimic the natural environment of the species are provided, while others have adopted materials and devices that do not necessarily resemble those present in the wild. Further study is needed on which system might be the most beneficial to animals in terms of ensuring good welfare.

7.3. Personnel involved in animal care and use

The relationship that develops between the care-giver and the animal has scientific as well as welfare implications (Davis and Balfour, 1992), and this relationship could be made into a more positive experience, for both animal and human, given due consideration. For example, the provision of a reward after an injection or other scientific procedure can result in a positive reponse to a potentially aversive stimulus (Bloomsmith *et al.,* 1998; Goodwin, 1997; Kessel-Davenport and Gutierrez, 1994; Klaiber-Schuh and Welker, 1997; Mendoza, 1999; Reinhardt, 1990a; Taff and Dolhinow, 1989; White *et al.,* 2000). This positive reward scheme also gives a positive reinforcement to human-animal interactions. Allowing staff adequate time to interact with the primates, especially when the animals are young, can help to assure the subsequent welfare of the experimental animal. However, it must be noted that handling by humans is likely to be stressful to non-human primates and appropriate measures need to taken to avoid negatively affecting their welfare.

Appropriate knowledge of the natural behaviour and biology of the species for which they are in charge is essential for personnel involved, at every level, in non-human primate care and their use in scientific procedures. Indeed it is a requirement under the EU Directive 86/609/EEC Article 16 for a competent person to care for the animals. An adequate training and education programme for all those involved, imparts information on the species-typical characteristics, and provides practical skills in husbandry techniques and experimental procedures to be performed, as well as occupational health issues such as bites, scratches and zoonotic diseases. A knowledge of normal conditions is crucial to recognise signs of illness, distress or abnormal behaviours and assists in identifying their origin in order to minimise the adverse effects on welfare. Institutions are responsible for adequate training and qualification of personnel involved in the care and use of non-human primates, as well as for providing information on health and safety for the staff. The education, training and competence of the technical staff, who look after the animals and who carry out the scientific procedures, is an important factor in securing good animal welfare and good science. In addition, poorly trained staff may run an increased risk of being injured when in contact with primates, and possible consequent exposure to zoonotic diseases. Specific training programmes for primate husbandry are needed as these animals are not domesticated, and differ greatly from other commonly-used laboratory animals, such as rodents and dogs.

Competence in a scientific technique is essential to carry out good science and protect animal welfare. FELASA (2000) have initiated a syllabus for a training programme, but the issue of assessing the competence of individuals carrying out a scientific procedure on an animal needs to be addressed.

Caretakers:

Personnel involved in the daily care of non-human primates are generally assigned to tasks summarised as follows (FELASA, 1995):

- Cleaning and sanitation of cages, rooms, enclosures, including furniture, equipment, environmental enrichment devices etc.,

- Removal and disposal of waste and dirty materials,

- Feeding the animals, i.e. providing them with the necessary nutrients and supplements,

- Monitoring and maintaining records of the environmental parameters and control of the optimal conditions, and checking functioning of the equipment (e.g. automatic watering device, air conditioning etc.),

- Observations of the animals and attention to any deviation from normal to be reported to the supervisor and veterinarian. The caretakers are in daily contact with the animals and are often the first to identify any sign of disease, injury, abnormal activity and behaviour, and improper intake of water and food,

- Handling and restraint of animals for examination, treatment and experimental procedures,

- Assistance in experimental procedures, necropsy, sample collection etc.,

- Provision and evaluation of furniture and devices as environmental enrichment.

In addition, the following elements could be considered: training of non-human primates to collaborate in health monitoring and experimental procedures, and interacting with the animals to promote a good working relationship and gain the confidence of the animals. Training primates to 'work' in a research project, habituating them to procedures and environments (e.g. the laboratory) rather than simply taking them out of their home environment and then carrying out a scientific procedure is likely to be better for both the animals' welfare and the science (Damon *et al*., 1986; Reinhardt, 1997).

The training of animals to a procedure so that it can anticipate to some degree what is going to happen has been shown to minimise the distress that may be caused in an experiment (Wiepkema and Koolhaas, 1993) and animal behaviourists have been influential in advancing this idea to the benefit of both science and the animals' welfare.

Technicians performing experimental procedures:

Besides acquiring an adequate competence and skill in the tasks mentioned above, personnel carrying out experimental procedures perform techniques associated with the experiment, such as the administration of substances, removal of body fluids, data collection, keeping records of responses to the procedures, peri-operative care, anaesthesia, analgesia, euthanasia, necropsy, etc. They are also responsible for taking appropriate measures to minimise factors interfering with the experiment and for taking action when adverse effects occur to the animal during or following the procedure. It is crucial that they are capable of recognising signs of pain and distress and assessing the welfare of the animals (Morton and Griffiths, 1985; FELASA, 2000) with appropriate reporting of any unexpected consequences.

Scientists:

The project leader and the researchers are responsible for designing and planning the experiments and for supervising the procedures performed. Although experimentation on non-human primates frequently entails various degrees of unavoidable pain or distress to the animal, investigators are required to anticipate, minimise, alleviate, and avoid conditions that threaten the welfare of the animals. They should also be aware of animals' behavioural responses to humans in order not to distress any animal (e.g. response by a primate to a direct stare from humans). In undertaking research, scientists are also obliged to consider the availability and applicability of alternative methods to the use of living animals.

Even though a formal animal care and use or ethical review evaluation procedure may not be in place within an institution, project leaders must provide an assurance that the experimental subjects will not be subjected to avoidable suffering (i.e. suffering which can be avoided through employing good practices), while still attaining the scientific objective.

Veterinarians:

Under the EU Directive and the European Convention a veterinarian or other competent person is charged with advisory duties in relation to the welfare of the animals. This means that only those veterinarians, with adequate training and experience in non-human primate medicine, should be responsible for the veterinary care of the animals. A comprehensive and careful programme of veterinary care includes policies and procedures regarding aspects of husbandry, nutrition, handling, enrichment, animal welfare, training of the animals, quarantine, hazard containment, occupational health, and safety (ILAR, 1998). Veterinarians define and develop a health monitoring programme in order to provide health and fitness tests for individual animals, and in order to maintain the good health of the colony by preventing spread of disease. The programme will also include protecting humans from possible injury or exposure to a zoonotic disease. Guidelines have been recently published on the health monitoring protocol of non-human primate colonies (FELASA, 1999). The veterinarian is also responsible for the welfare of the animals and for implementing procedures aimed at improving their welfare under the husbandry conditions in place, and minimising any pain and distress during the life of the animal from birth until death.

Ethologists

Ethology is the branch of biology in which behaviour and behavioural mechanisms are studied in a scientific framework using both descriptive and quantitative methods. Ethologists, i.e. persons formally educated in ethology and trained and experienced in the behaviour of non-human primates, can assist in defining procedures related to social dynamics, such as: social compatibility, group formation, separation and reintroduction of animals. In addition, ethologists can document and evaluate the psychological welfare of the animals and be responsible for the oversight of basic environmental enrichment. Furthermore, they can give advice on the implementation of an environmental enrichment plan. They may identify behaviours and activities that deviate from the species normal patterns, determine their cause and offer recommendations on the methods to correct them. Veterinarians and ethologists can work in tandem to ensure that animal welfare is safeguarded, as some diseases may lead to abnormal behaviours and vice versa.

7.4. Experimental facilities and procedures

Various housing systems are utilised depending on a facility's policy and on the type and duration of the experiments. A system still very commonly used is single housing that allows close observation and easy access to individual animals. The current European legislation (Directive 86/609/EEC) indicates minimal cage dimensions based on the weight of the primates, and does not take into account the species-specific behavioural needs, the arboreal nature of these animals, or their age (young animals need conspecifics to develop normal social behaviours and space to carry out play activities).

Single cages vary in design and dimensions depending on species, age, and the type of research programmes. They normally have moveable backs so that the animals can be safely restrained for anaesthesia, treatment, or experimental procedures (Taylor Bennett *et al*., 1995). Individual caging is also the most commonly used system to quarantine newly acquired non-human primates. Cages vary from minimal inclusion of accessories, such as perches, to the addition of environmental enrichment devices (playthings, swings, ropes, puzzle feeders, etc.). Individual caging is frequently selected for infectious disease research, experiments that involve surgery, pharmacological and toxicological studies, and vaccine production and control. In recent years, housing systems used in these research areas have been evolving from single to group housing, with larger and enriched cages and limiting individual caging exclusively to the time of the experiment. This allows animals to have access to a larger enclosure and to compatible conspecifics when single housing is not strictly necessary (Fuchs, 1997; Woolley, 1997).

The use of implantable telemetry devices has enabled the collection of physiological data in unrestrained animals housed in a social context (see "Behavioural indices" in Chapter 6.2). Since social interactions are considered to be one of the most important factors promoting the welfare of non-human primates, it is reasonable to consider that the adverse effects of social deprivation might profoundly influence experimental results. In some establishments, the training of primates to collaborate in minor interventions during experimental procedures has been successfully introduced to reduce the stress on the animals of handling and the risks of aggression to personnel. Training sessions, where positive rewards are offered to the animals, can contribute to creating trustful relationships between the animals and their caregivers (Reinhardt *et al*., 1991; Reinhardt and Cowley, 1992).

Connected cages or modular systems (two or more adjacent cages that can be connected when individual housing is not required) are also utilised either for stock or experimental animals, in that they enable the animals to be isolated only for the period necessary to perform the scientific procedure or for sample collection.

Group housing is generally utilised when animals are maintained for breeding and as stock, i.e. before, after or between experiments. In these cases, the animals may be housed in indoor-outdoor enclosures when the species involved can often easily acclimate to the local climatic conditions.

7.5. Welfare implications for primates in captivity

Even though some primates travel and search for food on the ground, most are arboreal and all primates seek shelter by climbing into trees where possible and, for example, when being chased by a predator. For primates in captivity, it is therefore not only the physical space of the cage that is important but also that the cage is furnished so that animals can make use of the space as advantageously as possible. As primates climb for security when chased, it is important that they can seek shelter in captivity by reaching a high position in their cage, preferably higher than the eye-level of their keepers.

Primates remain wild animals and, unlike the commonly used mammals, they have not adapted or been genetically selected for domestication, and on reaching adulthood they normally struggle for dominance. The interaction with primates in research should be based on positive training, which is possible because of their high intelligence. They can then habituate to their keepers so that interactions that occur during the research, such as handling and experimental procedures, can be as stress-free as possible. It should be emphasised, however, that tamed individuals may become dangerous for human beings. Such animals have lost any inhibition in their physical contacts with humans and they can severely bite their human handlers (and humans they come into contact with). It is worth habituating primates as early as possible to the presence and behaviour of human beings, but with care. The animals should be socialised with their conspecifics, so they learn from them which social behaviours are rewarded or punished

8. BREEDING AND SUPPLY

8.1. History of supply

Historically the supply of non-human primates worldwide for research and testing purposes took place in three phases. The first phase began in the 1950s when the search for a polio vaccine required the use of large numbers of non-human primates as experimental animals. This need was met by the importation of wild-caught (feral) stock, particularly rhesus macaques (Welshman, 1999).

The second phase started in the 1970s when many countries, notably India, introduced a ban on the export of monkeys. The reaction to this was two-fold. In many cases the research community shifted to the use of long-tailed macaques, which were still readily available from countries such as The Philippines and Indonesia. Secondly, some end-user countries, especially the USA, established their own breeding colonies (Welshman, 1999).

The third phase began in the late 1970s when it became clear that in order to conserve the feral monkey population and still ensure a continuing supply of simians for biomedical research, large-scale programmes of primate breeding needed to be initiated (Hobbs, 1972; Neurauther and Goodwin, 1972; Schmidt, 1972). This was accentuated during the 1980s by an awareness of conservation issues, and reinforced by the rapid disappearance of the natural habitats of monkeys in South-East Asia. In anticipation that countries still supplying wild-caught animals would prohibit the export of feral animals, breeding centres were established to supply captive-bred monkeys (Welshman, 1999).

8.2. Self-sustaining colonies

In order to obtain self-sustaining captive colonies, it is necessary to produce successful breeders at adulthood. To this end, individuals must grow in social conditions that mirror natural conditions. Mirroring, however, does not mean merely copying. The social environment should be adapted to the constraints of captivity. By maintaining groups of non-human primates in captive conditions, their demographic structures are artificially fixed and they are required to remain in close proximity to each other. In the wild, individuals establish dominance relationships to make their behaviours mutually predictable and to resolve conflicts. In a restricted space, however, dominance relationships can induce a social tension from which individuals cannot escape as they would in their natural environment in the wild. This may elicit stress, aggression, and impair reproduction. It follows that captive-born animals cope better with husbandry conditions than wild-caught animals (Ha *et al*., 2000). Special attention must, therefore, be given to the social needs of individuals, which will differ according to the relationships and the breeding systems used for each species.

Lesser mouse lemurs:

The species most sensitive to crowding are those who normally live solitary lives. When lesser mouse lemurs are maintained under high density, they may die from the stress caused by crowding (Perret, 1982). It has been found that dominant males suppress the sexual activity of subordinate males. Not only is the sexual behaviour of the latter inhibited, but dominant males also employ a urinary pheromone to inhibit the rise of blood testosterone levels in subordinates during the breeding season (Perret, 1992). Outside the reproductive period, lesser mouse lemurs may be kept in mixed groups that should not exceed a dozen individuals. Animals can sleep together in a small number of nest boxes but it is better to provide them with one nest box each, as individuals can then choose a partner. To improve breeding performance, a female in oestrus should be placed with several males in order to ensure a mating.

Owl monkeys:

Owl monkeys have to be maintained in male-female pairs. Adults should not be housed with adults of the same sex because of aggression (Wright *et al.*, 1989; Baer 1994), and neighbouring pairs threaten each other so it is preferable if they have no visual contact. Females can give birth every 9-12 months and males should not be removed after the birth because the mother can reject its infant if the father is not present to carry it. Nest boxes should be large enough to accommodate parents and offspring when asleep and offspring should be removed when they reach 2 years of age as after this age, severe conflicts may occur between parents and offspring (Wright *et al*., 1989).

Marmosets and tamarins:

The most successful method of breeding callitrichids is to house mature animals as male-female pairs and allow them to reproduce naturally (Epple, 1978; Evans 1983). Paired females give birth to and raise 2-3 offspring every 5-8 months under laboratory conditions (Gengozian *et al*., 1978; Koenig *et al*. 1990). If the offspring remain with their parents, the family increases steadily and so, in turn, the number of non-reproductive helpers. In cotton-top tamarins (*S. oedipus*), survival rates of offspring are higher in extended families compared with offspring (immatures) raised by a parent pair or in a nursery of peers (Johnson *et al*., 1991). In common marmosets (*C. jacchus*), survival rates were found to be better in groups of no more than 11 group members (Rothe *et al*., 1993). Larger family groups are usually unstable and suffer from social conflicts between females.

Besides family groups, marmosets and tamarins may be kept in captive groups of unrelated post-pubertal or adult animals (Abbott, 1993). Overt social conflict is responsible for the suppression of sexual behaviour in subordinate males. The dominant male imposes its status on all other males in the group through aggression and it attacks copulating males. The hormonal system of subordinate males is impaired, and they have lower plasma testosterone concentrations, and reduced sexual behaviour and fertility. In females the most dominant one suppresses the sexual activity of the others in the group and attacks them if they copulate. The reduced ability of subordinate females to secrete luteinising hormone (LH) from the pituitary gland stops ovulation. Rates of intra-sexual aggression may be elevated, especially towards unfamiliar conspecifics. Overt conflicts are more severe among females than males. In a study on the common marmoset, subordinate females had to be removed to avoid serious injury to them in three-quarters of newly formed groups (Abbott, 1984).

Squirrel monkeys:

Squirrel monkeys should be bred in social groups containing various age and sex classes. Their sexually segregated social structure is retained in captive populations. Adult females cluster into several subgroups, while adult males are less socially cohesive but form stable hierarchies. The formation of mixed male-female groups can induce breeding readiness; it modifies the timing of annual reproductive changes so that subsequent breeding seasons occur in the same months as those of the initial group formation (Mendoza *et al*., 1991). When individuals are singly housed but allowed to hear and smell other subjects from mixed groups, they still display similar reproductive annual changes (Schiml *et al*., 1999).

Larger social groups make a significant contribution to squirrel monkey welfare and reproduction (Mendoza *et al*., 1991). Compared with animals living in mixed male-female pairs, the presence of multiple females in a social group heightens the proportion of females exhibiting ovarian cyclicity and increases testosterone levels in males. Adult males and females that stay in mixed male-female pairs behave largely as if they are living alone - they are unaffected by separation from their mate and quite often do not reproduce. Mendoza *et al*. (1991) reported that a majority of females living in mixed male-female pairs never become pregnant whereas most group-housed females give birth. When females living in pairs conceive, about 40% produce viable offspring compared with 70% for group-housed females.

Macaques, baboons, vervets and capuchin monkeys:

In species forming multi-male social organisations, several unrelated adult males may be present in a captive mixed group. When housing space is limited to some dozens of cubic metres, however, the optimal number may be only one fully adult male with females. Having additional males in a small area may lead to them suffering from stress and wounding, and they could fail to mate. Several adult females should be present in a social group and allowed to raise their offspring.

As a general rule, the more space that is provided for a group, the better will be the welfare and health of its members. Allowing animals to escape the attention of others by increasing inter-individual distances or by being separated by visual obstacles can relieve social tension. The relationship between rates of aggression and the amount of space, however, is not a simple one (de Waal, 1989; Judge, 2000). An increase in the spatial density of animals often elevates the frequency of conflicts, but individuals may cope with a heightened social tension by increasing their rates of submission and appeasement behaviours, thus reducing the causes of conflict. Besides quantity, the quality of space is important. In one study in pig-tailed macaques, levels of aggression were lower in individuals housed in a single room in comparison with those housed in a double room with a partition wall in the middle. Although the latter had access to twice as much space, the partition impaired the male's ability to control female aggression (Erwin, 1979).

Several studies have reported a relationship between social status and reproductive success. The relatively crowded conditions of captivity may exacerbate the effects of social competition. Reproduction rates are often higher in dominant females compared with lower-ranking females, and subordinates may experience delayed first conception, reduced number of offspring and increased infant mortality (Abbott, 1993). In rhesus macaques one study found that the presence of the dominant female decreased the number of copulations in subordinates (Michael and Zumpe, 1984) whereas another study reported no link between female social status and the number of copulations (Wilson, 1981).

To keep self-sustaining populations in captivity on a long-term basis, it is necessary to maintain genetic variability and prevent the deleterious effects of inbreeding. The Guidelines of the Captive Breeding Specialist Group of the International Union for Conservation of Nature and Natural Resources (IUDZG and CBSG, 1993) state that:

1) the founder group of wild-caught animals should consist of at least several dozen animals;

2) the sex ratio of the reproduction individuals must remain as close as possible to 1:1, and social exchange of males should ensure such an effect in polygamous species;

3) inbreeding through mating in closely related individuals must be avoided; and

4) a small number of individuals unrelated to the population should be regularly added to the pool of animals.

8.3. Breeding systems

While there is usually an available supply of New World monkeys and most Old World monkeys, some shortages of common marmosets are observed, and the supply of macaques can be difficult. The breeding and export of macaques has become an important economic factor in many source countries and there is, therefore, a pressure to breed under economical conditions, which can ultimately impact on the quality and welfare of the animals. The International Primatological Society (IPS) has produced guidelines for the acquisition, care and breeding of non-human primates to define minimum standards, and to ensure a uniformity of animals bred and supplied from the different countries (IPS, 1993b).

Four different methods are generally used to produce self-sustaining primate populations:

- free-ranging island colonies,
- semi-free-ranging corral colonies,
- pen or run-type single-male harem colonies and
- colonies where animals are cage mated in pairs (Hendrickx and Dukelow, 1995a).

8.3.1. Free-ranging colonies, island-breeding

By the 1940s a free-ranging colony of rhesus macaques of Indian origin had been established on the island of Cayo Santiago, Puerto Rico (Carpenter, 1972; Rawlins and Kessler, 1986). It is one of the very few facilities that is dedicated as a unique site for the study of primate biology under semi-natural conditions. Much of what is known about rhesus macaque social and reproductive behaviour is derived from studies of this colony (Hendrickx and Dukelow, 1995a). Studies of the net reproductive rate over a period of 7 years (Rawlins and Kessler, 1986) suggest that semi-free-ranging rhesus macaques are more successful in producing live-born infants than those kept in smaller enclosures (Hendrickx and Dukelow, 1995b). This colony has recently become very important because in AIDS research it has been shown that rhesus macaques of Indian origin are a much better model for the disease than Chinese rhesus macaques, but very few animals of Indian origin are available due to the ban on exports by India.

Another very successful free-ranging population of rhesus macaques is located on a densely wooded island off the coast of South Carolina (Taub and Mehlmann, 1989). From 1979 when 1,400 animals were translocated there from the Carribean Primate Research Centre, the colony grew to roughly 4,000 animals and about 3,150 were shipped to other government biomedical programmes.

8.3.2. Corral breeding

The California Primate Research Centre (CPRC) and other Regional Primate Primate Research Centres in the USA have had an active breeding-programme in corrals since 1972 (Hendrickx and Hendrickson, 1988; Small and Smith, 1986). Macaques have been bred successfully in these enclosures, and large numbers of animals can be produced very economically in areas where the climate is suitable (Baskerville, 1999).

The disadvantages of keeping macaques in this way are those of identification of individuals, monitoring illness and injury, infection from indigenous parasites and diseases, capturing, associated adverse effects on welfare and determining parentage of offspring (Welshman, 1999).

8.3.3. Harem groups

A smaller scale method of macaque production is by the establishment of permanent harem groups, each in a separate pen or enclosure. There is wide variation in the composition of macaque, baboon and vervet harem groups reported in the literature (Valerio and Dalgard, 1975; Erwin, 1977; Goodwin and Coelho, 1982; Kessler *et al*., 1985). The most common keeping system in the US-Primate Centres are the 'corn-cribs', large metal structures originally constructed to store corn and with a large amount of vertical space. Continuously modified over time, they are used to keep harem groups of 12 to 24 animals (Hendrickx and Hendrickson, 1988). The harem group system is also very commonly used in Europe and in Asian countries. These systems of housing allow more accurate monitoring of health status and breeding. However, the restricted space means a greater potential for instability of the hierarchy, with subsequent harassment of particular individuals. This, in turn, can lead to lower ranking animals being deprived of access to food and water (Welshman, 1999).

8.3.4. Timed-mating strategies

To maximise conception rates, several timed-mating strategies have been used. They are based on the restriction of time the female and male are housed together during the ovulation period (Hendrickx and Kraemer, 1970). The most common mating schedule for both rhesus and long-tailed macaques is to place the female in the male's cage for 2 hrs every other day over a 3-day period (i.e. two times). Using this method, the conception rate for rhesus macaques exceeds 70%. However, several facilities have had very successful rhesus macaque breeding programmes by keeping all the males in one room (a stud room) and bringing the females there for mating without the need for such timed-mating strategies (Hendrickx and Dukelow, 1995b). When animals were singly housed timed-mating strategies were frequently used. When animals are group housed these strategies have implications for poor welfare due to the removal of animals from their social groups. Unless the time of mating needs to be accurately known for the scientific research being performed, timed-mating strategies should not be required.

8.4. Weaning

Natural weaning is a gradual process through which the infant primate becomes independent from its mother, firstly with regard to nutritional needs, then by gaining behavioural autonomy. As the infant grows, the diet is increasingly supplemented with solid food. Nutritional weaning age varies according to the body weight of the species. It occurs between the ages of 2 and 6 months in marmosets, tamarins, owl monkeys and squirrel monkeys, and takes place between the ages of 6 and 15 months in vervets, macaques, baboons and capuchins (Fedigan and Fedigan, 1988; Fragaszy *et al*., 1991; Mendoza *et al*., 1991; Hendrickx and Dukelow, 1995a, b). In the last months of the process, nutritional self-sufficiency is completed but the infant still suckles for reassurance as it is psychologically dependent on its mother. The birth of the next offspring often completes the process of weaning. Weaning represents a stressful stage for the infant since it implies some degree of rejection by its mother. In the context of the social group, the growing infant may seek comfort and help from other group members.

When primates are being bred for research there is a commercial pressure that the females produce as many offspring as possible, and to wean infants as early as possible, especially in the bigger species like macaques and baboons where development is slow. There is no specific scientific criterion, however, to determine at which age weaning would be optimal in terms of safeguarding welfare for each animal. In many breeding colonies, it is usual to separate and forcibly wean infant macaques at ages ranging from 3 months to one year. The age at which infants are weaned may have an effect on reproductive productivity, particularly in seasonally breeding species like rhesus macaques (Baskerville, 1999). It was found (Goo and Fugate, 1984) that the interbirth interval in female rhesus macaques was significantly related to weaning age, and that females who had their offspring weaned at 6 months had higher reproductive rates than those who were weaned at 8, 10 or 12 months. In Japanese macaques, females having stillborn infants had the shortest inter-birth interval (Kotera *et al*., 1975). On the other hand, Reinhardt (2002) asserted that the perceived benefits of permanent pre-weaning mother-infant separation were not supported by scientific data and that artificial weaning may be an economically unsound management practice. In a study of savannah baboons, separating infants at six months did not improve productivity of mothers; most females had resumed their reproductive cycles before infant removal (Wallis and Valentine, 2001). The benefit of early weaning on reproductive rates might be marginal. Since separation from the mother incurs negative psychological consequences for the infant (see Chapter 9), any slight increase in reproductive rate is insignificant compared to the abnormal behaviours induced in the offspring and the potential impact this may have on their subsequent use in science.

The maturation of primates is rather slow and infants are psychologically dependent on their mothers for a long period. Early weaning is very stressful. It has been demonstrated (Harlow and Harlow, 1965; Ruppenthal *et al*., 1976; Goldfoot, 1977) that infant rhesus macaques which had either been separated shortly after birth and raised in peer groups, or that had been raised with their mother in single cages for 3-12 months and subsequently allowed very limited daily access to other infants, showed poor reproduction performance, poor maternal behaviour and increased aggression as adults.

The stress of weaning at 4.5-6 months in pig-tailed macaques causes not only behavioural changes such as activity and sleep disturbances but also physiological changes for up to 28 days (Sackett and Terao, 1992). It was found (Goo and Fugate, 1984) that infant rhesus macaques weaned at 6 months were lighter in weight at 12 months than infants left with their mother until that time.

One suggestion is that the best compromise is to wean most infants at about 6 months, which allows good productivity, but to leave individuals who are performing poorly compared to their peers (e.g. based on behaviour, body weight etc.) with their mothers for a longer period (Baskerville, 1999).

Another system for the management of harem groups is to replace the existing females gradually by leaving young female offspring in their maternal group until they become sexually mature, but periodically changing the males to prevent excessive in-breeding. This system reflects what happens in wild troops (Baskerville, 1999) but has the lowest productivity of all described systems. The advantage, however, is that animals in this system show few social abnormalities, and so it is particularly suitable to establish permanent self-sustaining colonies.

8.5. Use of wild caught animals

The "International Guidelines for the Acquisition, Care and Breeding of Nonhuman Primates" of the International Primatological Society (IPS, 1993a) distinguish between three categories of origin of primates used in research:

1) 'Feral primates' consist of stock caught from the wild; these show the greatest genotypic and phenotypic diversity,

2) 'Captive-bred primates' have been bred and raised under more or less controlled conditions in captive colonies (whether in classical laboratory situations or in corrals),

3) 'Purpose-bred primates'- such primates are derived from stock which has been placed in semi-feral conditions, such as an uninhabited island previously free of primates, from which weaned individuals can be taken, as soon as a sustainable population has been achieved.

First generation of primates bred in captivity (F1 generation) is interpreted as being the first generation of offspring born in captivity from wild-caught parents (i.e. animals that have been caught in the wild and held in captivity for breeding purposes). It should not be necessary to replace breeding primates for research with wild-caught animals, as alternatives exist such as the exchange of animals between research breeding colonies. Exceptionally for the sake of conservation of a species it may be necessary to take animals from the wild (e.g. for the storage of gametes and embryos).

The sources of primates (breeding and supplying) for research include registered establishments within the EU, as well as island colonies with renewable breeding stock, some of which may occasionally source replacement breeders from the wild. Island breeding colonies exist in a semi-wild state, but for the purposes of classification these are considered as captive-bred.

The Philippines and Indonesia banned the export of wild-caught primates in 1994, but wild-caught animals have been sometimes used for breeding purposes. In this system, breeding animals are replaced by wild-caught animals after their reproductive phase has finished, sometimes not to maintain genetic diversity but for economic reasons. As all primate species are endangered to some extent and many are listed as such (IUCN, 2000 http://www.redlist.org/search/search-basic.html), there is a position that no wild-caught animals should be used, not even for breeding purposes (alternatives exist through captive-bred colonies exchanging animals). It is even more important to avoid capturing animals from the wild for animal welfare reasons, since trapping the animals in the wild often causes death and injuries and in all cases an enormous stress for the captured primates. Also the catching of wild animals risks introducing pathogens from the wild into breeding colonies. Moreover as the genetic background is unknown there is a further danger of introducing unwanted genetic chacteristics.

The IPS therefore discussed the CITES (Convention on International Trade in Endangered Species of wild flora and fauna) definition of 'captive-bred' during its congress in 1994. It was agreed that the term 'captive-bred' should only apply to those animals conceived and reared in a managed environment. The identification of any such animal must be known as must that of the mother and, if possible, the father. Individual life histories must be available, together with documentation of any viral, bacterial or parasitic infections and any health screening protocols that had been undertaken (Welshman, 1999). To discourage the use of wild-caught animals the biomedical community should only accept captive-bred animals that are of the second or higher generation bred in captivity as being classified as "purpose-bred". This would help to prevent the use of wild-caught animals as breeders and support the effort to eliminate early weaning systems, as in general early weaned primates do not become competent breeders (see chapter 9.4)

8.6. Accreditation of facilities

Accreditation of breeding facilities could help to ensure that standards of animal welfare and health are observed in breeding centres in Europe, as well as abroad. A system of accreditation would give the user of the animals some reassurance that the animals would meet health and quality standards that are necessary to carry out high quality science and ensure that good animal welfare is safeguarded. Some breeding facilities in non-EU countries have already received ISO 9000 accreditation.

In verifying criteria for accreditation, it may be difficult to decide whether a breeding female has been wild-caught or was purpose-bred, or if hygienic deficits have been compensated for by an excessive use of antibiotics. However, the opportunity to inspect facilities and to withdraw accreditation, could improve standards and lead to better science and animal welfare

9. SPECIFIC ANIMAL WELFARE PROBLEMS

All animals maintained in captivity are by definition constrained and their freedom to engage in the full panoply of species-typical behaviours is limited by physical considerations such as enclosure size and design. When non-human primates are maintained for purposes of research, it is particularly important to take into account the impact of their captive environment. Only then is it possible to conduct a proper assessment of the welfare impact to consider the balance between the overall impact of husbandry, laboratory maintenance and the necessary scientific procedures, and the possible beneficial outcome of the research for man and animals.

Some issues that need to be addressed are as follows.

- What are the requirements of the researcher?
- What are the requirements of the animals concerned?
- How can these two sets of requirements be reconciled?
- How to monitor and minimise the impact of husbandry, laboratory maintenance and scientific intervention on the welfare of the animal?
- Once identified and agreed, how should good practices be implemented?

9.1. What are the requirements of the researcher

This requires a robust analysis of the problem that a researcher is investigating and whether this is a fundamental investigation of an animal's biology or a regulatory requirement to identify the pharmacological profile of a particular drug. However, the questions to be asked are broadly similar.

- Can the necessary outcome be achieved without the use of animals?
- Why are non-human primates required to be used?
- Are there opportunities to consider the use of alternative animal species?

If the fundamental requirements for using a particular species have been established, there are a number of important questions that need to be considered. These include the availability of animals of the appropriate 'quality', for example, health status, age, genetic profile, weight, condition and level of biographical characterisation. Whether the animals are suitable for maintenance under the conditions necessary for conducting the study is also important. For example some studies will necessitate frequent intervention for drug administration or blood-sampling. Thus, an animal's prior history and housing and husbandry practices before, during, and after the scientific procedure need to be considered.

9.2. Positive aspects of husbandry: welfare and environmental enrichment

The unnatural restrictive environments and husbandry practices in research laboratories have raised a concern about the possible negative welfare aspects, both for reasons of ethics and of experimental validity. There is a growing appreciation that positive welfare conditions also reward in terms of good science (Chance and Russell, 1997). Positive welfare conditions can be achieved by programmes of environmental enrichment which are in line with the behavioural needs and natural inclinations of the respective species. It leads to the opposite of a life of boredom, frustration and apathy (see Wemelsfelder, 1984) and recently much consideration has been given to how such enrichment can be achieved. The two most relevant aspects are: i) the social environment, and ii) the physical environment.

9.2.1. The social environment - Social housing

Most primate species are highly social and live in complex societies. The position of an individual in the social network is determined by its sex, age, its dominance position and that of its close relatives, and its affiliative relationships, in the first place with kin. These, in turn are determined by the history of the group and its members, and its demographic and genealogical development. They provide an environment for an individual in which it can become absorbed and challenged. It meets competition and rivalry on the one hand, and affiliation, affection and enjoyable contacts (e.g. play) on the other. The harmonious fluctuations of excitement and tranquility, of stress and relaxation, determine the quality of that animal's life.

Having compatible companions is recognised as being one of a primate's most important needs: "The remarkable sociality of the primate order in general is the most relevant characteristic of their humane housing" (USDA, 1999), "Social deprivation should not be considered any more normal than say, water or food deprivation" (de Waal, 1991b), "A compatible conspecific probably provides more appropriate stimulation to a captive primate than any other potential enrichment factor" (IPS, 1993a).

Solitary housing clearly negatively affects many aspects of welfare including health, in comparison with housing in pairs or in groups. Thus aggression (Chase *et al*., 2000), abnormal behaviour and stereotypies (Bloomsmith *et al*., 1998; Bellanca and Crockett, 2001; Chase *et al*., 2000) are higher in socially impoverished conditions (Reinhardt *et al*., 1988; Line *et al*., 1990a; Bayne *et al*., 1991; Eaton *et al*., 1994; Baker, 1996; Kessel and Brent, 2001). This applies in particular to self-aggression, a pathological behaviour in which the monkey 'threatens' its own body and even bites itself, sometimes inflicting wounds as a result (Russell and Russell, 1985; Bushong *et al*., 1992; Jorgensen *et al*., 1998; Novak *et al*., 1998; Reinhardt, 1999; Reinhardt and Rossell, 2001). Cardiovascular physiology, however, was closer to the natural condition in these socially impoverished conditions (Coelho *et al*., 1991). Singly housed rhesus macaques showed long-term features of immunosuppression (Line *et al*., 1993; Lilly *et al*., 1999) and neuro-endocrinological indicators of stress-induced anxiety and of depression (Lilly *et al*., 1999). Reinhardt *et al.* (1990) showed that in a large colony of rhesus macaques, 23% of those caged individually required medical treatment, compared with only 10% of those housed in pairs.

Many studies for various species report an increase in good welfare indicators after singly-housed animals were transferred to a social situation (Reinhardt *et al*., 1988; Line *et al.,* 1990a; Kessel and Brent, 1997, 2001). These include decreased automutilation (Reinhardt, 1999), and decreased susceptibility to disease (Reinhardt, 1990b; Schapiro and Bushong, 1994), which also seems to be reflected in enhanced immune responses (Schapiro *et al*., 2000). In a study involving corn cribs, abnormal behaviour, age-directed activities and self-directed activities were all seen to decrease. Locomotion and normal behaviour as well as enrichment directed activities and social behaviour all increased (Kessel and Brent, 2001). Adult female rhesus macaques that were temporarily taken out of their group and that showed strong stress responses, recovered significantly faster when re-united with a preferred companion (Gust *et al*., 1994; Coe *et al*., 1982). Grooming a social partner lowered heart rate more than self-grooming in a pig-tailed macaque (Boccia *et al*., 1989). When offered the choice between food and social companionship, a normally-fed tufted capuchin monkey reliably preferred a companion. This indicates that social companionship is not a luxury but a necessity (Dettmer and Fragaszy, 2000). This is recognised in the recommendation of the National Research Council of the US (NRC/ILAR, 1998), namely that "Social interactions are considered to be one of the most important factors influencing the psychological well-being of most nonhuman primates".

The differences in various measures of physical and psychological welfare between singly-housed primates and those living in the wild clearly are of significance with regard to the general validity of research in such areas, given the fact that most of such data have been acquired from singly-kept animals (Schapiro *et al*., 2000; Rosenberg and Kessel, 1994). All this justifies the recommendations already made by, for instance, the Animal Welfare Institute (1979), and the International Primatological Society (1993a) that "monkeys should, unless there are compelling reasons for not doing so, be housed socially" (IPS, 1993a).

The presence of social partners is the major enrichment and socially-housed animals show both higher rates, and more variety, of activity, and less illness and pathological symptoms than singly-housed animal as already outlined. The benefits of living with social partners are clear, but not solely for the primates concerned. Hartner *et al*. (2001) reported that there was an important difference between singly- and socially-housed long-tailed macaques. Not only did the latter show less self-directed activity, they were also more at ease and more relaxed in handling and training procedures; in short, they were better animal models as they were less stressed and so gave more precise and relevant data.

Some individuals cannot be paired or integrated in a social group due to insurmountable incompatability with other animals and a solitary life may be less stressful for them (Coe, 1991; NRC/ILAR, 1998). Experimental and health constraints may also require the separation of individuals. When it can be explicitly justified that single housing is necessary, then limited regular access to a large complex area with conspecifics may be beneficial (Jaekel, 1989), or, at least, the opportunity to meet partners several times a week (Jerome and Szostak, 1987; Gilbert and Wrenshall, 1989). In one study, the provision of social stimulation heightened activity, and possibly also the frequencies of stereotypies (Schapiro *et al*., 1995). It should be verified, however, that individuals, when in close contact, are compatible, as when an animal is near a threatening partner, a subordinate individual may be stressed and develop abnormal behaviours (Lipman, 1992). In addition, frequent human attention in some forms and appropriate care can partly compensate for the detrimental effects of isolation (Baker, 1997; Wolfle, 1987; Choi, 1993; Bayne *et al*., 1993).

Where there is no alternative to single housing of primates, it is advisable, when possible, to allow animals to have tactile contacts with conspecifics through mesh (Crockett *et al*., 1997, 2001). Again, it should be checked beforehand that partners are compatible, as otherwise aggressive contact might cause wounds and injuries to fingers. In baboons, the blood pressures of companions able to contact each other have been found to be lower than those of conspecifics housed either singly or with social strangers (Coelho *et al*., 1991). Another option is to give animals the opportunity to meet partners several times a week (Jerome and Szostak, 1987; Gilbert and Wrenshall, 1989). If single housing of non-human primates cannot neither be avoided nor the consequent adverse effects on welfare minimised, euthanasia can be considered as an option to prevent prolonged poor welfare. This option may apply where repeated attempts to re-socialise the animal have failed and severe signs of social deprivation develop (e.g. self-mutilation, severe abnormal and stereotypic behaviours) and cannot be otherwise resolved.

9.2.2. Risks of social housing

Social housing can introduce social tensions (Reinhardt *et al*., 1986) and the risk of wounding through aggression (Rolland, 1991). Whether this is the case depends on a number of social factors. Baker *et al*. (2000) found in a study on chimpanzees comparing different housing systems that group-living chimpanzees incurred the highest level of minor wounding, but serious wounding levels were not affected by housing condition. They found that the major factor is the social composition (sex, age and method of rearing) of a colony.

Any relocation to an unfamiliar enclosure with different configurations, escape opportunities and places of concealment are all liable to increase hostility (Judge, 2000). The relationship between enclosure size, on the one hand, and crowding stress, fighting and injuries is a complex one (de Waal and Berger, 2000; Judge and de Waal, 1997). Thus Boyce *et al*. (1998) found that rhesus macaques living in a large outdoor enclosure during the summer showed a five-fold increase in injury incidence during confinement in a smaller indoor enclosure in winter. A similar result was found for baboons by Elton (1979). By contrast, levels of aggression and anxiety scratching did not differ when a group of hamadryas baboons was transferred between their spacious outside enclosure and their small indoor quarters (Judge *et al*., 2001). However, it should be noted that this species is not known for its aggressive traits. Similarly the chimpanzees of the Arnhem Zoo colony did not show an increase in agonistic behaviour in their much smaller inside hall. On the contrary, their level of affiliative interactions went up, seemingly buffering the 'expected' increase in tension (Nieuwenhuijsen and de Waal, 1982; Catlow *et al*., 1998). Caws and Aureli (2001) even found that space restriction by indoor confinement in chimpanzees reduced the level of aggression; "they seem to inhibit aggression by not joining ongoing conflicts and by selectively decreasing the targeting of common victims."

9.2.3. Group composition and *stability*

Social groups are dynamic networks. Sudden outbreaks of aggression are always possible, even in stable groups structured by kinship bonds in captivity, as seen in the wild (Samuels and Henrickson, 1983; Ehardt and Bernstein, 1986; Samuels *et al*., 1987). In macaque groups, for instance, traumas inflicted by conspecifics represent the main cause of veterinary intervention (Rolland, 1991).

Several studies have documented the importance of group composition. Thus Dazey *et al*. (1977) reported that in a group of pig-tailed macaques there was significantly less aggression between group-living females in the presence of adult males. The same has been found by Erwin (1979). He found that this was due to the exertion of a 'control role' by the dominant male. If the group had access to two rooms instead of one, there was a dramatic increase in aggression between the females because the male could no longer exert his role in inhibiting conflict. The above example also highlights the importance of a spatial structure.

A stable group composition is essential and frequent rearranging is disruptive and can lead to increased fighting and mortality. This was the case in a breeding colony of rhesus macaques where there was regular removal of pregnant females and introduction of non-pregnant females (Kaplan *et al*., 1980). Comparable observations are reported by Kessler *et al*. (1985).

9.2.4. *Visual withdrawal* and *escape options*

The structure and furnishing of the enclosure has an important influence on social interactions and relationships. In the natural situation, individuals or subgroups can avoid others by moving out of reach or out of sight. In the usual captive situation this possibility is greatly limited. Thus animals may not be able to evade stressful confrontations with their companions, yet the risk can be reduced considerably by appropriate structuring of the cages. In pair-housed rhesus macaques, it has been shown that partners spend more time in close proximity and in affiliative interactions when a privacy panel is provided (Reinhardt and Reinhardt, 1991).

Multiplying shelters and sources of food and water may lower social competition. Enriching the environment with perches and visual breaks also reduces aggression rates (Neveu and Deputte, 1996; Maninger *et al*., 1998; Nakamichi and Asanuima, 1998; Westergaard *et al*., 1999). Providing visual barriers and cover has proven to be an effective means for reducing aggression. This can be achieved in the form of barriers or screens behind which animals can hide, without the risk of being cornered, and allowing them to see others through peep holes without being seen themselves (Erwin, 1977; Ricker *et al*., 1995), and to escape to a place where their adversaries are not prepared to follow them (Maninger *et al*., 1998; Miller-Schroeder and Patterson, 1989; McCormack and Megna, 2001). The division of the living space in compartments is another technique and Westergaard *et al*. (1999) found that this led to significantly lower rates of wounding in rhesus monkey breeding groups. However, Erwin (1979) found the opposite effect in a study on pig-tailed macaques. Here the compartmentalisation of the space allowed females to express their mutual hostilities without the dominant male being able to exert his conflict-interfering control role.

These species-specific aspects emphasise a very important point, namely that the application of such measures should be selected on the basis of a good ethological understanding of the role patterns in the social structure of a given species (see chapter 6.3).

In nature, animals can decide to leave a group temporarily or definitively. They do so at a cost (leaving the security offered by being in the group) which their enemies are not prepared to take. Also in the captive situation one can devise structures that allow animals to escape from the hostility of companions. O'Neill-Wagner (1996) proposed that electric fencing may be a very economical and effective way to protect vulnerable animals. Such animals may accept the momentary risk of being shocked when wanting to escape, and to return when the behaviour of companions 'on the other side' indicates that it is safe to return. The shock wires protecting trees in the Arnhem Zoo Chimpanzee Consortium are, on rare occasions, used in similar ways (personal observation van Hooff) and the use of such barricades also informs caretakers of evolving tensions allowing timely measures to be taken to resolve this.

9.2.5. The physical environment

9.2.5.1. Cage size

Primates are amongst the most intelligent creatures, a characteristic that derives its adaptive value from their flexible and opportunistic way of life, in terms of both the exploitation of resources and their natural habitat that often requires locomotory versatility. The possibility to display these flexibilities in enclosures of adequate sizes and with appropriate furnishing is a condition for psychological welfare. The reliance on body weight in the existing guidelines as a determinant of cage size is inadequate. Far more important factors include species, age, sex, and individual biography of the animal and its previous experience. Another important factor to consider is the structure of the enclosure and the useable space. For most non-human primate species, the volume of available space and the vertical height of the enclosure are more important than floor area, due to the arboreal nature and the vertical flight reaction of these species.

The relationship between restricted space and abnormal behaviour has long since been realised (van Wagenen, 1950; Draper and Bernstein, 1963). Individual cages that restrict movement and do not permit climbing, jumping and running result in reduced weight and size, muscular atrophy (van Wagenen, 1950; Faucheux *et al*., 1978), reduced joint mobility (Turnquist, 1985), repetitive stereotyped movement patterns (Draper and Bernstein, 1963; Paulk *et al*., 1977; Kitchen and Martin, 1996), and in apathy and depression (van Wagenen, 1950). In general, provision of additional space, irrespective of the cage furnishings, leads to more movement and greater activity (Brent, 1992; Kerl and Rothe, 1996), as well as to better reproductive performance (Boot *et al*., 1985; Westergaard *et al*., 2000). In conclusion, enclosures that allow normal patterns of locomotion are an essential factor for the welfare of captive primates.

Even when the research absolutely demands that animals are temporarily housed in individual cages, these should contain perches installed at an appropriate height, offering a minimum of climbing opportunities, and the facility to avoid sitting on the floor. When they were housed in cages containing no perches, singly-housed long-tailed macaques spent significantly more time suspended from the cage wall (Shimoji *et al*., 1993). In addition the arrangement of cages should allow animals to move to a position higher than the level at which they perceive threatening factors, e.g. humans that may frighten them. The consequences of double-tier cage arrangements must also be considered (Heger *et al.*, 1986; IPS, 1993; Mahoney, 1992; NRC, 1996; Reinhardt and Reinhardt, 2000b). For example such cage arrangements may impair the natural flight reactions of primates and also contribute to poor cage illumination (Röder and Timmermans, 2002).

9.2.5.2. Cage structure and furnishings

It is evident that, in addition to the availability of space, the structure and furnishing of the available space greatly influences the behaviour of captive primates. The social importance of visual and physical barriers has already been noted. A diversification of the environment may offer incentives for exploration and play, and thus both prevent boredom and abnormal behaviours, such as stereotypies (self-aggression, coprophagy) as well as diverting animals from aggressive tendencies. This may be achieved through variation in environmental elements and by giving access to natural and suitable artificial structures and objects in the enclosure. Simply transferring animals from an indoor to an outdoor environment may have this effect, especially when the outdoor environment is more naturalistic. This has been documented for a number of species, e.g. chimpanzees (Clarke *et al*., 1982; Jensvold *et al*., 1999), gorillas (Goerke *et al*., 1987), mandrills (Fried and Whitehouse, 1992) and squirrel monkeys (Marriott *et al*., 1993). The beneficial effect is illustrated by a study on gorillas by Maple and Finlay (1987b): after being translocated from barren cages to a new naturalistic enclosure, play wrestling was recorded for the first time, and regurgitation and re-ingestion were no longer observed.

Existing cages can be modified to satisfy the need to explore, manipulate, locomote and be occupied in various ways, for instance, by supplying bedding materials, such as woodchips, straw and shredded paper, allowing nesting behaviour (e.g. chimpanzees: Brent *et al*., 1991). When small food items, such as grain, are scattered in these materials this stimulates prolonged occupation by foraging (chimpanzees: Baker, 1997; rhesus macaques: Bayne *et al*., 1992a). Such time-consuming foraging tasks temporarily distract the animal from showing abnormal behaviours (chimpanzees: Bloomsmith *et al*., 1998; rhesus macaques: Bayne *et al*., 1991, 1992b; pig-tail macaques: Chamove *et al*., 1984; Boccia, 1989; Boccia and Hijazi, 1998).

However, once all food has been retrieved or eaten, the subject may resume an habitual disorder. Inanimate enrichment, including feeding enrichment, has not been shown to cure subjects from behavioural pathologies, unlike animate enrichment. For additional reviews and data regarding this issue see the website database (http://www.awionline.org/Lab_animals/biblio/index.html)

Instead of easily consumable foods such as pellets, foods that require extensive manipulation, such as corn-on-the-cob, were effective in reducing the amount of stereotypy in singly-housed baboons (Nennett and Spector, 1989). Animals can be made to work for desirable food and in various zoos different types of provisioning devices have been installed. These devices require animals to be perceptually alert and to apply complicated motor skills in order to find, retrieve and process food items, for example, bamboo pipe feeders for tamarins (Steen, 1995) and artificial 'termite mounds' for chimpanzees that promote fetching and using tools (Nash, 1982). Such foraging tasks were also found to be effective in laboratory colonies (Boccia, 1989; Boccia and Hijazi, 1998). Perceptual and cognitive challenges can be presented by introducing food-puzzle foraging devices (Bloomstrand *et al*., 1986; Maki *et al*., 1989; Brent, 2001; Crockett *et al*., 2001).

Objects of various kinds can be presented as playthings. Usually the novelty effect wanes gradually (Line *et al*., 1991a, b; Line and Morgan, 1991). Destructible objects and materials maintain their fascination for longer because they keep on changing in shape and size as they are being manipulated (Brent and Stone, 1996). Foraging tasks and puzzles do not suffer from habituation (Poffe *et al*., 1995). A certain amount of unpredictiveness combined with commensurate announcing signals can keep animals on the alert. For instance, a signal indicating that food items are going to appear, but keeping the animal uncertain of when precisely. Alternatively requiring a speedy response before access to the food is shut off, but again keeping the animal uncertain about which of a number of access options should be chosen. It should be noted that this uncertainty associated with anticipation and alertness for competence does not normally lead to pathological stress.

9.2.6. Training as enrichment

Several studies on different species indicate that non-traumatic training tasks, apart from adapting the animals to experimental routines, can have a beneficial effect on welfare. Not only can this reduce the sensitivity of the animals to stressful circumstances and procedures (Elvidge *et al*., 1976), it can also promote the efficiency of these procedures because an animal can be encouraged to cooperate, for instance in procedures such as blood collection, physiological measurements or entering a restraining apparatus (Michael *et al*., 1974; Reinhardt, 1992; Schnell and Gerber, 1997). Physiological measurements can now be taken even without removing animals from their enclosure and restraining them (Reinhardt *et al.*, 1990, 1991; Reinhardt and Cowley, 1992). All this promotes safety and valid and efficient data collection, diminishing data variability and reducing the number of animals required to obtain statistically significant results. Although handling always involves some form of stress to the animal, by facilitating the ease and efficiency of procedures these training procedures do promote the good welfare of the animals and the carrying out of good science (Brockway *et al*., 1993; Chance and Russell, 1997; Hau and Carver, 1994; Klein and Murray, 1995).

Even comparatively short-lasting but regular exposure to an adequately enriched and varied environment can have long-lasting beneficial effects. Thus singly-housed long-tailed macaques showed marked behavioural improvements when they were given daily access for 15 minutes to a cage containing exercise and play equipment (Leu *et al*., 1993; Wolff and Ruppert, 1991). Comparable results were obtained by O'Neill (1989) and Storey *et al*. (2000) for rhesus macaques, and by Tustin *et al*. (1996) for Japanese macaques.

It is important to mention that measures should be adapted to the species-specific requirements and characteristics of a species. Thus the provision of opportunities for an individual animal to get away from others may not always lead to a reduction of aggression. The opposite may be true, for instance in groups of a species where the dominant male exerts a control role, interfering with, and punishing, individuals involved in conflicts (Erwin, 1986). In this situation aggression may increase when they can confront one another out of sight of the male.

9.3. Socialisation procedures

Interfering with the social relationships of individuals is an inevitable part of some husbandry and experimental procedures. This may lead to the formation of new groups from recently acquired animals for breeding, the grouping of immature animals to create pathogen-free colonies, the introduction of animals to avoid inbreeding, the re-introduction of subjects after completion of experiments that have needed temporary separation, and the re-pairing of individuals who have become incompatible.

Managing social groups of non-human primates is a difficult task that requires training in the species-specific behaviours, the consequences of any social disruption, and the procedures that allow the manipulation of individuals and groups. As stated by Visalberghi and Anderson (1993) "The range of possible reactions to social stimuli is considerably greater than to inanimate stimuli, going from enthusiastic and lasting acceptance to extreme injurious aggression. In general, it is easier to predict what an animal will do with something new than with somebody new." Each individual contributes to that unpredictability and the response of a group is a combined outcome of each of its members' unpredictabilities. Thus, it is understandable that the same human intervention may actually produce different consequences in two apparently similar groups. Given that there are no rules that hold true in all situations, any introduction or reunion of animals must be carefully planned and monitored. Compatibility and incompatibility between individuals are crucial when devising socialisation procedures. The breeding and supplying establishments should be involved in any socialisation programme as they can initiate it when the animals are young.

One method of dealing with the possibly harmful consequences of first encounters, upon introduction to a group, is to blunt the canine teeth of adult males. However, exposing the pulp cavity of a tooth could lead to the development of an abscess, and the extraction of canine teeth can damage the jaw bones, as they have long roots and their extraction can lead to infection with consequent negative effects on welfare (NRC/ILAR, 1998). It has also been proposed to use sedative drugs to reduce aggression during first encounters (Moran *et al*., 1993). It should be borne in mind that the situation is highly demanding for animals and the drugs used may interfere with the animals' physical and cognitive responses. Moreover, it is difficult to find a dosage that does not handicap the animals too much. The use of anxiolytics presents grave risks and should be prohibited as they tend to remove an animal's normal inhibitions (cause a disinhibition). This may decrease an animal's fear of a more dominant animal and lead to an increased aggression and consequent implications for poor welfare.

9.3.1. Pairing individuals

When group-housing is not possible, animals may at least live in pairs. Even the presence of only one other companion can replace the social group to a considerable extent. Where two individuals are kept together they need at least twice as much space as that required for singly-housed animals, to allow the subordinate to increase its distance from the dominant companion in case of social tension and incompatibility, although compatible pairs may require less space (Reinhardt, 1994b, 1998; Reinhardt and Reinhardt, 2000a). When establishing pairs, knowledge of natural sex and age-class affinities in the species is necessary. In species constituting strong breeding pairs like callitrichids, for instance, males and females are more tolerant of each other than same-sex individuals. As a general rule, pairing is much easier if the individuals are younger, but pairing immatures is not risk-free. On the other hand pairing between adults and immatures has been shown to be successful in a majority of cases (Reinhardt *et al*., 1995; Majolo *et al*., 2001). Pairing is easier in marmosets, tamarins, and squirrel monkeys than in macaques and baboons. Pairing of unfamiliar adults without due care raises a high probability of injurious aggression in the latter species. In addition, the use of a progressive socialisation procedure minimises the likelihood of wounding (Reinhardt *et al*., 1995). Compatibility between prospective cage-mates should be assessed through a series of gradual steps. Firstly, both individuals should be allowed to become familiar with each other in adjacent cages permitting visual and auditory communication. At this stage, it should be checked whether one individual establishes a clear dominance relationship, through the expression of assertive behaviours and threats by one partner, and the display of avoidance behaviours and submission signals by the other. Individuals exhibiting mutual aggression should not be considered suitable partners. After such screening, individuals showing complementary dominance-subordination behaviours may be reunited in a cage other than their previous home-cages, to weaken the assertiveness of both partners. An additional intermediate step may be added, that of individuals being allowed to contact each other through wire mesh before reunion. This socialisation procedure has proven to yield high rates of successful pairings, even among animals who had been singly-housed for long periods. In several macaque species, pairs appear compatible in the majority of cases (Line *et al*., 1990a; Crockett *et al.*, 1994; Eaton *et al*., 1994; Reinhardt, 1994a, 1998; Reinhardt *et al*., 1995; Byrum and St. Claire, 1998; Watson, 2002).

Although the above adult/adult pairing procedure was developed in macaques, it would be valuable to apply it to other primate species. An additional precaution is to house pairs of males in male-only areas since the presence of females may trigger sex-related aggressive competition (Coe, 1991; Reinhardt *et al*., 1995). Also, when pair-mates have been temporarily separated, a brief stage of non-contact familiarisation diminishes the likelihood of conflict on reunion (Reinhardt *et al*., 1995; Jackson, 2001).

9.3.2. Establishing groups

The formation of groups can be a most dramatic event for animals. Difficulties are similar to those encountered in the formation of pairs but enhanced by the higher number of individuals involved. The same factors as previously mentioned affect the probability of success of group formation i.e. species, personality, experience, age, sex and familiarity of individuals. Reuniting animals familiar to each other is the easiest way of constituting groups (Erwin, 1986; Vermeer, 1997). In squirrel monkeys, severe fights are uncommon at group formation even with animals unfamiliar to each other (Williams and Abee, 1988; Lyons *et al*., 1994; Mendoza *et al*., 1991). Mixing young macaques does not raise serious difficulties (Reinhardt *et al*., 1995) but attempts to establish new groups of adult macaques, baboons and vervets have produced a long record of deep trauma, deaths and group disbanding (Else, 1985; Else *et al*., 1986; Line *et al*., 1990b; Clarke and Blanchard, 1994; Reinhardt *et al*., 1995). These species appear quite xenophobic; they behave hierarchially, and individuals can make powerful coalitions and join against others. Escalated aggression due to these coalitions is a major concern when forming new groups of macaques and baboons.

The integration process should be conducted in an unfamiliar area enriched with many objects to distract the attention of individuals. It should not include 'dead ends' but rather circular escape routes and visual barriers (Watts and Meder, 1996; Westergaard *et al*., 1999). Food and water should be available from several locations to prevent some individuals from monopolising a single source. The number of people viewing the initial encounter should be limited to avoid contributing to the tension of animals. All means necessary to separate animals should have been prepared in advance. However, some aggression is likely and individuals should be allowed some time to resolve conflicts. The staff should always be able to intervene and terminate the process as soon as it appears that serious physical injury may occur.

In species forming multi-male/ multi-female groups, the main method used to form new groups has been to simultaneously release all the unknown individuals together. This provokes a general disorder with many individual conflicts, but the overall goal is to prevent the formation of coalitions that would target the aggression on a few victims (Bernstein and Gordon, 1977; Erwin, 1986). A staged procedure has also proved to yield a lower level of wounding in several cases (Westergaard *et al.*, 1999; Wallis and Hartley, 2001). Animals are first socialised in small groups for several days and once they are stabilised, they are merged into a larger group. It may be advisable to first constitute unisexual subgroups that are allowed to establish hierarchies, and then to reunite sexes (Mendoza *et al.*, 1991). The presence of females in oestrus must be avoided when several males are present. Blunting canine teeth can decrease the severity of wounds during initial encounters but if the harassment persists, even cutting the canine teeth will not prevent serious injuries (Clarke and Blanchard, 1994; NRC/ILAR, 1998).

Merging two pre-existing groups will provoke violent fights between two strong coalitions. This strategy has produced a number of failures in various species and is not advisable (Erwin, 1986; Rhine and Cox, 1989; Watts and Meder, 1996).

9.3.3. Removal and *introduction of individuals*

When conflicts arise and persist in a group, careful monitoring should identify the animals responsible for the attacks. The removal of aggressors can bring peace back into the group (Reinhardt *et al.*, 1987a; Judge *et al.*, 1994), but, in some cases, removing key individuals from the social network can destabilise the whole group. Sometimes, it is advisable to remove the victim (Vermeer, 1997) but often a new animal then replaces the previous one as a victim and target for aggression (NRC/ILAR, 1998). A removed individual can be returned to the group if it is harmed only occasionally. If, however, it suffered from chronic harassment before removal, the chances of a successful reintegration are low as the initial aggressors are still present in the group. As some experimental procedures require that group members be temporarily removed, the longer an individual is away the riskier is the return. If a significant re-ordering of the group structure occurs in its absence, it may be difficult for an individual to reclaim its former social position (Bernstein *et al.*, 1974; Gordon *et al.*, 1992; NRC/ILAR, 1998). The outcome of the reintroduction depends on the social status of the individual and it is easier for group members having a high rank or many allies. If a new group has to be constituted with animals originating from an established group, the best way to avoid de-stabilising the original group is to remove individuals as subgroups of kin-related partners, following the maternal lines (Bernstein and Gordon, 1977).

In most species, the introduction of strangers into a social group may elicit considerable aggression from the group members (Bernstein *et al*., 1974; Morland *et al*., 1992; Reinhardt *et al*., 1995; Watts and Meder, 1996). The difficulties are similar to those encountered in pairing and forming groups from unfamiliar individuals, with the additional problem that many individuals may support each other in targeting a single newcomer. Newcomers should be allowed time to explore and habituate to the introduction area in the absence of the host group (Watts and Meder, 1996). A staged procedure may be advisable to familiarise a newcomer with different subsets of the host group before introducing it to the whole group.

An individual challenging every group member meets a stronger resistance than another accepting immediate low rank and trying to establish relationships (Bernstein *et al*., 1974). This explains why adult individuals, especially males, may meet repeated attacks. As a general statement, new adult males should be introduced only into a group where no other adult males are present (Bernstein *et al*., 1974; Watts and Meder, 1996). This is true even in tufted capuchin monkeys and squirrel monkeys, where the introduction of unfamiliar immatures and adult females raise only low levels of aggression, but if resident males are present, they direct strong aggression against the male intruder (Fragaszy *et al*., 1994; Williams and Abee, 1988; Cooper *et al*., 1997). Similarly, in marmosets and tamarins, introducing a new adult, either male of female, into a family group is rarely successful (Watts and Meder, 1996).

It is worth noting that the introduction of unweaned infants is possible provided that conditions are favourable (Watson and Petto, 1988). In many species, a lactating female that has just lost her offspring will generally be ready to adopt another infant. Introducing an infant in such circumstances leads to a high likelihood of successful fostering (Marsden and Vessey, 1968; Taub *et al*., 1977; Thierry and Anderson, 1986).

9.4. Detrimental consequences of social disruption

Any separation, introduction or change in membership induced by husbandry and experimental procedures is liable to induce stress and negative welfare consequences. Each time a monkey is separated from its companions, it will incur short-term and long-term negative consequences irrespective of age - infancy, adolescence or adulthood. On the other hand, the introduction of individuals with no prior experience of one another generates uncertainty, which is a potent elicitor of psychological and physiological stress (Mendoza *et al*., 1991).

9.4.1. Separation of infants

The impact of separation from the mother is quite profound in the infant primate and is well-documented in infant macaques. They typically display a biphasic response characterised by an initial stage ('protest') of hyperactivity associated with distress vocalisations, followed by a depressive stage ('despair') featured by social withdrawal, a decrease in play, and the development of a typical slouched posture (Mineka and Suomi, 1978; Capitanio, 1986). This is accompanied by physiological disturbances in the regulation of heart rate, body temperature, sleep patterns, cortisol secretion and the immune system (Laudenslager *et al*., 1981; Reite *et al*., 1981; Kaplan, 1986; Coe, 1993). The intensity of the response depends on several factors such as age, species, novelty of the environment and presence of other companions. The presence and care provided by group mates may buffer the detrimental effects of the loss of the mother figure (Kaufman and Rosenblum, 1969; Drago and Thierry, 2000). Providing separated infants with companions or surrogate mothers alleviates distress and depressive behaviours (Harlow and Harlow, 1965; Coe *et al*., 1985; Hennessy, 1985; Koyama and Terao, 1992). Although behavioural signs appear less marked in squirrel monkeys and tufted capuchin monkeys, they are accompanied by physiological effects similar to those found in macaques (Coe *et al*., 1985; Coe, 1993; Mendoza *et al*., 1991; Byrne and Suomi, 1999).

According to the guidelines of the IPS (1993 a,b), young individuals should not be separated from their mothers at an early age (i.e. less than 6 months). They should remain in contact for one year to 18 months in monkeys like macaques, baboons and capuchins. The guidelines of the Primate Vaccine Evaluation Network also state that infants should not be weaned before 6 months and recommend separation at 12 months old (Poole and Thomas, 1995).

On a long-term basis, rearing infants in isolation induces pervasive behavioural problems. They develop abnormal behaviour patterns like motor stereotypies, bizarre postures, self-clasping or self-aggression. Later in life, they appear unable to respond appropriately to conspecifics, they display abnormal reactions to stimuli, heightened fear or aggression, and inadequate mating and parental behaviour (Mitchell, 1970; Capitanio, 1986). Several reports indicate that social deprivation may also alter neurobiological systems (Struble and Riesen, 1978; Kraemer *et al*., 1984). This pathology persists into adulthood and cannot be cured, although re-socialisation with companions may decrease the frequencies of abnormal patterns. Long-term effects may differ according to species; squirrel monkeys appear less affected by early social deprivation than macaques (Hennessy, 1985).

Allowing infants to grow with their mothers in a social group is necessary to warrant normal behavioural development. In the absence of the mother, the presence of peers or adult conspecifics from an early age, and daily contacts with them, may promote a relatively normal development (Champoux *et al*., 1991; Ruppenthal *et al*., 1991; Worlein and Sackett, 1997). Infant macaques reared with peers do not show the self-clasping and stereotypies shown by the single reared infants. However, they may display excessive mutual clinging, fear and aggression. In rhesus macaques, peer-group reared females show a 25% probability of failure to rear their first infant. This contrasts with less than 5% in females reared by their own mother. Moreover, most females reared in isolation exhibit inadequate maternal care (Ruppenthal *et al*., 1976). A female macaque needs to be reared by an adult female, or observe other adult females caring for infants, to perform at least the basics of maternal care. Contact with conspecifics, either with peers prior to adulthood or with one's own infant later in life, greatly reduces the probability of inadequate maternal care (Ruppenthal *et al*., 1976). Marmosets and tamarins who have been removed from their groups before they had the opportunity to help their parents care for infants also have a lower likelihood of rearing their own offspring successfully (Snowdon and Savage, 1989).

9.4.2. Social disruption in juvenile and *adult individuals*

Disruption of social bonds invariably provokes signs of distress in juvenile primates. In rhesus macaques, removing juveniles from their social group induces an acute stress as measured by adrenal cortisol response, and a long-term depression of the immune systems that lasts for several months (Gordon *et al*., 1992; Gust *et al*., 1992; Lilly *et al*., 1999). Even several-year-old juveniles may undergo depressive behaviours if they are separated from their mothers (Kaplan, 1986). The responses of young macaques become worse if separations are repeated (Mineka *et al*., 1981). When individuals are removed along with other companions and placed together in a peer group, their stress is attenuated (Coe, 1991; Gust *et al*., 1996).

Among adult individuals, the signs of distress induced by separation from familiar partners are more conspicuous in marmosets and tamarins than in rhesus macaques and squirrel monkeys (Gust *et al*., 1994; Mendoza *et al*., 1992; Norcross and Newman, 1999; Shepherd and French, 1999). In rhesus macaques, however, females introduced into a new breeding group show elevated adrenocortical responses for as long as three months after relocation (Goo and Sassenrath, 1980). Re-uniting individuals with prior companions generally relieves the stress of separation. However, the return to the social group after several months of absence has the potential to induce stress and a depression of the immune system, depending on how the individual is received by its group members (Gordon *et al*., 1992; Gust *et al*., 1993).

Social interactions involved in the formation of dominance relationships can alter hormonal (e.g. cortisol) and autonomic activity in various primate species in a manner dependent on the relative rank attained by each individual (Mendoza *et al*., 1991). Group formation, separation, reunion or any event modifying attachment bonds and dominance relationships may produce behavioural and physiological signs of distress for a long time afterwards (Raleigh *et al*., 1984; Steklis *et al*., 1986; Coe, 1993). Frequent moves increase aggression by preventing the establishment of stable hierarchies. On a long-term basis, unstable social conditions impair immune responses and increase the susceptibility to infection and disease (Kaplan, 1986; Coe, 1993; Capitanio *et al*., 1998; Ha *et al*., 1999).

10. ANIMAL HEALTH

The primary focus of this report is the welfare of primates used in research, although some relevant animal health issues are briefly outlined in this chapter. It is clear that the health of non-human primates can impact on their welfare as well as the science, since animals that are in poor health will, by definition, also have poor welfare. Veterinarians, with adequate training and experience in non-human primate medicine should be primarily responsible for their veterinary care. A comprehensive and careful programme of veterinary care includes policies and procedures regarding aspects of: husbandry, nutrition, handling, enrichment, animal welfare, training of animals, quarantining newly-introduced animals, hazard containment, and occupational health and safety (ILAR, 1998). Veterinarians may define and develop a health monitoring programme in order to provide health and fitness tests for individual animals, and in order to maintain the good health of the colony by preventing the spread of disease. The programme will also include protecting humans from zoonoses. Comprehensive guidelines have recently been published on the health monitoring protocol of non-human primate colonies (FELASA, 1999). For effective research healthy animals are needed and purpose-bred animals should have a more assured health status than wild-caught animals. The veterinarian is also responsible for the welfare of the animals and for implementing procedures aimed at improving their welfare and minimising pain and distress. For primates in particular, a health programme will include consideration of the mental health of the animals and ways of improving this, as well as their physical health (Weber *et al*., 1999).

On occasions it will be necessary to carry out periodic fitness checks on animals e.g. before they are used in breeding programmes, or used in a research project. Such checks would be facilitated if each animal was uniquely identified and easily identifiable (FELASA, 2002, www.felasa.org). An individual file (so-called 'passport') that might accompany an animal wherever it goes could include details such as identity number, species, sex, generation of captive breeding, genealogy, date and place of birth, date of acquisition, origin (country and institution), age of weaning, history of transportation, breeding scheme employed, reproductive history (e.g. number of offspring, pregnancy diagnosis, veterinary interventions), present and previous housing system (type, size and structure of the enclosure), composition of the group (number of adult males and females, juveniles and infants), rank in the group, presence and type of environmental enrichment, research project history (e.g. starting and ending dates of the experimental protocol, nature and severity of procedure, handling technique, details of involvement of the animal in any training programme and the ability demonstrated, those scientists or groups responsible for the project), and any injuries, negative experiences, or particular characteristics or preferences of the animal concerned. If the animal has had any pathological investigation, a copy of the pathologist's report should be attached.

It would be beneficial if these files on individual non-human primates were supplied to the institutions where the animals were to be used, together with general information regarding the establishment of origin itself. These could include name and location of the establishment, the purpose for which the animals were kept (e.g. breeding for internal experimental purposes and/or as supplier for other institutions, with or without commercial interests), and details of animal care and routine procedures. The retrospective review of such individual files would give a valuable insight on the history and eventual fate of primates used in research.

The formal establishment of a comprehensive health control programme is essential to reduce the risk of transmission of zoonoses to personnel and scientists handling the animals, and help to safeguard the health and, consequently, the welfare of primates at the breeding site, during transport and at the research centre. In addition, variables of the health status might influence the outcome of an experiment and so should be known and documented. Any health control programmes may need to be amended to take into account developments in the use of non-human primates in biomedical research as well as the emergence of potential new pathogens. A significant number of non-human primates bred for research may be the first generation offspring of parents captured in the wild and held in captivity for breeding, and so may be potential carriers of microbiological agents endemic in wild populations. In any event, primates are also susceptible to many of the same infectious agents as humans and, therefore, may acquire those through close contact with humans. The following are examples of examinations that could be performed in the context of a comprehensive health programme.

Physical, behavioural and clinical examination:

This examination could include general signs of good clinical condition: body weight and body condition score, temperature, appearance, signs of genetic abnormalities or diseases, behavioural observations when on its own and with group (e.g. evidence of position in hierarchy, stereotypies, aggression, specific companions), temperament, ease of handling and whether the animal is trained to cooperate in procedures. Immunological tests (e.g. Tuberculin test) may complete the physical examination and should be performed upon arrival and subsequently every 6 months or yearly.

A management strategy for dealing with such problems as fight injuries or nutritional imbalances, which may be encountered with increasing use of foraging and group housing, should be developed and incorporated into any primate health management programme. The benefit of social housing is that the environment is dynamic, unpredictable and variable so there is little habituation, but there are increased risks of infection, wounding and competition for food. With good management strategies these risks can be minimised but not altogether removed (Schapiro and Bushong, 1994).

Laboratory tests:

Laboratory tests, in conjunction with observation of a quarantine period, could help to identify health problems, allowing appropriate control and treatment measures to be instituted to safeguard health and welfare. Tests should be performed upon arrival of the animals at the research centre and subsequently at regular intervals. The following investigations are examples of procedures that may be carried out (Weber *et al.,* 1999) although individual control programmes will be modified at each facility depending on the risk e.g. a closed colony may experience a lower risk of introducing infection than one regularly importing animals.

Tests could include the following.

- haematology for signs of infection, leukaemia etc.;

- biochemical tests for enzyme, hormone, metabolite levels for example;

- urinary tests;

- serology to check for disease exposure, immunity, carrier status etc.;

- bacteriological tests with regard to *Campylobacter*, *Leptospira*, *Mycobacterium*, *Salmonella*, *Shigella*, *Yersinia*, *Pseudomonas*, *Mycoplasma* as examples;

- virological tests for example concerning Herpesviruses, Hepatitis A and B, Simian virus 40 (SV40), Simian haemorrhagic fever, Ebola Reston-Marburg viruses, Simian immunodeficiency virus (SIV), Simian T-cell lymphotrophic virus (STLV-1), Simian retrovirus type D virus (SRV/D), Foamy virus, Monkeypox virus, Lyssavirus (Rabies virus), Yellow fever;

- parasitological tests for ectoparasites, such as mites and lice, and endoparasites, for example *Entamoeba histolitica*, *Toxoplasma gondii*, *Giardia* spp., *Plasmodia* spp, *Strongyloides stercoralis*, *Trichuris* spp., *Prostenorchis elegans*, *Pneumonyssus sinicola*, and fungal tests; and

- genetic profiling, for example using DNA probes, in order to identify animals which may carry a genetically recessive disease or particular genotype, which could be relevant to their use in research.

11. TRANSPORT

One of the main threats to good welfare regarding importing non-human primates from overseas is their prolonged transport. Even though some improvements have been made concerning the shipment containers and their equipment during the last few years, transport causes an enormous stress for the animals (Wolfensohn, 1997; Prescott 2002). In contrast to the transport of farm animals, there has been little systematic research designed to assess the impact of transport on non-human primates (Wolfensohn, 1997) although there has been much speculation on the potential impact of this practice. The Scientific Committee on Animal Health and Animal Welfare has already produced a report on the welfare of animals during transport, which gave details for horses, pigs, sheep and cattle (SCAHAW, 2002). A report is in preparation considering the welfare during transport of other species not considered in that previous report.

The transport procedure may start at the breeding centre some two to three weeks before shipment. The animals are separated from their groups and taken into single cages for medical investigations and quarantine. At the end of this period they are placed into transport crates that are very small. The size of these crates for smaller species is only 25x40x50 cm, and for young macaques it is 30x50x65 cm. If they are being imported from outside the EU they can spend a minimum of 36 hours in these crates but it is often more than 50 hours. This is the time it takes for the journey to the airport, to check in and load, the flight to the European destination, to check out with customs and after appropriate veterinary checks, and transport to the end-destination. During this time food and drink are restricted, they can be exposed to an extreme range of temperatures, and draughts and noise cannot always be avoided. The animals may sometimes have to wait on the runway for hours before they are loaded into the aircraft. Land journeys can also be very stressful for the animals. As only one example, most road transport vehicles are not fully air-conditioned and the animals may be exposed to extremes of temperature and humidity.

Another factor is that some international airlines have in recent years decided to cease transporting non-human primates. Possible contributory factors to such decisions may have been safety concerns following the shipment of a consignment of primates infected with an Ebola-like virus in the early 1990s, as well as campaigning by animal rights groups. Consequently it may be more difficult to import non-human primates and this can have serious welfare implications if transport conditions are not optimised. To safeguard the welfare of non-humn primates during transport, staff that are sufficiently trained or experienced in the transport of non-human primates, and the necessary expertise and infrastructure are important considerations. IATA Guidelines can be a useful tool to advise airlines of specific considerations regarding the transport by air of non-human primates (www.iata.org).

There is some work in progress on monitoring the behavioural and biomedical sequelae of transport (see chapter 12.1) but it is clear that it must have negative effects on welfare. Diarrhoea, which is the main clinical problem during quarantine of imported primates, may be due in part to the stress of transport.

12. SPECIFIC USES IN SCIENCE

12.1. Sourcing of Animals/Quality Assurance Issues

Broadly speaking, apart from marmoset and chimpanzee production, there is a significant shortfall between the requirements for research and the production of other species of primates, notably macaques, within Europe, and research institutions are obliged to import animals from overseas to satisfy requirements. Sourcing animals raises issues regarding animal quality, animal welfare and transport stress (Wolfensohn, 1997; Prescott, 2002).

As discussed in chapter 4, there are difficulties in assessing the number of primates bred in Europe for use in research and predicting the number and species required for future research needs. Although the number of animals used in research and development is difficult to predict, it may not fall and could even rise over the next 10 years. This is because the development of pharmaceutical products may become more dependent upon experiments with animals whose genomic basis most closely resembles that of humans (e.g. gene therapy, cancer research, genomic basis of neurological diseases, new vaccines).

A ‘zero option’ for non-human primate use in Europe has been suggested (Balls, 1995), proposing that the use of primates be gradually reduced to zero over the next 10 years or so. In considering this option the possible consequences of doing so, without the use of validated alternative methods in place, must be carefully assessed as otherwise human health could be jeopardised. For example, primates are used in testing polio vaccine safety and not to do so could result in the use of a vaccine that either fails to induce an adequate immunity in children, or puts humans at risk of disease because the virus retains some virulence. An alternative to the use of primates for this testing, using a transgenic mouse, is being developed but has not yet been adequately validated for regulatory acceptance.

Apart from changes in the overall numbers of primates used, the balance of species used could be altered. It might, for example, be possible to use marmosets rather than long-tailed macaques in some areas of regulatory testing. Such a step would, of course, be dependent upon the regulatory acceptability of the marmoset in this context. If this were to occur, the need to import the current large numbers of long-tailed macaques would decline and breeding of marmosets within Europe could be increased accordingly.

The factors that influence the selection of species of primate for research and testing are diverse and include practical considerations such as availability of subjects, background data, regulatory acceptability, and species-specific biological attributes and propensities. Selection of a particular species undoubtedly reflects a balance of these factors. For example, regarding the use of marmosets in regulatory tests, there may be difficulties concerning the lack of historical background data for this species, availability of animals, high individual variation (files on individual non-human primates might help in this regard see Chapter 10), stress experienced on dosing or handling and unsuitability for specific procedures such as repeated blood sampling. A thorough appreciation of the advantages and disadvantages of a particular species relative to other primate, as well as non-primate, species, is of the utmost importance.

It is also important for the researcher that the species-specific attributes which influenced the selection of a particular species as a research model and the quality and welfare of the experimental animals are safeguarded (Röder and Timmermans, 2002). It will also be important to anticipate possible future requirements for genetically modified primates for research as well as research involving stem cells from non-human primates. Such issues will inevitably arise in the future and consideration should be given to the predicted trends in research and associated ethical issues. For the foreseeable future, research involving non-human primates in Europe may continue to necessitate the importation of animals for research and breeding stock from overseas. The issues of quality and health status of non-human primates for research purposes are important considerations with regard to imports. The level of characterisation of primates in research will also very much depend upon scientific requirements of the investigation, for example, histocompatability loci (MHC) typing might be a very important consideration in many areas of immunological research but would not generally be considered as being required in regulatory testing.

12.2. Legal and regulatory issues concerning the use of non-human primates in research

12.2.1. Laws regulating the use of non-human primates in Europe

In addition to the scientific justification of research and the potential benefits that may accrue, the impact on the animals should be taken into account when deciding which species should be used, especially an assessment of the impact on the animal's welfare. Experiments involving primates as defined in Directive 86/609 are subject to the same requirements as those undertaken on other species. In particular, the Directive specifically states that efforts must be undertaken to replace animal experiments with alternative methods. Furthermore, in Directive 86/609/EEC (Article 7) it is stated that "in a choice between experiments, those which use the minimum number of animals, involve animals with the lowest degree of neurophysiological sensitivity, cause the least pain, suffering, distress or lasting harm and which are most likely to provide satisfactory results shall be selected".

The requirement that efforts must be taken to replace animal experiments with alternative methods, was subsequently highlighted by the 50% reduction target proposed in the European Commission's 5th Environmental Action Programme but not ultimately adopted. Directive 86/609/EEC specifies that the use of these species is permitted only when it could be shown that no replacement alternatives could be used in place of an *in vivo* study and the objective of the study would not be achieved by using another species. Sometimes, more restrictive regulations are adopted by individual countries. In the UK, for example, the use of primates in studies requires specific authorisation from the Home Office and if animals are to be kept for long-term studies then users are strongly encouraged to group house them.

Under Directive 86/609/EEC only purpose-bred primates can be used, and special exemption has to be obtained in order to import wild-caught animals. In some countries, endangered species can only be used in studies to ensure the survival of that species, or additionally, for example, for essential biomedical research when no other suitable species could be found. In addition, the use of wild-caught primates would be considered only in specific and exceptional circumstances and, as only one example, in the UK would be referred to an Animal Procedures Committee, as is any study on primates which might entail procedures that cause substantial severity. The use of an Old World species is only considered when a New World species could not be used, due to the difficulty in providing for the behavioural needs of Old World species rather than a selection based on cognitive abilities. When animals are imported from third countries, the importer must provide proof that they have been purpose-bred. In some countries when the severity limit for a protocol has been exceeded, the experiment (e.g. animal dosing) is required to be stopped. However such end-points will vary between countries. Although the great majority of toxicity studies are terminal, because of the necessity to examine tissues and organs for pathology, re-use may be possible after some pharmacokinetic, toxicokinetic and metabolism studies.

The CITES regulation adds an additional control over trading of primates and all primates that are listed on either Appendix I or Appendix II of the CITES Treaty are endangered species. This means that they are either in danger of extinction or may reach that category in the foreseeable future, unless action is taken to protect current populations. Conservation issues may also influence the use of non-human primate species in research, separate from all welfare considerations.

12.2.2. Main biomedical areas using non-human primates

Primates are required in safety testing of pharmaceuticals and other chemicals, in the production and quality control of vaccines, in the testing of dental materials, in the neurovirulence testing of polio vaccines, and in fundamental biomedical research.

A comparison can be drawn between the statistics for 1999 on the use of non-human primates for experimental purposes in individual Member States (EC, 2002, see Chapter 4) and corresponding data data for 1996/1997 (EC, 1999; Bottrill, 2000). Although in 1999 the UK and France were still confirmed as the major users of non-human primates (35% and 25% respectively of the total number were used in these two countries), a significant increase (+21%) in primate use was reported for Germany, representing in that year the third major European user (23%). The remaining animals were mainly used in Italy, Belgium (both 5%) and The Netherlands (3.5%), whilst in 5 out of the 15 reporting Member States no non-human primates had been used.

In 1999, the greatest proportion of non-human primates (53%) was used for toxicological and other safety evaluations, followed by their use in research and development of products and devices for human medicine, dentistry and veterinary medicine (26%), and in biological studies of a fundamental nature (18%). In total, approximately 95% of non-human primates used in 1999 were used for regulatory requirements, either for the production and quality control of products and devices or in toxicological studies.

It is noteworthy that 97% of non-human primates used in 1999 for toxicological and other safety evaluation were used for the development of products or devices for human medicine, dentistry and veterinary medicine, and no animals were used in the fields of chemicals, agrochemicals, food and additives, cosmetics, toiletries, and household products.

Animals used for fundamental research in 1999 were distributed as follows: research involving the human nervous system and mental disorders (15%), human cancer (3.6%), human cardiovascular diseases (2.4%), other human diseases (79%). It is likely that a large proportion of this group of ‘other human diseases’ includes research into the mechanisms of HIV infection, AIDS, the development of anti-HIV vaccines, and other re-emerging infectious diseases (e.g. malaria, tuberculosis etc.). Other areas include research into shock, including septic shock, development of techniques, mainly for PET (Positron Emission Tomography) scans, investigations into reproductive function, dental research, immunological, anatomical and histological investigations, organ transplantation, investigations of coeliac disease, diagnostic procedures, ophthalmology and metabolic diseases. Finally, a number of animals were used for studies on ageing, hepatic cirrhosis, and gene delivery.

12.2.3. Regulatory requirements for the use of non-human primates

There are two different steps in the research and development process where primates are used; pharmacology studies to investigate efficacy, and safety studies requested by regulators. Studies may have to be performed on primates when efficacy cannot be established in other species. Regulators from all the three major geographic areas (Europe, US, and Japan) defined a list of pharmacological and toxicological investigations that are necessary to define safety and metabolic patterns of new drugs in animals. Based on that data, safety margins can be calculated for their use in humans. According to ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) Guidelines that were adopted in 1995 (ICH 3, Closing Report issued in Yokohama), the toxicity of all new drugs should be investigated following both a single administration (acute toxicity) and repeated exposure that best mimics the therapeutic use in man. In addition, toxicological effects on the reproductive system and potential adverse effects on major organs and systems (CNS, cardiovascular, excretory, gastrointestinal, etc.) need to be investigated in animals throughout the development phases of new drugs.

It states that both single and repeated-dose "toxicity tests must be conducted on at least two mammalian species of known strain using equal number of both sexes", one being a non-rodent. In the selection of species, it is desirable that, with regard to the metabolism and the pharmacokinetics of the substance (including the biotransformation of the product), the species chosen should be as closely similar to man as possible within the usual spectrum of laboratory animals used for safety testing. In the definition of the number of animals needed, regulators indicate that the size of the experimental groups should be such that all toxicologically important effects due to the treatment should be revealed, and should also be large enough to permit taking animals at intervals before the end of the study without interfering with the final evaluation of the study.

For studies aimed at revealing reproduction toxicity in mammalian species, the predominant species used are rats and rabbits, both for practical reasons (length of pregnancy, litter size, etc.) and the large amount of background knowledge available for these species. Although primates are not generally used for these studies having several disadvantages (insufficient historical background data, often numbers too low for detection of risk), there could be a case for their use in reproductive toxicity testing. In these studies the objective is to characterise a relatively specific or probable reproductive toxicant, rather than detect a hazard, and primates may be the only sensitive species.

A very similar approach to detect potential adverse effects was established for biotechnology products, such as hormones, cytokines, blood products, monoclonal antibodies, vaccines, etc. For these particular classes of compounds, selection of the animal species should be based also on their immunoreactivity and species-specific pharmacological effects. Pre-existing knowledge, where available, on the suitability of animal species in relation to specific product groups should be taken into account. Where it is not possible to predict the value of a particular animal species for safety testing, initial investigations may be carried out in any of several rodent and non-rodent species, including primates.

12.2.3.1. Safety testing of human pharmaceuticals and other chemicals

International Guidelines and regulations for testing the toxicity of pharmaceuticals require that safety data are obtained in a second non-rodent species for acute, subchronic and chronic toxicity testing. Although the dog is usually the default non-rodent species and in some cases is also the preferred species, primates need to be used in cases where the dog is very sensitive to the effects of the test compound or has a very different metabolism from that seen in humans. In most cases, unless contra-indicated on scientific grounds, when a primate species needs to be used the usual choice is the macaque or the marmoset. The macaque is likely to be the species of choice where there are background data on the material or similar materials in the macaque. When the test material is shown to be different between the two species, or due to technical limitation, usually the smaller species is used (marmoset).

An important point to note is that primates have become the automatic second default non-rodent species to be used when the dog is inappropriate, since regulators are less willing to accept data obtained from pigs or ferrets and may still require such studies to be repeated in primates (Weber, 1997). The Japanese Ministry of Health and Welfare Guidelines (1995) state that the dog is often the appropriate non-rodent species in acute toxicity studies, but that monkeys may also be considered. The species selected should be the most suitable to characterise the intrinsic toxicity of the test substance. For repeat-dose toxicity studies, the non-rodent species should be capable of demonstrating the principal pharmacological effect of the test substance, but it is also important to take into account similarity to the species used in the single-dose studies. European regulations do not identify a specific non-rodent species, while the US FDA has not published any formal guidelines on the testing of pharmaceuticals in animals. In general, study protocols are designed to satisfy regulatory agencies throughout the world, although there are differences in the minimum numbers of animals that are acceptable per study. Among regulatory agencies the US Food and Drug Administration (FDA) is generally considered to have the most extensive requirements, as evidenced by the following example. European requirements specify a group size of 6 animals of both sexes to be used in sub-chronic toxicity studies in non-rodents, but the FDA may require 8 or more animals per group. Longer-term supplementary animal studies may be required during Clinical Phases II and III, and if the drug is intended for chronic use in man, then studies of 29-32 weeks may be required, but the FDA may insist on a 52-week study. Chronic non-rodent studies require four animals per sex in each group, giving a minimum of 40 animals per study, although the FDA may require up to 56 animals to be used.

The development of human-specific biotechnological products, may in some cases result in substances which do not show cross-reactivity even in macaques. For example regarding HIV, it has been demonstrated that macaques are not the appropriate model to mimic the chronic form of the disease in humans, although they are used in other parts of AIDS research.

Although there are no specific references to non-human primates as the non-rodent species in European, US or Japanese regulations on toxicity testing of industrial or agricultural chemicals, the Guidelines for Toxicity Testing of Chemicals issued by MITI (the Japanese Environmental Agency) specifically mention the monkey as well as the rat, rabbit and dog as suitable species for toxicokinetic studies, and state that these studies should use the same species as used in other toxicological tests of the chemical.

In regard to food additives, the dog, pig and non-human primate are referred to in the Reports of the Scientific Committee for Food: Safety Assessment Guidelines, published by the European Commission in 1980 (SCF, 1980), in a statement that sub-chronic and chronic studies in these species may need to be extended to 1.5-2 years. The Presentation of an Application for Assessment of a Food Additive Prior to its

Authorization published by the European Commission in 1989 mentions that dogs or non-human primates may be useful for chronic toxicity studies "when the nature of the toxicity or the procedures required necessitate the use of large species". The US FDA Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food (Red Book) of 1982 mentions the rabbit, dog, cat and primate as possible species used, in addition to rodents for acute toxicity testing. However, the 1993 Draft Red Book II assumes the dog to be the usual second species.

12.2.3.2. Biotechnology-Derived Pharmaceuticals

The International Conference on Harmonisation (ICH) Guideline S6 *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* states that the specific characteristics of these products may preclude the use of rats and dogs, and the species selected must be one which expresses the relevant receptor or demonstrates a similar tissue cross-reactivity profile to that of human tissue. In addition, the guideline discusses the problems that might arise from the production of neutralising antibodies to the test substance. While these sections of the guideline do not refer specifically to primates, the comments nevertheless imply that these might be the only appropriate species in certain cases. The selection of the species for these studies is based on the results of a tissue cross-reactivity screen.

12.2.3.3. Testing of dental materials

The testing of dental materials falls under the field of two International Standards, ISO 7405:1997 Dentistry - Preclinical evaluation of biocompatibility of medical devices used in dentistry - Test methods for dental materials, and the 20-part ISO 10993:1997 Biological evaluation of medical devices. ISO 10993 does not include any tests on primates, but three tests, all terminal, are listed in ISO 7405. Monkeys, dogs, ferrets and miniature pigs are listed as alternatives, but the choice of species, and indeed the choice of which tests to perform, is left up to the company making the submission.

12.2.4. Production and *quality control in polio vaccine*

The production and quality control of polio vaccine, specifically the attenuated oral vaccine, is of special interest to any consideration of the use of primates in Europe, because these animals are used on a large scale in this area and because many of the vaccine manufacturers are based in Europe. Principal species used are the African Green monkeys and long-tailed macaques for the production and quality control mainly in neurovirulence testing. Monkeys are also used for the neurovirulence testing of live mumps, measles and rubella vaccines. However, the test is carried out only on individual seed lots approximately every 5-10 years, in contrast to the necessity of testing each final batch of oral polio vaccine.

Addressing the issue of monkeys, the European Pharmacopoeia recommends that manufacturers produce larger seed lots which will last for many years, specifically to reduce the numbers of animals used for testing. Following the implementation of alternative biotechnology methods, testing of some vaccines in monkeys was eliminated (e.g. Hepatitis B vaccine).

Two types of polio vaccines are available, the inactivated Salk vaccine (inactivated polio vaccine, IPV) and the attenuated Sabin vaccine (oral polio vaccine, OPV). Both can be produced in primary monkey kidney cells, in a monkey kidney cell line (Vero) or in human diploid cell cultures. OPV is cheaper to produce and is administered by the more convenient oral route as opposed to the injection required with IPV.

According to the EU Pharmacopoeia, each lot of OPV has to be tested in monkeys before being released for use, to guarantee that the vaccine does not contain the neurovirulent wild-type virus.

IPV is used routinely in the Netherlands, Canada and Scandinavian countries, as well as for the vaccination of immunocompromised individuals. In the rest of Europe, the US and most of the rest of the world OPV was, and still is, the vaccine of choice, although the US Centers for Disease Control and Prevention and the American Academy of Pediatrics have announced that only the IPV is to be used in children from January 1, 2000.

Polio vaccines were first produced in primary kidney cell cultures from wild-caught rhesus macaques. Following the discovery in the 1960s that batches of the vaccine were contaminated with the SV40 (Simian virus 40) virus, greater attention was given to ensuring that the animals used were as virus-free as possible. One solution was to use captive-bred long-tailed macaques. Other companies shifted to using wild-caught African Green monkeys from Barbados that, due to their historical origin, have remained relatively virus-free- for example they are free from SV40 and SIV (Simian immunodeficiency virus).

In contrast to polio vaccines, where the majority of manufacturers use monkey kidney cells (Griffiths, 1999), other virus vaccines are mostly produced in human diploid cells (Hayflick, 1999).

Based on estimations made by manufacturers, about five million doses of vaccine may be produced from the kidneys of one monkey, and one monkey is used to test 2.5 million doses, giving a total of three monkeys used for the production and testing of five million doses. When vaccines are produced in cell lines, one monkey is required to test every 0.5 million doses, giving a total of ten monkeys required to test five million doses. Although technically it might be possible to produce lots larger than 5 million doses, this would require regulatory approval that would have to be preceded by a parallel validation and testing

Since the early 1960s, human diploid cells (WI-38 cells) have been used for the production of polio virus, followed by other strains such as MRC5, TIG1 and 2BS, but only in the 1970s did the use of such cells become accepted. Meanwhile, the fibroblast-like Vero cell line had already been established from the kidney tissue of an African Green monkey. Since the DNA of these cells may contain endogenous tumour virus sequences and may undergo further changes and release oncogene products or other growth-promoting proteins (Griffiths, 1999), the cells are checked for the presence of viral DNA and tested for tumourigenicity.

While testing of IPV is necessary to detect the presence of residual live virus, this may be done in primary monkey kidney cells or in the cell lines used for vaccine production. For OPV, monkeys are used to test neurovirulence. This test is conducted both on the seed lot, and on each monovalent bulk, i.e. on each of the three polio vaccine serotypes, which together make up the complete vaccine. Monkeys are injected with the test vaccine or reference preparation intraspinally, or in the case of Japanese regulations, intracerebrally and observed for 17-22 days. They are then killed for histological examination of the nervous system tissue. Current requirements only state that animals should be killed when they become moribund or severely paralysed. The monkeys usually begin to suffer from paralysis after only a short period, however, the observation period of 17-22 days is considered to be necessary in order to ensure that histopathological signs of neurovirulence have developed.

The severity of the lesions induced by the vaccine is scored in order to assess whether its pathogenicity is different from that of the reference preparation. The production of a trivalent final bulk according to the requirements of the European Pharmacopoeia involves the test has being carried out at least three times in a total of 110 monkeys. Primates are used for this purpose, as they are the only species that are naturally susceptible to the virus. Long-tailed macaques are used for historical reasons, but African Green monkeys can also be used.

Although the potency test required by the European Pharmacopoeia is conducted in chickens or guinea pigs, it should be noted that the US requirements (CFR 630.3, 1993) are that potency testing must be carried out in monkeys. The US requirements for monkeys to be used in the potency testing of IPV may have increased relevance following the decision that only IPV is to be used for vaccinating children in the US. If any of the US vaccine supplies are to be provided by European manufacturers, they will need to be tested in monkeys. Nevertheless, any consideration of the lack of harmonisation between Europe and the US must take into account the criticism of the current European test, namely that the immune responses of guinea pigs and chickens are not comparable with that of humans. However, the cited source for this statement (Minor, 1990) also suggests that the immune response of monkeys may differ from that of humans. The response of rats is considered to resemble the human response, and therefore this species might be a suitable alternative to the use of monkeys. The PEI report also raised the possibility of using suitable strains of mice for this purpose. Current initiatives are focusing on the use of guinea-pigs for combined testing. Although a WHO collaborative study did not succeed in validating an *in vitro* method for the measurement of IPV D-antigen (Wood *et al*., 1994, 1995), the method is still considered to hold promise once modifications have been introduced. Sawyer *et al*. (1997) have reported the development of a series of monoclonal antibodies which may be useful for the improved standardisation of this assay. There may also be prospects in the long term for developing a test based on the observation that human peripheral blood lymphocytes can be stimulated to produce serotype-specific antibodies against wild-type polio virus *in vitro*.

Based on a report of the WHO Expert Committee on Biological Standardization (1999), transgenic mice could offer a reliable alternative to the use of monkeys in testing neurovirulence. Following the full validation of the procedure and the establishment of a new international reference material for the assay, manufacturers and national control authorities would be encouraged to use transgenic mice instead of monkeys for neurovirulence testing. Another method currently under serious consideration is the MAPREC assay (Mutant Analysis by PCR and Restriction Enzyme Cleavage), to detect the presence of mutations that are associated with a reversion to neurovirulence in type 3 vaccines. This assay is already well-established and widely used by a number of manufacturers and control authorities to characterise virus seeds and monitor production consistency. The major advantage of the MAPREC assay is that it does not require the use of any animals.

12.3. Modifying the use of primates in scientific experiments

There are practical ways in which the use of primates might be improved, from the viewpoint of gaining more scientific information from the use of individual animals, while also reducing any suffering caused to the animal by their use in research. One of these ways may be to have specialised centres that are well-equipped in terms of facilities and expertise. Such a concentration of resources could well produce better science as well as improved animal welfare.

The concept of the Three **R**s aims to ensure that animals are only used when no **R**eplacements are available; that the number of animals used is **R**educed to the minimum needed to achieve the scientific objective; and that the experiments are **R**efined so that only the minimum degree of animal suffering is caused. These three aims are legally mandated within the EU through the Directive that regulates research using animals (EU Directive 86/609/EEC). Research projects should be evaluated in detail for their application of the Three Rs principle, and for the standards of experimental design and research. However, conflicts may arise where pharmacopoeial requirements might require more suffering than is strictly necessary to achieve the scientific objective (e.g. rabies, pertussis, polio, erysipelas and tetanus vaccine potency testing).

There is the opportunity to reduce the number of animals used in scientific experiments, and to refine these experiments so that less suffering to primates is caused e.g. through improved husbandry, better experimental design, and the use of earlier endpoints thus minimising the degree and duration of suffering. In recent years there has been a major change in available knowledge and attitudes due to the rapid development of animal welfare science (Broom and Johnson, 1993). The result is that refinement possibilities are now much more sophisticated and the third **R** of refinement has become more applicable.

The recognition and assessment of pain and distress in animals impacts on how humane endpoints in research are defined and implemented. Humane endpoints, that is when an animal is killed or withdrawn from an experiment, may be the point at which the scientific objective has been achieved, or when an animal is no longer scientifically useful (Hendriksen and Morton, 1999).

The development of initiatives to identify the earliest point at which an experiment can be terminated (define endpoint criteria) is of major importance, as to prolong the experiment causes animals to suffer unnecessarily and for no scientific benefit i.e. it causes 'avoidable' suffering (Morton, 2000; OECD, 2001).

Similarly, designing experiments carefully in a way that causes less harm can be beneficial to the animal's welfare. It involves both a statistical (Festing *et al.,* 2002) and a practical approach not involving statistics (Morton, 1998) for example, whether drugs are effective with minimum insults before greater ones are applied (e.g. a noxious stimulus when testing an analgesic, tumour size in anti-cancer therapy).

The requirements of the researcher will, of course, be dependent upon the nature of the research being undertaken. If, for example, the experimental protocol necessitates animals being singly housed, maintained under high levels of biocontainment or restrained for prolonged periods, the researcher has particular responsibilities and wherever possible needs to seek creative solutions to mitigate any adverse effects on welfare of the experimental situation. This is important not only from an animal welfare perspective but also significantly impinges upon the quality of the research output.

The use of restraint chairs for non-human primates is a case in point. 'Primate chairs' in a plethora of designs and with various degrees of restraint are routinely used in some areas of research, for example to facilitate single cell recording from conscious animals in neurophysiological research or to enable time-critical blood sampling in pharmacokinetic studies. There are, however, numerous reports which cite adverse electrophysiological, neuroendocrine or immunological sequelae as a consequence of such restraint (Bouyer *et al.,* 1978; Gauquelin-Koch *et al.,* 1996; Golub and Anderson, 1986; Mason, 1972; McNamee *et al.,* 1984; Morrow-Tesch *et al.,* 1993; Morton *et al.,* 1987; Nakamura *et al.,* 1982; Rabot *et al.,* 1997; Wheeler *et al.,* 1990). Moreover there are clear suggestions that habituation to the chair does not prevent the adverse biological impact of the procedure.

It is essential that the potential impact on the animal is acknowledged and taken into account during the assessment of the welfare impact of the research being undertaken, as well as any potential problems in the interpretation of the results. There will be situations when the use of some form of restraint is unavoidable and in such circumstances, there is an imperative to investigate alternative designs that address an animals' physiological and morphological propensities and to also reduce the degree of restraint required by pursuing options for training subjects to co-operate with experimental procedures.

Similarly, the need for long term single housing must always be critically examined and generally considered very much as an exception rather than the rule. Options for pair or group housing during periods appropriate to the experimental protocol should be investigated where practicable.

Food and water deprivation is frequently used in studies that require animals to exhibit conditioned behaviours in order to gain access to appetitive rewards. Such deprivation is not always required if the reward offered is sufficiently attractive to maintain performance: Pearce *et al*. (1999) have trained marmosets to respond to stimuli in order to gain access to a preferred foodstuff (banana milkshake) that is not encountered elsewhere in the diet. This reward has been used to sustain daily performance on the task for up to 18 months. It also has to be recognised that deprivation itself may have adverse effects on an animal's physiological as well as psychological welfare, which in turn may affect the scientific data being collected.

As discussed in chapter 4.4, prioritising and supporting collaborative projects could ensure the best use of primates, decreasing total number of animals required and safeguarding animal welfare. This approach could also help to promote good practices between participating laboratories. The sharing of in-house data, where commercial interests allow, and better reporting of experiments in the scientific literature (Morton, 1992) could also help to reduce and refine the use of primates and other animals in scientific experiments. This could involve reporting 'negative results' and providing details of any suffering to the animals, and how it can be recognised, avoided and alleviated. The provision of more precise and accurate details in scientific papers could also promote the best use of animals in science. Several papers have been criticised for giving inadequate details, leading to the work being repeated in another laboratory (Smith *et al*., 1997), as well as for insufficient or inadequate analysis of the data (Festing, 1992, 1994) and, regrettably also for poor science (Hampson *et al*., 1990; FRAME/CRAE, 1987).

Furthermore, new developments in science increasingly enable more data to be gained from animals. Non-invasive methods such as the use of NMR, PET, and CAT scanning give the opportunity to gain new and more relevant data. The miniaturisation of research methodology so that more results can be obtained from a single sample or better profiling in drug studies can be made as more samples can be taken, has been a significant advance. The major advances in telemetry and data logging are providing more accurate and valuable scientific information, as studies can now be performed on conscious animals for prolonged periods, while they are in their own cage or in another familiar environment.

However, the impact of some of these 'advances' on the animals have to be balanced against the potential for repeated use of that animal, as well as the pain and distress caused by implanting the electronic device in the first instance as well as the burden of carrying such a device in or on its body.

13. CONCLUSIONS[1]

Husbandry

1. Even though primates are taxonomically placed within a single order, a great variation exists between species. In order to improve the welfare of primates in captivity, knowledge of the life and adaptation of the species under natural conditions is essential (Ch. 5).

2. As with other mammals in captivity, primates have basic physiological needs, as well as behavioural needs associated with living in groups, adapting to their surroundings, and security and socialisation during the neo-natal period (Ch. 5).

3. Most primates are highly social and intelligent animals and their cognitive skills have been shaped by evolution to find and handle food, and to relate to other individuals in a social group. Having social partners is one of the most significant needs of primates and they develop abnormal behaviour patterns when socially deprived. Providing social partners is an important way to provide stimulation to animals and to enrich their environment (Ch. 5 and 9).

4. Primates need an enriched and stimulus-enhanced environment in captivity to explore, manipulate, play, forage and search for food; merely satisfying minimum space requirements is inadequate (Ch. 7). They need some unpredictability in their environment, allowing them to make choices and have some control over any likely outcome. Primates normally move and live to exploit to a maximum the potential of tri-dimensional space available to them. Enclosures that allow normal elaborate patterns of boisterous locomotion (e.g. outdoors) are essential to ensure good welfare of captive primates (especially if young) (Ch. 9).

5. Dominance hierarchies can be expressed through feeding order in primates and so some animals may not receive sufficient access to food. Therefore, it is important that all animals in a group have adequate access to food resources (Ch. 7).

[1] Conclusions are numbered and a figure in brackets indicates the relevant chapter from which they have been drawn.

6. Improvements have been made in captive primate housing conditions beyond the currently required standards, but despite this, some of these conditions may still only partly meet the animals' needs with respect to behavioural, physical and physiological requirements (Ch. 8).

7. Outdoor housing can be used for primates, particularly stock and breeding animals, and sometimes experimental animals, in combination with indoor housing, as it is beneficial for their welfare. However, the climate has to be suitable and the animals provided with a choice of indoor or outdoor accommodation. This approach increases the variety of stimuli in an animal's external environment but raises some concerns relating to disease control (exposure to disease vectors, wild birds etc.) (Ch. 7)

8. When primates cannot express their normal behaviour and satisfy their needs to show certain behaviours, either because of a lack of environmental diversity, or an insufficient amount of space, they develop abnormal behaviour patterns (e.g. stereotypies) (Ch. 9). When manifestations of inappropriate and abnormal behaviours are observed they tend to be severe but there is evidence that they can be, at least partly, ameliorated by attending to that animals' social and environmental needs, and by husbandry modification (Ch. 6).

9. Since primates are usually social animals, single housing is always detrimental to their welfare, and placing them in cages in double-tiers impairs their natural vertical flight reaction and contributes to poor illumination of cages (Ch. 7). The consequences of social deprivation can be especially negative for infant macaques raised in isolation, as they may become fearful and aggressive in adulthood (Ch. 9).

10. Aggression and competition are a normal part of primate social life but in captivity primates are confined, and an individual may not be able to escape from the aggressor. Providing visual barriers and cover has proven to be an effective means of reducing aggression. Modifying the composition of a social group is sometimes necessary but the consequences are often difficult to predict. When changing group composition or introducing individuals to each other, there is always a risk that animals will fight and inflict wounds on each other, thus resulting in poor welfare (Ch. 9).

11. The behaviour and responses of animals depend not only on individual characteristics (e.g. age, sex, personality) but also on an animal's rearing experience, history, rank in the group, and relationships with conspecifics and handlers. The management of primates needs a good knowledge about the biography of the individuals. The advice of an ethologist in any enrichment programme and on socialisation procedures would be beneficial (Ch. 9).

12. Social instability is stressful and has negative behavioural, physiological, and immunological effects in primates (Ch. 9). The composition of a social group may be disrupted, for example, when an animal has to be removed for health or experimental reasons. Re-introduction of these animals needs to be carefully monitored, and sometimes it may not be possible because of potential adverse welfare consequences caused by aggression on re-introduction to the group (Ch. 7). The use of anxiolytics and blunting of canine teeth in primates, to limit the effects of aggression upon introduction of animals to social groups, can have serious adverse effects on their welfare (Ch. 9).

13. It is possible to assess primate welfare through a range of general measures but more research needs to be carried out to determine the appropriate measures for each species (Ch. 6). Moreover, there is a lack of integrated research programmes into housing and husbandry of the various primate species, as well as environmental enrichment. This is important as it may impact on both the animals and on the research being carried out on them (Ch. 7).

14. Detailed data on the care and use of primates would assist studies aimed at safeguarding their welfare. Although some data is collected within the EU, further information could be provided on the country of origin of primates used, the number maintained for scientific, stock and breeding purposes, the system of housing, the severity of experimental procedures performed, the scientific justification for their use, as well as the selection of a particular species (Ch. 4).

15. The exchange and dissemination of technical information would help to ensure good welfare and to identify good practices relating to husbandry, rationale for use, severity of procedures, sharing of tissues and experimental data, and validation of alternatives to their use and any re-use (Ch. 4).

Breeding and supply

16. In terms of the welfare of macaques, the best system of management is to have harem groups and to replace the existing females gradually by leaving young female offspring in their maternal group until they become sexually mature. The males have to be changed periodically to prevent excessive inbreeding. While this system has the lowest productivity of all described systems it has the considerable advantage that animals show few social abnormalities, and so it is a particularly suitable system to establish permanent self-sustaining colonies and the provision of high quality animals for science (Ch. 8).

17. When individual primates are kept in single cages for prolonged periods and infants are reared without peer contact their welfare is poor. Infants raised under this system are subsequently seriously abnormal both socially and sexually. Moreover, early weaning and separation is very stressful and such animals often show poor reproductive performance, poor maternal behaviour and increased aggressiveness when adults (Ch. 8).

18. As welfare is poor where wild-caught primates are brought into captivity, purpose breeding and a system of breeder accreditation would help to promote good animal welfare. It would also give scientists reassurance that the animals would meet health and quality standards that are necessary to carry out good and humane science (Ch. 9).

Human-primate interactions

19. All primate species are wild animals and are not domesticated, and so close contact with humans is likely to be stressful. Socialisation of these animals is important for them to adapt to captivity, to develop normal social relationships with conspecifics, and to become habituated to human beings (Ch. 7).

20. Considerable stress can be caused to primates if caretakers and research staff are not familiar with the biology including the behaviour of the species. Staff training and

competence are therefore very important to ensure appropriate handling and care of animals (Ch. 7).

21. In many cases experimenters and keepers can produce better science and reach their goals with better animal welfare by obtaining the cooperation of animals and investing in good relationships with them (e.g. training to co-operate in procedures, provision of rewards), rather than using restraint and coercion (Ch. 7 and 9).

Animal Health

22. The establishment and coordination of animal health programmes within primate research, breeding and holding facilities will help to safeguard the health and welfare of both the primates and in-contact humans, and will provide information on identifying and applying good practices (Ch. 10).

Transport

23. The transport of primates can be extremely stressful, especially prolonged transport from overseas, and can result in very poor welfare for a variety of reasons e.g., confined space, long journey duration, deprivation of food and water, possibility of experiencing extreme temperatures, exposure to draughts and noise. Very limited scientific data are available on the amount of transport-related stress experienced by non-human primates (Ch. 11).

Scientific aspects

24. The carrying out of research in specialised centres that are well-equipped in terms of facilities and expertise could produce better science as well as improved animal welfare (Ch. 12).

25. Chimpanzees and other Great Apes have considerable emotional, cognitive and social abilities and are particularly susceptible to mental distress in captivity. This may also apply to other species but insufficient research has been carried out to clearly confirm this. The level of cognition and consciousness of chimpanzees and other Great Apes poses ethical questions regarding their use in invasive experimental research. If Great Apes are kept in captivity they need to be kept in ways that provide for all their needs within the context of the overall scientific objectives (e.g. isolation of animals may be required for certain infectious disease research) (Ch. 5).

26. The main biomedical research areas using primates are safety testing of pharmaceuticals, quality control of vaccines, and fundamental research. At present some scientific procedures require the use of primates e.g. polio or Hepatitis C vaccine production, HIV research, investigations into higher cognitive function (Ch. 12).

27. The use of primates in EU Member States is permitted only when replacement alternatives do not exist or have not been validated but new trends may lead to an increased requirement for their use in research involving HIV/AIDS, tuberculosis and malaria (Ch. 12).

28. Poor primate welfare will impact negatively on any scientific data collected and is very likely to increase the number of animals required, therefore, good animal welfare needs to be encouraged whenever primates are used (Ch. 9). There is always a need to carry out an assessment of the welfare impact of an experimental procedure on the species proposed to be used (Ch. 12).

29. There are inadequate strategies in place to establish and maintain non-human primate tissue banks and primate-derived cell culture collections in order to optimise the use of this material. A limited and strictly controlled re-use of primates offers the potential to reduce the total number of primates used in research (Ch. 4).

30. For regulatory toxicity tests only purpose-bred primates are used in the EU (Ch. 12).

31. There is a need for a strengthened and more formal network to serve as a focus for non-human primate research matters in Europe. Such a network could promote good practices through informed discussion on the use and alternatives to the current use, and strategies to recognise and assess the level of severity imposed by scientific procedures and systems of husbandry. This would also help to avoid any unnecessary duplication of experimental work carried out in different countries (Ch. 4).

32. Although harmonisation of experimental protocols for safety testing has been largely achieved, no clear definition of early and humane endpoints has been established for many protocols (Ch. 12).

14. RECOMMENDATIONS[2]

Husbandry

1. Where primates are kept in captivity and used in science, the needs of the species, including the need to satisfy physiological, physical and behavioural needs, should be recognised and catered for in their husbandry. For example their management and housing should be designed to facilitate socialisation and formation of normal social relationships with their conspecifics (Ch. 5).

2. A rich and stimulating environment should be provided to cater for the intelligence and curiosity of primates (Ch. 5 and 9). Requirements and recommendations regarding housing conditions should be based on scientific evidence concerning the effects on animal welfare, but where scientific evidence is lacking, guidelines and codes of practice should be based on good practices (Ch. 9).

3. If Great Apes are kept in captivity they should be kept in ways that provide for all their needs within the context of the overall scientific objectives (Ch. 5).

4. All housing of primates should be designed to allow the expression of species-typical behaviours and postures. Enclosures for non-human primates should be equipped with

[2] Recommendations are numbered and a figure in brackets indicates the relevant chapter from which they have been drawn.

one or more elevated resting surfaces (to a position higher than the level at which they perceive threatening factors, e.g. humans) and installed in such a way that an animal can sit on them comfortably. Perches or shelves should be provided in all cages. Arboreal species should be given adequate vertical space to allow the expression of normal locomotory behaviour. Primates should not be placed in double-tiered caging unless the cage arrangement permits adequate vertical movement for the animal (Ch. 9).

5. For animals housed in groups the environment should be furnished with devices minimising social competition and favouring the escape and privacy of threatened individuals. Animals should have adequate access to food resources so that monopolisation and feeding-related serious aggression and conflict do not occur, therefore multiple feeding points are usually necessary (Ch. 9)

6. When deciding how to house primates, including the need to show certain behaviours, a variety of criteria including the biology of the species, age, sex, and an individual's history based on its previous experience should be considered, as opposed to simply applying a mathematical standard based on body weight (Ch. 9).

7. Whenever possible a combination of both indoor and outdoor housing should be provided for all animals, where it has no adverse welfare consequences for the animals concerned or the science. When outdoor housing is chosen a programme of disease control should be implemented, to take into account the added health risks due to direct contact with the outside (Ch. 9).

8. Where group housing is applied, the natural social organisation of the species should be taken into account. The composition of a social group should be maintained as stable as possible in order to minimise the risk of aggression associated with social disruption. The membership of paired and socially-housed groups of primates should be as stable as possible to provide optimal conditions regarding animal welfare and health, and to allow the production of reliable scientific results (Ch. 9).

9. Since re-introduction of animals can create situations adversely affecting animal welfare, before an animal is removed, consideration should be given to whether it will be re-introduced and, if so, in what way. Care should always be taken when re-introducing individuals into a group and the behavioural responses of all animals should be observed for the first few hours, and then periodic observations should be carried out more frequently than normal until compatibility seems assured (Ch. 9).

10. Primates should not be housed singly unless fully justified by health considerations (for the animal or human handler) or research procedures, as advised following an ethical review process. If primates have to be singly housed, the animals should have visual, olfactory and auditory contact with conspecifics and the period of single housing should be adopted only for the minimum time period required (Ch. 9).

11. Following a period of single housing all efforts should be made to re-socialise the animal to minimise the adverse effects on welfare that result from being singly housed (Ch. 9).

12. An appropriate welfare and health programme involving veterinarians and ethologists should be established at each institution using primates in research (Ch. 10).

13. An environmental enrichment programme should be drawn up by the institution responsible for the animals, and implemented by all those involved in their care. An ethologist should advise on any enrichment and socialisation programme, and this programme should also involve veterinarians (Ch. 9).

Breeding and supply

14. For as long as the use of primates in research is necessary, only purpose-bred animals should be used. Such purpose breeding should be planned in order to meet the projected research requirements and breeding centres should be accredited (Ch. 8, 12). Only animals of the second or subsequent generation bred in captivity should be accepted as being classified as 'purpose-bred' and supplied for research. Any exceptions should be based on their approval following an ethical review process (Ch. 8).

15. Primates should not be imported from outside the EU until a specific scientific use or essential breeding use for them has been approved, to avoid prolonged journeys or their being held for prolonged periods in holding stations before being sent to their final destination. When imported they should move directly to the final destination and not via third parties to be 'sold on', where this may involve additional transport and consequent adverse effects on their welfare. A possible exception is where quarantine measures preclude delivery to their ultimate destination (Ch. 11).

16. In considering breeding strategies, special attention should be given to the social needs of individuals, which will differ according to the species, their relationships, and the breeding systems used for each species (Ch. 8).

17. Macaques should not be weaned and separated from their mothers before they are 10-12 months of age and they should then be placed into peer groups. Animals destined to become future breeders should be left with their mothers until they are no longer dependent on them for food and have had time to learn important behaviours such as mothering. In principle this is likely to be true for other primate species apart from macaques, but there is less scientific data available (Ch. 8 and 9).

18. Those animals destined as future breeders should be kept in socially-structured groups until maturity, as this is the best way to establish long-term breeders that will lead to self-sustaining colonies (Ch. 8).

19. When establishing breeding colonies, preferably semi-free-ranging or corral breeding systems should be chosen. All harem groups should be closely supervised to avoid aggression. Timed-mating strategies should not be followed unless the time of mating needs to be precisely known for scientific purposes (Ch. 8).

20. Suppliers should provide users with all the information that is important for the welfare and the health of the animals and for working safely with the animals supplied (Ch. 10- see also Recommendation 31).

Human-animal interactions

21. Since primates are not domesticated, they should be habituated as early as possible to the presence and behaviour of humans. and so unnecessary physical contact should be

avoided because it is stressful. However, that does not preclude training primates to cooperate in experimental procedures which can reduce stress and so provide for better welfare (Ch. 9).

22. Within the constraint of human safety, experimenters should aim to build up a positive relationship with primates being used in their research. When performing experimental procedures they should use rewards and positive reinforcements rather than coercion (Ch. 9).

23. Selection of suitably trained staff together with a comprehensive training programme in the social management of primates and the requirements of species and individuals should be part of the policy of all primate facilities. Training programmes should be revised periodically to include the most up-to-date knowledge of the different aspects of the care and use of animals, including their behaviour (Ch. 9).

24. The animal care staff should carefully monitor newly-grouped animals, and regularly monitor established groups in order to intervene at an early stage when an animal suffers from attacks by conspecifics (Ch. 9).

25. Those in charge of primates in breeding and supply establishments should be aware of the welfare requirements of species and individuals, and manage their breeding systems to ensure good welfare (Ch. 9).

Transport

26. Persons involved in the transport of primates (e.g. by air) should be informed of the requirements for the transport of primates, and appropriate trained staff, equipment and facilities are required (Ch. 11).

27. Based on available scientific data, conditions during transport should be modified to minimise adverse effects on welfare. Primates should only be transported when their welfare can be good and transport conditions optimised e.g. direct flights by the shortest possible route, minimising waiting times, creating acceptable environmental conditions, good dietary care, and ensuring competence of those handling the crated animals (Ch. 11).

28. In order to avoid poor welfare due to prolonged transport from overseas, the supply of primates for research within Europe should ideally be met from European breeding programmes. The planning of this breeding programme should be in line with the projected requirements for the future use of primates in research so that neither a shortfall nor a surplus of animals is created. If institutions using primates in research were located close to such breeding/holding centres the necessity to transport primates over long distances would be additionally reduced and the consequent adverse effects on their welfare reduced (Ch. 11).

29. Importation and movements of primates should be coordinated between institutions to facilitate the sharing of facilities and allow a number of smaller consignments to be synchronised and moved at the same time. This should reduce the total number of consignments and optimise the allocation of resources and expertise at the time of transport to safeguard animal welfare (Ch. 11).

Animal Health

30. Cooperation and sharing of information on animal welfare and health should be encouraged between institutions using primates in research and should involve veterinarians and ethologists. An appropriate welfare and health programme should be established at each institution using primates in research.

31. Each non-human primate should have an individual history file (‘passport’) that gives a detailed biography for each primate, including any previous pathological investigation. The file should accompany that animal if it is moved between institutions. Information from these individual files should be used to form part of a database to analyse primate care and use in practice, and to review the adequacy of the systems in order to establish good practices. This history file should record all basic information for each animal in a colony including reproductive and medical information, and also social information, i.e. all social partners, rank in the group, moves and events that have occurred in the life of that animal, including any previous pathological investigations, and details concerning the compatibility and incompatibility of individuals (Ch. 9 and 10).

Scientific aspects

32. The carrying out of research in specialised centres that are well-equipped in terms of facilities and expertise should be encouraged, to promote good scientific and husbandry practices, which should result in good science and good animal welfare (Ch. 12).

33. Coordination between research centres and promotion of tissue banks and data exchange networks should be encouraged as a means to reduce the number of primates required to be used in research (Ch. 4).

34. Animals should be acclimated to their surroundings and habituated to the procedures carried out on them when this will reduce the stress they experience and improve the reliability of the scientific results (Ch. 9).

35. Harmonisation of experimental protocols should continue, e.g. establishing the group size of experimental protocols and defining experimental and humane endpoints. In addition, criteria for deciding when euthanasia has to be performed or the animal has to be withdrawn from a study should be clearly established (Ch. 12).

36. According to international guidelines the toxicity of all new drugs should be investigated at least in two mammalian species, one being a non-rodent. A critical evaluation on the use of a second species is required and its use fully and satisfactorily justified for the species chosen (Ch. 12).

37. Replacement alternatives to the use of primates should be resourced, developed, and then validated and implemented as a priority. Where primates are used in research their use should be refined so that as little suffering as possible is caused to an animal – using both *in vivo* (e.g. by the use of a species with a lower neurological sensitivity) and *in vitro* alternatives. Possible future requirements for the use of genetically modified primates should be anticipated and the consequences for primate welfare carefully considered. In terms of animal welfare, the criterion to be used when deciding which species should be used is the extent of poor welfare that is likely to result (Ch. 12).

38. A number of objective measures of animal welfare should be characterised, appropriate concerted research conducted, and information collected in order that good practices be identified and then applied in research involving primates (Ch. 6). The results should then be disseminated perhaps through the use of animal care guidance and Codes of Good Practice to ensure good welfare.

39. The use of primates in research and their maintenance for scientific purposes in an institution should be considered by an appropriate ethical review process (Ch. 12).

40. Due to their similarities with humans and their status as endangered species, special considerations should apply to any proposed use of chimpanzees in invasive biomedical research. The possible use of Great Apes in biomedical research, clinical research aimed at the treatment of an individual Great Ape or research that will benefit the species as a whole, will all require careful consideration and justification (Ch. 5).

41. Project leaders should give an assurance that the experimental subjects will not be caused avoidable suffering within the context of the scientific objective. The rationale for the research and projected harms and predicted benefits should be assessed by an independent ethical review process (Ch. 12).

42. Cooperation and sharing of information on animal welfare and health should be encouraged between institutions using primates and should involve veterinarians, ethologists, animal care staff and scientists (Ch. 10 and 12).

43. The exchange of information between ethical review systems should be facilitated and encouraged, helping to harmonise primate use, and avoiding duplication of research between different countries (Ch. 12).

44. To better inform assessments of the welfare of primates used in research in the EU, collection of data should additionally include a detailed breakdown of the number and species of non-human primates used (Ch. 9), for example specific categories of:

- Prosimians;
- within New World monkeys individual categories such as marmosets, tamarins and other New World monkeys,
- within Old World monkeys individual categories such as rhesus macaques, long-tailed macaques, other macaques and other Old World monkeys;
- Great Apes;
- the number of primates maintained for scientific and/or breeding purposes.

45. Particular attention should be given to classifying both ‘use’ and ‘re-use’ of primates in experiments, as well as to clarifying definitions of ‘re-use’, its impact on science, animal welfare, the total number of primates used, and setting limits on any re-use (Ch. 4).

46. Regarding experiments involving the use of primates, consideration should be given to the necessity of the research, the ethical issues involved, and promoting the welfare of the animals used (Ch. 4).

47. The impact of the scientific procedures on the welfare of the animals, and data on the severity of procedures should be collected through a retrospective reporting system. Data should also be collected on the impact of the conditions of husbandry and care on the welfare of the animals, including data on the adverse effects, such as stereotypies, morbidity, mortality (Ch. 4).

48. The coordination and concentration of resources and expertise should be promoted between institutions using primates in research in different countries. This would facilitate the implementation of various recommendations already outlined (e.g. avoiding duplication of research, implementing good practices, exchange of information, use of tissue banks etc.) (Ch. 12).

15. FUTURE RESEARCH

In order to meet the physiological, physical and behavioural needs of a given primate species in captivity, further study is needed on their emotional, cognitive and social abilities, their self-awareness, and their susceptibility to mental distress in captivity. Research is also needed for the commonly used non-human primate species on their physiology, environmental preferences, behavioural repertoire, social organisation and behavioural ecology in the wild in order to establish good practices. There is a need for investigation of physiological and ethological stress measures that reliably reflect an individual animal's physiological and behavioural status in a given husbandry situation. It is not the intention of the Committee to recommend an increase in the number of primates used in research. However, certain critical gaps in the available scientific knowledge are highlighted below, since these limit the ability to recommend precise environmental, housing and husbandry parameters to ensure good welfare. In particular, further research is needed on the welfare impacts of:

- different housing systems (e.g. dimensions and design of enclosures, type of equipment provided) and husbandry procedures used;
- environmental enrichment techniques (e.g. devices provided, mode and time of presentation etc.);
- methods used to train animals to cooperate during experimental and husbandry procedures;
- various capture and restraint procedures used for non-human primates;
- weaning and separation from the mother;
- whether the welfare needs of chimpanzees in captivity are greater than other primate species;
- the assessment of primates' welfare in breeding establishments;
- the assessment of primates' welfare during transport and the optimal conditions that ensure good welfare.

As a priority, research work is needed on the development, validation and acceptance of alternatives to the use of primates in research (e.g. use of transgenic rodents for toxicity testing).

16. EXECUTIVE SUMMARY

The Scientific Committee on Animal Health and Animal Welfare was asked to prepare a report on the welfare of non-human primates used in scientific procedures, and to propose how the welfare of these animals could be improved by taking into account the most recent scientific information available. It was not within the Committee's mandate to review the ethical issues of whether or not primates should be used in research.

In 1986 the Council adopted Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes which seeks to improve the controls on the use of laboratory animals, to set minimum standards for their housing and care, and addresses in broad terms the training of personnel handling animals and supervising experiments. It also aims at replacing animals with non-animal methods wherever possible, as well as encouraging the development and validation of such replacement methods. Where animals have to be used, the Directive aims to ensure that it is only the minimum number, and that any animal suffering is the minimum necessary to achieve the scientific objective. Since the Directive dates back more than 15 years, some provisions require revision based on more recently available scientific data and current good practices. Improving animal welfare will often lead to more effective research in terms of its reliability and accuracy, while at the same time it has the potential to reduce the numbers of animals used and to minimise any suffering that may be caused by the scientific protocol.

The Report of the Scientific Committee is divided into chapters that cover the scale of experimental use of non-human primates in the EU, their general biology, general welfare assessment, current husbandry practices, breeding and supply issues, specific welfare problems, animal health issues, transport, and specific issues relating to their use in science. These are followed by conclusions and recommendations, priorities for future research, and an executive summary.

Recommendations of the Report include the collection of more detailed data on the use of primates in research within the EU, including a retrospective reporting system on the severity of procedures carried out. Coordination between research centres and the exchange of information will help to identify good practices regarding safeguarding the welfare of non-human primates in research. The management and housing of non-human primates in captivity could also be modified to ensure good welfare and provide for their physiological, physical and behavioural needs, through the provision of a stimulus-rich environment and appropriate care. Staff should be adequately trained and be competent in the care and handling of primates. Only purpose-bred animals should be used in research, and breeding systems should be designed to ensure good welfare. A combination of indoor-outdoor housing is recommended where it has no adverse welfare and health consequences and is compatible with the scientific use. It is concluded that since non-human primates are social animals, single housing is always detrimental to the animal's welfare. It is recommended that each primate should have a detailed individual file with records relevant to its life history (including health records) and use. A number of recommendations are made regarding minimising the adverse effects of prolonged transport on the welfare of non-human primates. A network between facilities using non-human primates in research could also coordinate discussion on matters relating to the use of non-human primates, identify good practices and safeguard their welfare. This would facilitate the exchange of technical information regarding their use in research and help to avoid duplication of their use, enable sharing of resources, facilitate the development and validation of alternatives, and help implement the Three Rs (Replacement, Reduction and Refinement). A number of areas where further research is required are also highlighted.

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18. ACKNOWLEDGEMENTS

This report of the Scientific Committee on Animal Health and Animal Welfare is substantially based on the work of a working group established by the Committee and chaired by Prof. D.B. Morton. The working group drafted the report, which was then reviewed and revised by the Scientific Committee on Animal Health and Animal Welfare. The Scientific Committee is solely responsible for the final text, including the conclusions and recommendations. The members of the working group were as follows:

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