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Primate Welfare Meeting

27 October 2010

Animal welfare, Natural history and captive care, Future directions in primate research

Welcome

Dear Colleagues,

Welcome to the sixth NC3Rs Primate Welfare Meeting. This meeting brings together scientists, veterinarians, animal care staff, facility managers and policy makers with a common interest in the welfare of laboratory-housed non-human primates. The broad aims of the meeting are to –

- support the development and implementation of refinements in primate care and use
- provide evidence that can be used to promote improvements in primate welfare and direct welfare research
- bring people together to establish new contacts and for exchange of views and information on primate issues

The Primate Welfare Meeting is just one of many activities of the NC3Rs focused on the use of non-human primates in research (see www.nc3rs.org.uk/primatewelfare and www.nc3rs.org.uk/primatesabpi).

This year's meeting includes talks from international speakers on a variety of topics, from new methods of assessing primate welfare to opportunities to reduce primate use in the development of biotherapeutics. It also provides unique opportunities to talk first-hand to researchers working with macaques and marmosets in the field, and to share your views on continuing professional development needs for the laboratory primate research community.

We are pleased that this meeting has again attracted so many delegates, including several from overseas. We hope you will take this chance to make new contacts and to exchange ideas for the refinement of primate care and use.

Where further research is needed to develop and validate new refinements, the NC3Rs is keen to support this via its research funding schemes www.nc3rs.org.uk/researchfunding

Thanks to everyone for your interest and have a great day.

Mark Prescott

Dr Mark Prescott
Programme Manager, NC3Rs

Vicky Robinson

Dr Vicky Robinson
Chief Executive, NC3Rs

Agenda

09.30 – 10.00	**REGISTRATION and COFFEE**
10.00 – 10.10	**WELCOME and INTRODUCTION** *Professor Rodney Phillips, University of Oxford*
	ANIMAL WELFARE
10.10 – 10.40	**Refining a macaque feeding programme to increase food accessibility for low ranking animals and to improve group welfare** *Dr Moshe Bushmitz, BFC Israel Ltd., Dr Corri Waitt & Dr Paul Honess, University of Oxford*
10.40 – 11.10	**Attentional bias: a new method for assessment of captive primate welfare** *Dr Emily J Bethell, Dr Amanda Holmes, Professor Ann MacLarnon & Dr Stuart Semple, Roehampton University*
11.10 – 11.40	**Considerations for rehoming non-human primates: life after the lab** *Mr Keith Morris, MRC Human Reproductive Sciences Unit*
11.40 – 12.00	**COFFEE**
	NATURAL HISTORY AND CAPTIVE CARE
12.00 – 12.30	**How should a long-tailed macaque behave?: lessons from natural history for enriching captive macaques** *Dr Michael Gumert, Nanyang Technological University*
12.30 – 13.00	**Incorporating natural adaptations of common marmosets to improve their welfare in captivity** *Dr Maria de Fatima Arruda, Federal University of Rio Grande do Norte, Brazil & Professor Hannah Buchanan-Smith, University of Stirling*
13.00 – 14.00	**LUNCH**
	FUTURE DIRECTIONS IN PRIMATE RESEARCH
14.00 – 14.15	**Continuing professional development needs for the laboratory primate research community** *Dr Mark Prescott, NC3Rs*
14.15 – 14.45	**Refinement of the use of food and fluid control as motivational tools for macaques used in behavioural neuroscience research** *Dr Mark Prescott, NC3Rs*
14.45 – 15.15	**Tackling the challenges of NHP use in safety assessment: combining experience, data and regulatory change** *Dr Kathryn Chapman, NC3Rs*
15.15 – 15.45	**Evaluation of the reuse potential of non-human primates for non-definitive studies during pre-clinical development of biotherapeutics** *Dr Manoj Rajadhyaksha, Pharmacokinetics, Dynamics and Metabolism. Pfizer. Inc.*
15.45 – 16.15	**Non-human primate research trends in the USA** *Professor Joseph Kemnitz, University of Wisconsin-Madison*
16.15 – 16.30	**DISCUSSION and CLOSING REMARKS**
16.30 – 17.30	**RECEPTION**

Refining a macaque feeding programme to increase food accessibility for low-ranking animals and to improve group welfare

Dr Moshe Bushmitz, BFC Israel Ltd, Dr Corri Waitt, Department of Zoology, University of Oxford & Dr Paul Honess, Department of Veterinary Services, University of Oxford

For captive primates, feeding is probably the most significant event in their daily lives; it has an enormous impact on the daily pattern of behaviour. Any feeding program should determine: how many times a day to feed and at what time; what types of food and what proportion of the daily food ration to give at each feeding; and how to disperse the food in the cage. Sometimes these are based on what has been done historically at the facility or on what caregivers feel is best, instead of on careful analyses of how these factors directly impact the animals and especially the low-ranking ones.

This project aimed to assess how dividing the food type and amount across feedings affects the behaviour of breeding groups of long-tailed macaques (*Macaca fascicularis*). The overall goal was to optimize feeding procedures to: a) minimize competition during feedings to reduce stress in the times preceding, during and following feeding; and b) improve access to and distribution of food, especially for low-ranking animals and weaned infants. Over 80 hours of data on the behaviour of six breeding groups were collected using scan sampling over a 3 week period before, during and after feeding. The study compared current feeding practices (three feedings per day of 10%, 20%, 70% of the daily food ration) with an experimental condition featuring a more even distribution of the food (three feedings of 30%, 30%, 40% of the daily food ration). This modified distribution of food resulted in improvements in the animals' behaviour and a decrease in competition for food. The study also investigated weight changes in infants given access to a "feeding shelter".

Attentional bias: a new method for assessment of captive primate welfare

Dr Emily J Bethell, Dr Amanda Holmes, Professor Ann MacLarnon & Dr Stuart Semple, Centre for Research in Evolutionary Anthropology, Roehampton University

One important, but hard to measure, aspect of animal welfare is psychological wellbeing. Keeping captive primates in a state of good psychological wellbeing will help refine the animal models we use, and reduce the number of animals used in research, due to greater retention. Psychologically healthy animals may also be easier and safer to work with. Recently, a number of studies have provided evidence that measuring 'cognitive bias' may provide a powerful tool for assessing animal psychological wellbeing. Cognitive bias has been well studied in humans, and describes the way in which changes in affective state are characterised by changes in cognitive processes. For example, people who are anxious are faster to detect threatening stimuli than are non-anxious individuals. This enhanced vigilance for threatening information leads to further increases in anxiety which may ultimately result in clinical levels of anxiety. To date, animal studies have demonstrated affect-mediated cognitive bias in birds, rats and dogs. We present data on an aspect of cognitive bias that has not previously been tested in a non-human animals (specifically, attentional bias), together with the first study of affect-mediated cognitive bias in a non-human primate. Eight rhesus macaques were shown (aggressive-neutral) picture pairs of conspecific faces, and their gaze towards the faces was coded. Following a veterinary inspection, which served as a stressor, macaques showed a different pattern of gaze towards the aggressive-neutral face pairs compared with when no stressor had been given. We discuss our findings in terms of existing vigilance and avoidance theories of attentional bias for threatening information in humans, and suggest the method presented provides a valuable means of measuring psychological wellbeing in non-human primates.

Considerations for rehoming non-human primates: life after the laboratory

Mr Keith Morris, MRC Human Reproductive Sciences Unit, Edinburgh

The idea of re-homing laboratory animals bred for research is not a new one. Companies involved in feeding trials and non-terminal studies have been relocating animals, particularly cats and dogs, to good homes as domestic pets for many years. It is also not unknown for animal technicians and carers to rehome a favourite rodent, rabbit or guinea pig. However, the rehoming of laboratory non-human primates (NHPs) is much more controversial and demands a great deal of careful thought. At a time when most large zoos are solely interested in breeding endangered or attractive species for conservation or public attraction, it is rarely possible to find homes for the more common laboratory NHPs, such as the common marmoset and macaque species. This presentation will highlight important considerations for successfully rehoming groups of non human primates, including selection of suitable animals, evaluation of potential homes, transportation issues and legal requirements.

How should a long-tailed macaque behave?: lessons from natural history for enriching captive macaques

Dr Michael Gumert, Nanyang Technological University

Long-tailed macaques (*Macaca fascicularis*) are a common laboratory primate, and are by far the top traded non-human primate into the research industries of developed nations. In Southeast Asia, long-tailed macaques acclimate easily to living near people, and this attraction is likely related to their common usage in captivity. They are easy to locate and obtain, and survive well in captivity being relatively less stressed around humans compared to some other primate species. Long-tailed macaques are long-lived, intelligent, and highly social. As such, there are numerous ethical and welfare considerations for maintaining physically and psychologically healthy captive macaques. I will cover aspects of their natural behavior, to provide captive care experts with information useful to animal-care decisions. Long-tailed macaques are generalist omnivores, living in a variety of habitats and feeding on fruits, vegetation, insects, small animals, shell fish, and human foods. Long-tailed macaques live in large social groups of highly variable size, ranging from 4 to several hundred, with most groups skewed in favor of females. Females are philopatric and remain in their natal groups, while males emigrate at sexual maturity and change groups throughout their live every several months to few years. During emigration, males live alone or in small all-male groups for up to several years. All long-tailed macaque groups are despotic and nepotistic, and thus social patterns are structured by dominance hierarchies and matrilineal clans. Kin relationships are important to social rank, as individuals rely on aggressive support from their families during conflict. Females reach sexual maturity at age 3-4 and can give birth once every year or two. Having a live span of 20-30 years, they can have a highly fecund reproductive career. Consequently, captive managers need to be concerned with reproductive management. Population growth is also a concern in natural populations that interface with human societies. Several techniques have been attempted to control populations, including sterilization and culling. In captivity, sterilization is more practical than in field conditions since the animals are medically cared for and easy to monitor. Another issue in captivity is managing boredom and providing animals with enrichment. Across the natural range of long-tailed macaques, various behavioral variants are found that can provide insight into the types of activities that would be most enriching to macaques. In some populations, they engage in behavior such as food washing, food rubbing, tooth flossing, tooth picking and numerous forms of object manipulation. A common form of object manipulation is stone handling, and in one region, off the west coast of Thailand and Myanmar, a sub-species of long-tailed macaque (*Macaca fascicularis aurea*) customarily uses stone tools to process shellfish and nuts. In other parts of their natural range, macaques have been found to fish in Kalimantan and Sumatra, to bath in hot springs in Lombok, and to utilize caves in Timor-Leste. Knowledge of behavior in natural settings can help captive care specialist plan innovative and dynamic housing and husbandry paradigms beneficial to the well-being and enrichment of their captive macaques.

Incorporating natural adaptations of common marmosets to improve their welfare in captivity

Dr Maria de Fatima Arruda, Department of Physiology, Federal University of Rio Grande do Norte (UFRN), Brazil & Professor Hannah Buchanan-Smith, Department of Psychology, University of Stirling

The common marmoset, *Callithrix jacchus*, is the most frequently used New World primate in laboratory research and testing, due to its small size, apparent breeding success, and easy handling which make it comparatively inexpensive to keep. However, there are considerable welfare problems associated with marmoset use in laboratories, which include marmoset wasting syndrome and large litters with negative consequences for both dam and infant survival, and also potentially for the scientific output given the variation in rearing which may include early deprivation. This presentation will summarise the natural history of marmosets to inform welfare decisions for housing and husbandry in the laboratory. The field data come from marmosets that have been followed in their natural environment systematically since 1991 by researchers at the UFRN, Natal, Brazil. The implications for welfare are based on over 25 years of experience of working with marmosets in captive settings. Common marmoset adaptability is demonstrated from the types of habitats they can live in - from coastal Atlantic forest, caatinga (semi-arid scrub forest) and urban areas, to exotic species plantations where resources show strong seasonality between dry and wet seasons. Group size ranges from 5 to 17 individuals, whose flexibility permits adjustable responses to physical and social pressures in those variable conditions. They are cooperative breeders and live in stable family groups comprised of a reproductive pair and their siblings usually born from sequential births. Our long-term monitoring of groups, besides recording monogynous groups, has also recorded polygynous ones. Subordinate individuals from neighbouring groups have been recorded copulating during intergroup encounters; the subsequent pregnancy does not result in successful reproduction, sometimes even involving infanticide perpetrated by the dominant female. Migration is an important event in marmoset dynamics and reproductive vacancy is in general filled by individuals that have migrated from neighbouring groups. The dominant male and other adult males are the most involved in all forms of infant care – carrying, supervising and transferring food to the infants. Sometimes subordinate females are prevented from caring, an aspect of the competitive relations between the dominant and other females in the group. An adult weighs about 320 g and infants are born weighing around 30 g. Common marmosets are omnivorous and eat fruit, animal prey (mostly insects) and exudates. Exudate is used aseasonally and is obtained from the branches and trunks of specific trees which are visited systematically in the group's daily range. The activity budget includes social interactions and exploration which are usually distributed during the day in periods of fruit/gum tree exploration, foraging for insects and resting with extensive grooming bouts, The day is ended by moving very subtly to the sleeping site, which in general is up high in a tree and can be used just occasionally or regularly, probably related to the perceived pressures of the environment. These data on the natural adaptations and flexibility of the social organization and dynamics of the species, and consequently how individuals respond to social and ecological pressures/factors, are an important tool to support the management of the species to promote good welfare which is critical for ethical reasons, financial reasons and also for good science.

Continuing professional development needs for the laboratory primate research community

Dr Mark Prescott, NC3Rs

It is generally acknowledged that laboratory personnel responsible for the use and care of non-human primates (NHPs) require special knowledge and practical skills, and the highest standard of training, because of the animals' complex behavioural, social, physiological and psychological needs, and the ethical considerations involved in their use. The Weatherall report[1] concluded that a strong case can be made for increasing the training period of scientists and technicians working with NHPs beyond the short course currently given in the UK, and that this should be supported by continuing professional development for all those involved with NHP research. In this short presentation, voting keypads will be used to survey the audience about their training and continuing professional development needs.

References

1. Weatherall D, Goodfellow P, Harris J, Hinde R, Johnson L, Morris R, Ross N, Skehel J, Tickell C (2006) *The use of non-human primates in research: A working group report chaired by Sir David Weatherall FRS FMedSci*. London, UK: The Academy of Medical Sciences, Medical Research Council, The Royal Society, Wellcome Trust

Refinement of the use of food and fluid control as motivational tools for macaques used in behavioural neuroscience research

Dr Mark Prescott, NC3Rs

Control of food or fluid intake is commonly used in behavioural neuroscience experiments using macaques in order to motivate the monkeys to perform extended sequences of responses on behavioural tasks while electrophysiological recordings from the brain are made. The control may involve strict scheduling of the time for which food or fluid is available, or a reduction in the total amount of food or fluid provided per day – either way, hunger or thirst becomes a key motivator for reliable performance.

Depending on how they are implemented, controls of food or fluid can elicit physiological and behavioural responses that may compromise animal health and psychological well-being. Food or fluid control may also have an indirect impact on animal welfare if it affects husbandry. Coupled with the relatively lengthy periods of time over which behavioural neuroscience experiments are conducted, these issues make use of food and fluid control protocols the subject of much concern and debate.

To address these issues, the NC3Rs convened an expert working group comprising senior neuroscientists, veterinarians, animal care staff and members of the Animals (Scientific Procedures) Inspectorate to review the available scientific literature and produce recommendations for refinement. The group's report[1] sets out good practice based on the available information and expertise. It also highlights the gaps in knowledge that need to be addressed to ensure that, where food or fluid control is necessary, the protocols are as humane as possible. The NC3Rs will be working with the scientific community to identify how the data gaps and research priorities can best be addressed.

References

1. Prescott MJ, Brown VJ, Flecknell PA, Gaffan D, Garrod K, Lemon RN, Parker AJ, Ryder K, Schultz W, Scott L, Watson J, Whitfield L (2010) Refinement of the use of food and fluid control as motivational tools for macaques used in behavioural neuroscience research: Report of a working group of the NC3Rs. *Journal of Neuroscience Methods*, doi:10.1016/j.jneumeth.2010.09.003 [Epub ahead of print]

Tackling the challenges of NHP use in safety assessment: combining experience, data and regulatory change

Dr Kathryn Chapman, NC3Rs

Approximately 92 per cent of the non-human primates (NHPs) used in the UK are in pharmaceutical development and the majority of these are used to assess the safety and toxicity of new drugs. Over the last five years, the NC3Rs has been working with the pharmaceutical and biotechnology industry to assess opportunities to minimise NHP use. By sharing experience and data, approaches have been developed to reduce NHP use in pharmacokinetic studies for candidate selection, abuse potential studies and preclinical safety testing of monoclonal antibodies (mAbs).

By co-ordinating international working groups comprised of pharmaceutical companies, contract research organisations and regulators we have provided practical guidance on mAb development and an evidence base for change in practice[1,2,3]. By sharing data we have identified opportunities to minimise the number of NHPs used per mAb, by reducing the number of recovery animals, dose groups and chronic studies.

To explore further the potential for reducing the number of dose groups in chronic toxicology studies, we have investigated toxicological effects at different dose levels for 70 mAbs in nonclinical development from a wide range of therapeutic areas. Initial analysis of these data provides evidence that there are cases where fewer NHPs may be used, for instance in oncology indications or for biosimilars. The presentation will include an overview of the NC3Rs/industry collaborative projects and a discussion of the future of NHP use in drug development.

References

1. Chapman K, Pullen N, Graham M, Ragan I (2007) Preclinical safety testing of monoclonal antibodies: the significance of species relevance. *Nature Reviews Drug Discovery* 6: 120-126

2. Chapman K, Pullen N, Coney L, Dempster M, Andrews L, Bajramovic J, Baldrick P, Buckley L, Jacobs A, Hale G, Green C, Ragan I, Robinson V (2009) Preclinical development of monoclonal antibodies: considerations for the use of non-human primates. *mAbs* 1 (5): 505-516

3. Chapman K, Pullen N, Andrews L, Ragan I (2010) The future of non-human primate use in mAb development. *Drug Discovery Today* 15 (5-6): 235-242

Evaluation of the reuse potential of non-human primates for non-definitive studies during pre-clinical development of biotherapeutics

Dr Manoj Rajadhyaksha, Pharmacokinetics, Dynamics and Metabolism. Pfizer. Inc.

Non-human primates (NHP) are primarily used in pharmaceutical research when it is scientifically justified. There are regulations both in the EU as well as in the US with respect to the ethical use of NHPs for the advancement of science and for the development of human life saving pharmaceutical medicines. Although, most research continues to be done primarily in smaller vertebrates, in some cases NHPs are the only relevant species for a given therapeutic with respect to pharmacological activity, similarities in metabolic pathways with humans or sometimes special regulatory requests that are prompted due to the need to provide additional evidence of safety or efficacy.

The advent and growth of biotherapeutics in the past 10 years has led to a significant and unsustainable increase in the use of NHPs. Several pharmaceutical companies have exponentially increased their monoclonal antibody (mAb) based portfolio. Further the trend of using fully human mAb makes NHPs the only relevant species, to avoid obvious immunogenicity. This has led to a worldwide shortage of NHPs, especially the Old World monkeys. The heightened industry demand has also resulted in a steep increase in the cost of NHPs per head. The surge in NHP use has also led to several issues for the sponsors, like limitations of vivarium space and increase in per diem cost of animal care. Unlike small molecule study time frames, the mAb therapeutics tend to have longer half lives thereby requiring longer recovery periods and significantly expanding the study duration, further putting stress on the factors mentioned above.

It can be easily realized that one of the reasons why there is a significant accumulation and use of NHPs for biotherapeutic development is due to the existing dogma that "NHPs can never be reused for biotherapeutics as they would be considered primed with the first biotherapeutic and would elicit an anamnestic response to the second biotherapeutic, should it be tested in the same animal". This tenet is based on the assumption that such primed animals may develop anti-drug antibodies and may negatively influence the pharmacokinetic and pharmacodynamics of the second biotherapeutic. Our team designed experiments that questioned this assumption. Results from these studies have led us to suggest that NHPs can be immunologically characterized and this characterization may help distinguish between animals that have reuse potential versus those that may not. Efforts currently are exerted to identify biomarkers that can further refine this discrimination and provide definitive capabilities to identify animals that can be reused for biotherapeutic development.

Non-human primate research trends in the USA

Professor Joseph Kemnitz, University of Wisconsin-Madison

The use of nonhuman primates (NHPs) in research continues to provide important insights into primate biology and discoveries resulting in significant improvements in human health and quality of life. In the USA most of the academic research using NHPs is done under the auspices of the National Center for Research Resources (NCRR), which includes the network of National Primate Research Centers (NPRCs). The NCRR-supported primate research facilities maintain approximately 26,000 monkeys of 20 species. They have breeding programs and are largely self-sufficient in terms of animal needs. Rhesus macaques predominate at these centers and are used for biomedical research related to HIV/AIDS, reproductive biology, neuroscience, aging and metabolism. There is increasing interest in the use of cynomolgus macaques of Mauritian origin for vaccine studies and common marmosets for studies of metabolism. In 2009, 24,414 NHPs were imported into the USA, somewhat fewer than in the preceding four years, primarily by commercial entities for use in the pharmaceutical industry. Of these 92% were cynomolgus macaques and the majority came from China. There is increasing use of NHP in studies of stem cell research and regenerative medicine, including cardiac tissue repair and potential therapies for spinal cord injury and neurodegenerative diseases, as well as diabetes and blood cell reconstitution. The development of informatics tools is augmenting increased effort in sharing NHP resources and promoting best practices, both within the USA and internationally, including substitution of species other than NHPs when appropriate.

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