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Refinement of the use of non-human primates in scientific research. Part I: the influence of humans

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Abstract

The welfare of non-human primates used in scientific research must be safeguarded to promote scientific validity and for ethical reasons. Welfare can be improved by the refinement of practice, particularly if these refinements are applied to every aspect of the life of an animal used in the laboratory, from birth to death with the aim of both minimising harm and maximising well-being. Many refinement methods have been described in nationally and internationally accepted guidelines on laboratory practice, but awareness of these guidelines is not universal. In Part I of this review, we examine the influence of humans on non-human primates and summarise and evaluate methods of refinement that are or could be used to reduce suffering and improve welfare. In particular we focus on staff selection, education and training, human–animal bonds, staff communication, and training primates. In Parts II and III, refinements of housing, husbandry and experimental procedures are reviewed.

Keywords: *animal welfare, human–animal bonds, positive reinforcement training, refinement, staff education, staff selection*

Introduction

In their seminal text The Principles of Humane Experimental Technique, Russell and Burch (1992) described their concept of refinement, explaining that inhumanity arising as a direct result of the use of animals in procedures and occurring as an indirect result of the use of animals in science should be reduced as far as possible. In this paper we follow Russell and Burch's (1992) definition of inhumanity which can be summarised as the infliction of distress. It is clear that Russell and Burch intended that the principle of refinement should be applied to all aspects of the animal's life in the laboratory, from birth to death. Despite the clear and in-depth discussion in Russell and Burch's book, numerous definitions and interpretations of refinement exist in the literature, many of which are regressive with respect to the original concept. In other cases, the view of refinement has progressed since its inception to include not only the minimisation of inhumanity, both direct and contingent, but also the maximisation of well-being. In an effort to harmonise the conception of refinement and to facilitate progression of its use, Buchanan-Smith *et al* 2005 have proposed a definition into which the essence of Russell and Burch's original concept and the most progressive ideas of refinement are incorporated. This definition is as follows:

> "Any approach which avoids or minimises the actual or potential pain, distress and other adverse effects experienced at any time during the life of the animals involved and which enhances their well-being" (Buchanan-Smith *et al* 2005)

In this report we concentrate on refinement of the use of non-human primates (henceforth primates) in science, with a focus on Europe. In 2001, more than 11 000 primates were used in Europe, the majority of which were Old World monkeys (Rennie & Buchanan-Smith 2005). Additional animals are held in captivity for breeding and supply purposes. Data from European primate-user countries indicate that primates are used mainly in toxicology and safety evaluations, applied studies for human and veterinary medicine and fundamental studies (Rennie & Buchanan-Smith 2005). Like some other laboratory-housed mammals and birds, primates have complex cognitive capacities and social lives (Box 1991). Combined with the fact that laboratory-housed primates have not been intentionally bred to be adapted to laboratory conditions as have some rodents (Roder & Timmermans 2002) they may be more likely to suffer and may also have a greater capacity for suffering than some other laboratory-housed animals (Smith & Boyd 2002). In this review we follow Mason's (1991, p 104) characterization of suffering, which she states is synonymous with poor well-being and "concerns mental states experienced by the animal as unpleasant".

One of the principle barriers to the use of the latest refinement techniques is the lack of dissemination of information regarding their implementation. The following review is the first of three papers considering refinement techniques that can be applied to the use of primates in laboratories from birth until death. In these reviews we examine methods of refinement which may be used to minimise inhumanity, maximise well-being and which have the potential to do both. In many cases the refinements discussed here are recommended in guidelines available internationally. In this review we consider refinement of the impact of humans on laboratory-housed primates.

Influence of humans on the refinement of laboratory practice

The competence of staff of all levels involved in the care and use of laboratory-housed primates is probably the most important factor influencing welfare and scientific validity. Positive interactions between staff and animals are known to improve health and welfare and increase the ability of the animals to cope with stress (Bayne *et al* 1993; Bloomsmith *et al* 1997, 1999; Baker 2004). Ensuring that staff members have a positive influence on psychological and physical well-being has been suggested to be the single most important refinement that can be applied in the laboratory environment (Petto *et al* 1992). The effects of staff on welfare and science are dependent upon the education, training and attitude of staff to the animals and to their work (Bayne 2002).

Selection of staff

Although many aspects of the care of laboratory animals can be learned through education and training, the best animal care workers are probably those who have a positive attitude towards the animals. In order to ensure that staff with the right attitude are chosen to care for laboratory-housed primates, the person's motivation for accepting the post must be considered during the selection process. An interest and regard for animals must be considered a priority (Bayne 2002 for primates; Chang & Hart 2002; Wolfle 2002 for animals in general) but it is also essential to understand the importance of carrying out tasks properly (Wilson *et al* 1995). Staff should therefore have an interest in science in order to have an understanding of the motivation for the research being carried out (Bayne 2002). It is also important to see how the prospective worker reacts to primates and how the primates react to them. In some cases the animals' behaviour towards candidates may be taken into account during staff selection and may form part of the basis on which workers are selected: the animals choose the staff by behaving positively towards them (Arluke & Sanders 1996).

Staff education and training

When the right staff have been selected, they must be trained to a high standard. Knowledge and competence may only be gained through appropriate education and hands-on training of those involved. Appropriate education and training is a requirement of the European Directive 86/609/EEC (European Union [EU] 1986), although no indication is given of how this should be achieved. Guidelines published by the Federation of European Laboratory Animal Science Associations (FELASA) provide an outline of curricula for four different courses to teach staff at all levels, from technicians to scientists and specialist laboratory animal workers (Wilson *et al* 1995; Nevalainen *et al* 1999, 2000), and we refer the reader to these guidelines for full discussion of the issues.

An understanding of the laws controlling the use of animals in science is essential. It is important that all staff are aware of their responsibilities towards their animals and that they are also aware of the responsibilities of others. Although many of the principles of general management and husbandry procedures are common across species, different species may have very different biology and specific physiological and behavioural needs (Mason & Mendl 1993; Wolfensohn & Honess 2005). These differences affect all aspects of the animals' life in the laboratory environment, from the type of food they require, their response to changes in their environment to their behavioural and physiological responses to procedures. Education in the biology and ethology of the relevant species is also imperative, so that changes in species-specific behaviour and indicators of good and poor welfare can be recognised (Hau 1999; European Commission [EC] 2002). A sound knowledge of the behavioural and physiological requirements of the species is invaluable in the development of enrichment and training programmes and can be applied during routine monitoring of animals. Good practice in the care and husbandry of laboratory animals of all species, including the different species of primates, is provided in The UFAW Handbook on the Care and Management of Laboratory Animals (Poole 1999). Such information should be made available to all staff, to ensure that the best known methods of care are used.

Monitoring of animals and their environment is a legal requirement (EU 1986). Training must be given to ensure that such checks are carried out properly and records are kept and reviewed to ensure that changes are instituted when required. However, although formal education and training are extremely important, there can be no substitute for experience and it has been recognised that technicians, who work closely with the animals, are often the first to notice the changes indicative of an effect of a procedure (Wolfle 2002). The ability to recognise the significance of, sometimes subtle, changes in behaviour is also essential for the evaluation of methods used to improve welfare (Bayne 2002). The FELASA guidelines suggest that individuals should be tested both on theory and on their competence in an examination at the culmination of each stage of training (Wilson *et al* 1995; Nevalainen *et al* 1999, 2000) and such tests are a requirement according to legislation in some European countries including the UK and the Netherlands (Home Office 1986a; Anon 1997).

Human–animal bonds

During daily interactions in the laboratory, members of staff learn to recognise the individual characteristics of their animals. Primates are also able to recognise individual humans (Sands & Wright 1982) and show preferences for individuals with whom positive interactions have occurred (Bloomsmith *et al* 1997) and may exhibit signs of fear and aggression towards those humans that have become associated with negative experiences (McKinley 2004). Thus, habituation to handlers is specific and not generalised to all handlers (in rats, Davis 2002; in primates, McKinley 2004) and individual members of staff develop relationships or positive bonds with individual primates (Waitt *et al* 2002). The greater the recognition and understanding of an individual's behaviour the greater the bond (Hart 1996) and the more time that is spent interacting positively with an individual, the stronger that bond becomes (Arluke & Sanders 1996; Herzog 2002). The development of such bonds has traditionally been frowned upon as it is considered to introduce problems, both in terms of experimental variation and in terms of the effect on staff when favoured animals are used in studies or are euthanised (Wolfle 2002). Thus, traditionally animals were not named but were given a number (Wolfle 2002). Despite this, those working with primates often either used the animal's number as a name, or named animals without the name being officially recognised and therefore presented in scientific studies (Wolfle 2002).

The recognition of handlers by primates represents a significant variable in experimental paradigms. If the animal is able to predict a positive or negative event on the basis of the presence of a particular person, his/her reaction to that individual may have a profound effect on his/her responses in the experiment (Reinhardt *et al* 1997a; Waitt *et al* 2002). It has more recently become accepted that the development of bonds between animals and their human carers has a positive effect on welfare and can, as a result, reduce the handler-related variability in studies. For example, Waitt *et al* (2002) found that stump-tailed macaques that showed affiliative behaviour towards caregivers exhibited less abnormal behaviour than those which avoided or were aggressive towards caregivers. Unstructured affiliation between human handlers and captive macaques and chimpanzees has a strongly positive influence on their well-being (Bayne *et al* 1993; Baker 2004). Further, Bayne *et al* (1993) found that, in rhesus macaques, the use of species-specific affiliative signals and food provisioning stimulated positive interactions between staff and animals and resulted in a significant reduction in the occurrence of abnormal behaviours. Further, in work reported by Markowitz and Line (1989), the quiet presence of humans that occasionally provided treats, but mainly watched behaviour, resulted in a considerable reduction in abnormal behaviour associated with humans entering the colony room. The reduction of handler-associated stress will in turn reduce experimental variability (Schapiro 2000). The development of positive relationships between the primates and their handler also reduces the likelihood of injuries to staff, thus increasing safety (Heath 1989). The ability to recognise the, sometimes subtle, effects of experiments on animals is greatly improved by the development of close working relationships with study primates. Thus, the accuracy of the data collection can be increased and the adverse effects of experiments reduced as deviations from normal may be identified earlier (animals in general, Wolfle 2002). Scientists should therefore also be encouraged to form positive, or at least neutral, relationships with the animals on their study. The use of names for individuals is considered to facilitate the development of positive relations as it provides a verbal reference point by which the animal can be identified and discussed (Scott 1990; Bayne 2002), resulting in the use of the relative pronoun 'who' not 'that' (Segal 1989), encouraging more empathetic handling and increasing the motivation to provide enrichments and other innovative, welfare-enhancing modifications to protocol (animals in general, Chang & Hart 2002). Difficulties arise in naming individuals in colonies consisting of several hundreds of primates, especially when individuals are group housed, individual recognition is not visually easy, and both primate and staff turnover are high. It is recommended that a highly visible means of visual recognition is used (Rennie & Buchanan-Smith 2006). Positive interaction with the animals in their care also increases staff morale, which is also only likely to enhance animal well-being (Waitt *et al* 2002). However, managers should be aware that the technicians who have developed relationships with their animals are the same technicians who have to perform procedures that may cause pain and suffering and they may have to euthanise primates with whom they have bonded. The potential role of counselling in such situations should be addressed.

Development of staff communication

Communication between staff at all levels is essential to ensure that the most is made of the network of care that is provided for the animals and that a culture of care is maintained. However, this network of communication can break down. For animals in general, care workers are key members of the team in scientific studies (Wolfle 2002) as they spend the most time with the animals and are often the first to identify subtle changes in the behaviour of the experimental animals. However, because these members of staff often develop the strongest bonds with the animals and, in many establishments, feel that their expertise is not properly recognised, there can often be poor communication between project leaders, scientists and animal technicians (Chang & Hart 2002; Wolfle 2002). The use of meetings to inform technicians about the science in which their animals are being used, and the results of these studies, has been suggested in order to increase the understanding of those involved in the care of the animals (Chang & Hart 2002). Such meetings could also be used to allow technical staff to communicate problems arising during studies or to discuss strategies that could be used to improve welfare. These sessions may thus help to reduce the barriers that result from hierarchical systems of work. Communication between members of the care staff can also be used to ensure that monitoring is consistent between staff members. Regular cross-checking of check-sheets within a team of staff can ensure that consistency is maintained and that desensitisation to the degree of suffering does not occur over time. The movement of staff between studies can also help to ensure that consistency is maintained (EC 2002), although it should be noted that such changes may impact on staff morale if they are moved away from preferred animals or projects.

Training of primates as a refinement

Training primates to co-operate with routine scientific, husbandry and veterinary procedures has been found to reduce fear, anxiety and distress associated with almost every aspect of laboratory practice (Reinhardt *et al* 1995; Prescott & Buchanan-Smith 2003). It is also accepted that the reduction of stress and removal of apprehension in relation to procedures can reduce the perception of pain and other aversive experiences, thus indirectly improving welfare (The Biological Council Animal Research & Welfare Panel 1992; Laule 1999). The minimisation of such adverse effects reduces the cost and risk of experimentation from both the animals' and scientists' point of view (Laule 1999). The introduction of training programmes also increases the frequency of positive interactions between care staff and primates (Bloomsmith *et al* 1998). As a result, the careful use of training can result in improved physical and psychological well-being, higher staff morale, increased breeding success and efficiency of husbandry procedures (Laule 1999) and a reduction in stress-related experimental variation (Schapiro 2000). Thus, the number of animals required to obtain reliable results can be reduced (The Biological Council Animal Research & Welfare Panel 1992; EC 2002). Also the number of blood samples that can be obtained within a short period of time can potentially be increased, within physiological limits, as each sample is associated with less stress than in non-trained animals (Schapiro 2000).

The ethical and scientific reasons for incorporating training into routine laboratory procedures are strong and its use is recommended in legislative and professional guidelines (eg Home Office 1986b; International Primatological Society 1993). However, it must be noted that the method by which training is accomplished has a considerable influence on the degree to which welfare is improved. Despite recognition of the scientific and ethical benefits of training (eg Prescott & Buchanan-Smith 2003) its use is not as widespread as might be expected (Prescott *et al* 2005). One of the main reasons for this appears to be that scientists are unwilling to try new methods when those they already use work sufficiently well and because alternative methods appear to require greater expenditure of time and money. This is particularly true with the smaller species of primate as handling them is relatively easy and poses little risk to the handler (McKinley *et al* 2003). Larger primates (eg macaques) have been trained more often and for a wider range of tasks than smaller primates (eg marmosets) because they are considered more dangerous, they live longer and are thus likely to be kept for longer in the laboratory and thus the time investment involved in training these primates is considered to be more worthwhile (Desmond & Laule 1994). However, we do not consider these factors as justification and smaller, more nervous primates have the potential to benefit as much from appropriate training. Although the financial and time investments required to undertake training programmes have been evaluated in several studies (eg Reinhardt *et al* 1995; McKinley *et al* 2003; Schapiro *et al* 2005), this information has not been widely disseminated in the past. Thus, the perceived barriers of financial and time costs remain (Prescott & Buchanan-Smith 2003; Prescott *et al* 2005). Guidelines on the use of training in the laboratory were published by The Biological Council Animal Research & Welfare Panel in 1992. Further explanation and examples of the use of training to achieve specific goals are provided in this document. A special issue of the Journal of Applied Animal Welfare Science provides details of the use of positive reinforcement training (PRT) in primates (Prescott & Buchanan-Smith 2003). A list of behaviours that have been successfully trained in either laboratories or zoos, or both, is given with references in Table 1.

Methods of training

There are two main methods of training that have been used either exclusively or in combination (Laule 1999). Both rely on the principles of operant conditioning (Laule 1999) in which animals learn associations between their own behaviour and the consequences of performing that behaviour (Roper 1983). The ability of animals to learn about the consequences of their actions and therefore to have control over their environment has evolutionary significance. Animals that are able to learn are better able to adapt to their environment and should thus have a survival advantage over those that cannot. Because of this, the inability to respond to changes in the environment may be highly stressful and the provision of an opportunity to exert control over their environment has been found to reduce stress, as indicated by an associated reduction in activity of the hypothalamo-pituitary-adrenal (HPA) axis (Weiss 1968). Thus, PRT has the potential to improve welfare by providing the animal with choices, some degree of control and hence predictability (Markovitz 1982 and see Bassett & Buchanan-Smith in press for a review of the welfare aspects of predictability and control in primates).

Negative reinforcement training and punishment

Negative reinforcement training (NRT) is commonly used to induce co-operation in laboratory-housed primates (Laule 1999). During NRT, the animal learns to perform a behaviour in order to avoid an aversive stimulus. The negative reinforcer may be anything from electric shock, as was used in early studies of operant learning (eg Garcia & Koelling 1966), to the threat of capture with a net or loud noises (Phillippi-Falkenstein & Clarke 1992). Negative reinforcement increases the performance of a desired behaviour and should not be confused with punishment, where the aversive stimulus is applied after the performance of a specific behaviour in order to reduce the likelihood of its recurrence. The scope of NRT to improve welfare is limited as the animal learns to co-operate with aversive procedures in order to avoid an even more aversive stimulus. Thus, the choice is forced, real control is limited and the animal is subject to stress from both the procedure and the threat of the aversive stimulus used to enforce co-operation. Further, the types of behaviours that can be

Table 1 List of references for scientific and routine veterinary and husbandry procedures that can be trained using positive reinforcement training to minimise stress.

Tasks for which positive reinforcement training can be used		References
Scientific procedures	Restraint	Moseley & Davis 1989; Laule 1999
	Venipuncture	Priest 1990; Reinhardt 1997b; Schapiro *et al* 2005
	Collect urine samples	Visalberghi & Anderson 1999; McKinley *et al* 2003
	Collect saliva samples	Lutz *et al* 2000; Cross *et al* 2004
	Collect semen samples	Colahan & Breder 2003; Schapiro *et al* 2005
	Injection	Priest 1991; Philipp 1995; Schapiro *et al* 2005; Videan *et al* 2005b
	Oral administration	Savastano *et al* 2003
	Topical application	Reinhardt & Cowley 1991
Generation of data	Touch screen	Crofts *et al* 1999
	Bar press	Scott *et al* 2003
General husbandry	Weighing	McKinley *et al* 2003; Savastano *et al* 2003
	Relocation (transport cage or shifting)	Reinhardt 1992a, b*; Klein & Murray 1995; Scott *et al* 2003
	Identification (microchip reading)	Savastano *et al* 2003
	Separation	Savastano *et al* 2003
	Stationing (staying at a given place)	Savastano *et al* 2003; Schapiro *et al* 2003
	Improve socialisation	Schapiro *et al* 2001
	Co-operative feeding	Bloomsmith *et al* 1994
	Affiliative interactions	Schapiro *et al* 2001
	Reduce abnormal behaviour	Laule 1993; Schapiro *et al* 2001
Veterinary care	Palpation	Savastano *et al* 2003
	Stethoscope	Savastano *et al* 2003
	Joint manipulations	Colahan & Breder 2003
	Mouth/teeth inspection/cleaning	Philipp 1995; Colahan & Breder 2003
	Treatment of surface wounds and skin diseases	Young & Cipreste 2004
	Temperature	Colahan & Breder 2003
	Ear examination	Savastano *et al* 2003
	X-ray	Colahan & Breder 2003
	Ultrasound	Savastano *et al* 2003
	Pinworm assessment	Schapiro *et al* 2005
	Infant care	Philipp *et al* 2001; Colahan & Breeder 2003

*Combined with negative reinforcement training.

trained using NRT and punishment techniques are limited. Only the prevention of some unwanted behaviours (such as when the animal may endanger him/herself, another animal or the trainer) and reinforcement of spontaneously occurring behaviours, generally escape responses, can be trained in this way (The Biological Council Animal Research & Welfare Panel 1992). Despite these limitations, NRT has been used with success and is most commonly reported as a means of obtaining co-operation during capture and relocation. For example, Luttrell *et al* (1994) reported that the negative reinforcement of shouting and arm-waving was used to induce rhesus macaques to co-operate reliably in a capture procedure using a chute system. Similarly Phillippi-Falkenstein and Clarke (1992) used poles banged against the pen to induce rhesus macaques to enter a chute system for faecal sampling.

Although the use of punishment is never recommended (The Biological Council Animal Research & Welfare Panel 1992), its use may be considered more acceptable in circumstances where the trainer, subject or other animals will be in danger if the behaviour (such as aggression) occurs (The Biological Council Animal Research & Welfare Panel 1992). In these circumstances compliance must be 100% reliable as one occurrence of the behaviour may result in injury or death. Although the rationale behind the use of punishment under these circumstances is more acceptable, positive alternatives to punishment and NRT should always be sought (The Biological Council Animal Research & Welfare Panel 1992).

Positive reinforcement training

In PRT, rewards are used to increase the performance of a preceding behaviour. Thus, by association, the animal learns to perform a certain behaviour or series of behaviours, in response to a cue from the trainer, in order to receive something desirable, for example a preferred item of food, verbal praise, a preferred toy or social access (Laule 1999). It was traditionally considered necessary to deprive subjects of food in order to increase motivation to obtain rewards (Roper 1983) but this practice is unnecessary (Scott 1990) and it should always be ensured that subjects are given their full ration of food that meets their nutritional requirements adequately (Scott 1990; Desmond & Laule 1994). Care must be taken, however, that training sessions do not result in over-indulgence in preferred foods and it has been recommended that training rewards are counted as part of the animal's balanced diet (Scott 1990). However, even under these circumstances, if training is carried out prior to normal feeding times, when animals are hungry and/or the food reward is highly desirable, aggression between cagemates may result. Such aggression can be avoided by timing training sessions so that they occur after the primates have been fed and by avoiding the most desirable food rewards (McKinley *et al* 2003).

For any potentially aversive task, habituation should be used. Habituation is the waning of a response as a result of repeated stimulation, without fatigue. It is important to allow laboratory-housed primates to habituate to aspects of the environment or procedures (eg the sound of clippers, restraint in a sling, confinement in a transport container) in order to minimise individual variation and thus reduce experimental variation. At a very simple level, PRT can be used for example to reduce neophobia and aversion by associating novel or aversive stimuli with rewards, a process known as desensitisation (Laule 1999). For example, Moseley and Davis (1989) described a process by which marmosets and owl monkeys were desensitised to the presence of humans and experimental apparatus using positive reinforcement, rewarding the animals for calm behaviour when the handler or apparatus was present. In order to train the animal effectively, the trainer must have the animal's attention and so reinforcement of sitting still and watching the trainer should be the first step towards instigating an effective training regime (Laule 1999). Training sessions should be short. McKinley *et al* (2003) found that a maximum session length of 10 minutes, ending sooner if the marmoset had earned 12 rewards, was suitable although in subsequent studies the maximum was set at 8 minutes with no decrease in the speed with which the marmosets learnt (McKinley 2004). Schapiro *et al* (2003) used session lengths of 15 minutes with group-housed macaques (thus each macaque was individually trained for a considerably shorter period within this 15 minutes). The key point is that session length should be short enough to maintain the animal's interest and to ensure that excessive quantities of food rewards are not given, creating potential weight problems, but optimum length varies between species and individuals (Savastano *et al* 2003).

Timing of the reward is extremely important in PRT. The reward must be given as soon as the behaviour is performed to ensure that the correct behaviour is reinforced and no opportunity to learn the wrong response is given (Scott 1990). In circumstances where this is not possible, the trainer should use a conditioned 'bridging' stimulus (Laule 1999). This stimulus is a previously irrelevant cue (eg a vocalisation like 'good') which the animal is trained to associate with the receipt of a reward simply by pairing the signal with the reward. The bridging stimulus can later be used to indicate to the animal that the response it has made was correct and that the reward will follow. In effect, the bridging stimulus becomes the reward. This ensures that the correct response is rewarded. Bloomsmith *et al* (1994) used PRT and bridging stimuli to reduce aggression in a group of captive chimpanzees. The alpha male was trained using PRT to sit and stay whilst other members of the group were fed and was rewarded with the verbal communication 'good' when he remained still and calm. The command 'no' was also used when aggression occurred and the chimpanzee was rewarded when he/she stopped and sat down. The bridging stimuli were necessary in this training programme as the trainers had to carry out training from outside the enclosure and as the chimpanzee was not always within easy reach and therefore could not always be rewarded instantly; the bridge informed the animal the instant he/she performed the requested behaviour.

Positive reinforcement training can also be used to reinforce naturally occurring behaviours in a trial and error learning situation (The Biological Council Animal Research & Welfare Panel 1992). For example, in group-housed animals it can be very useful to train animals to go to and remain beside a 'target'. Each animal can be given its own target within the enclosure and be trained, using trial and error learning and positive reinforcement, to go to and to stay touching the object when a cue is given by the trainer. This behaviour is called 'stationing'. In this way the trainer can gain access to each individual in the group separately (Laule 1999).

In contrast to NRT, PRT can also be used to shape complicated behaviours that would not occur spontaneously. In order to train very complicated behaviours, a schedule of PRT described as shaping or successive approximation can be used. The subject may be trained to perform progressively more complex stages of a desired behavioural response. When each stage is performed reliably in response to a cue from the trainer, the next stage can be attempted, gradually progressing towards performance of the whole response (Laule 1999). For example, McKinley *et al* (2003) described a programme of successive approximation in which marmosets were trained to scent-mark at a specific site, depositing a few drops of urine into a vial. The marmosets were first trained to associate a bridging stimulus of clicking (made using the tongue) with a food reward. They were then observed, continuously watching for naturally occurring scent-marking. When scent-marking occurred the clicking cue was made and a reward was given. When the rate of scent-marking increased in response to clicking, a verbal request was given as the marmoset moved towards scent-marking sites. When the marmoset would scent-mark on request, rewards were given only when he/she scent-marked at one or two specific sites. Collection vials were then placed in holes drilled at the scent-marking site so that the urine sample could be retrieved. Samples were successfully collected on 94.6% of occasions and reliability was obtained in three to 13 sessions in an average of 52 minutes per pair. McKinley *et al* (2003) used a similar process to train marmosets to sit on scales placed in their home cage. McKinley *et al* (2003) found that the time taken to train subjects to sit on the scales was shortest in those marmosets that already accepted hand feeding. This finding is supported by other authors who found that familiarity with humans improved learning ability (Laule *et al* 1996). Scott (1991) also found that allowing visitors into colony rooms, and allowing them to hand feed common marmosets, provided a means of desensitising the monkeys to the presence of unknown humans and was thought to increase the speed with which their animals adapted to training. However, ease of training is dependent upon the type of behaviour required and McKinley *et al* (2003) found that the time taken to train scent-marking for urine collection was longest in those marmosets that would already feed from the hand as these animals showed no fear of the trainer and therefore no associated increase in scent-marking, a behaviour increased by stress (Bassett *et al* 2003).

As PRT involves only positive interactions, its use has been found to reduce the stressfulness of procedures (Videan *et al* 2005a) and to increase the confidence of animals in the presence of human handlers (EC 2002; Bassett *et al* 2003; McKinley 2004). As a result, relationships between primates and their human carers are developed and improved and the stress of interactions is reduced (Bassett *et al* 2003). It is widely considered that the development of positive relations between handler and animal and the minimisation of fear greatly reduce the risk of handling large, strong animals from both the handler's and animal's point of view. Placing an animal in a situation in which it perceives threat and can find no means of escape may induce dangerous and aggressive defence behaviours (Reinhardt 2003) and may cause the animal to injure him/herself as it attempts to escape (Poole *et al* 1999). This is especially true in the case of larger primate species because of their strength and because many species have large canine teeth.

Positive reinforcement training relies on the voluntary co-operation of the subject in the procedure and the animal is therefore provided with far greater control over the event than those trained using NRT. For this reason it has been proposed that the process of training itself can act as an enrichment, as animals voluntarily take part and must work in order to obtain rewards and develop cognitive skills (Scott 1990; Laule & Desmond 1998). This was demonstrated by Crofts *et al* (1999) who adapted traditional Cambridge Neuropsychological Test Automated Battery apparatus to fit the home cage. The traditional apparatus required that the marmoset subject be removed from its home cage and placed in an isolated testing chamber in a procedure room. In contrast, the adapted apparatus used in this study was attached to the front of the home cage so that the subject could perform the test, but access to the home cage was always maintained. Thus, the subject chose to co-operate with the test in order to obtain a food reward. Crofts *et al* (1999) reported no loss of accuracy in the test despite the potential distraction of the home colony room environment. Co-operation was obtained without food restriction and, in contrast to NRT, provided the animals with a real choice between two non-threatening options.

Although there are obvious benefits to providing laboratory primates with means of controlling their environments and enrichment opportunities, problems may arise if training is stopped in between experiments (Bloomsmith *et al* 2001). It has been shown that the withdrawal of control, following a period where control has been given, can result in even greater activation of the HPA axis than that observed in animals that were never given the opportunity to control their environment (Weiss 1968). It must also be noted that PRT is likely to be most effective when the task to be trained is enriching or neutral (eg problem solving, stationing, weighing). If the task is potentially aversive (eg venipuncture), the sole use of PRT may be less feasible, at least initially. For example, Bowell *et al* (2005) found that marmosets trained to enter a transport box and be separated from the social group for 5 minutes took significantly longer, or refused to enter the box, when attempts were made to capture them in the same transport box to be removed for blood sampling.

Combined use of negative reinforcement training and positive reinforcement training

In many studies NRT and PRT have been used in combination to induce co-operation with potentially aversive procedures. For example, Wolfensohn and Honess (2005) described the procedure for training macaques to stand for intramuscular injection whilst socially housed within a large room. Reinhardt (1991) and Reinhardt and Cowley (1991) used NRT and PRT in a successive approximation programme to train macaques to present a limb for blood sampling, although more recent protocols describe the sole use of PRT for blood sampling (Schapiro *et al* 2005; Videan *et al* 2005b) and these should be used in preference. In the earlier studies movement towards the front of the cage was initially induced using the squeeze-back mechanism of the home cage, reducing the cage to half its original size. When the subject was standing near the opening in the front of the cage one of its legs was grasped and held until resistance ceased. The macaque was then rewarded and released. When the subject moved to the front of the cage reliably and the limb could be held without resistance, the squeeze-back mechanism was used to reduce the cage to two-thirds of its original size, until the subject co-operated with the procedure voluntarily. Desensitisation to the actual sampling procedure was then achieved by rewarding the macaque for tolerating successive approximations of blood sampling. The average time invested in training the macaques to present a limb for blood sampling was 40 minutes although there was considerable variation within the group (16–74 minutes). These successes undoubtedly reduce the adverse effects of the sampling procedures, once reliable presentation for sampling has been established.

However, although NRT increases the speed with which training of these procedures may be accomplished, the process of training involves force and is likely to be stressful initially. Exclusively positive programmes of training have been used to train large primates to co-operate with a variety of complex practices including blood sampling (eg Priest 1990; Laule *et al* 1996; Schapiro *et al* 2005), injection (Schapiro *et al* 2005; Videan *et al* 2005b), application of test substances to the skin (Reinhardt & Cowley 1991), semen sampling (Schapiro *et al* 2005) and for assistance with suckling infants (Priest 1990, and see Table 1). Similarly, PRT has been used exclusively to train marmosets to co-operate with laboratory procedures (eg McKinley *et al* 2003). It must be recommended therefore that in order to reduce stress from procedures to an absolute minimum, the primates should be habituated and desensitised, and positive reinforcement alone should initially be attempted (The Biological Council Animal Research & Welfare Panel 1992; Desmond & Laule 1994). Although PRT should be incorporated into laboratory routines as it has been shown to be practical, and beneficial to both the animals and the science, it may be necessary to resort to a combination of NRT and PRT if the procedures are aversive and time is limited (eg toxicology, Schapiro *et al* 2005).

Personnel requirements for successful training

The use of PRT is a mutually positive experience for trainer and trainee and can dramatically improve the standard of care and the morale of care workers in the laboratory (animals in general, Kiley-Worthington 1990). Good trainers require patience and must have a natural affinity and empathy with the individual they are trying to train (Laule 1999). Young and Cipreste (2004) argued that calm demeanour, consistency in behaviour and an ability to analyse their own behaviour are other important characteristics. It should be recognised that not all personnel have characteristics that make good trainers and that the suitability of individual trainers must be assessed before selection for intensive training duties (The Biological Council Animal Research & Welfare Panel 1992). Problems arising during training can usually be overcome and the capacity for innovation is a highly desirable trait in a trainer. Potential trainers must also be educated in the behavioural ecology of the species concerned (Colahan & Breder 2003). Laule (1999) suggested that training can be carried out most effectively if a hierarchical system of training responsibilities is laid out. She suggested that an overall training supervisor should have the ability to design training programmes and to solve any problems should they arise. Several senior trainers should work under the supervisor and be able to train more complex behaviours and advise the supervisor on the progress of training. Finally, all care staff should have an understanding of the key concepts of training and positive reinforcement so that they are able to maintain trained behaviours and to train simple new behaviours, for example to move animals between cages during routine husbandry. Thus, it should be possible for training to be reinforced during every interaction between care staff and primates during all routine husbandry and scientific procedures. In this way training can become part of the routine of the laboratory and the 'extra' costs associated with specific programmes are diminished (Laule 1999). It is also considered important that all external staff, including vets and managers, have an understanding of the basic principles of the training techniques used in that laboratory, so that the trust of the trainee is not undermined during more unusual procedures. Although it may not be possible to implement continuous routine use of PRT for all primates in all laboratories due to perceived time constraints, even increased positive human interaction (treat feeding) and/or a small amount of training several times a week will improve welfare (eg Bayne *et al* 1993; Bloomsmith *et al* 1999; Waitt *et al* 2002; Bassett *et al* 2003; Baker 2004).

Conclusions and animal welfare implications

The nature of human–animal interactions affects every aspect of the use of primates in research. Care workers should be selected for their positive attitude to the animals and have an interest in science. Education and on-the-job training are essential and competence should be tested. Courses like that outlined by FELASA should be used and regularly revised. Good lines of communication are vital between staff with different responsibilities. The development of human–animal bonds increases the well-being of primates and staff morale and can improve science. However, there is a need for the development of guidelines for the initiation and maintenance of such positive interactions to ensure that they can be achieved safely, especially if aversive procedures are involved. Furthermore, the use of names for individuals, even in large colonies of primates, would assist in improving human–primate bonds, but if not readily identifiable through individual characteristics, suitably visible forms of identification are required to facilitate recognition.

Technicians using PRT, which induces the expression of a behaviour by rewarding that behaviour when it occurs, find it a rewarding experience, and it can lead to positive changes in the attitude towards animals. Furthermore, the animal can be trained to actively co-operate with routine husbandry and veterinary procedures, and with research procedures and data collection, in order to gain the reward. The animal has control over whether he/she participates and complicated series of behaviours can be trained. This has the potential not only to enhance well-being, but may also improve the quality of scientific research. NRT induces expression of a behaviour in order to avoid exposure to an aversive stimulus. The range of behaviours that can be trained in this way is limited as the animal has to conform and has no control. Punishment should be given only to prevent extremely dangerous behaviour.

The use of PRT, particularly with smaller primates, remains limited in the research community. Possible reasons include lack of information about the costs, both financial and in staff time, inertia of tradition and a lack of understanding of the benefits that can be accrued. Detailed information is needed regarding the time and financial investment necessary to train behaviours, and further research is required on the optimal age to train, session lengths and the role of social learning. The need for further research should not deter wider application of PRT. There is considerable evidence, some of which has been summarised in this review, which indicates the importance of human–animal interactions and demonstrates the potential impact of staff in the refinement of practice in laboratories. Thus, technicians and scientists should be fully aware of the impact that they have and use it to ensure that their influence on their animals' well-being is positive.

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