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Selective breeding of primates for use in research: consequences and challenges

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Abstract

Primates are bred in captivity for a number of purposes, from zoo-based captive breeding programmes for conservation to breeding for biomedical research. In each case, breeding animals that are fit for purpose, either as viable candidates for reintroduction or as valid research models, has presented challenges and resulted in steep learning curves. The breeding of animals for biomedical research has become increasingly focused on the production of animals that are less stressed by captive (specifically laboratory) environments. This is because elevated, particularly chronic, stress responses can result in altered physiological, neurological and behavioural states that have the potential to compromise the validity of scientific results. Selective breeding in captivity to, for example, maximise production, select for docile temperament or specific genotypes for biomedical research, is likely to be counter to natural selective pressures for evolutionary fitness. Given that many natural selective pressures active in the wild are absent in captivity, this paper reviews the selective breeding of primates (especially Old World monkeys) in captivity, its potential negative effects, and options that exist for ameliorating these negative effects.

Keywords: *animal welfare, biomedical research, breeding facilities, macaques, Old World primates, selective breeding*

Introduction

Primates are bred in captivity for a variety of reasons. In zoos it is for potential reintroduction (eg golden lion tamarins [*Leontopithecus rosalia*]; Kleiman *et al* 1986) and to improve scientific understanding about the reproductive biology of endangered species (eg aye-aye [*Daubentonia madagascariensis*]; Coffman *et al* 1993, woolly monkeys [*Lagothrix lagotricha*]; Mooney & Lee 1999). In biomedical research, primates are bred to provide research subjects, with individuals either representing their species (in its own right) or acting as models of disease or process in humans (see various contributions in Wolfe-Coote 2005). In both instances, the animals produced by these breeding programmes exhibit traits which are the result of both planned and unplanned selective breeding, the nature and diversity of the programme's founder population, and the effect of captive conditions and husbandry.

This paper focuses on the breeding of primates, particularly macaques (*Macaca* spp), for biomedical research though it will inevitably make reference to the breeding of primates in other contexts. It highlights many significant welfare effects of planned and unplanned selective breeding under artificial, captive conditions and ways in which some of these challenges might be addressed. Most examples are taken from the literature but additional information is drawn from the breeding colony of long-tailed macaques (*Macaca fascicularis*) of Bioculture Ltd (BCM) on Mauritius.

Recent estimates for the number of primates being used globally in biomedical research place the figure at around 200,000 (Carlsson *et al* 2004). This figure is likely to have risen since 2004 and also does not include animals held, either not 'on study' or in breeding facilities. Therefore, the total number of primates dedicated to research is likely to be nearer 400,000. Under some regulatory frameworks (eg UK, EU) there is a ban on the use of wild-caught primates for research, save in exceptional circumstances (Prescott & Jennings 2004). This position is based on three major points which together have increased the demand for captive-bred high health status animals:

- Wild caught individuals suffer significantly more under restrictive captive conditions and imposed husbandry regimes than captive-bred animals (Crockett *et al* 2000; Ha *et al* 2000);
- Captive-bred animals have better known health status and clinical histories (Bourne & Golarz de Bourne 1975); and
- Self-sustaining breeding centres help reduce the impact on wild populations (Morton *et al* 2005) and are strategic resources (Wolfensohn 1997).

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A thorough review of the history of the development of the use of primates in research is provided by Fridman (2002). Whilst research centres were established as early as 1913 (Tenerife, Canary Islands) and 1923 (Pastoria station, Pasteur Institute, French Guinea), the first *ex situ* primate centre focused on research and breeding was established in the Soviet Union (Sukhumi Primate Centre) in 1927 (Fridman 2002; Dewsbury 2006). However, the strategic establishment of *ex situ* primate breeding and research centres was started in the USA as early as 1916 (Yerkes 1916). As a result of the energies of Robert Yerkes, the Anthropoid Experiment Station of Yale University was opened in 1930 in Florida for the breeding and study of chimpanzees (Yerkes 1935). This facility has become one of the most important primate breeding and research centres in the world having moved to Emory University (Georgia, USA) and being renamed: The Yerkes National Primate Research Center. By 1968, there were seven Regional Primate Research Centers in the USA (California, Oregon, New England, Tulane, Wisconsin, Washington, Yerkes) and an eighth (Southwest) was added in 1999 (Johnsen 1995; Fridman 2002). In the UK, perhaps the first breeding centre established was at Cambridge University in 1959 (Anderson & Simpson 1979). Other primate centres established in Europe include: the Dutch Primate Centre (Biomedical Primate Research Centre, Rijswijk, The Netherlands) in 1970 (JARAM van Hooff [2009] citing Cicero [1988]); the German Primate Centre, (DPZ: Deutsche Primatenzentrum, Gottingen, Germany) in 1977 (www.dpz.gwdg.de); Centre de Primatologie (Strasbourg, France) in 1978 (http://pin.primate.wisc.edu/idp/idp/entry/126); and the Istituto di Neurobiologia e Medicina Moleculare/Italian National Research Council (INMM CNR: Rome, Italy) in 1981 (http://www.euprim-net.eu/management/con_inmm.htm). In 2006, eight European primate facilities established EUPRIM-NET to form a virtual European Primate Centre; sharing resources and promoting and implementing the 3Rs (www.euprim-net.eu).

The combination of the establishment in 1973 of CITES (Convention on International Trade in Endangered Species), the 1978 embargo on primate exports from India (previously supplying up to 100,000 rhesus macaques [*Macaca mulatta*] per year to the USA), and the 1981 World Health Organisation opinion on the need for self-sustaining breeding colonies, increased the pressure for breeding in importing countries. It also led to the establishment of facilities for breeding primates in many countries with a history of the export of wild-caught indigenous primates including Indonesia (eg Tinjil Island, 1988: Kyes 1993), Philippines (SICONBREC, 1983: Hobbs 1989), Mauritius (Bioculture 1985: Stanley 2003), and a number of countries in continental Asia (eg China, Vietnam, Nepal etc: Prescott & Jennings 2004; Morton *et al* 2005). For example, long-tailed macaques, widely distributed in Malayo-Indonesia and Indochina, were introduced to Mauritius by the Portuguese in the 1500s (Tosi & Coke 2007). It is generally accepted that the small founder population originated from Java based on pelage (Sussman & Tattersall 1981) and mitochondrial DNA (Lawler *et al* 1995) comparisons. However, while not totally rejecting a Javan origin, recent phylogenetic analysis indicates a Sumatran origin (Tosi & Coke 2007). As an alien species it has had a significant impact on Mauritius's endemic wildlife and agriculture (particularly sugar cane production: Tattersall *et al* 1981; Stanley 2003) and initial population control centred on bounty killing and extensive culling. However, since 1985, trapping for use in biomedical research has been used. In most cases these animals are incorporated into breeding colonies and then either their F1 or F2 offspring exported for research, primarily to the USA and Europe.

Breeding practices and consequences

Breeding for production

There are a number of housing/grouping configurations used in the captive breeding of primates. These vary from solitary housing with timed breeding (monitoring female reproductive status and moving her to a breeding male's cage for mating around ovulation), permanent or semi permanent pairs, small harem groups (eg outdoor cages including corn cribs, breeding rooms), expansive corrals, and free-ranging island settings (eg Cayo Santiago, Puerto Rico). In the wild, macaques typically live in multi-male-multi-female groups. Female macaques have strong social dominance structures with related individuals forming one or more matrilines within the group with a small number of breeding males (approximately 1–4) (Fooden 1991; Hill & Okayasu 1996; Fooden 2000). There is usually a positive relationship between dominance rank and male reproductive success, which is negatively related to the number of male competitors (Cowlishaw & Dunbar 1991; De Ruiter *et al* 1994). Young males leave the natal group on maturing, forming peer groups or moving into existing groups (Melnick *et al* 1984). Traditional captive breeding has typically weaned all infants out of the natal group often for production or space availability reasons.

Group housing has a number of benefits in terms of efficiency (staff time) and cost (caging infrastructure) savings as well as assisting with regulatory compliance and developmental benefits for the animals (Wallis & Valentine 2001; Wolfensohn & Honess 2005). However, while it is not uncommon to house breeding animals in groups it is rare that the composition of the group, or changes to it over time, reflect the situation present in the wild. For example, immigration and emigration opportunities do not exist in all but the most expansive of configurations. However, it has been noted that Japanese macaques (*M. fuscata*) escaping, or attempting to escape, from corrals were predominantly young males; matching the pattern of natural emigration from natal groups in the wild (Lehman & Taylor 1992). In addition, where groups are kept as harems and males may hold group tenure for life, the ability of females to exercise mate choice is significantly limited or non existent. Under such conditions, sexual selective pressures that commonly operate between female and male polygamous primates (Kappeler & Van Schaik 2004) cease to exist and the artificial selection of males by their human keepers takes over. Males are then selected for a range of characteristics including research model traits (eg genetic), health status, and temperament.

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It is the authors' experience that fear of intragroup aggression appears to be the major reason why adult males are not moved between captive breeding groups on a regular, non-essential basis. This aggression could manifest itself in infanticidal behaviour by the new male or fights between adults resulting in trauma injuries requiring veterinary attention. This instability may in turn have an impact on productivity. However, in the wild, male tenure of a breeding group may last only two to three years (the time it takes his daughters to mature). Macaque breeding systems appear to be strongly driven towards a regular replacement of breeding males for genetic and inbreeding avoidance functions (Zumpe & Michael 1996). This is achieved through a reduction in reproductive behaviour with familiar mates which can be reversed by a novel partner (Zumpe & Michael 1984; Goy 1992; Zumpe & Michael 1996). Aggression, including infanticide, is not uncommon in primates during group takeovers even in the wild, however in captivity a combination of careful planning (including of male suitability and maturity), gradual familiarisation and introduction, monitoring and intervention, and temporarily flooding the housing with visual barriers can successfully minimise aggression, injury and instability (eg Watts & Meder 1996; Honess & Marin 2006b; Jennings *et al* 2009).

Under well-designed, high health, high welfare captive breeding strategies it is possible to achieve high production levels that may exceed those reported from the wild. For example, at BCM, the average birth rate is 70% (minimum: 58%, maximum: 102.3%) which compares favourably with birth rates reported for wild long-tailed macaques of 71% in good years, and 38% in bad (van Noordwijk & van Schaik 1999).

Interest in theoretical aspects of differential maternal investment (Trivers & Willard 1973; Silk 1983) has led to examination of secondary sex ratio in a number of primate species. In particular, researchers have examined the effect of social rank on sex ratio at birth. It would appear that wild and captive contexts can produce contradictory evidence for the debate; for example, *M. fascicularis* is one of a number of primate species that in captivity show a more skewed sex ratio toward male births among high-ranked females than low-ranked females, which is not born out in the wild (Bercovitch 2002). It has also been suggested that females may produce more males when subjected to 'stress' and also when they have surplus resources (McGinley 1984) and it may be that captive conditions combine these factors (Bercovitch 2002).

Birth and birth weight

It is clear that housing conditions and stress can have a dramatic effect on pregnancy outcomes for captive-bred primates. Prenatal mortality (stillbirths) for primates housed indoors ranged from 5.9–20% (in several Old World species, including five macaque species) compared to 2.7% in free-ranging rhesus macaques; a difference that may be attributable to housing conditions (Hendrickx & Dukelow 1995). Cage size itself has been demonstrated to have an effect on pregnancy outcomes in female long-tailed macaques housed in 45 × 45 × 60 cm (length × breadth × height) (68% successful) versus 70 × 70 × 100 cm (90% successful) (Boot *et al* 1985). It should be noted that the former cage size falls below any currently acceptable caging for macaques in Europe or the USA, indeed the bigger cage is below existing EU/UK standards.

Genetics studies have demonstrated the heritability of birth weight in macaques (eg Ha *et al* 2002). It is therefore not surprising that the reproductive performance of a daughter can be influenced by her own mother's birth weight, with birth weight being a feature of particular matrilines; more dominant matrilines produce heavier offspring (Price & Coe 2000). Females born light produce their first infant about one year later than others and carry more risk of stillbirth and light or premature neonates. In view of this, it might be suggested that breeding selection should favour those matrilines with heavier daughters at birth. Price and Coe (2000) suggest there may be a link with prenatal stress, therefore if more than one matriline exists in a breeding group the dominance relationship between them will most likely ensure that one is always dominant over the other and the subordinate matriline will therefore produce light daughters at birth. Further support for the role of social stress is provided by Ha *et al* (2002) who found that birth weights were lower in group-housed animals than in those housed singly. This potentially provides a conflict for those wishing to maximise psychological well-being as well as production. However, it should be noted that the mean birth weight reported in this study for infants of socially-housed animals (468.5 g) is not meaningfully lower than that reported elsewhere for this species (473 g; Lee 1999) and may not therefore indicate reduced welfare. Indeed, the mean birth weights reported by Ha *et al* (2002) for singly-housed females' infants at 513 and 501 g are considerably higher than the weight reported by Lee (1999) and is likely to reflect reduced feeding competition and (although Ha *et al* do not define the size of the single caging; likely to be around the regulated size of 0.56m^2 × 0.81 m high [NRC 1996]) decreased activity in smaller caging.

Weaning

Natural weaning is a process involving a gradual withdrawal of milk resources and care allocation, over a period of weeks or months, from the infant by the mother (Lee 1996). The timing of weaning is largely determined by bodyweight and is predicted by the infant's weight at birth (Lee 1999). In practice, for most macaque species, this point is reached at about one year of age (Reinhardt 2002). In captive breeding 'weaning' typically refers to the permanent removal of the infant from its mother. It is common practice for this to take place at about 6 months of age, although increasingly recommendations are that it should take place around 12 months (NC3Rs, IPS Guidelines). Other factors that are taken into consideration when planning the weaning are: i) the animal's bodyweight (at BCM: not less than 1.2 kg), and ii) readiness for weaning of any half-siblings with which they are housed (Wolfensohn & Honess 2005).

The perceived wisdom in many facilities is that early weaning (3–8 months) is necessary to break lactational

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amenorrhea and return females to breeding condition (Wallis & Valentine 2001; Reinhardt 2002), as well as to reduce risk of vertical transmission of B-virus (Mansfield 2005). Although Kotera *et al* (1975) (for Japanese macaques [*Macaca fuscata*]) found that early weaning (from 3 months) increased female productivity, these findings compared populations on islands for which insufficient information was presented to ensure that this observation was not confounded by other factors. Indeed, only one study (Goo & Fugate 1984; *M. mulatta*) has demonstrated experimentally improved productivity with early weaning (6, 8 and 10 months versus 12 months) but the authors also point out the highest production rates they found are still lower than those reported for wild rhesus macaques. On the negative side, this study also reported a weight difference (average: 200 g) at 12 months between those weaned at six and 12 months though this did not translate to any difference in survival between these groups at two years of age. There is also evidence that contradicts the suggestion that early weaning increases productivity: in baboons (*Papio hamadryas*), mothers of naturally weaned infants had on average shorter (though not significantly so) intervals for a number of parameters (eg interbirth interval) which would improve production compared to those whose infants were weaned at around six months (Wallis & Valentine 2001). There is also evidence that mothers of early weaned infants suffer stress or depression that could hinder their ability to return to breeding condition. For example, bonnet macaque (*Macaca radiata*) mothers with infants weaned at six months exhibited apathy, restlessness and poor appetite (Nagarajan *et al* 2004). Not least there is a substantial body of research which demonstrates the negative consequences for the primate infant that is separated prematurely from its mother, in terms of its psychological development, future social and reproductive behaviour, and reactivity to stressors (eg Mineka & Suomi 1978; Wallen *et al* 1981; Mineka *et al* 1986; Higley & Suomi 1989; Goin & Gust 1998; Latham & Mason 2008).

A number of enlightened breeders are beginning to retain at least some of the female offspring within their natal group with the intention of creating naturalistic matrilineal groups with a periodic replacement of the breeding male(s). Over time, groups originally composed of largely unrelated females become increasingly homogeneous in relatedness as expanding group size can be managed by splitting the group along matrilines. This strategy, mimicking that in the wild, promises a number of significant benefits in breeding rate (via mate-boredom alleviation; Zumpe & Michael 1984), maternal education (especially of primiparous females; the most important factor in mothering quality: Tsuchida *et al* 2008), reduced aggression among females (due to inheritance of rank) and between males and females (female protection via kinship-based coalitions) (Gouzoules & Gouzoules 1987). All of these benefits will be accompanied by a general reduction in stress levels.

Since January 2008, BCM has been examining the consequences of retaining selected females in their natal groups (selection is based on their mother being in the colony more than 10 years and having a production rate of above 80%, ie 8 births in 10 years). To date, none of the retained females (217 of a total of 321) have received treatment of aggression-related injuries. The weaned animals, also without significant injury, are still in peer groups, being below the age at which they are formed into breeding groups.

Breeding for models

Primarily due to their phylogenetic proximity to humans, and in the absence of alternative options, non-human primates continue to be used as research models for a range of human medical conditions. There are significant physiological and anatomical similarities between them; however, it has long been recognised that for animals to be valid research models they must be both clinically and psychologically healthy. As discussed above, there is a substantial body of literature on the negative psychological and developmental consequences of maternal deprivation, raising animals in inappropriate or socially deficient environments, and keeping adults in social isolation or inappropriate groupings.

There are a number of natural variations among even closely related primate forms that can inform their selection as research models. For example, rhesus macaques from two different origins account for most of the rhesus macaques used in research: Indian and Chinese. While currently classified as the same species (2 Indian and 4 Chinese subspecies: Groves 2001) there are nevertheless differences between these forms, not least in their diagnostically different genetics which allows identification of the ancestry of captive animals (Smith 2005). In fact, mitochondrial DNA, but not nuclear DNA (Groves 2001), suggests that Chinese rhesus may be more closely related to both the Japanese (*M. fuscata*) and the Taiwanese (*M. cyclopis*) macaques than to rhesus macaques from India (Smith *et al* 2007). Evidence also exists of the genetic differentiation between captive and wild populations of rhesus macaques in China, as a result of captive breeding strategies (Satkoski *et al* 2008).

The significance of differences between Indian and Chinese rhesus were seen when attempts to use more Chinese rhesus in AIDS research, in response to reduced availability of those of Indian origin, uncovered a different response to SIV infection. Those of Chinese origin survived significantly longer than those of Indian origin (Trichel *et al* 2002) with Chinese rhesus representing a better model for HIV infection in humans (Ling *et al* 2002). Significant genetic differences also exist between populations of long-tailed macaques, in particular between those from the Philippines and those from Indochina. Those from Mauritius exhibit the lowest genetic diversity of any long-tailed macaque population (Smith *et al* 2007) and differ from Asian forms in a range of morphological characteristics related to their maturation and larger body size (Drevon-Gaillot *et al* 2006). Mauritian macaques may represent a valuable model for the study of diabetes as some individual free-ranging macaques exhibit a predisposition to diabetes as a result of a high sugar diet (Tattersall *et al* 1981).

While it is not yet possible to breed usable numbers of genetically modified primates for specific disease models

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(eg Parkinson's disease), recent research has not only demonstrated the feasibility of producing transgenic primates (Chan *et al* 2001) but also that germline transmission of a transgene is possible (Sasaki *et al* 2009). Inevitably, this raises new and significant ethical questions for the selective breeding and use of primates in research (Cyranoski 2009).

Primates are however already selectively bred in captivity as models for a range of human conditions, including atherosclerosis and arteriosclerosis. One study examined the effect of selective breeding on cholesterolemic response in baboons (*Papio* spp) (McGill *et al* 1988). Breeders were selected for their high or low blood lipoprotein cholesterol concentrations in response to diets high in cholesterol and fat. Six males and 64 females were formed into six breeding groups of either high or low responders. The direct animal costs in this selective breeding programme can be seen in that of 96 live births (over 32 months) 32 subsequently either died or were excluded from the study for health reasons (McGill *et al* 1988). Baboons (*Papio cynocephalus cynocephalus* and *P. c. anubis*) have also been used to selectively breed lines with significantly differing (high/low) blood pressure (Carey *et al* 1993). These models were produced for the comparative study of physiological, biochemical, metabolic and genetic factors involved in the control of blood pressure. Heritability of another condition was demonstrated by selectively breeding animals with either high or low historical intraocular pressure associated with glaucoma (Dawson *et al* 2003).

Biomedical research has also identified value (eg for HIV and SIV research) in selectively breeding primates to produce offspring that have identical MHC (major histocompatibility complex) genes. This process is facilitated by breeding from a source with naturally restricted MHC diversity, such as Mauritian long-tailed macaques (Mee *et al* 2009). The MHC gene family is known to play an important role not just in the immune system (Slierendregt *et al* 1993), but also in inbreeding avoidance and co-operation via kin recognition (Brown & Eklund 1994), and reproductive success (Knapp *et al* 1996). Knapp *et al* (1996) found that shared parental MHC antigens predicted over 70% of pregnancy loss in less reproductively successful pigtail macaques (*Macaca nemestrina*) and conclude that identification of MHC genes could benefit primate breeding colony management. Similar reproductive consequences may arise from breeding that consciously or unconsciously selects for identical MHC genes thereby counteracting natural selective pressures for MHC diversity with resulting benefits for reproductive success.

Breeding for health

Since the beginning of formalised primate breeding there has been an awareness of the dangers to both human and animal health of bringing them close together in artificial, confined and often indoor environments. This problem has been addressed through a mixture of hygiene and health practices, screening and controls. Establishing the clinical health of animals and staff is a starting point for the welfare of both, however these practices can themselves have significant impacts on welfare, particularly when they are disproportionate. For example, keeping monkeys on grid floors may limit the accumulation of faeces, urine and waste food but it also limits the provision of enrichment opportunities that a scattered forage, forage substrate or deep litter can provide (Anderson & Chamove 1984). Equally, single-housing of animals may prevent wounding or transfer of many infections but prevents species-typical social behaviour and elevates stress and abnormal behaviour levels (Novak & Suomi 1988; Reinhardt & Reinhardt 2000; Honess & Marin 2006b). While frequent cleaning and health screening, and the wearing of high levels of Personal Protective Equipment (PPE), will keep pathogen transfer down, the intensity of operation and barrier equipment can be reduced when working with animals of a high defined health status enabling more welfare-friendly practices (Wolfensohn & Honess 2005).

There are a number of pathogens which non-human primates can carry which have significant health implications for humans as well as the ability to confound programmes of research (Mansfield 2005). Among the most important of these are simian herpes B (B virus) and Ebola viruses; both of which are associated with high rates of fatality in humans. Breeding primates that are free of defined pathogens (specific pathogen free: SPF) has been the goal of many captive breeding facilities and while the processes involved do not represent selective breeding in terms of focused altering of the genetic profile of the colony, nevertheless this is likely to be the result over time. The breeding of SPF primates for research was, in the first instance, largely driven by the need to produce healthy animals for human occupational health reasons. There was an increasing perception of the risk of simian herpes B virus in macaques that were experimentally (or naturally) infected with HIV or other retroviruses (SIV, STLV-1 and SRV), causing immunodeficiency and activation and shedding of B virus (Johnsen 1995). Efforts to prevent maternal infection of infants has frequently meant that animals produced for SPF breeding stock are removed from their mothers at, or shortly after, birth and then hand-reared. However, this strategy can result in the development of clinical and behavioural problems as well as significant extra husbandry burdens (Mansfield 2005). In addition to wishing to avoid the exceptionally high welfare burden of early weaning and hand-rearing it would appear that leaving the infant with its mother until it is 8–12 months old has additional benefits of transferred immunity from the mother and the fact that most do not seroconvert until two-years old or later (Mansfield 2005). Mansfield (2005) details a strategy for the formation of an SPF macaque colony in which infants are weaned at 8–12 months and then singly housed until initial testing results are reported, at which point those testing seronegative are placed in peer groups of 3–4 animals and B virus tested every three months for a minimum of two years before then being formed into breeding groups at around three-years old. If any individuals test seropositive then it is recommended that the whole

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group is returned to the conventional (non-SPF) colony. The seronegative animals remaining in the SPF colony continue to be tested regularly up to the production of Level 2 SPF offspring. Most SPF colonies maintain a regime of screening and testing on at least an annual basis. It should be pointed out, however, that there are still consequences of peer-, rather than hand-, rearing for breeding animals, including deficient maternal behaviour and lower infant survival, when compared to breeders raised in their natal group (Goin & Gust 1998).

In the most extreme examples of the production of gnotobiotic animals (ie with no pathogens, or only those of known identity) animals have to be delivered by caesarean section and maintained, probably alone, in expensive isolating housing (Bourne & Golarz de Bourne 1975). Monkeys raised in these conditions typically develop substantial behavioural problems and may become withdrawn and fail to complete or attempt experimental tasks (Bourne & Golarz de Bourne 1975).

The establishment of an SPF colony gives sufficient security for staff health and it is then possible, with appropriate staff training (eg early recognition of aggression and stress) to relax barrier systems enabling closer interaction, assisting the socialisation and training of the animals (Wolfensohn & Honess 2005). The alternative strategy is to work with animals bred from a founder population naturally free of the pathogens which SPF breeding is designed to eradicate. This has the benefit of SPF status without the need for the derivation practices which can compromise welfare. One example is the long-tailed macaques (*M. fascicularis*) on Mauritius which are free of Ebola, B virus, SIV, SRV and STLV-1.

Breeding for temperament

In captive breeding there may be active or inadvertent selection for animals with docile, less aggressive temperaments (Mehlman *et al* 1994) because they are easier to manage. Equally, more aggressive animals may get culled-out as they present an additional risk to cage mates or staff.

Temperament selection also relates to the refinement of procedures. The increasing uptake of positive reinforcement training to reduce the need for chemical and physical restraint, benefits animal welfare but also increases model validity and the quality of research (Jennings *et al* 2009). However, it has also been established that there are differences in training success between animals of different temperament; more exploratory animals being easier to train than those that are more inhibited (Coleman *et al* 2005). However, selection of animals for ease of training may be at odds with other efforts to select for less aggressive individuals: serotonin levels (higher levels of which are associated with affiliative and friendly behaviour) are negatively correlated with tendencies towards more aggressive and risk-taking behaviour (Mehlman *et al* 1994). Therefore, selection for passivity for husbandry and social management may be selecting for animals that are harder to train. Indeed, there is also evidence that in long-tailed macaques, friendly, affiliative and explorative behaviour are positively correlated with serotonin-binding potential (via PET scan) in different sides of the anterior cingulated cortex (Shively *et al* 2006). Selection of animals for their docile, friendly temperament, potentially at the expense of inquisitiveness, a trait positively correlated with training success (Coleman *et al* 2005), might therefore be expected to have an impact on the application of training for clinical and husbandry procedures. It is also likely to affect the ability to train animals for data collection, for example in behavioural neuroscience, although this has not yet been tested.

Animal welfare implications and conclusion

Captive breeding of primates for biomedical research has reached a crossroad; there is no indication that demand for research subjects is decreasing; to the contrary, it is anticipated to rise (Carlsson *et al* 2004). There are therefore pressures on breeding facilities to meet this demand while at the same time complying with demands for the highest standards of health and welfare and restricting the captive generation (second generation or later) of supplied animals.

The argument that high standards of health and welfare have beneficial effects for research quality is not a new one (Poole 1997). In recent years, there have been significant increases in understanding of the impact of housing and husbandry, via elevated stress, on welfare and the quality of science (eg Honess & Marin 2006a,b). It can also be seen, as discussed above, that both production levels and model quality are compromised by poor welfare in the breeding context. There are inevitable restrictions placed on management practices when trying to breed primates in captivity. The social and reproductive systems of the species are the product of many millions of years of natural selection and to work with, rather than against, their adaptations is likely to produce less stress and hence better production and better research models.

The selection of animals from high health status stock not only benefits research validity and occupational health but can also positively influence the use of expansive housing systems and the quality of interaction that care and research staff have with the animal, with significant animal welfare benefits (Wolfensohn & Honess 2005). If these animals are from naturally high health status stock the animal welfare and animal waste issues associated with some SPF derivation practices are also avoided. Where animals are selectively bred for specific research models raising specific welfare challenges, this must receive separate, specific justification, as required by many regulating bodies. This paper highlights the importance of refining breeding practices as part of the overall package of welfare improvements for animals being used in, or to supply, laboratory research.

References

Anderson DM and Simpson MJA 1979 Breeding performance of a captive colony of rhesus macaques (*Macaca mulatta*). *Laboratory Animals 13*: 275-281

Anderson JR and Chamove AS 1984 Allowing captive primates to forage. *Standards in Laboratory Animal Management, Part 2* pp 253-256. UFAW: Wheathampstead, Herts, UK

Bercovitch FB 2002 Sex-biased parental investment in primates. *International Journal of Primatology 23(4)*: 905-921

https://doi.org/10.1017/S0962728600002244 Published online by Cambridge University Press

Boot R, Leussink AB and Vlug RF 1985 Influence of housing conditions on pregnancy outcome in cynomolgus monkeys (*Macaca fascicularis*). *Laboratory Animals 19(1)*: 42-47

Bourne GH and Golarz de Bourne MN 1975 Breeding monkeys for biomedical research. In: Bourne GH (ed) *The Rhesus Monkey, Volume III: Management, Reproduction and Pathology*. Academic Press: London, UK

Brown JL and Eklund A 1994 Kin recognition and the major histocompatibility complex: An integrative review. *The American Naturalist 143(3)*: 435-461

Carey D, Kammerer CM, Shade RE, Rice KS and McGill HC Jr 1993 Selective breeding to develop lines of baboons with high and low blood pressure. *Hypertension 21(6)*: 1076-1079

Carlsson HE, Schapiro SJ, Farah I and Hau J 2004 Use of primates in research: A global overview. *American Journal of Primatology 63(4)*: 225-237

Chan AWS, Chong KY, Martinovich C, Simerly C and Schatten G 2001 Transgenic monkeys produced by retroviral gene transfer into mature oocytes. *Science 291(5502)*: 309-312

Coffman BS, Hess WR, Glander KE, Feeser PE and Simons EL 1993 Management of a breeding colony of aye-ayes (*Daubentonia madagascariensis*) at the Duke University Primate Center. *AAZPA Regional Conference Proceedings 1993*. *American Association of Zoological Parks and Aquariums* pp 161-167. 2-4 May 1993, Pittsburgh, PA, USA

Coleman K, Tully LA and McMillan JL 2005 Temperament correlates with training success in adult rhesus macaques. *American Journal of Primatology 65(1)*: 63-71

Cowlishaw G and Dunbar RIM 1991 Dominance rank and mating success in male primates. *Animal Behaviour 41*: 1045-1056

Crockett CM, Shimoji M and Bowden DM 2000 Behavior, appetite, and urinary cortisol responses by adult female pigtailed macaques to cage size, cage level, room change, and ketamine sedation. *American Journal of Primatology 52(2)*: 63-80

Cyranoski D 2009 Marmoset model takes centre stage. *Nature 459(7246)*: 492

Dawson JC, Dawson WW, Cunningham BE and Lambrou GN 2003 Developing open angle intraocular hypertension: Early results of selective breeding in the Florida Monkey Colony. *Investigative Ophthalmology and Visual Science 44(5)*: 1118.

De Ruiter JR, van Hooff JARAM and Scheffrahn W 1994 Social and genetic aspects of paternity in wild long-tailed macaques (*Macaca fascicularis*). *Behaviour 129*: 203-224

Dewsbury DA 2006 *Monkey farm. A history of the Yerkes Laboratories of Primate Biology, Orange Park, Florida 1930-1965*. Bucknell University Press: Lewisburg, PA, USA

Drevon-Gaillot E, Perron-Lepage M-F, Clément C and Burnett R 2006 A review of background findings in cynomolgus monkeys (*Macaca fascicularis*) from three different geographical origins. *Experimental and Toxicologic Pathology 58(2-3)*: 77-88

Fooden J 1991 Systematic review of Philippine macaques (primates cercopithecidae: *Macaca fascicularis* sub spp). *Fieldiana Zoology 64*: 1-44

Fooden J 2000 Systematic review of the rhesus macaque, *Macaca mulatta* (Zimmermann 1780). *Fieldiana Zoology 96*: 1-180

Fridman EP 2002 *Medical primatology: History, biological foundations and applications.* Taylor & Francis: London, UK

Goin DL and Gust DA 1998 Peer-rearing influences subsequent maternal behavior and infant survival in a newly formed herpes B-virus negative rhesus macaque group. *Primates 39(4)*: 539-543

Goo GP and Fugate JK 1984 Effects of weaning on age on maternal reproduction and offspring health in rhesus monkeys (*M. mulatta*). *Laboratory Animal Science 34*: 66-69

Gouzoules S and Gouzoules H 1987 Kinship. In: Smuts B, Cheney D, Seyfarth R, Wrangham R and Struhsaker T (eds) *Primate Societies* pp 299-305. University of Chicago Press: Chicago, USA

Goy RW 1992 The mating behavior of primates: Estrus or sexuality. In: Itoigawa N, Sugiyama Y, Sackett GP and Thompson GKR (eds). *Topics in Primatology: Behavior, Ecology, and Conservation*, *Volume 2* pp 151-161. University of Tokyo Press: Tokyo, Japan

Groves CP 2001 *Primate Taxonomy*. Smithsonian Institution Press: Washington, USA

Ha JC, Robinette RL, Almasy L and Dyke B 2002 Genetics and caging type affect birth weight in captive pigtailed macaques (*Macaca nemestrina*). *American Journal of Primatology 56*: 207-213

Ha JC, Robinette RL and Davis A 2000 Survival and reproduction in the first two years following a large-scale primate colony move and social reorganization. *American Journal of Primatology 50(2)*: 131-138

Hendrickx AG and Dukelow WR 1995 Breeding. In: Taylor Bennett B, Abee CR and Hendrickson R (eds) *Nonhuman Primates in Biomedical Research: Biology and Management* pp 428. Academic Press: London, UK

Higley J and Suomi S 1989 Temperamental reactivity in nonhuman primates. In: Kohnstamm G, Bates J and Rothbart M (eds) *Temperament in Childhood* pp 153-167. Wiley: New York, USA

Hill DA and Okayasu N 1996 Determinants of dominance among female macaques: Nepotism, demography and danger. In: Fa JE and Lindburg DG (eds) *Evolution and Ecology of Macaque Societies* pp 459-472. Cambridge University Press: Cambridge, UK

Hobbs KR 1989 The SICONBREC project: Conditioning and breeding facilities for the cynomolgus monkey (*Macaca fascicularis*) in the Philippines: A review after the first five years. *Animal Technology 40(1)*: 55-68

Honess PE and Marin CM 2006a Behavioural and physiological aspects of stress and aggression in nonhuman primates. *Neuroscience and Biobehavioral Reviews 30(3)*: 390-412

Honess PE and Marin CM 2006b Enrichment and aggression in primates. *Neuroscience and Biobehavioral Reviews 30(3)*: 413-436

Jennings M, Prescott MJ, Buchanan-Smith HM, Gamble MR, Gore M, Hawkins P, Hubrecht R, Hudson S, Jennings M, Keeley JR, Morris K, Morton DB, Owen S, Pearce PC, Prescott MJ, Robb D, Rumble RJ, Wolfensohn S and Buist D 2009 Refinements in husbandry, care and common procedures for non-human primates: Ninth report of the BVAAWF/FRAME/RSPCA/UFAW Joint Working Group on Refinement. *Laboratory Animals 43(Supplement 1)*: 1-47

Johnsen DO 1995 History. In: Taylor Bennett B, Abee CR and Hendrickson R (eds) *Nonhuman Primates in Biomedical Research: Biology and Management* pp 428. Academic Press: London, UK

Kappeler PM and Van Schaik CP 2004 Sexual selection in primates: review and preview. In: Kappeler PM and Van Schaik CP (eds) *Sexual Selection in Primates*. Cambridge University Press: Cambridge, UK

Kleiman DG, Beck BB, Dietz JM, Dietz LA, Ballou JD and Coimbra-Filho AF 1986 Conservation program for the golden lion tamarin: Captive research and management, ecological studies, education strategies, and reintroduction. In: Benirschke K (ed) *Primates: The Road to Self-Sustaining Populations* pp 959-979. Springer-Verlag: New York, USA

Knapp LA, Ha JC and Sackett GP 1996 Parental MHC antigen sharing and pregnancy wastage in captive pigtailed macaques. *Journal of Reproductive Immunology 32*: 73-88

Kotera S, Tanaka T, Tajima Y and Nomura T 1975 Establishment of an island breeding colony of Japanese monkeys as a laboratory animal. *Laboratory Animal Handbooks 6*: 95-105

Kyes RC 1993 Survey of the long-tailed macaques introduced onto Tinjil Island, Indonesia. *American Journal of Primatology 31(1)*: 77-83

Latham NR and Mason GJ 2008 Maternal deprivation and the development of stereotypic behaviour. *Applied Animal Behaviour Science 110(1-2)*: 84-108

Lawler SH, Sussman RW and Taylor LL 1995 Mitochondrial DNA of the Mauritian macaques (*Macaca fascicularis*): An example of the founder effect. *American Journal of Physical Anthropology 96(2)*: 133-141

Lee PC 1996 The meanings of weaning: Growth, lactation, and life history. *Evolutionary Anthropology 5(3)*: 87-98

Lee PC 1999 Comparative ecology of post natal growth and weaning among haplohrine primates. In: Lee PC (ed) *Comparative Primate Socioecology* pp 111-136. Cambridge University Press: Cambridge, UK

Lehman SM and Taylor LL 1992 Natural migration patterns predict escapes from a colony of Japanese macaques (*Macaca fuscata*). *Laboratory Primate Newsletter 31(3)*: 3-8

Ling, B, Veazey RS, Luckay A, Penedo C, Xu K, Lifson JD and Marx PA 2002 SIV_{mac} pathogenesis in rhesus macaques of Chinese and Indian origin compared with primary HIV infections in humans. *AIDS 16*: 1489-1496

Mansfield K 2005 Development of specific pathogen free nonhuman primate colonies. In: Wolfe-Coote S (ed) *The Laboratory Primate* pp 621. Elsevier Academic Press: London, UK

McGill HC Jr, McMahan CA, Mott GE, Marinez YN and Kuehl TJ 1988 Effects of selective breeding on the cholesterolemic responses to dietary saturated fat and cholesterol in baboons. *Arteriosclerosis, Thrombosis, and Vascular Biology 8(1)*: 33-39

McGinley MA 1984 The adaptive value of male-biased sex ratios among stressed animals. *The American Naturalist 124(4)*: 597-599

Mee ET, Badhan A, Karl JA, Wiseman RW, Cutler K, Knapp LA, Almond N, O'Connor DH and Rose NJ 2009 MHC haplotype frequencies in a UK breeding colony of Mauritian cynomolgus macaques mirror those found in a distinct population from the same geographic origin. *Journal of Medical Primatology 38(1)*: 1-14

Mehlman PT, Higley JD, Faucher I, Lilly AA, Taub DM, Vickers J, Suomi SJ and Linnoila M 1994 Low CSF 5-HIAA concentrations and severe aggression and impaired impulse control in nonhuman primates. *American Journal of Psychiatry 151(10)*: 1485-1491

Melnick D, Pearl M and Richard A 1984 Male migration and inbreeding avoidance in wild rhesus monkeys. *American Journal of Primatology 7*: 229-243

Mineka S and Suomi SJ 1978 Social separation in monkeys. *Psychological Bulletin 85(6)*: 1376-1400

Mineka S, Gunnar M and Champoux M 1986 Control and early socioemotional development: Infant rhesus monkeys reared in controllable versus uncontrollable environments. *Child Development 57(5)*: 1241-1256.

Mooney JC and Lee PC 1999 Reproductive parameters in woolly monkeys (*Lagothrix lagotricha*). *Zoo Biology 18*: 421-427.

Morton WR, Kyes KB, Kyes RC, Swindler DR and Swindler KE 2005 Use of the primate model in research. In: Wolfe-Coote S (ed) *The Laboratory Primate* pp 405-415. Elsevier Academic Press: London, UK

Nagarajan P, Venatesan R, Mahesh Kumar MJ and Majumdar SS 2004 Suppression of lactation in post-weaning *Macaca radiata* females by bromocriptine under laboratory conditions. *Laboratory Primate Newsletter 43(1)*: 12-13

Novak MA and Suomi SJ 1988 Psychological well-being of primates in captivity. *American Psychologist 43(10)*: 765-773

NRC (National Research Council) 1996 *Guide for the Care and Use of Laboratory Animals*. National Academic Press: Washington DC, USA

Poole TB 1997 Happy animals make good science. *Laboratory Animals 31*: 116-124

Prescott M and Jennings M 2004 Ethical and welfare implications of the acquisition and transport of non-human primates for use in biomedical research and testing. *ATLA 32(Supplement 1)*: 323-327

Price KC and Coe CL 2000 Maternal constraint on fetal growth patterns in the rhesus monkey (*Macaca mulatta*): The intergenerational link between mothers and daughters. *Human Reproduction 15(2)*: 452-457

Reinhardt V 2002 Artificial weaning of Old World monkeys: Benefits and costs. *Journal of Applied Animal Welfare Science 5(2)*: 151-156

Reinhardt V and Reinhardt A 2000 Social enhancement for adult nonhuman primates in research laboratories: A review. *Laboratory Animal 29(1)*: 34-41

Sasaki E, Suemizu H, Shimada A, Hanazawa K, Oiwa R, Kamioka M, Tomioka I, Sotomaru Y, Hirakawa R, Eto T, Shiozawa S, Maeda T, Ito M, Ito R, Kito C, Yagihashi C, Kawai K, Miyoshi H, Tanioka Y, Tamaoki N, Habu S, Okano H and Nomura T 2009 Generation of transgenic non-human primates with germline transmission. *Nature 459(7246)*: 523-527

Satkoski J, George D, Smith DG and Kanthaswamy S 2008 Genetic characterization of wild and captive rhesus macaques in China. *Journal of Medical Primatology 37(2)*: 67-80

Shively CA, Friedman DP, Gage HD, Bounds MC, Brown-Proctor C, Blair JB, Henderson JA, Smith MA and Buchheimer N 2006 Behavioral depression and positron emission tomography–determined serotonin 1A receptor binding potential in cynomolgus monkeys. *Archives of General Psychiatry 63*: 396-403

Silk JB 1983 Local resource competition and facultative adjustment of sex ratios in relation to competitive abilities. *American Naturalist 121*: 56-66

Slierendregt BL, Kenter M, Otting N, Anholts J, Jonker M and Bontrop RE 1993 Major histocompatibility haplotypes in a breeding colony of chimpanzees (*Pan troglodytes*). *Tissue Antigens 42(2)*: 55-61

Smith DG 2005 Genetic characterization of Indian–origin and Chinese–origin rhesus macaques (*Macaca mulatta*). *Comparative Medicine 55(3)*: 227-230

Smith DG, McDonough JW and George DA 2007 Mitochondrial DNA variation within and among regional populations of longtail macaques (*Macaca fascicularis*) in relation to other species of the *fascicularis* group of macaques. *American Journal of Primatology 69*: 182-198

Stanley MA 2003 The breeding of naturally occurring B virus-free cynomolgus monkeys (*Macaca fascicularis*) on the island of Mauritius. *International Perspectives: The Future of Nonhuman Primate Resources* pp 46-48. National Academies Press: Washington, USA

Sussman R and Tattersall I 1981 Behavior and ecology of *Macaca fascicularis* in Mauritius: A preliminary study. *Primates 22(2)*: 192-205

Tattersall I, Dunaif A, Sussman RW and Jamieson R 1981 Hematological and serum biochemical values in free-ranging *Macaca fascicularis* of Mauritius: Possible diabetes mellitus and correlation with nutrition. *American Journal of Primatology 1(4)*: 413-419

Tosi AJ and Coke CS 2007 Comparative phylogenetics offer new insights into the biogeographic history of *Macaca fascicularis* and the origin of the Mauritian macaques. *Molecular Phylogenetics and Evolution 42(2)*: 498-504

https://doi.org/10.1017/S0962728600002244 Published online by Cambridge University Press

Trichel A, Rajakumar P and Murphy-Corb M 2002 Species-specific variation in SIV disease progression between Chinese and Indian subspecies of rhesus macaque. *Journal of Medical Primatology 31*: 171-178

Trivers RL and Willard DE 1973 Natural selection of parental ability to vary the sex ratio of offspring. *Science 179*: 90-92

Tsuchida J, Yoshida T, Sanaki T and Yasutomi Y 2008 Maternal behaviour of laboratory-born, individually reared long-tailed macaques (*Macaca fascicularis*). *Journal of the American Association for Laboratory Animal Science 47(5)*: 29-34

van Noordwijk M and van Schaik C 1999 The effects of dominance rank and group size on female lifetime reproductive success in wild long-tailed macaques, *Macaca fascicularis*. *Primates 40(1)*: 105-130

Wallen K, Goldfoot DA and Goy RW 1981 Peer and maternal influences on the expression of foot-clasp mounting by juvenile male rhesus monkeys. *Developmental Psychobiology 14(4)*: 299-309

Wallis J and Valentine B 2001 Early vs natural weaning in captive baboons: The effect on timing of postpartum estrus and next conception. *Laboratory Primate Newsletter 40(1)*: 10-13

Watts E and Meder A 1996 Introduction and socialization techniques for primates. In: Kleiman DG, Allen ME, Thompson KV and Lumpkin S (eds) *Wild Mammals in Captivity: Principles and Techniques* pp 67-77. University of Chicago Press: Chicago, USA

Wolfe-Coote S 2005 *The Laboratory Primate. The Handbook of Experimental Animals.* Blackwell Publications: Oxford, UK

Wolfensohn SE 1997 Brief review of scientific studies of the welfare implications of transporting primates. *Laboratory Animals 31(4)*: 303-305

Wolfensohn SE and Honess PE 2005 *Handbook of Primate Husbandry and Welfare.* Blackwell Publications: Oxford, UK

Yerkes RM 1916 Provision for the study of monkeys and apes. *Science 43(1103)*: 231-234

Yerkes RM 1935 Yale laboratories of primate biology, incorporated. *Science 82(2139)*: 618-620

Zumpe D and Michael R 1984 Low potency of intact male rhesus monkeys after long-term visual contact with their female partners. *American Journal of Primatology 6*: 241-252

Zumpe D and Michael R 1996 Social factors modulate the effects of hormones on the sexual and aggressive behavior of macaques. *American Journal of Primatology 38*: 233-261

https://doi.org/10.1017/S0962728600002244 Published online by Cambridge University Press