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A brief history of primate research: Global health improvements and ethical challenges

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ABSTRACT

Humans have benefitted from close relationships with animals for hundreds of thousands of years. However it has only been in relatively recent times that they have made use of the scientific investigation of animals; their anatomy, physiology and response to disease in attempts to alleviate human suffering. Scientists rapidly realized the value of primates as research models – their evolutionary proximity to humans making them better predictors, or models, of human biology. Systematic studies using primates began in the last century and massive demand for research subjects almost caused the extinction of some important wild populations. This resulted in initially ex situ and then latterly in situ breeding centers, purpose-breeding animals for biomedical research. Primate research typically follows that using less sentient animals (generally rodents) in which mechanism and proof of principle are established before examining effect and safety in primates. The quality of life of millions of people has rested on progress from primate research. The broader society has become more concerned with how we treat animals and use of animals in research has come under particular scrutiny. The actions of extremists have threatened not only the continued use of primates in research, but also the property, welfare, and occasionally, lives of those that have committed their careers to studying primates to aid humanity. This commentary examines the history of primate research and discusses key advances as well as important lessons learnt about the ethics surrounding the use of primates in research.

KEY WORDS: ***Primate research; Biomedical research; Ethical challenges; Primate welfare; Translational research; Health benefits***

THE DEVELOPMENT OF PRIMATE BREEDING AND RESEARCH FACILITIES

Man's interest in, and recording of, the internal biology of other living animals dates back thousands of years to Classical times and includes those who laid the foundations for modern medicine, such as Galen and Aristophanes[1]. The incorporation of non-human primates into systematic studies aiming to alleviate human suffering starts much later, in the 1900s. Primates became the focus of a whole range of investigations covering everything from anatomy to physiology and behaviour.

In a world where the experimentation on fellow humans became an important moral and ethical issue the close relationship between human and non-human primates, first conclusively argued by Darwin[2], formed the logical basis of learning more about human biological systems through the study of analogous species. More recent empirical evidence of similarities between humans and their closest living relatives, both from modern genetic approaches and phylogenetic reconstruction, emphasises the importance of animal, especially primate, models for valid research. Essentially, the greater the evolutionary proximity of the model to humans the better the predictive value of research findings in the animal when translating results to humans.

Estimates from 2004 are that around 200,000 primates per year are used in research[3]. In 2010 it was estimated that nearer 400,000 primates globally were dedicated to research, if animals held in breeding facilities and those not currently on study were included[4]. Despite these apparently high numbers, primates account for only a very small proportion of all animals used in research. In the EU this is around 0.1%[5].

Demand for primates for research escalated when they proved essential in the successful development of the polio vaccine. This characterised the large-scale use of primates in research and vaccine development when, in the USA in the 1950s-60s, as many as 1.5 million rhesus macaques (*Macaca mulatta*) may have been used for fundamental polio research and vaccine development. For this programme of research, around 100,000-200,000 rhesus macaques, per year, were exported from India to the USA[6-8]. Over-exploitation of wild populations of this species led to concerns about local, or even national, extirpation and resulted in an export embargo by India in 1978[4]. The plight of this species and the extensive extraction of other primate species from the wild led to concerns about the sustainability of supply for research and the trade's conservation impact and in 1981 the World Health Organisation (WHO) called for a move towards self-sustaining breeding facilities in habitat countries to produce healthy research models without threatening wild populations[9].

The earliest primate facilities

Prior to the establishment of the first significant *in situ* breeding facilities, a number of important breeding and research facilities had already been established outside habitat countries, predominantly in USA and Europe. Probably the first *ex situ* primate breeding/research facility was the Anthropoid Research Station established on Tenerife in the Canary Islands in 1913[10]. The facility was overseen by Wolfgang Köhler who conducted seminal research there on the ability of chimpanzees to use tools and solve problems (e.g. stacking crates to reach suspended bananas). Köhler recognised the importance of keeping primates in social contexts, concluding that "A chimpanzee kept in solitude is not a real chimpanzee at all"[11]; an important observation that can be extended to all primates and which is now established in the most important regulations governing primate research. These stipulate the keeping of primates in a minimum of a compatible conspecific pair, unless specific justification is provided[12,13].

Other primate research/breeding facilities followed including the Pasteur Institute's Pastoria Station in Kindia, French Guinea that functioned from 1923 until the 1960s and was at one time directed by Albert Calmette[14]. Calmette is famous for his role in the development of the BCG tuberculosis (TB) vaccine and for developing the first snake antivenom. Primates at Pastoria were used in a broad range of medical research including vaccine development for TB, typhus, and polio and for the study of a range of tropical diseases including malaria and trypanosomiasis[14].

The first facility to be developed outside the African realm was the Sukhumi Primate Centre, in the Soviet Union in 1927, which was initially stocked with chimpanzees and baboons. The centre, which still conducts research today, is in the modern-day country of Georgia. One of the cofounders was Ilya Ivanov, infamous for his research interest and attempts to create human-ape hybrids to test Darwinian Theory[15].

However, probably the most important of the early facilities was the Anthropoid Experiment Station in 1930 developed by Robert Yerkes of Yale University[16]. This facility was established in Florida in, perhaps, the most tropical climate in the continental USA to approximate the climate of the natural range of the centre's primates. The centre was established with some chimpanzees from Pastoria Station[14] and aimed, initially, to conduct research into chimpanzee, and later rhesus macaque, psychology and physiology. It was later renamed the Yale Laboratory of Primate Biology and in 1965 was taken over by Emory University and moved to the State of Georgia. This centre was the seed from which the United States' network of eight National Primate Research Centres grew over the next 34 years. Now this network comprises the most substantial ex situ primate research and breeding resource in the world.

Several other key breeding/research facilities became established over the next few decades as authorities and researchers became concerned about securing an adequate supply of animals for their research needs. As noted in Honess et al[4] these included facilities in the UK (1959), Holland (1970), Germany (1977), France (1978), Italy (1981), as well as in Japan (Primate Research Institute, 1967[17]), and China (Yunnan 1982[18]).

In situ breeding

The expansion of primate research and the call for self-sustaining, in situ, breeding facilities resulted in the establishment of several important enterprises. The first of significance was the Simian Conservation Breeding and Research Center (SICONBREC; Makati, Philippines), which was established in 1983 to breed, and condition long-tailed macaques (*Macaca fascicularis*) under natural conditions for research purposes[19].

SICONBREC was followed by the establishment of Bioculture in Mauritius in 1985 where the capture and breeding of long-tailed macaques from the invasive, introduced population presented an ideal humane population control method[20]. Bioculture was the first of several breeding enterprises on the island. The breeding operation was established with trapped long-tailed macaques that were, and continue to be, major agricultural and biodiversity pests. These monkeys presented a particular challenge for those seeking to preserve Mauritius' endemic and native wildlife, particularly a number of famously endangered bird species (e.g. pink pigeon, *Columba mayeri*; echo parakeet, *Psittacula eques*; Mauritian fody, *Foudia rubra*), some of which were subject to predation by the monkeys[21,22]. Increasing pressure on populations of long-tailed macaques in their natural range, largely from extraction for research, and from habitat loss[23], makes introduced populations outside their natural range the best candidates for utilisation as a research resource as foreseen by Kavanagh[6].

The third of early *in situ* breeding ventures was the imaginative Tinjil Island Natural Habitat Breeding Facility, established in Indonesia in 1987[9]. The aim of this facility, in introducing a small population of screened long-tailed macaques to an island with no existing monkey inhabitants, was to allow the monkeys to breed naturally to produce simian retrovirus- (SRV) and TB-free animals for research as well as to help conserve natural populations[9].

Despite the relatively early establishment of research facilities in habitat countries (e.g. Pastoria[14], Tigoni Primate Research Centre, Kenya 1958[24]) the expansion of *in situ* breeding facilities only followed the success of SICONBREC, Bioculture, and Tinjil with centres being established most notably in Asia (e.g. Vietnam, Cambodia, China), but also in the Caribbean (e.g. St Kitts, Barbados) and Latin America (Peru)[8].

BIOMEDICAL ADVANCES FROM PRIMATE STUDIES

The expansion of primate research, with the attendant need to breed animals to reduce pressure on wild populations, was identified early on as essential to enabling continued accumulation of medical benefits for society[7]. Apart from increased understanding about primate, and hence human, biology from basic, or fundamental, research there have been numerous direct health benefits from the biomedical research conducted with primates. Most notable of these is the development of the polio vaccine[25] resulting in the almost total global eradication of this devastating disease, though a small but significant number of cases continue to appear in some of the poorest communities in the world (e.g. in Africa)[26]. Primates are also used extensively in toxicology to determine safe and efficacious drug doses and potential side effects.

As detailed by many resources including UAR and Bushmitz[27] primate research has played a critical role in the development of treatments for a range of important diseases and conditions including: HIV/AIDS, Parkinson's disease, leprosy, typhoid, rheumatoid arthritis, congenital cataracts, and cancer chemotherapy. Of recent highlight has been the development of a therapy for Ebola (ZMapp)[28].

As noted above in the case of polio, primate-based research has led to the development of vaccines for the prevention of a number of diseases including: yellow fever, measles, hepatitis B, anthrax, chikungunya, and tuberculosis. There is also important progress in the development of vaccines for Ebola[29] and malaria[30]: both in advanced clinical trials.

Other advances include the discovery of many blood and plasma components, including the Rhesus factor so important for successful blood transfusions. Primate research played a central role in the development of safe and successful intensive care technology for premature babies and medical imagining (e.g. MRI scanners), modern anaesthetics, corneal transplants, In vitro fertilization, and many aspects of stem cells and their potential therapeutic uses[27].

Among some of the most exciting new areas where primate research has been essential and where successful translation to human patients can be seen is in the area of biological cybernetics. Fundamental primate neuroscience studies have laid the foundations for production of neuromotor prosthetic limbs in both nonhuman primates and humans[31-33]. These devices can be operated under neural control by the person wearing them[34,35]. Visually dramatic was the use of a robotic exoskeleton produced by the Walk Again Project (http://virtualreality.duke.edu/project/walk-again-project/) to enable a paraplegic young man to kick the first ball of the World Cup in Brazil in 2014[36]. Advances in this area, that would not have been possible without primate research, promise life-changing benefits for amputees and those with paralysis, for whom, without these benefits, independent living might not be possible.

It is clear that primate research has made significant contributions to medical advances that have saved, or made positive changes to, the lives of millions of people, but the benefits are not limited to humans. Just one example is that Ebola is having a devastating impact on already threatened populations of wild apes in central Africa[37]. Vaccines developed through research and testing in macaques and chimpanzees represent an opportunity to save some of these threatened populations[38].

ETHICAL CHALLENGES RAISED BY PRIMATE RESEARCH

Primate research presents significant ethical challenges, both for those conducting the research and for the general public in whose name the work is permitted and licenced. Their close phylogenetic relationship to humans means that while on the one hand they represent good scientific models, on the other hand they are cognitively sophisticated and may suffer in many of the same ways that a human would, when subjected to circumstances such as: social isolation, loss of control and research procedures. It is vital therefore that the authorities and institutions that permit and oversee primate research do so only where the balance of benefit of the research for society (and animals) appropriately outweighs the cost incurred by the animals: the cost: benefit analysis. This ethical consideration of the research together with implementation of the 3Rs (Reduction, Refinement and Replacement[39]) is at the heart of guidance and regulation covering animal research in many contexts (e.g. Europe[12] and the USA[13]).

Despite the regulatory burden and scrutiny to which primate research is subjected, it still draws strong attention from the Animal Rights movement. This movement has a central tenet, which opposes human ownership of, and dominion over, any animal and this results in opposition to animal research[40]. The work of Harry Harlow in investigating the developmental consequences of early maternal deprivation in rhesus monkey infants[41,42] has been a focal point for opposition to primate research[43]. Primate research in this area continues to be under significant pressure from the Animal Rights movement and has, in at least one case, resulted in extensive independent scrutiny and subsequent rebuttal of allegations by the funders who highlight the importance of primate research generally and of this specific area of epigenetic research[44].

There will always be varying degrees of success of primate research projects and, despite the efforts of those overseeing research there will always be variation in the attention of researchers to animal welfare and ethical issues related to their research. While the latter requires constant attention and (re-) education, this should take the form of the enforced application of the 3Rs, using animal welfare science and best practice in the care and management of the primate subjects and the employment of the most refined, high welfare research techniques. What is needed is engagement of dedicated animal welfare groups and animal welfare scientists with the research community to protect animal welfare rather than extremist action which threatens individual security, corporate or institutional viability, and not least the potentially life-saving, or quality-of-life-enhancing, benefits that are derived from well-justified, well-regulated, and animal welfare-protecting primate research.

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