NHP Study: Evidence from Europeans for Medical Progress and Antidote-Europe

Introduction

Europeans for Medical Progress (EMP) and Antidote-Europe are two scientific organisations concerned with human health protection, and not with animal protection. We very much welcome this inquiry, though with some reservations that it is being overseen by four organisations which actively promote and defend NHP research. We must state at the outset our informed, professional opinion that animal models of human diseases are so poorly predictive of the human situation that, on balance, they result in more human harm than benefit. This is true not just for species such as mice and rats but also for our closest evolutionary relatives, despite the *prima facie* genetic and biochemical similarities of many NHP species to humans.

We show in this document many examples of the false promise of NHP research and the human harm that reliance upon it has caused. We also discuss the merits of alternative forms of research and testing that are much more relevant to human medicine, and which should be adopted as a matter of urgency in preference to primate models which, quite simply, have failed to deliver despite decades of opportunity. We do not deny that, historically, there may have been examples of medical progress that have relied upon NHP experiments. These successes, however, must be assessed alongside the failures and the human harm that has resulted from them. If the failures outnumber the successes, as we believe they do by a significant margin, then it is time to replace the model with the technologically superior, more predictive methods of research that are now available.

Non-Human Primates in Pre-Clinical Drug Testing / Toxicology

The major use of NHPs remains as the 'second species' in pre-clinical safety assessment of new drugs. Marmosets are often the species of choice – not due to any outstanding scientific properties, but because they are small, cheap and relatively easy to house and breed[1]. In fact, the validity of NHP use in this way has been questioned recently in several quarters:

- The Toxicology Working Group of the House of Lords Select Committee on Animals in Scientific Procedures stated 'the formulaic use of two species in safety testing is not a scientifically justifiable practice, but rather an acknowledgement of the problem of species differences in extrapolating the results of animal tests to predict effects in humans,' and 'the reliability and relevance of all existing animal tests should be reviewed as a matter of urgency[2].'
- The Animal Procedures Committee asserted that NHP use is only justifiable if 'the data obtained are both valid (relevant for humans) and necessary in order for a safety assessment to be made.' They then implicitly question this by urging that 'the predictive value of data from primate studies should be investigated by comparing the results of pre-clinical and clinical studies on drugs that have progressed to clinical use[3].'
- The Boyd Group concluded that 'any use of NHPs in research and testing requires very strong justification' and recommended that the APC 'examine retrospectively *any* application or licence to use non-human primates, with a view to informing future ethical judgements[4].'
- The Nuffield Council on Bioethics concluded that 'there is a need for continuing review of the scientific case for using animals in research and testing. It is axiomatic that any such use should be accompanied by active and critical reflection on the validity and relevance of the models and research studies[5].'

Despite pre-clinical safety testing in animals, very often including NHPs, the attrition rate of drugs entering human clinical trials is 92%[6]. Many drugs that do pass the clinical trial phase to reach the market place have a questionable safety profile: adverse drug reactions (ADRs) remain the fourth biggest killer in the western world, despite apparent safety in animal (often NHP) models[7]. Important examples include:

- Hormone Replacement Therapy – prescribed to millions of women, and thought to protect against heart disease and stroke on the basis of NHP experiments, HRT is now known to *increase* the risk of these diseases, as well as breast cancer in humans. The Chairman of the German Commission on the Safety of Medicines described HRT as 'the new Thalidomide.' It has caused up to 20,000 cases of breast cancer over the past decade in Britain alone[8].
- AIDSVAX – after successful results of this HIV vaccine in chimpanzees, it failed to protect any of the 8000 human volunteers in clinical trials.
- Teratology (risk of birth defects) – in the wake of Thalidomide, animals, often NHPs, have been used to assess the risk of foetal damage during pregnancy as a result of exposure to drugs and other chemicals. Results from NHPs correlate with known human teratogens only 50% of the time, less even than results from more evolutionarily distant species such as rats, hamsters and ferrets[9,10]. Aspirin, for example, is teratogenic in monkeys though not in humans.
- Asthma – Isoprenaline doses, derived from animal data, were too high for humans and killed thousands of people; mainly children. An attempt to replicate this in NHPs was completely unsuccessful[11].
- Opren (for arthritis) killed 61 people and harmed over 3500, despite showing no problems in NHPs[12].

- Flosint (another arthritis drug) caused hundreds of severe ADRs and several deaths, despite being well tolerated in NHPs[13].
- Carbenoxalone (for gastric ulcers) caused heart failure, which could not be replicated in NHPs[12].
- Amrinone (for heart failure) caused severe haemorrhaging in 20% of long-term patients, despite showing no warning signs in NHPs[14].

These statistics and examples are of no surprise when one considers comprehensive studies of comparative drug toxicology, which have revealed levels of discordance between results from animals and humans of between 67 and 96%[15,16]. These studies show that animal (or NHP) based toxicology is not predictive of human response; providing correct predictions less often than a coin toss.

Among scientists in academia and in the pharmaceutical industry itself, the inability of animal-based pre-clinical models (including NHPs) to assess human ADMET properties (how a drug is Absorbed, Distributed, Metabolised and Eliminated, and its Toxicological properties) has been acknowledged for decades:

- '…the present tests are well known to us but that does not make them good. There may be better tests around, but we have no incentive whatsoever to look for them at the moment. In fact, quite the reverse [because of the fear that regulatory agencies will require the new tests in addition to the current ones][17].'
- 'It has been obvious for some time that there is generally no evolutionary basis behind the particular-metabolizing ability of a particular species. Indeed, among rodents and primates, zoologically closely related species exhibit markedly different patterns of metabolism[18].'
- William Bains, chief scientific officer of Amedis Pharmaceuticals in the UK estimates that 50% of all drugs in development fail to progress to the market because of problems associated with ADMET and 50% of all drugs that do make it to market have problems associated with ADMET[19].
- Tom Patterson, chief scientific officer at Entelos, likened the current practice of drug testing in humans during clinical trials to making airplanes, trying to fly them, and marketing the one that does not crash[19].
- 'One of the major challenges facing the drug discovery community is the limitation and poor predictability of animal-based strategies....many drugs have failed in later stages of development because the animal data were poor predictors of efficacy in the human subject… One of the overriding interests of the pharmaceutical and biotechnologies industry is to create alternative development strategies that are less reliant on poor animal predictor models of human disease…Although the species [chimpanzees] share more than 98.9% gene identity [with humans], the expression of genes in the brain was more than five-fold greater in humans than in the chimpanzees....Differences from mice were even greater. These differences reinforce the importance of using human disease models in drug discovery as a real predictor of human efficacy… Discovery of drugs that act on the human central nervous system, are best studied in human-cell based systems[20].'

Non-Human Primates in Human Disease Research

NHP research on the three leading killers; heart disease, cancer and stroke, has failed to yield insights about the diseases or drugs to treat them. The scientific literature is replete with examples of NHP data confounding human disease research by conflicting with known human data or by leading research up 'blind alleys,' or even by causing human harm when translated to the clinic. Looking briefly at some of the major areas of NHP use:

- **Stroke** occurs as a result of atherosclerosis, but atherosclerotic plaques do not form in NHPs. Artificial induction of stroke-like situations in NHPs have served as a model of stroke research for decades, despite critical physiological differences such as collateral blood flow. Significant species-specific and even strain-specific differences in response to ischaemic injury exist[21], and despite dozens of candidates, not a single effective therapy has been successful in humans, despite efficacy in NHPs[22-24].
- **Parkinson's Disease (PD)** has been studied using neurotoxic chemicals to induce superficial PD-like symptoms, predominantly in marmosets and macaques. Fundamental differences in the onset, type, and persistence of symptoms exist in all models, in addition to physiological differences such as the absence in NHPs of Lewy Bodies. Species differences are known to play a role in the clinical expression as well as in the cellular specificity of the lesions; for example, striatal degeneration in humans is frequently associated with dyskinesia, whereas striatal excitotoxic lesions alone are not sufficient to induce dyskinesia or chorea in NHPs. Also, the time course of nerve cell degeneration, which normally evolves over several years in neurodegenerative diseases in humans, is for practical reasons replaced by a much shorter period of time in NHP models[25]. The major breakthroughs for PD have been via epidemiology, clinical studies, genetic research, human tissue studies and autopsies. Space precludes detail here, but these have resulted in the discovery that levodopa crosses the blood-brain barrier then converts into dopamine, that its efficacy in treatment of PD patients diminishes due to progressive degeneration of the D3 dopamine receptor, and that there seem to be a number of genetic and environmental predispositions/causes. Additionally, deep-brain

stimulation (DBS), often claimed to have been developed through NHP experiments, was actually discovered serendipitously in a human patient and owes nothing to NHPs for its advancement[26,27].

- **Alzheimer's disease (AD)** is another human ailment for which progress has been confounded and hampered by animal (including NHP) research. Many scientists have spent years trying to create a 'good' AD animal model; not only has this been a failure[28-30], but we have made very little progress in understanding the various pathologies associated with the disease. For example, mouse experiments suggested that tau protein was unlikely to be of any importance, though this is now known to be highly species-specific[31], and plaques and tangles in the brain are the hallmark of Alzheimer's disease in humans but not in monkeys[32]. Human clinical research, epidemiological studies and *in vitro* techniques gave rise to the cholinergic hypothesis for AD, and revealed AD-associated decrease in choline acetyltransferase (ChAT) activity, and links with the presenilin 1, presenilin 2 and APOE-e4 genes, and vitamin B12/folate deficiency and high fat/high cholesterol diets. None relied on the use of NHPs or other animals.

  NHP use can also cause direct human harm, in addition to delaying progress and diverting research funds from more relevant methods. The once much-vaunted AD 'vaccine' AN-1792 (AIP-001) dramatically slowed brain damage in an AD mouse model, and 'was well tolerated when tested in several animal species, including monkeys' in experiments prior to clinical trials[33,34]. Despite the encouraging NHP data, clinical trials were suspended following CNS-inflammation and ischaemic strokes in 15 participants[35].

  All the above is true because, quite simply, genes in the brains of humans and non-human primates, including chimpanzees and rhesus monkeys, differ in their levels of activity. In other words, the differences in brain activity between humans and monkeys can be traced right down to the molecular level. This supports the thesis that all animal species exhibit unique biological activities that arise from their particular genetic make-up. Interestingly, the *human genes* exhibit greater protection against activity-related damage, as compared with monkey brains. This could help to explain why humans live longer than non-human primates and also why humans are more susceptible to age-related neurodegenerative diseases, such as Alzheimer's and Parkinson's[36]. Other major differences between humans and NHPs, particularly neurological differences, are now being elucidated that explain definitively why the latter can not serve as disease models for human beings. With regard to AD, humans and great apes for example possess a particular type of projection neuron in the anterior cingulate cortex, which is known to be severely affected in the degenerative process of Alzheimer's disease[37]. Also, the neuropeptide galanin that regulates cholinergic basal forebrain (CBF) function differs in its chemoanatomic organisation across species: in monkeys, all CBF neurons coexpress galanin, whereas in apes and humans galanin is found within a separate population of interneurons that are in close apposition to the CBF perikarya[38]. Because galaninergic fibres hyperinnervate CBF neurons in AD inhibiting acetylcholine release in the hippocampus, it may exacerbate cholinergic cellular dysfunction in AD. This difference could be critical when attempting to create an NHP AD model.

  It is perhaps because of such evidence that many experts are now concluding that, in the words of Dr John Xuereb, director of the Cambridge Brain Bank Laboratory, 'Alzheimer's, Parkinson's and other neurodegenerative diseases occur in humans and it is in human tissue that we will find the answers to these diseases' (BBC Radio Cambridge, 2002).

- **AIDS** – NHPs do not develop AIDS when infected with HIV. Despite this fact, NHPs continue to be used in HIV/AIDS research, often with the 'related' simian immunodeficiency virus (SIV), or an artificial hybrid of the two (SHIV). As with so many artificially-induced animal models of human diseases, the differences are too profound to allow any resulting data from them to be extrapolated to humans[39]. For example:

  *Infection progresses at a different rate in SIV/SHIV infected monkeys compared to HIV-infected humans.

  *Some proteins from the coat of the virus have vaccine-like effects in monkeys, but not in people.

  *Chimpanzees have an alteration in their DNA that makes their immune systems detect and respond to HIV and SIV viruses differently[40].

  *The lymph nodes of HIV-infected people undergo structural changes and contain deposits of the virus; neither occurs in chimpanzees[41].

  *Humans and chimpanzees have different ratios of crucial blood cells called T-lymphocytes.

  *There are important differences in the cellular receptors involved in the infection process[42].

  Because of these and many other differences, none of 30-plus vaccines (mostly tested in NHPs) has proved safe and effective in over 70 clinical trials. Recently, the 'Aidsvax HIV vaccine failed to protect 8000 high-risk human volunteers despite proving efficacious in chimpanzees[43].' In fact, some candidate anti-virals screened using *in vitro* methods have gone directly into humans with little supportive *in vivo* data from prior animal experiments. One of the reasons is that there is no predictive animal model for HIV infection in humans[44]. Some scientists have acknowledged that even chimpanzees are unlikely to prove useful as animal models for understanding the mechanism of infection or means of treatment[45]. Dr Thomas Insel, as director of the Yerkes Primate Centre, admitted that 15 years of work in chimps has produced little data relevant to humans[46]. The US Government, following a 10 year expert review, concluded that chimpanzees are a deficicient model and redirected $10 million of funding. Dr Bolognesi of Duke University, USA, stated 'No

animal models faithfully reproduce...HIV infection and disease in humans, and the studies of experimental vaccines in animal models...have yielded disparate results[47].' In the opinion of a US-based group of researchers, 'the testing of vaccines and drugs in more animals will not be helpful if in the end these animals do not closely resemble humans. Even a vaccine that has 100% efficacy in [NHPs]… might still be ineffective in humans. Conversely, a proficient vaccine developed in humans might never show benefit in the animal models[42].' Dr Mark Feinberg, a leading AIDS researcher, summed it up thus: '*What good does it do you to test something [a vaccine] in a monkey? You find five or six years from now that it works in the monkey, and then you test it in humans and you realise that humans behave totally differently from monkeys, so you've wasted five years.'*

In common with many other human diseases, everything we know about HIV and AIDS has been discovered without relying on animal models. Effective HIV protease-inhibitor and nucleoside-analogue drugs were conceived and developed using *in vitro* and *in silico* methods[48-53], some of which are known to have ADMET properties that vary wildly between animal species, and that can be particularly dissimilar in NHPs[54].

Infectious disease research in NHPs or indeed, in any animals other than humans is almost guaranteed to fail because infectious agents are highly species specific. For instance, chimpanzees are essentially immune to the human AIDS virus, Hepatitis B and C viruses, the malaria parasite and many other pathogens to which humans are susceptible. The Handbook of Animal Models of Infection, (Academic Press 1999 p7) observed: *'Up to this very day, all infectious diseases affecting humans are far from having appropriate animal models and, even in those cases where such infections are possible, the symptoms observed in animals and the course of the disease are often very different from those encountered in humans.'* The recent anthrax attacks in the US mail were initially not taken seriously enough because experiments on monkeys showed the bacterium not to be fatal until 8-10,000 spores are inhaled. When people died from much smaller doses it became apparent that this does not apply to humans. Dr. Albert Sabin, inventor of the polio vaccine, swore under oath before the US Congress that: *'…prevention [of polio] was long delayed by the erroneous conception of the nature of the human disease based on misleading experimental models of the disease in monkeys[55].'*

Space precludes an appraisal of the use of NHPs in multiple sclerosis, cancer, epilepsy, brain function and behavioural research, amongst many others. For the purposes of this submission, it is sufficient to state that there is a similar pattern throughout all areas of NHP research: a lack of predictivity for humans, and a confounding dataset that often contrasts with what is subsequently discovered in humans.

The Biological Basis of Human/NHP Differences

The differences between NHPs and human beings are clear to see, not just in the list of points made here, but more simplistically just by looking at individuals from all primate species. Depending on the methods of calculation humans are 97-99% genetically identical to chimpanzees, our closest evolutionary relative. Yet the physiological and biochemical differences that manifest due to this relatively small degree of genetic variation are immense[56-59]. On a superficial level we don't look alike or behave similarly; on a deeper level our biochemical differences mean that we suffer from different diseases, respond in different ways to infectious agents, have different metabolisms, and find different substances toxic. In short, an awful lot of subtle biochemical differences combine to make us very different indeed.

We are now learning why this is so, and it carries through to NHP use in biomedical research: NHPs are just too different from human beings to serve as 'surrogate' humans in this way. They cannot be predictive of the human situation; one cannot rely on data from NHP experiments when extrapolated to humans. NHP research can be 'tweaked' in order to retrospectively correlate with and 'confirm' human data, but this should not be taken as evidence of its worth. When *extrapolated* to humans, NHP research has caused untold amounts of harm, a fraction of which is detailed here; directly by causing human suffering and death, and indirectly by delaying medical progress and diverting research funds from more appropriate methodology.

Those small genetic differences between us explain why this is the case. Some of these differences lie within the structural genes, i.e. those genes that make proteins and enzymes that 'make up' the body and allow it to function. Tiny differences can completely change a gene's function and ability to do its job. Most of the differences, however, are now known to lie within the regulatory regions of our DNA; particular genes and sections of DNA that are involved in turning other genes 'on' and 'off' and modifying how their products do their jobs and interact with one another, in response to a variety of signals and stimuli. These can act highly promiscuously, and exert 'avalanche' effects upon hundreds of other genes. A small difference, therefore, can have far-reaching and extreme effects. For example, striking differences have been found in the levels of gene expression between humans and chimps in the brain and liver[60].

The Way Forward

Many scientific techniques exist which perform significantly better than NHP-oriented research, and are directly responsible for the great strides we are now making towards treating and curing the most widespread and debilitating human diseases. Batteries of human-based tests provide reliable and relevant information on which to base further research and to speed the translation of research to the bedside.

These technologies include microarrays and other DNA technologies; proteomics and metabolomics; mathematical and computer modelling; epidemiology;,human clinical research; myriad *in vitro* molecular biological techniques; microfluidics devices harbouring many types of human cells in an almost 'natural' environment and interacting with one another; and many more. Studies of brain function and neurological disorders account for much NHP research, yet the most dramatic differences between us and other primates are in the brain. Human brains can now be studied non-invasively using a huge array of imaging techniques such as positron emission tomography (PET), magnetoencephalography (MEG), magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS), EROS (event-related optical signals), VBM (voxel-based morphometric analysis) and single photon emission computed tomography (SPECT). These enable the conscious brain to be observed while engaged in a variety of cognitive tasks (eg. talking, singing, reading, writing) of which NHPs are not even capable. Subtleties such as musical ability and memory skills can be identified, highlighting the redundancy of knowledge to be gained from NHPs. The Academy of Life Sciences at Aston University is an example of progress to be gained from multidisciplinary human clinical research.

Perhaps the most exciting technology with regard to drug development is 'microdosing,' in which nanogram doses of new drugs are traced through the human body. Employed as 'Phase 0' clinical trials, microdosing provides extensive information about a drug's pharmacokinetic properties in a human environment and has already been endorsed by the FDA (April 2005) and the European Agency for the Evaluation of Medicinal Products (January 2003)[61]. The APC recommended that the use of microdosing in place of NHPs should be encouraged. Several companies exist whose mission is to develop and/or test drugs in an exclusively human context, such as Pharmagene: (quote) 'no animal species is sufficiently similar to man to act as a wholly reliable surrogate.' Indeed there is extensive evidence that the use of animal (non-human) tissue can result in the generation of potentially misleading information' and Biopta, whose rationale is 'proof of concept in man.'

Time for Objectivity

The limitations of nonhuman primate research and the risk of excessive faith in its results have not yet been widely appreciated by many. For a variety of political reasons, few scientists openly question whether primate models are a reliable research method. One of the main obstacles to open discussion and debate is that researchers, threatened by those who oppose their modus operandi, believe that best strategy is to defend *all* animal research regardless of its actual value[62,63] and to discourage and actively suppress criticism from within their ranks[64-67].

We believe it is time for objectivity, transparency and honesty in the assessment of NHP models and their contribution to medical science. Only by ensuring this can we be confident that we are utilizing scientific technology to the full, performing the best translational research possible, and making real progress towards the relief of human suffering and disease.

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