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Chimpanzee Research: An Examination of Its Contribution to Biomedical Knowledge and Efficacy in Combating Human Diseases

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Detailed reviews of all papers involved in this citation analysis can be found in the supplement accompanying this paper.

SUMMARY

Research on captive chimpanzees incurs considerable animal welfare, ethical and financial costs. Advocates of such research claim these costs are outweighed by substantial advancements in biomedical knowledge, and that the genetic similarity of chimpanzees to humans enables the former to make critical contributions to preventing, diagnosing and combating human diseases. To assess these claims, we examined the disciplines investigated in 749 studies of captive chimpanzees published from 1995-2004 inclusive, and subjected 95 randomly selected papers to a detailed citation analysis:

49.5% (47/95) of papers had not been cited at the time of this study; 38.5% (34/95) were cited by 116 papers that did not describe well-developed methods for combating human diseases; 14.7% (14/95) of these chimpanzee studies were cited by (a total of 27) papers describing well-developed prophylactic, diagnostic or therapeutic methods for combating human diseases. Close examination of these 27 human medical papers revealed that *in vitro* research, human clinical and epidemiological investigations, molecular assays and methods, and genomic studies, contributed most to their development. Duplication of human outcomes, inconsistency with other human or primate data, and other causes resulted in the absence of any chimpanzee study demonstrating an essential contribution, or, in most cases, even a significant contribution of any kind, towards the development of the described human treatment.

INTRODUCTION

In a recent plea for increased research on captive chimpanzees, VandeBerg and Zola (VandeBerg and Zola 2005) asserted in *Nature* that, "*Many advances from biomedical research with chimpanzees have been published in the past one to two years, demonstrating that rapid medical progress pertinent to a wide range of human diseases is being made through the use of chimpanzees.*"
Claims such as these, made particularly by many researchers that currently use non-human primates (NHPs) or have used them in the past, are usually based on the ostensible similarities of chimpanzees to humans. Of all NHPs, the common chimpanzee (*Pan troglodytes*) and bonobo ("pygmy chimpanzee," *Pan paniscus*) are genetically most similar to humans. Though estimates initially suggested this similarity was around 98.5 - 99%, more recent analyses suggest the figure may be in the region of 95 - 96% (Britten 2002; Varki and Altheide 2005). Either way, these figures suggest that chimpanzees would be the most likely non-human species to be of assistance in the development of diagnostic or therapeutic techniques for combating human diseases. NHPs are used in areas of research as diverse as hematology, immunology, virology, pharmacology (Herodin *et al*., 2005), and neurotoxicology (Evans 1990), to investigate potential bio-terrorism agents such as Ebola and Lassa viruses, anthrax and the plague (Patterson and Carrion 2005), and even to examine the physiological effects of the environment in space (Pesquies *et al*., 1978).
Chimpanzees specifically have recently been involved in research in most of these areas, but chiefly in studies into acquired immunodeficiency syndrome (AIDS) and hepatitis C virus (Herodin *et al*., 2005).

Research on captive chimpanzees remains controversial, however, with opponents citing numerous and varied animal welfare, ethical, scientific and financial concerns (Sauer 2000; Thew 2000). Because of these concerns, some form of scientific evaluation and objective appraisal of the necessity and human benefits derived from research on captive chimpanzees is imperative. Notably, captive chimpanzee research must be regarded as a "special case;" most of the public, and indeed much of the scientific community, agree that the associated ethical cost at the very least demands a results-oriented pay-off in the form of substantial, tangible, human medical progress. Determining the scientific justification for chimpanzee research is paramount: if it exists, then concerns can be addressed and weighed against benefits. The argument to end chimpanzee research may become too strong to be effectively countered, if scientific justification is hard to come by other than in the form of speculative claims emanating from individuals closely involved in it.

A first step in assessing the merits of research on captive chimpanzees is to obtain a clear picture of the biomedical disciplines examined by such research. Some work has already been done in this area: based on 184 grant abstracts filed in the Computer Retrieval of Information on Scientific Projects (CRISP) database and 89 journal articles cited in PubMed (the U.S. National Library of Medicine's premier bibliographic database), Conlee *et al.* (Conlee *et al.*, 2004) provided some initial indications of the disciplines investigated by chimpanzee research within the U.S. In addition, Carlsson *et al.* (Carlsson *et al.*, 2004) surveyed 2,937 articles published in 2001 describing 4,411 NHP studies using over 41,000 animals worldwide, though only a small minority of these were studies of chimpanzees.

Here we assess the utility of chimpanzee research *in combating human disease*, using a two-phase approach: 1) we determined the frequency with which chimpanzee research published in peer-reviewed journals was cited by papers describing human prophylactic, diagnostic or therapeutic methods (using the Cochrane Collaboration's guidelines for systematic reviews (Higgins and Green 2005) where appropriate), and 2) we quantitatively and qualitatively assessed the nature and importance of the contributions provided by the cited chimpanzee studies. The survey was limited to major biomedical bibliographic databases likely to contain human medical papers, and attention was focused on research on captive chimpanzees because such research has raised the most concerns.

METHODS

We searched three biomedical bibliographic databases for papers describing research involving living chimpanzees or chimpanzee tissue from 1995 to 2004 inclusive: CAB Abstracts, the most comprehensive bibliographic database covering the applied life sciences, containing over 4.5 million records (Anonymous 2006*a,b*); EMBASE, the Excerpta Medica database, which is a biomedical and pharmacological database containing over 10 million records (Anonymous 2006*c*); and Medline, the premier medical and allied health profession database, containing over 12 million records (Anonymous 2006*d*). Jointly these databases included over 6,000 biomedical journals and thousands of other scientific documents sourced from more than 140 countries. Where appropriate, we also applied the Cochrane Collaboration's guidelines for systematic reviews (Higgins and Green 2005), applying many of their recommendations including those regarding protocol development; data collection, analysis and interpretation; and report content and structure.

All titles, abstracts, and associated fields were searched for "chimpanzee," "bonobo," "*Pan troglodytes,"* and "*Pan paniscus,"* limiting the search to documents with abstracts. These included:

- Studies of captive chimpanzees;
- Studies of biometric information taken from captive chimpanzees, such as MRI scans;
- Studies of fresh or preserved chimpanzee tissues, other than those specified below.

They excluded:

- Studies of free-living chimpanzees;
- Veterinary case reports of the diagnosis, treatment or post-mortem examination of naturally-ill chimpanzees, whether in captivity or not;
- Genome studies (excluding those of experimentally infected chimpanzees);
- Studies of skeletal anatomy (museum specimens were often used);
- Studies of cell lines (although cell samples obtained from captive chimpanzees were included);
- Studies of chimpanzee blood where the source was not specified;
- Secondary analyses of data obtained in primary studies.

From 749 chimpanzee studies that met the inclusion criteria, we randomly selected a subset of 100 studies using the "Research Randomizer" random number generator (www.randomizer.org). This was done for logistical reasons; performing a detailed citation analysis for 749 studies is a mammoth undertaking. Four of these citing papers were not available through the bibliographic databases used, and one additional study was cited only by a paper for which no abstract was available. Our analysis criteria (including a requirement for readily-accessible papers with published abstracts) led to these studies being excluded from further consideration, leaving 95 chimpanzee studies in the analysis. This sample size represents a number exceeding the sample size required to achieve statistical significance, based on the normal

approximation to the binomial distribution for a 95% confidence level with an error of plus or minus 10%.

These 95 studies were examined to determine the frequency with which they were cited by papers subsequently published in peer-reviewed journals indexed by the named bibliographic databases, as of January 2006. The species and biomedical disciplines that were the focus of these citing papers were also determined.

In particular, where abstracts of citing papers described prophylactic, diagnostic or therapeutic methods with clear potential for combating human diseases, the full-text of the citing articles (human subjects) was reviewed to determine the contribution of the cited chimpanzee study to the development of the method described, in comparison with other cited sources of knowledge. In each case, both the entire citing and cited papers were thoroughly examined, related articles sought (via direct links from literature databases and also via specific new database searches) to determine how the method had progressed since publication of the citing paper, and (where appropriate) clinical trial data obtained to assess the relevance and application of the method to human clinical practice. The contribution of a cited chimpanzee study was assessed by appraising the context of its citation, and by scanning all the references in the citing paper to derive the main contributors to the findings reported by it.

RESULTS

Using the specified search terms, 2400 abstracts were found dating up to 28th August 2005. Of these, 749 were studies of captive chimpanzees or chimpanzee tissue that met our inclusion criteria.

We classified the areas of investigation of all 749 chimpanzee papers into several categories as follows:

48.5% (363/749) of these were biological investigations, and 41.5% (311/749) were virology experiments (**Figure 1**). Biological investigations comprised nine disciplines, of which the most frequent were cognition/neuroanatomy/neurology (36.6%, 133/363) and behavior/communication (20.7%, 75/363) (**Figure 2**). Virological investigations involved 30 different types of virus, of which the most frequent were hepatitis C virus (HCV) and human immunodeficiency virus (HIV), each of which comprised 31.2% (97/311) of all virology experiments (**Figure 3**).

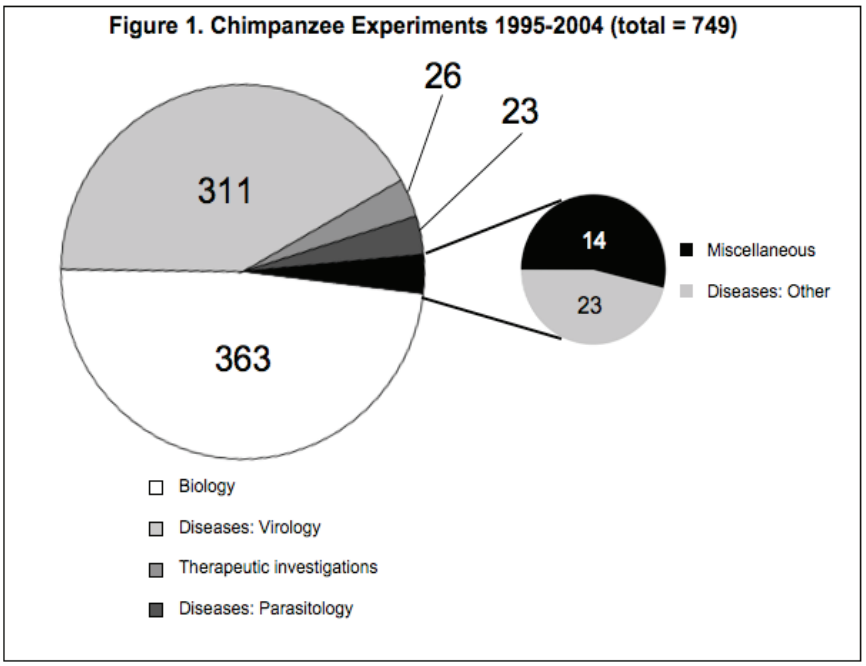

Figure 1: 2400 abstracts describing chimpanzee studies were found, dating from 1995 to 2004. Of these, 749 were studies that met the inclusion criteria. 48.5% (363/749) were biological experiments, and 41.5% (311/749) were virology experiments. A further 10% belonged to a variety of other categories.

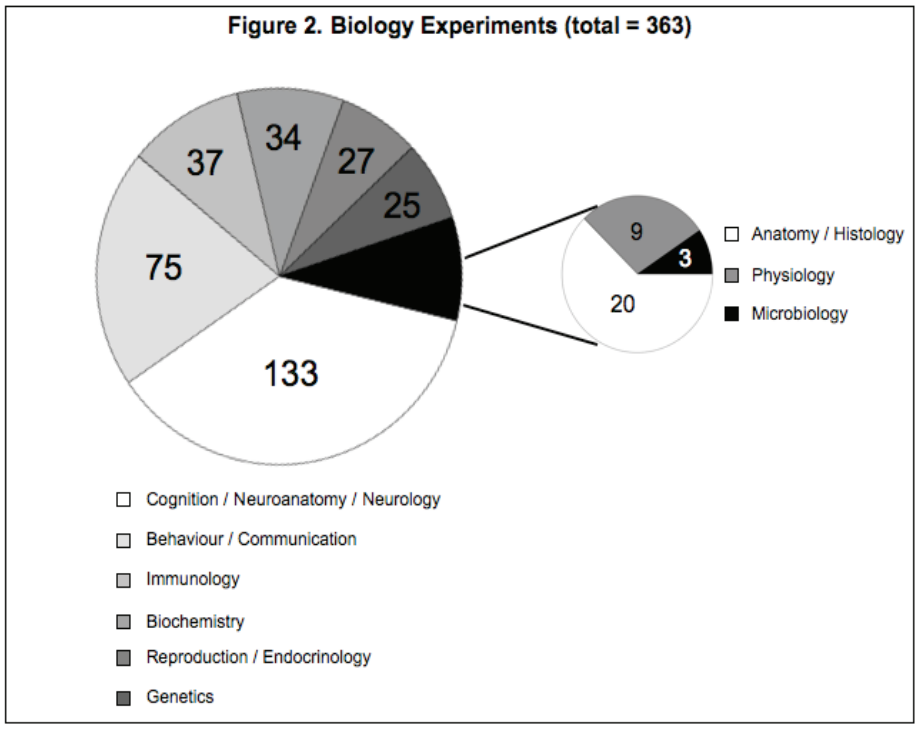

Figure 2: Biological investigations constituted 48.5% of chimpanzee experiments that met the inclusion criteria, performed between 1995 and 2004 inclusive. These were conducted in nine disciplines, of which the most frequent were cognition/neuroanatomy/neurology (36.6%, 133/363) and communication/communication (20.7%, 75/363).

Therapeutic investigations comprised 3.5% (26/749) of all chimpanzee experiments, of which almost two-thirds (16/26) investigated the pharmacological properties of a variety of compounds (**Figure 4**). Other investigations included the testing of surgical techniques or prostheses, anesthesiology, and toxicology of compounds other than pharmaceuticals. Parasitology experiments comprised 3.1% (23/749) of the total (**Figure 5**). Eight parasitic species were examined, of which the most frequent were the malaria protozoa *Plasmodium falciparum* and *P. ovale* (26.1%, 6/23), the roundworm *Onchocerca volvulus* (21.7%, 5/23), and the flatworm *Schistosoma mansoni* (17.4%, 4/23).

Other diseases and miscellaneous experiments combined comprised 3.5% (26/749) of all chimpanzee experiments, of which the most frequent were investigations of laboratory/husbandry techniques (42.3%, 11/26) and endotoxemia (30.1%, 8/26) (**Figure 6**). Three radiation studies were performed, and four other diseases were investigated: benign prostatic hyperplasia, Creutzfeldt-Jakob disease, gastrointestinal bacteriology (*Bacillus thuringiensis*), and tuberculosis (*Mycobacterium tuberculosis*).

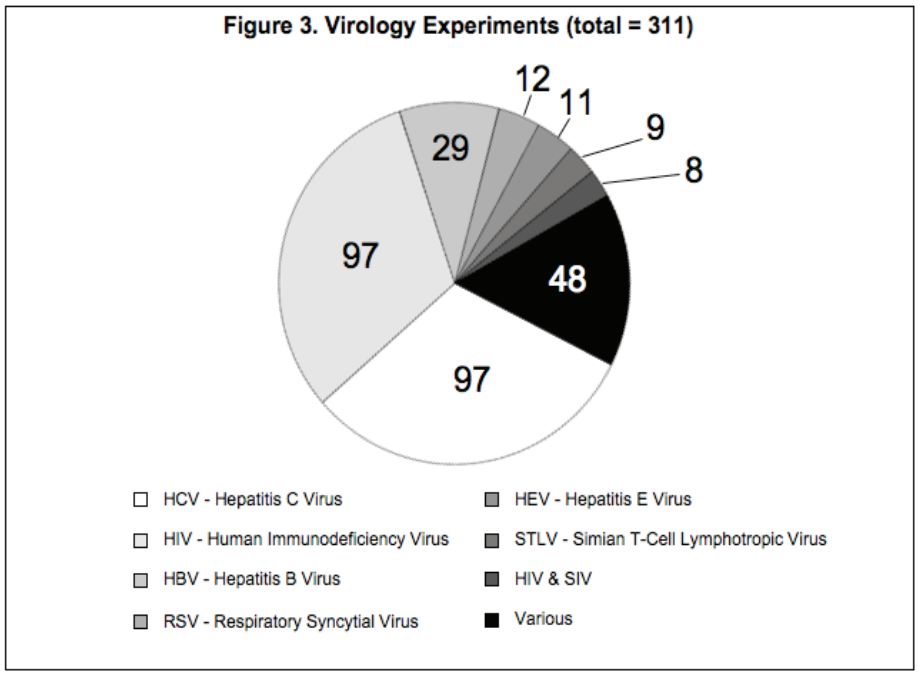

Figure 3: Virological investigations constituted 41.5% of chimpanzee experiments that met the inclusion criteria, performed between 1995 and 2004 inclusive. They were conducted in 30 disciplines, of which the most frequent were hepatitis C virus (HCV) and human immunodeficiency virus (HIV), each of which comprised 31.2% (97/311) of all virology experiments.
HCV = hepatitis C v, HIV = human immunodeficiency v, HBV = hepatitis B v, RSV = respiratory syncytial v, HEV hepatitis E v, STLV = simian T-cell lymphotropic v, SIV = simian immunodeficiency v, TTV = transfusion-transmitted v, FV = foamy v (human and simian FV), HAV = hepatitis A v, GBV-B = a close relative of HCV affecting tamarins, HV = herpes v, IV = influenza v, PIV = parainfluenza v, HCMV = human cytomegalovirus, HGV = hepatitis G v, HMPV = human metapneumovirus, H/S TLV = human/simian T-cell leukemia v, LCV = lymphocryptoviruses, RV2 = rhadinovirus (or gamma-2-herpesvirus) genogroup 2, VZV = varicella-zoster v, WMHBV = woolly monkey hepatitis B v.

Citations of chimpanzee studies

Notably, 49.5% (47/95) of these chimpanzee studies were not cited by any subsequent papers (**Figure 7**) (95% confidence interval for proportion of papers not cited in the original population of 749 papers = [0.395-0.595]. In other words, if this sampling was done repeatedly, one could be 95% certain that the proportion of chimpanzee studies not cited by any subsequent papers would be between these values, i.e. 39.5%-59.5%).

The remaining 48 chimpanzee experiments were cited by 143 papers for which abstracts were available. Some of these citing papers focused on humans alone; others did so in combination with other species, namely: bacteria (*Escherichia coli*); pigeons (*Columba livia*); bottlenose dolphins (*Tursiops truncatus*); dogs (*Canis familiaris*); Asian elephants (*Elephas maximus*); mice (natural or genetically-modified); pigs, and, unsurprisingly, a large variety of primate species: African green monkeys

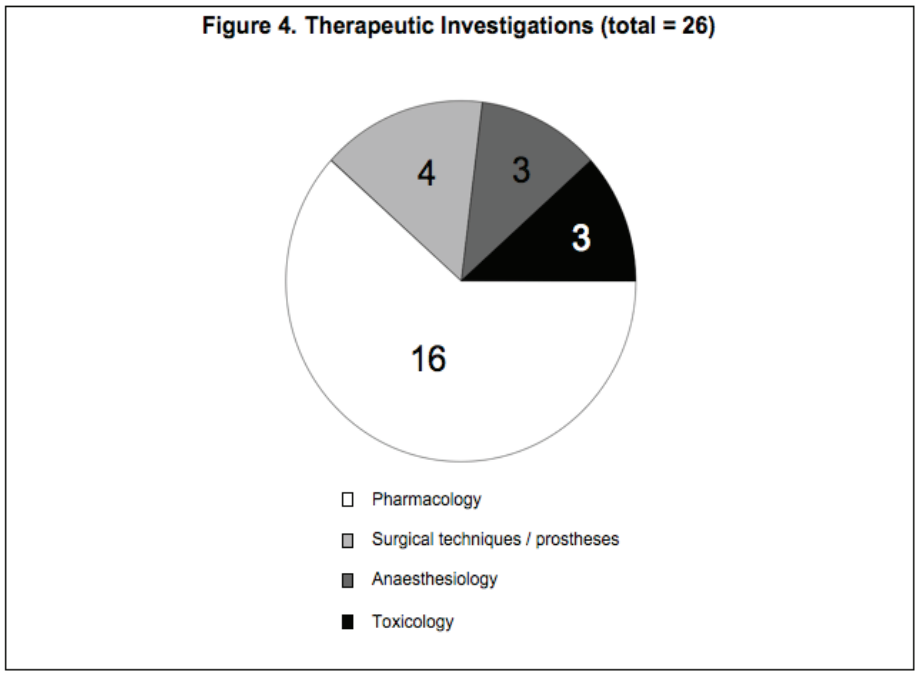

Figure 4: Therapeutic investigations comprised 3.5% (26/749) of all chimpanzee experiments, of which 61.5% (16/26) investigated the pharmacological properties of various compounds. Other investigations included the testing of surgical techniques or prostheses, anesthesiology and toxicology experiments.

(*Chlorocebus aethiops*); chimpanzees (*Pan troglodytes* or *Pan paniscus*); common marmosets (*Callithrix jacchus*); cotton top tamarins (*Saguinus oedipus*); cynomolgus macaques (*Macaca fascicularis*); Japanese macaques (*Macaca fuscata*); rhesus macaques (*Macaca mulatta*); squirrel monkeys (*Saimiri sciureus*); tufted capuchin monkeys (*Cebus apella*); olive baboons (*Papio anubis*); orangutans (*Pongo abelii* and *Pongo pygmaeus*) and western lowland gorillas (*Gorilla gorilla gorilla*).

A variety of biological disciplines were explored in these citing papers, with the hepatitis and human immunodeficiency viruses (HIV) featuring most prominently. Others included (in alphabetical order): asthma, autism, behavior, benign prostatic hyperplasia, cancer, chronic obstructive pulmonary disease (COPD), coxsackievirus B3, Epstein-Barr virus (EBV), genetic studies, human parainfluenza virus type 3, immunology, Kawasaki disease, laboratory techniques (including gene expression profiling and cDNA microarray interpretation), leukemia, malaria, neuroanatomy, neurology, organ transplantation, pathology (clinical), psychology, respiratory syncytial virus (RSV), rheumatoid arthritis (RA), rhinovirus colds, simian immunodeficiency virus (SIV), systemic lupus erythematosus (SLE), surgical techniques (cardiac allografts), toxicity (arsenic, transmissible spongiform encephalopathies (TSE)), and non-specific virology.

In addition to the 49.5% of papers in our random sample that were not cited, 35.8% (34/95) of those chimpanzee studies were cited only by papers (a total of 116) that did

not describe well-developed prophylactic, diagnostic or therapeutic methods for combating human diseases (**Figure 7**).

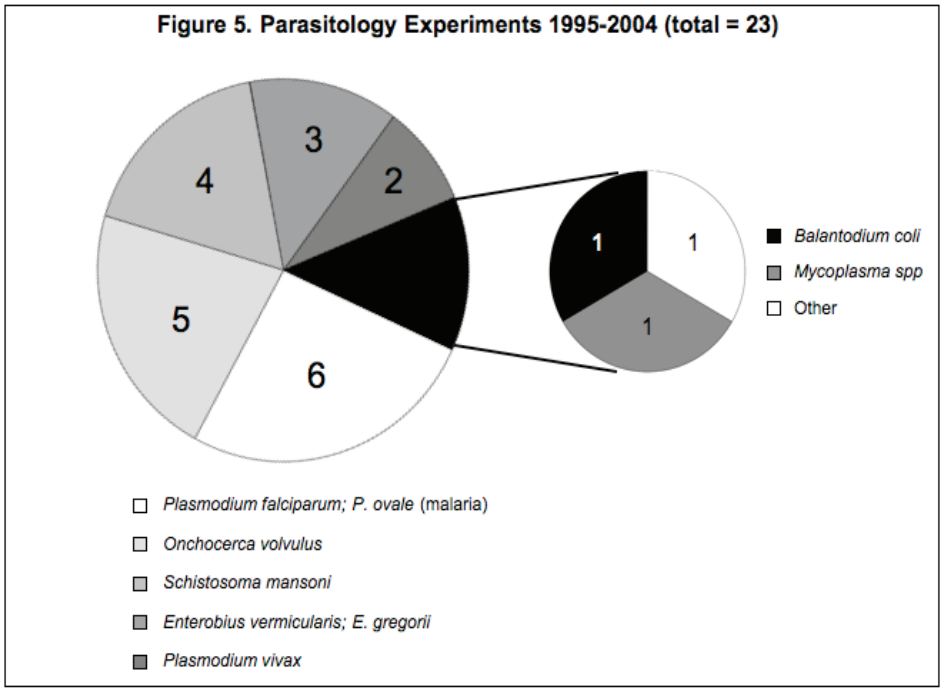

Figure 5: Parasitology experiments comprised 3.1% (23/749) of all chimpanzee experiments. Eight parasitic species were investigated, of which the most frequent were the malaria protozoa *Plasmodium falciparum* and *P. ovale* (26.1%, 6/23), the roundworm *Onchocerca volvulus* (21.7%, 5/23), and the flatworm *Schistosoma mansoni* (17.4%, 4/23).

Papers describing human prophylactic, diagnostic or therapeutic methods

Only 14.7% (14/95) of our random sample of chimpanzee studies were cited by a total of 27 papers that described human prophylactic, diagnostic or therapeutic methods. Of these, 5 described diagnostic methods and 22 described prophylactic and/or therapeutic methods for combating human diseases, which were either fully developed for human use or in the latter stages of development at the time of publication (**Figure 7**). Diseases examined in these citing papers included cancer (non-specific), COPD, EBV, hepatitis viruses A through G (HAV through HGV), hepatocellular carcinoma, HIV, malaria, organ transplant rejection, RSV, RA, rhinovirus colds, SLE and TSE. 63.0% (17/27) of these human medical papers were wide-ranging reviews of up to 300 studies, in which the cited chimpanzee study made only a minor contribution – as discussed later.

Detailed reviews of each of the 27 papers citing the 14 chimpanzee papers from our random sample (that had described human prophylactic, diagnostic or therapeutic methods) were carried out, to determine the contribution of the chimpanzee studies to the human prophylactic, diagnostic or therapeutic method described in the citing paper. These can be found in the supplement to this paper; a summary of the papers

citing the chimpanzee studies from our random sample, and of the cited chimpanzee studies, is provided in **Table 1**.

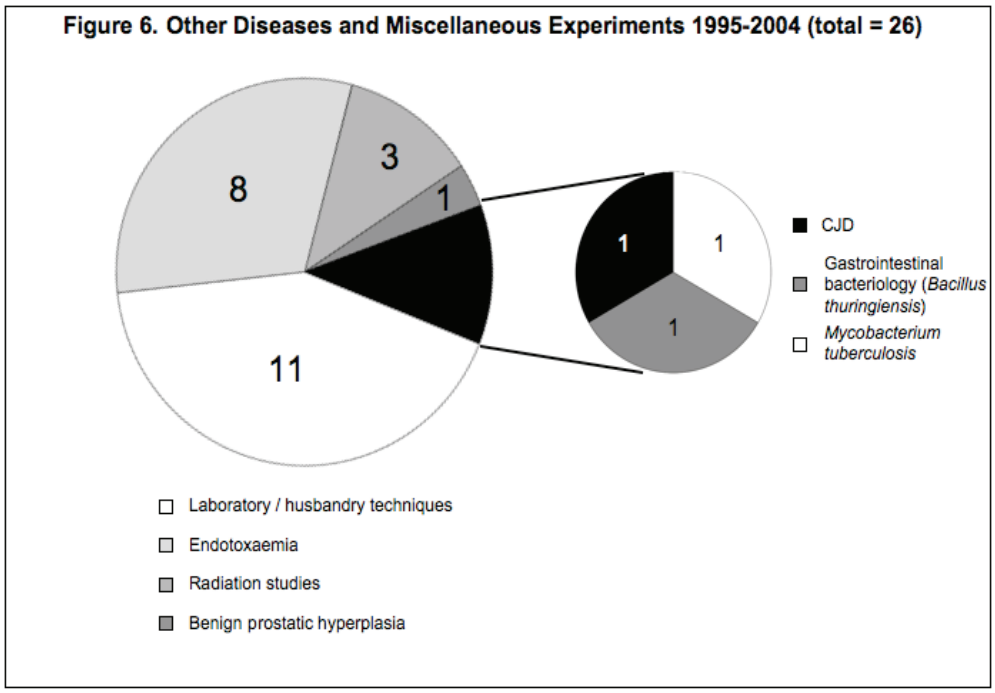

Figure 6: Other diseases and miscellaneous experiments comprised 3.5% (26/749) of all chimpanzee experiments when combined, of which the most frequent were investigations of laboratory/husbandry techniques (42.3%, 11/26) and endotoxemia (30.1%, 8/26). Three radiation studies were also conducted, and four other diseases were investigated, namely benign prostatic hyperplasia, Creutzfeldt-Jakob disease, gastrointestinal bacteriology (*Bacillus thuringiensis*), and tuberculosis (*Mycobacterium tuberculosis*).

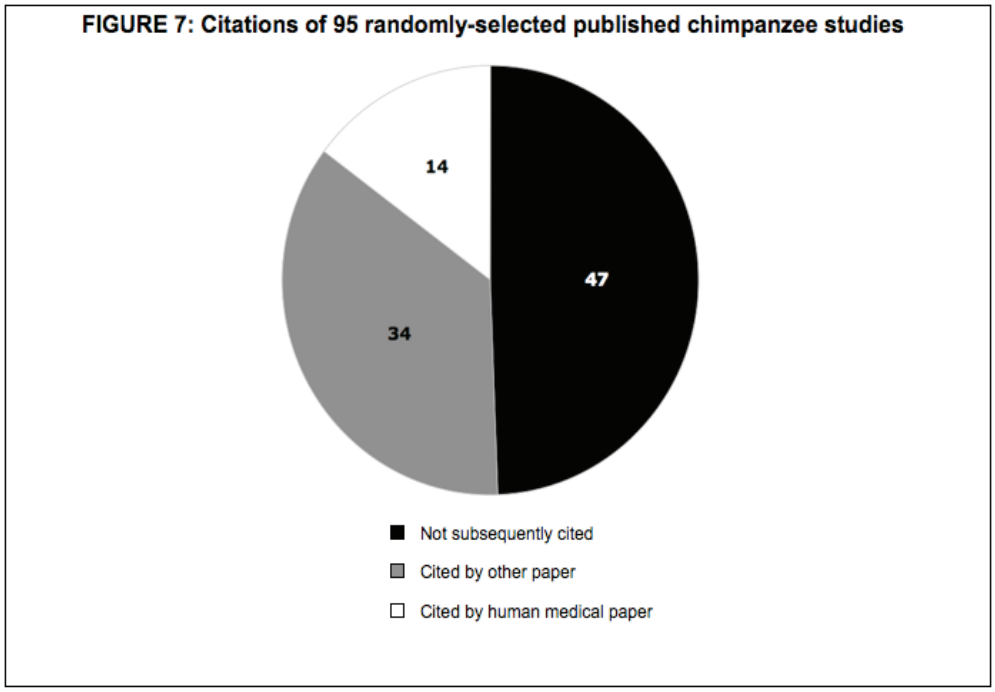

Figure 7: Citations of 95 randomly selected published chimpanzee studies. 49.5% (47/95) of these papers had not been subsequently cited in the scientific literature; (95% confidence interval for proportion of papers not cited in the original population of 749 papers = [0.395-0.595]). The remaining 48 chimpanzee experiments were cited by 143 papers. 35.8% (34/95) of these were cited only by 116 papers that did *not* describe well-developed prophylactic, diagnostic or therapeutic methods for combating human diseases. Just 14.7% (14/95) of our random sample of chimpanzee studies described human prophylactic, diagnostic or therapeutic methods, and these were cited by a total of 27 papers.

TABLE 1

CITING PAPER					CITED PAPER	
No.	**Paper**	**Type**	**Topic**	**No. References**	**Paper**	**Times Cited**
1	Tong & Stone (2003)	Review	Cancer (non-specific): therapeutic	155	Brams *et al*. (2001)	6
2	Suzuki *et al*. (2001)	Research paper	COPD: prophylactic	28	Huguenel *et al*. (1997)	6
3	Khanna *et al*. (1999)	Review	Epstein-Barr virus: prophylactic	112	Bertoni *et al*. (1998)	2
4	Koff (2002)	Review	HAV & HBV: prophylactic	85	Ogata *et al*. (1999)	5
5	Regev & Schiff (1999)	Review	Hepatitis viruses A-G: prophylactic & therapeutic	71	Mast *et al*. (1998)	13
6	McMahon *et al*. (2005)	Research paper	HBV: prophylactic	38	Ogata *et al*. (1999)	5
7	Karayiannis (2003)	Review	HBV: prophylactic & therapeutic	300	Pancholi *et al*. (2001)	5
8	Hüssy *et al*. (1997)	Research paper	HCV: diagnostic	24	Wang *et al*. (1996)	8
9	Feld & Hoofnagle (2005)	Review	HCV: therapeutic	91	Bigger *et al*. (2001)	10
10	Nakano *et al*. (1999)	Research paper	HCV: therapeutic	26	Wang *et al*. (1996)	8
11	Worm & Wirnsberger (2004)	Review	HEV: prophylactic methods	133	Mast *et al*. (1998)	13
12	Obriadina *et al*. (2002)	Research paper	HEV: diagnostic	32	Mast *et al*. (1998)	13
13	Kim & Wang (2003)	Review	Hepatocellular carcinoma: diagnostic	81	Bigger *et al*. (2001)	10
14	Armbruster *et al*. (2002)	Research paper	HIV: prophylactic & therapeutic	25	Conley *et al*. (1996)	10
15	Armbruster *et al*. (2004)	Research paper	HIV: prophylactic & therapeutic	27	Conley *et al*. (1996)	10
16	Bardsley-Elliot & Perry (2000)	Review	HIV: prophylactic & therapeutic	130	Grob *et al*. (1997)	2
17	Hone *et al*. (2002)	Review	HIV: prophylactic	108	Conley *et al*. (1996)	10
18	Sleasman & Goodenow (2003)	Review	HIV: prophylactic & therapeutic	93	Conley *et al*. (1996)	10
19	Yang *et al*. (1998)	Research paper	HIV: diagnostic	28	Conley *et al*. (1996)	10
20	Gallo (2002)	Review	HIV: therapeutic	258	Goh *et al*. (1998)	10
21	Moore & Hill (2004)	Review	Malaria: prophylactic	104	Pancholi *et al*. (2001)	5
22	Matthews *et al*. (2003)	Review	Organ transplant rejection: therapeutic	87	Newman *et al*. (2001)	2
23	Kneyber & Kimpen (2002)	Review	RSV: prophylactic	150	Crowe *et al*. (1999)	1
24	Hepburn *et al*. (2003)	Research paper	Rheumatoid arthritis: therapeutic	15	Newman *et al*. (2001)	2
25	Turner *et al*. (1999)	Research paper	Rhinoviral colds: prophylactic	34	Huguenel *et al*. (1997)	6
26	Gescuk & Davis (2002)	Review	SLE: therapeutic	77	Brams *et al*. (2001)	6
27	Brown (2005)	Review	TSE: diagnostic	26	Cervenakova *et al*. (2003)	1

Table 1: The twenty-seven medical papers citing publications from our random sample of 95 chimpanzee studies. Relevant details of each citing paper are summarized, along with information concerning the actual chimpanzee study cited in each case and the number of times these chimpanzee studies had been cited in total, at the time of our analysis. COPD = chronic obstructive pulmonary disease; HAV–HCV = hepatitis viruses A–C; HEV = hepatitis E virus; HIV = human immunodeficiency virus; RSV = respiratory syncytial virus; SLE = systemic lupus erythematosus; TSE = transmissible spongiform encephalopathy.

DISCUSSION

Contributions made by chimpanzee studies

For a variety of reasons, the chimpanzee studies from our random sample were found to be incidental to most of these human medical papers (**Table 2**).

TABLE 2

Reason for lack of contribution of chimpanzee study to human prophylactic, diagnostic or therapeutic method	Total number of reviews in category (of 27)	Specific reviews in category
Redundant (concurrent human experiments/"confirmations" of human data)	14	1, 5, 8-14, 16, 20, 24, 25, 27
Method not developed further (possibly due to chimpanzee/human differences)	7	2, 22-27
Chimpanzee study peripheral to human method described	7	3, 4, 6, 13, 15, 21, 25
Historical citation with no direct relevance	3	2, 17, 19
Inconsistent with data from other NHP studies	3	7, 17, 26
Inconsistent with human data	2	18, 24
Purely speculative in nature	2	3, 14
May have helped establish need for new diagnostic method but did not contribute further to its development.	1	12

Table 2: **Reasons why the random sample of chimpanzee studies in our analysis did not contribute to the human prophylactic, diagnostic or therapeutic methods described in papers citing them.** Each review detailed in this analysis fits into one or more of the eight categories shown. The total number of reviews in each category is shown, along with the specific reviews as numbered in the results section of this study. It should be noted, however, that due to the complex and overlapping nature of the studies and these categories, this table could not be considered to be exhaustive and all-inclusive.

In fourteen cases (Reviews 1, 5, 8-14, 16, 20, 24, 25 and 27; see Supplement) the chimpanzee studies appeared to be redundant, as humans or human sera were studied concurrently, or because they only served to confirm observations previously made in humans. In seven cases (Reviews 2 and 22-27) the method explored in the cited chimpanzee study was not developed further, sometimes because later clinical trials in humans failed to demonstrate safety or efficacy, contrary to positive results in chimpanzees. In seven cases (Reviews 3, 4, 6, 13, 15, 21 and 25) the chimpanzee study examined a disease or method peripheral to the prophylactic, diagnostic or therapeutic method described. In three cases (Reviews 2, 17 and 19) the chimpanzee study merely illustrated an historical finding, or was cited during historical discussions of attempts to combat the disease in question. In three cases (Reviews 7, 17 and 26) chimpanzee studies yielded results inconsistent with data from other NHP studies, while in two cases (Reviews 18 and 24) they yielded results inconsistent with human data. In two cases (Reviews 3 and 14) the cited chimpanzee studies were purely speculative in nature and had therefore not contributed to the concrete findings of the citing papers. In the remaining case (Review 12) the chimpanzee study may have helped establish the need for a new diagnostic method but did not contribute further to its development.

Five chimpanzee studies were cited by multiple human medical papers. The paper by Bigger *et al*. on the effects of HCV in chimpanzees (Bigger *et al*., 2001), for example, was peripheral to Kim and Wang's paper (Kim and Wang 2003) describing a diagnostic method for the detection of HCC (Review 13), and served only to confirm what had already been observed in earlier human studies cited by Feld and Hoofnagle's paper (Feld and Hoofnagle 2005) on therapeutic methods for combating HCV (Review 9).

Conley *et al.*'s study (Conley *et al.*, 1996) of the prophylactic use of hMAbs in chimpanzees challenged with HIV-1 was also cited by five medical papers. In two studies of prophylactic and therapeutic methods for combating HIV (Armbruster *et al*., 2002; 2004), prior positive results in the cited chimpanzee study suggested a potential field of further development with respect to hMAb choices used in combination prophylactic and therapeutic regimes (Reviews 14 and 15). The cited chimpanzee study did not, however, play an integral role in the citing studies, the purpose of which was to examine the safety, immunogenicity and pharmacokinetics of hMAb protocols in clinically healthy HIV-1-infected human volunteers. In papers by Yang *et al.* (Yang *et al*., 1998) and Hone *et al.* (Hone *et al*., 2002) describing the development of vaccines and a diagnostic method respectively for combating HIV, the cited chimpanzee study served only to demonstrate that effective HIV antibodies can indeed neutralize HIV in chimpanzees, to varying degrees, although conflicting results were observed in six other NHP studies cited by Hone *et al* (Reviews 17 and 19). Other than through such peripheral means, the cited chimpanzee study did not contribute to the development of these prophylactic and diagnostic methods. The contribution of this study towards the development of prophylactic and therapeutic methods for combating HIV reviewed by Sleasman *et al.* (Sleasman and Goodenow 2003) was similarly limited by inconsistency with other cited human data (Review 18).

Mast *et al.*'s paper (Mast *et al.*, 1998) describing the poor concordance, sensitivity and variable efficiency of previously available HEV assays in chimpanzees, particularly against different HEV strains, was cited by Regev *et al.*'s review (Regev and Schiff 1999) of prophylactic and therapeutic options for combating HAV, HBV, HCV, HEV, HGV and TTV (Review 5), as well as by Obriadina *et al.*'s paper (Obriadina *et al.*, 2002*a*) describing the development of a diagnostic technique for the detection of HEV (Review 12). The chimpanzees in Mast's study were used as both positive and negative controls, though both were redundant for more relevant positive and negative human controls in the form of human sera were available concurrently. Additionally, one of Mast *et al.*'s key outcomes was the highly discrepant existing HEV assay results from U.S. blood donors that were presumed HEV negative, necessitating great caution when interpreting positive assay results. This outcome relied exclusively on human results.

Newman *et al.*'s paper (Newman *et al.*, 2001) demonstrating the safety and efficacy of Keliximab, a primatized IgG1 anti-CD4 mAb in modulating T-cell receptor responsiveness in chimpanzees, was cited by two medical papers. In Matthews *et al.*'s review (Matthews *et al.*, 2003) of therapeutic strategies designed to thwart organ transplant rejection, it was hoped that the targeting of cell-surface receptors might result in T-cell inactivation, thereby delaying allograft rejection because T-cell activation is central to the inflammation and tissue damage that precedes it (Review 22). Hepburn *et al.* (Hepburn *et al.*, 2003) also described a clinical trial of Clenoliximab, an anti-CD4 mAb antibody proposed for the treatment of RA (Review 24). However, a later phase II human clinical trial of an analogue drug (Zanolimumab) failed to demonstrate efficacy at combating the disease, resulting in abandonment of the development of this drug for RA patients and casting doubts on the efficacy of anti-CD4 mAbs in decreasing allograft rejection.

A paper describing chimpanzee studies of DNA-based vaccines (Pancholi *et al.*, 2001) was cited both by Karayiannis' review of the prophylactic and therapeutic options available for combating HBV (Karayiannis 2003) (Review 7), and by Moore and Hill's review of strategies for the development of a malaria vaccine (Moore and Hill 2004) (Review 21). In the former case, inconsistency with other chimpanzee and NHP results limited the utility of the cited chimpanzee study, while in the latter the disease and vaccination strategies explored were too disparate from those investigated in the cited chimpanzee study to accord it other than peripheral relevance.

Wang *et al.*'s study of the reactivity of humans and chimpanzees to various epitopes of HCV H strain structural proteins (Wang *et al.*, 1996) was cited by both Hüssy *et al.*'s paper investigating a diagnostic method for HCV (Hüssy *et al.*, 1997) (Review 8), and by Nakano *et al.*'s paper investigating therapeutic options for HCV (Nakano *et al.*, 1999) (Review 10). However, in both cases only the human outcomes within this chimpanzee study contributed to the citing medical paper. In fact, the cited chimpanzee study highlighted differences in the immune response of humans and chimpanzees to HCV.

Several authors of human medical papers or cited chimpanzee studies identified potential problems associated with attempts to extrapolate chimpanzee results to human outcomes. For example, in their study of prophylactic methods for combating

EBV, Khanna *et al.* (Khanna *et al.*, 1999*a*) stated that, "*It would be a mistake to assume that experimental results obtained in these ... primate models had direct relevance to vaccine formulations that might offer protection against infectious mononucleosis [one of the main targets for a vaccine]*." In his review of prophylactic methods for combating HAV and HBV, Koff (Koff 2002) described the cited chimpanzee study as potentially *complicating* our understanding of escape viruses. Wang *et al.* (Wang *et al*., 1996) identified key differences between the immune response of humans and chimpanzees to HCV infection. When commenting on the failure of a test drug to demonstrate efficacy at combating (T-cell dependent) RA in a phase II clinical trial, despite prior efficacy of an analogue drug in modulating T-cell receptor responsiveness in chimpanzees, Newman *et al.* (Newman *et al*., 2001) stated that, "*...results to date illustrate the profound difficulties in translating animal model success to the clinical arena."* Development of this test drug for RA patients was discontinued.

Sources contributing to human medical papers

Techniques featuring most frequently in the development of the prophylactic, diagnostic or therapeutic methods described in the 27 medical papers detailed above included *in vitro* studies, human clinical and epidemiological studies, molecular assays and methods, and genomic studies. Methods featuring particularly prominently included:

- *In vitro* studies in at least 18 papers, utilizing for example: HeLa cells; human adenoid explants; human respiratory epithelium (embryonic lung fibroblasts); human T-cells; LCLs; and rodent cell lines. Several viral studies used *E. coli* and baculoviruses in conjunction with *Sf9* insect cells as vectors for viral delivery and expression.

- Human clinical and epidemiological studies in at least 15 and six papers, respectively.

- Molecular methods in at least eight studies, including: ELISA; immune electron microscopy; PCR; radioimmunoassay; Western blot; and several assays designed for the diagnosis of TSEs: a combination of competitive antibody capture and CE; CDI; SIFT; and an immuno-PCR assay.

- Chimpanzee studies were, of course, cited by all of the medical papers. Other animal models were cited more prominently in five medical papers, including: transgenic and natural mice, rats, hamsters, guinea pigs, goats, sheep, cows, mink, woodchucks and NHPs (orangutans, baboons, cynomolgus macaques and rhesus macaques). Several of these species were cited in only one paper describing diagnostic methods for combating TSEs (Brown 2005), either as sources or recipients of TSE-infected tissues.

- Genomic techniques such as differential display, suppression subtractive hybridization, representational difference analysis, serial analysis of gene expression and microarray analysis (for example of viral genomes) featured prominently in four medical papers.

A detailed examination of the level of contribution of the various animal models other than chimpanzees is beyond the remit of this paper. Citation of animal models other than the chimpanzee in this review does not necessarily reflect a tangible contribution to any study: it simply conveys its inclusion in a citing paper, the merit of which must be addressed in the manner of similar citation analyses and systematic reviews that have been conducted recently by various research groups (such as Pound *et al*. (2005), Bailey *et al*. (2005), Knight *et al* (2006), Perel *et al*. (2006) and Hackam *et al*. (2006)). Our evaluation was confined to the involvement of chimpanzees only.

Human utility of medical papers citing chimpanzee studies

Based purely on their appearance in the bibliographies of biomedical papers, research on captive chimpanzees or chimpanzee tissues appears to have contributed towards a large range of biomedical disciplines. But citations and involvement in research programs are not a definitive indication of the necessity and value of a particular approach or specific study or dataset, for which an in-depth assessment of each citing paper and cited chimpanzee study is required. For example, papers may be cited due to their negative contribution to an area of knowledge, for comparison to other paradigms, and so on. Or, where citations of chimpanzee research arguably indicate a positive contribution to the overall outcome, alternative methods may well have been available and superior.

In our analysis, over three-quarters (21 of 27) of the medical papers did not describe prophylactic, diagnostic or therapeutic methods for combating human diseases that were sufficiently developed for routine human use and efficacious in a sizeable proportion of human patients. Most of the putative vaccination strategies described were far from completion and implementation: for example, one combination chemotherapeutic protocol for HCV did not achieve sustained viral clearance in half of chronically infected patients treated (Review 9), and when describing the development of vaccines against RSV (which have been explored using a substantial number of animal studies over many years), Kneyber *et al.* (Review 23) (Kneyber *et al.*, 2002) stated that *"it will probably be at least another 5 to 10 years before any routine vaccination against RSV becomes daily practice."*

In at least three cases (Reviews 2, 24 and 25), drugs being tested failed to progress to the market following initial animal or human trials, indicating concerns over human safety and/or efficacy. In one case (Review 8) the sensitivity of the diagnostic assay in question was lower than that of the traditional assay, while in three other cases (Reviews 12, 19 and 27) the diagnostic assays were not ready for routine medical use.

Several reports described vaccines in successful use for some time, such as the combination HAV and HBV vaccine Twinrix (Review 4), and well-established therapeutic methods such as the use of rIFN-α for chronic HCV infection (Review 5), Nevirapine in HIV patients (Review 16), and Cyclophosphamide for the treatment of SLE (Review 26). In one case a single vaccine candidate for the prevention of HEV that had passed a phase I clinical trial was being tested in a field trial in Nepal (Review 11), though further tests were considered necessary to determine its long-term efficacy.

CONCLUSIONS

Advocates of research on captive chimpanzees claim it has been of critical importance during our struggles against major human diseases such as AIDS, hepatitis and cancer (VandeBerg and Zola 2005) – even though it continues in only a small number of nations, and indeed is banned or severely restricted in the UK, the Netherlands, Sweden, New Zealand, Austria and Japan. A ban is also being considered by the Swiss government as well as the European Union. Moreover, proponents insist that it must remain a cornerstone of future biomedical research, and that it is an indispensable facet of research that, if prohibited in the U.S., will see human beings suffer and jeopardize or nullify possible future treatments or cures for human disease.

To be made with such conviction, these claims require strong evidence. It is generally accepted that only a small fraction of scientific results, whatever the discipline and however they were achieved, ever translate to human medical benefit or could ever be remotely applicable to clinical practice. Nevertheless, that research is pursued for the sake of knowledge itself, and also partly because we do not know how applicable any area of investigation might be in the future. However, chimpanzee research is a special case as testified to by not only public and scientific opinion, but also by various policies and laws in the U.S. Research using chimpanzees has an ethical cost way above biomedical research involving bacteria and yeast, for example: passage of the CHIMP (Chimpanzee Health Improvement, Maintenance and Protection) Act in the U.S. in 2000, as well as the many countries limiting the use of great apes, acknowledges a different moral status for chimpanzees and raised the bar regarding the ethical considerations that the scientific community (as well as the general public) confers upon chimpanzees.

Both science and the public acknowledge that chimpanzees have varied and advanced cognitive and emotional abilities; they can be taught human languages such as American Sign Language and demonstrate complex nonverbal communication patterns. They are capable of reasoned thought, abstraction, generalization, symbolic representation and have a concept of self, and they exhibit a broad range of emotions and experience mental as well as physical pain. Chimpanzees (as well as other great apes) in captivity show a range of behavioral abnormalities and measurable signs of distress (psychopathology), which can result from early separation of infants from their mothers, sensory-motor deprivation or social isolation over prolonged periods of time (Brüne *et al*., 2006).

Quite aside from these characteristics of chimpanzees that arguably make them worthy of a human level of moral consideration, the question remains: Has chimpanzee research made a positive contribution to human health to scientifically justify their continued use in spite of the ethical objections of many? Or has that contribution been limited or even negative? And, overall, has it expedited medical progress or hindered it? If the net contribution of chimpanzee experiments to human medicine has been negligible, or negative, or if there are current and nascent research avenues that are more promising and relevant, then there is a *human*-based ethical argument for it to end. For if species differences have led to confounding data, blind alleys and false dawns for new human therapies, then humans too have suffered as a

result of misleading data from experiments involving chimpanzees – both directly and indirectly.

Proponents of chimpanzee research, however, claim that it is precisely the differences that can make chimpanzees so useful. If biochemical differences can be identified and used to elucidate *why*, for example, chimpanzees respond differently to HIV, hepatitis viruses, the malaria parasite and so on, they argue that these can be used as a foundation on which to build future research and target new drugs. There are two responses: one is that the analysis of such differences does not have to involve invasive research on captive chimpanzees, but can instead use biological samples taken from chimpanzees at sanctuaries, during routine and necessary operative procedures, physical examinations and/or post mortems. The second is that science has the tools to elucidate the molecular differences between *humans* that vary in their responses to infectious agents and diseases. Further, by minimizing extraneous differences and maintaining such investigations in a human context, they promise to deliver tangible results more precisely, accurately quickly and effectively.

Regardless of the findings of analyses such as this study, proponents of chimpanzee research may point to their involvement in, for example, hepatitis B and C research in a bid to demonstrate that not all chimpanzee experimentation has been of little or no use. The argument of the *necessity* of their involvement in hepatitis research and the development of vaccines is a fierce one with strong claims on both sides of the debate, but is not relevant to this review. No matter the veracity of claims on either side; this review seeks to examine the value of chimpanzee experimentation over *recent* years in order to assess its utility prospectively, and determine if there is a scientifically valid reason to support its continuation.

For both ethical and scientific reasons, there is widespread unease about captive-chimpanzee research within the scientific and wider communities. The fact that several countries highly active in sophisticated biomedical research have banned or severely limited research and testing using great apes testifies to this: most recently, in the UK, an independent inspector stated that a new primate research centre in Cambridge should not be built, on the basis that the proposed research to take place there could not be demonstrated to be in the national interest. In the Netherlands, the last research establishment in Europe housing chimpanzees was closed, after the Dutch minister for science announced that it was not scientifically necessary.

In summary, our review identified no studies of captive chimpanzees that made an essential contribution, or, in a large majority of cases, a significant contribution of any kind towards papers describing well-developed prophylactic, diagnostic or therapeutic methods for combating human diseases, including major diseases such as AIDS, cancer and hepatitis. At best, it has on occasion made a minor contribution to a small number of research projects, though an assessment of the crucial nature of this input and possible alternatives to the use of chimpanzees in each instance was not in the scope of our analysis. Additionally, it seems that data from chimpanzee experiments correlate with the human situation in only a small minority of cases. It therefore follows that reliable extrapolation of such data to humans is impossible, even potentially hazardous; statistically, it cannot be considered *predictive* of the human

condition or response. Retrospective correlations are useless, once the human data are known, and "confirmatory" studies in chimpanzees must be deemed similarly futile.

Far from augmenting biomedical research, chimpanzee experimentation appears to have been largely incidental, peripheral, confounding, irrelevant, unreliable and has consumed considerable research funding that would have been better targeted elsewhere. We call upon regulatory and funding bodies to take these data into account when considering the future of chimpanzees in research and testing, and likewise the U.S. government when considering the permanent retirement of chimpanzees currently held in U.S. laboratories and the status of the chimpanzee breeding moratorium.

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