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Chimpanzee experiments: Questionable contributions to biomedical progress

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Abstract
Biomedical research on captive chimpanzees incurs substantial animal welfare, ethical and financial costs, which advocates claim yield substantial advancements in biomedical knowledge. However, of 95 experiments randomly selected from a population of 749 published worldwide between 1995 and 2004, 49.5% (47/95) were not cited by any subsequent papers, demonstrating minimal contribution toward the advancement of biomedical knowledge generally. The remaining 48 cited chimpanzee experiments were distributed fairly evenly across the decade. Only 14.7% (14/95) were cited by 27 papers that abstracts indicated described well developed methods for combating human diseases, of which 63.0% (17/27) were wide-ranging reviews of 26-300 (median 104) references. Detailed examination revealed that *in vitro* studies, human clinical and epidemiological studies, molecular assays and methods, and genomic studies, contributed most to the development of these medical methods. No chimpanzee study made an essential contribution, or, in most cases, a significant contribution of any kind. Given their profound animal welfare and bioethical costs, the approval of experiments of such questionable merit indicates a widespread failure of the ethics committee system. The demonstrable lack of benefit of most chimpanzee experimentation indicates that a ban is warranted in those remaining countries—notably the US—that continue to engage in it.

Keywords: animal experiment, animal research, chimpanzee, bonobo, *Pan troglodytes*

Introduction

Chimpanzees are the species most closely related to humans, and consequently, are more likely than any other species to be predictive of human outcomes when used in toxicity testing and biomedical research. In a prominent plea in *Nature* for increased funding for such research, Vandeberg and colleagues (2005) stated that it has been of critical importance during our struggles against major human diseases.

However, research on captive chimpanzees is highly controversial, with opponents citing animal welfare, ecological, ethical, scientific and financial objections (Sauer, 2000; Thew, 2002). Some believe it is precisely the genetic similarities of chimpanzees to humans which are claimed to make them so useful as experimental models that also confer upon them a similar ability to suffer (e.g. De Waal, 1982 & 1996; Goodall, 1986), and that it is unethical to confine and experiment on them (Sauer, 2000; Goodall & Bekoff, 2002; Thew, 2002).

To gain a clear overview of the biomedical disciplines investigated via research on captive chimpanzees or chimpanzee tissues, I surveyed three major biomedical bibliographic databases and examined published studies conducted worldwide from 1995-2004. I focused on research on captive chimpanzees, particularly when invasive, because such research has raised the most concerns.

To assess the utility of such research in advancing biomedical knowledge generally, I randomly selected a subset of chimpanzee experiments from the worldwide population, and determined the frequency with which they were cited by papers subsequently published and included within these bibliographic databases. To assess the utility of chimpanzee research in combating human diseases in particular, I determined the frequency with these randomly-selected chimpanzee studies had been cited by papers describing prophylactic, diagnostic or therapeutic methods efficacious in combating human diseases.

Methods

I searched three biomedical bibliographic databases for published papers describing research conducted on living chimpanzees or chimpanzee tissues from 1995 to 2004 inclusive:

1. CAB Abstracts: the most comprehensive bibliographic database covering the applied life sciences, containing over 4.5 million records (Anon., n.d. a & b);

2. Embase, the Excerpta Medica database: a biomedical and pharmacological database containing in excess of 10 million records (Anon., n.d. c); and,
3. Medline: the premier medical and allied health profession database, containing over 12 million records (Anon., 2005).

I sought to determine the frequency with which chimpanzee research was cited by papers describing human medical techniques. Hence, my survey was limited to major bibliographic databases likely to contain such papers. Primate-specific databases such as Primate Lit were excluded.

I sought to assess the value of research on captive chimpanzees, particularly when invasive. Consequently, I included studies of captive chimpanzees or their tissues, and excluded veterinary medical case reports of naturally ill chimpanzees, most genome studies, studies of skeletal anatomy—which frequently used museum specimens, and studies of cell lines (although I did include cell samples, such as peripheral blood mononuclear cells, obtained from captive chimpanzees).

749 chimpanzee studies met these inclusion criteria. Resource constraints prevented detailed examination of all studies; hence an appropriate sample size was required from which to estimate the proportion subsequently cited by other published papers. The relatively small population of 749 studies necessitated the use of the normal approximation to the hypergeometric distribution. The minimum sample size required to achieve 95% confidence intervals with an accuracy of at least plus or minus 10%, was 86 (Morris, n.d.; Guenther, 1973; Green, 1982). The 'Research Randomizer' random number generator (www.randomizer.org) was used to generate a sample of 100 chimpanzee studies, of which five were excluded due to incomplete data.

The remaining 95 randomly-selected studies were examined to assess their citation frequencies, and where abstracts of citing papers described prophylactic, diagnostic or therapeutic methods with clear potential for combating human diseases, the complete medical papers were reviewed to determine the contribution of the cited chimpanzee study in comparison to other cited sources of knowledge.

Results

Disciplines investigated in chimpanzee studies

As of 28th Aug. 2005, 2400 abstracts were located using the specified search terms. 749 of these were found to describe studies of captive chimpanzees or chimpanzee tissues that met the inclusion criteria, of which 48.5% (363/749) were biological experiments, and 41.5% (311/749) were virological experiments (Fig. 1).

Biological investigations were conducted in nine disciplines, of which the most frequent were cognition/neuroanatomy/neurology (36.6%, 133/363) and behavior/communication (20.7%, 75/363) (Fig. 2). Virological investigations were conducted in 30 disciplines, of which the most frequent were hepatitis C virus and human immunodeficiency virus (HIV), which both comprised 31.2% (97/311) of all virology experiments (Fig. 3).

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 experiments included the testing of surgical techniques or prostheses, anesthesiological and toxicological investigations (Fig. 4). 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) (Fig. 5).

Other diseases and miscellaneous experiments together comprised 3.5% (26/749) of all chimpanzee experiments. The most frequent were investigations of laboratory/husbandry techniques (42.3%, 11/26) and endotoxemia (30.8%, 8/26). Radiation studies were also conducted, and four other diseases were investigated, namely benign prostatic hyperplasia,

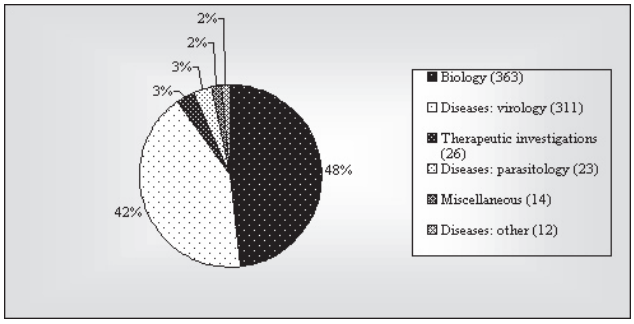

Fig. 1. Chimpanzee experiments 1995-2004 (total 749)

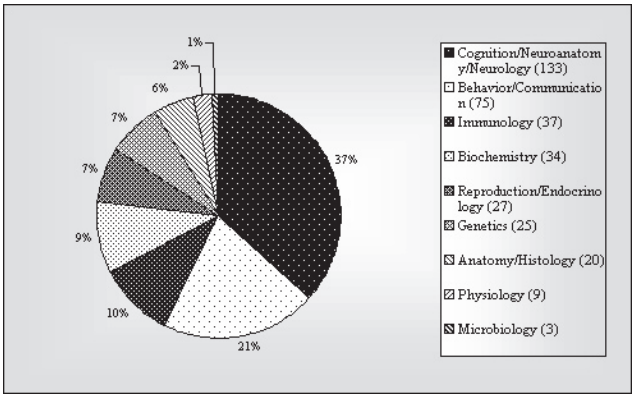

Fig. 2. Biology experiments (363 of 749)

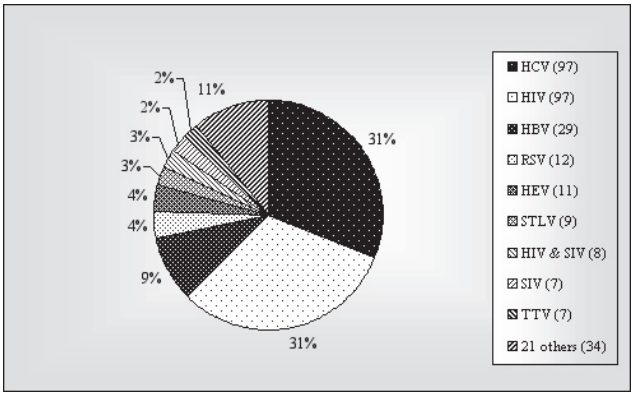

Fig. 3. Virology experiments (311 of 749)

Others: Six: FV. Four: HAV. Two each: GBV – B, HIV & HV, IV, PIV, Noroviuses. One each: Bacteriophages, Dengue v., Ebola v., HCMV, HGV, HMPV, H/S TLV, LCV, Papillomaviruses, RV2, Rhinovirus, VZV, WMHBV, Unspecified.

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 = GB virus B, 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.

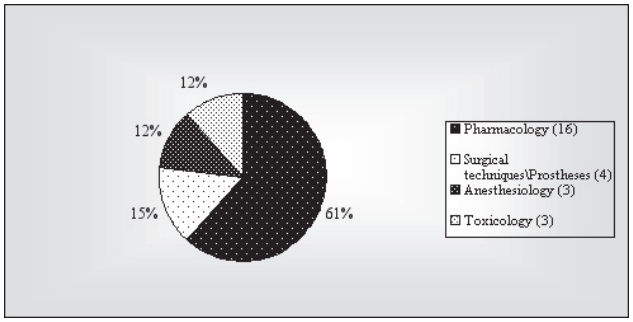

Fig. 4. Therapeutic investigation (26 of 749)

Creutzfeldt-Jakob disease, gastrointestinal bacteriology (*Bacillus thuringiensis*) and tuberculosis (*Mycobacterium tuberculosis*) (Fig. 6).

Citations of chimpanzee studies

Ninety five chimpanzee studies were randomly selected from the population of 749 published between 1995-2004. Of these, 49.5% (47/95; 95% CI = 39.6 – 59.4%) were not cited by any subsequent papers (Fig. 7). The remaining 48 cited chimpanzee experiments were distributed fairly evenly across the decade (Fig. 8). 38.5% (34/95) were cited only by 116 papers that clearly did *not* describe well developed methods for combating human diseases. Only 14.7% (14/95) were cited by 27 papers with abstracts that

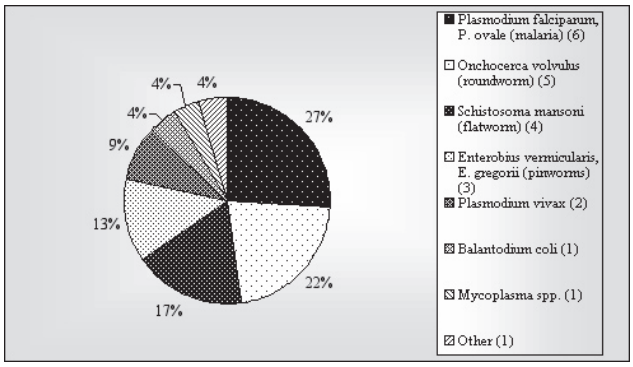

Fig. 5. Parasitology experiments (23 of 749)

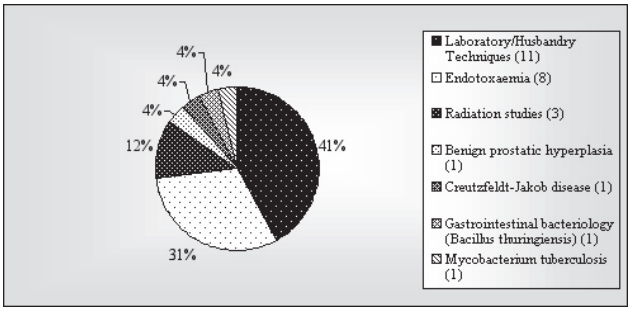

Fig. 6. Other diseases and miscellaneous experiments (26 of 749)

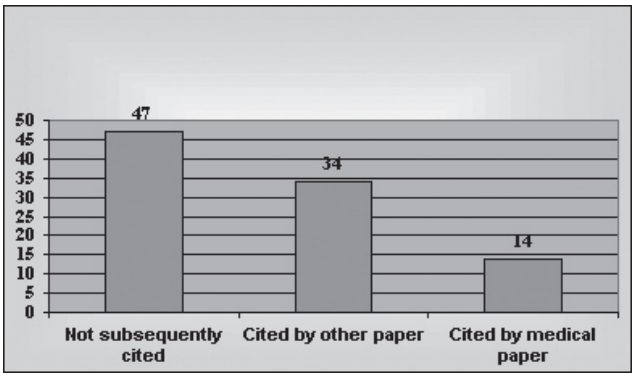

Fig. 7. Citations of 95 randomly-selected published chimpanzee studies

appeared to describe diagnostic (5) or prophylactic and/or therapeutic methods (22) with clear potential for combating human diseases.

Diseases examined included cancer (non-specific), chronic obstructive pulmonary disease, Epstein-Barr virus, hepatitis viruses A through G, hepatocellular carcinoma, HIV, malaria, organ transplant rejection, respiratory syncytial virus, rheumatoid arthritis, rhinovirus colds, systemic lupus erythematosus and transmissible spongiform encephalopathy (TSE) (Knight 2007a).

Discussion

Contributions of chimpanzee studies toward advancements in biomedical knowledge

49.5% of published chimpanzee studies were not cited by any subsequent papers. Given that much

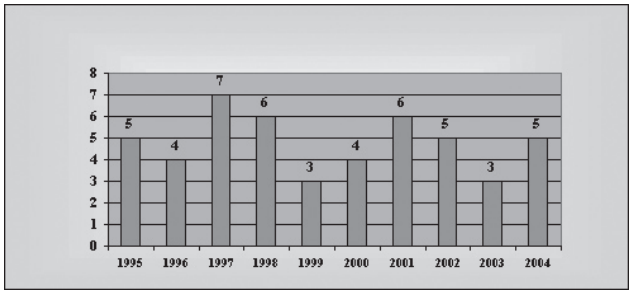

Fig. 8. Chronological distribution of 48 cited chimpanzee studies

research of lesser significance is not published at all, these published experiments can be assumed to be those with the greatest potential for advancing biomedical knowledge. Consequently, these results indicate that the majority of captive chimpanzee research generates data of questionable value, which makes little obvious contribution toward the advancement of biomedical knowledge.

Sources contributing to medical papers

Only 14.7% of published chimpanzee studies were cited by 27 papers with abstracts that appeared to describe methods with clear potential for combating human diseases. Detailed examination of these 27 papers revealed that *in vitro* studies, human clinical and epidemiological studies, molecular assays and methods, and genomic studies, featured most prominently in the development of these medical methods. For example:

- *In vitro* studies, such as of human T-cells, HeLa cells, human respiratory epithelium (embryonic lung fibroblasts), human adenoid explants, lymphoblastoid and rodent cells lines, were used in at least 18 papers.
- Human clinical and epidemiological studies were used in at least 15 and six medical papers, respectively.
- Molecular methods, such as immune electron microscopy, radioimmunoassay, polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA), Western blot, and several assays designed for the diagnosis of TSEs: a combination of competitive antibody capture and capillary electrophoresis, conformation-dependent immunoassay, screening for intensely fluorescent targets, and an immuno-PCR assay, were used in at least eight medical papers.
- Genomic techniques, such as serial analysis of gene expression and microarray analysis, e.g., of viral genomes, suppression subtractive hybridization, representational difference analysis, and differential display, featured more prominently in four medical papers.
- Several viral studies used *E. coli* and baculoviruses in conjunction with *Sf9* insect cells as vectors for viral delivery and expression.
- Chimpanzee studies were, of course, cited by all of the medical papers. Additional animal models were cited more prominently in five medical papers, including genetically modified and unmodified mice, rats, hamsters, guinea pigs, sheep, goats, cows, mink, woodchucks and other primate species (baboons, orang-utans, cynomolgous monkeys and rhesus macaques). Several of these species were only cited in one paper by Brown (2005) that described diagnostic methods for combating TSEs, either as sources or recipients of TSE-infected tissues.

  A detailed examination of the level of contribution of the various animal models other than chimpanzees is well beyond the scope of this study. However, as Brown (2005) stated,*"... it is always problematic to what extent such models reflect the human situation."*

Contributions of chimpanzee studies toward advances in human healthcare

The randomly selected chimpanzee studies proved to be of peripheral relevance to most of these 27 citing medical papers for a variety of reasons. 63.0% (17/27) were found to be wide-ranging reviews of 26-300 (median 104) references, to which the cited chimpanzee study made only a small contribution. In 12 cases the cited chimpanzee studies appeared redundant, as humans or human sera were studied concurrently, or because they only served to confirm previous human observations. In seven cases the methods explored in the chimpanzee study were not developed further, sometimes because later human clinical trials failed to demonstrate safety or efficacy, contrary to positive chimpanzee results. In five cases the chimpanzee study examined a disease or method peripheral to the medical method described. In most of the remaining cases the chimpanzee study yielded results inconsistent with human or other primate data, or merely illustrated historical findings, or was cited only to discuss human outcomes that were described concurrently, within the cited chimpanzee study.

Factors limiting the medical utility of chimpanzee studies

Several authors of human medical papers or cited chimpanzee studies identified potential problems with the extrapolation of chimpanzee results to human predictions. Despite great similarities between the structural genes of chimpanzees and humans, important differences between our regulatory genes result in differences in protein expression of around 20% (Glazko *et al.,* 2005), yielding marked phenotypic differences, that appear to result in altered

susceptibility to, etiology and progression of various diseases; altered absorption, tissue distribution, metabolism and excretion of chemotherapeutic agents; and altered toxicity and efficacy of pharmaceuticals (Bailey, 2005). In conjunction with distortions of normal physiology resulting from stressful laboratory environments and procedures, these are the most likely causes of the observed lack of utility of chimpanzee research during the development of medical methods efficacious in combating human diseases.

Conclusions

Of 95 randomly-selected published chimpanzee studies, half were not cited by any subsequent papers, demonstrating minimal contribution toward the advancement of biomedical knowledge generally. Only 14.7% (14/95) were cited by a total of 27 papers with abstracts that appeared to describe medical methods with clear potential for combating human diseases. However, detailed examination of each medical paper revealed that almost two-thirds were wide-ranging reviews to which the cited chimpanzee study made only a small contribution. In fact, no chimpanzee study made an essential contribution, or, in a disturbing majority of cases, a significant contribution of any kind, toward the development of these medical methods.

The advanced sensory, cognitive, communicative and social abilities of chimpanzees (De Waal, 1982 & 1996; Goodall, 1986 & 1995; Whiten & Byrne, 1988; Byrne, 1998; Hare *et al.,* 2000; Tomasello *et al.,* 2003) confer upon them a profound ability to suffer when born into unnatural captive environments or captured from the wild—as many older research chimpanzees once were—and when subsequently subjected to confinement, social disruption, and involuntary participation in potentially harmful biomedical research. The financial costs are also particularly high.

Research ethics committees are generally expected by society and required by legislation to allow only those experiments in which the benefits are likely to exceed the costs. By approving these experiments on the basis of unfounded assumptions about their likely benefits, the ethics committees responsible failed in their duty to society, and to the animals they were charged with protecting. The approval of such large numbers of these experiments indicates a widespread failure of the ethics committee system.

The demonstrable lack of benefit of most chimpanzee experimentation and its profound animal welfare and financial costs justify a ban in those remaining countries—notably the US—that continue to conduct it.

Despite the low human medical utility of chimpanzee experiments indicated by these results, it remains true that chimpanzees are the species most closely related to human beings. Hence, it is very likely that other species are even less efficacious when used as experimental models of humans in biomedical research and toxicity testing. Indeed, at least 25 published systematic reviews have confirmed the poor utility of other laboratory species in contributing toward advancements in human healthcare or toxicological assessments (Knight, 2007b). Accordingly, the redirection of biomedical resources toward the further development and implementation of non-animal research methodologies appears warranted.

Acknowledgements

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