Petition for Rulemaking
U.S. Department of Health & Human Services

To Set Criteria for Determining when Chimpanzees are No Longer Needed for Research and Must be Retired and Sent to Sanctuary as Required by the Chimpanzee Health Improvement, Maintenance, and Protection Act, 42 U.S.C. §283m. (CHIMP Act)

Flo, 55 years old, is believed to be the oldest chimpanzee now living in a U.S. laboratory.

July 18, 2012

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Purpose and Rationale

This Petition requests the Secretary of Health and Human Services to exercise its authority under the CHIMP Act (42 U.S.C. §283m [formerly 42 U.S.C. §287a - 3a]) to amend the implementing regulations for that statute, 42 C.F.R. Part 9, by including new criteria for "determining" when chimpanzees in laboratories are "not needed" for research and are therefore to be retired to sanctuary.

The Co-Petitioners include the **New England Anti-Vivisection Society—**a national organization founded in 1895 and dedicated exclusively to protecting animals in laboratories, and that spearheaded national efforts on behalf of chimpanzees in 2004; the **North American Primate Sanctuary Alliance—**an alliance of chimpanzee sanctuaries which meet the standards of care and accreditation set forth by the Global Federation of Sanctuaries, and includes Save the Chimps, Fauna Foundation, Center for Great Apes, Chimp Haven, Chimps Inc., Chimpanzee Sanctuary Northwest, and the Primate Rescue Center; **Save the Chimps—**the largest chimpanzee sanctuary in the world founded by the late Dr. Carole Noon and currently home to roughly 300 chimpanzees, the majority of whom are from the former Coulston Foundation and U.S. Air Force; **Fauna Foundation—**the first and only Canadian sanctuary for chimpanzees, including the first HIV-infected chimpanzees to be retired from U.S. research from the Laboratory for Experimental Medicine and Surgery in Primates, New York University, and chimpanzees from behavioral research use; **Animal Protection of New Mexico—**an organization dedicated to animal protection and currently focused on advocacy on behalf of the chimpanzees at the Alamogordo Primate Facility, New Mexico; the **Kerulos Center—**an organization committed to using science and ethics to inform animal care and conservation and cultural change; and **Senator Bob Smith—**lead sponsor of the Senate version of the 2000 CHIMP Act.

Relatively few chimpanzees have been retired since the CHIMP Act was enacted in 2000 even though: 80-90% of chimpanzees now in laboratories are not in active research protocols; use of chimpanzees for biomedical research has declined dramatically; chimpanzees have been determined to be "unnecessary" in nearly all areas of current biomedical use; a significant number of chimpanzees in laboratories are elderly and/or unfit for research; retiring chimpanzees to sanctuary would be economically beneficial to the American public—in tax dollar savings and reallocation of remaining federal funds to more promising areas of biomedical research; and retirement to sanctuary would also be beneficial for the chimpanzees' psychological and physical well-being.

Because the Secretary has not defined criteria for determining when chimpanzees are "not needed" for research and therefore must be retired pursuant to the statute, labs have been allowed to decide for themselves which chimpanzees, if any, to retire. This approach creates a conflict of

interest as the laboratories housing and maintaining chimpanzees receive federal funding to do so and, therefore, have a financial motivation to hold chimpanzees and continue to receive such housing and maintenance grants. In addition, the numbers of chimpanzees originally anticipated for retirement to federal sanctuary by NIH have not been retired, and NIH has indicated that it does not anticipate retiring any more chimpanzees. Thus, the current system is not working, as outlined in the Petition's Introduction.

As set forth in this Rulemaking Petition, the Secretary clearly has the authority under the CHIMP Act to issue criteria for determining whether a chimpanzee is "not needed" for federally funded research and trigger the requirement that any so-determined chimpanzee be retired to sanctuary. This Petition requests that the Secretary adopt clear regulations to determine when chimpanzees are "not needed" and to oversee the appropriate application of such criteria and the timely process of retirement to sanctuary.

Proposed Criteria

This Petition proposes scientifically and factually based standards by which to define when chimpanzees in laboratories are "not needed" in research within the meaning and intent of the CHIMP Act. These criteria include: (1) chimpanzees held or proposed for research in which chimpanzees have been determined to be unnecessary; (2) chimpanzees who have not been assigned to a research protocol in ten years; and (3) chimpanzees who are unfit research models (including elderly chimpanzees; chimpanzees who have previous use histories, multi-use histories, or incomplete medical record histories to accurately account for any and all previous use; and chimpanzees with chronic, severe, or multiple physical or psychological illness(es)). Because of the importance of social groups staying together, for both the chimpanzees' psychological and physical well-being, criteria should further specify that if a chimpanzee is determined to be "not needed" and therefore obliged to be sent to sanctuary, a family or significant group member should accompany the chimpanzee to live at the sanctuary even if the family or group member has not likewise been determined to be "not needed" him or herself.

(1) Chimpanzees held or proposed for research in which chimpanzees have been determined to be unnecessary in the research:

The Institute of Medicine's (IOM) 2011 recommendations adopted by the National Institutes of Health (NIH) set strict parameters for when a chimpanzee may be considered "necessary" for research. The IOM Committee foresaw a decreasing scientific need for chimpanzee studies. As discussed in this Petition, the IOM found that "most current use of chimpanzees for biomedical research is unnecessary."

In addition, further evidence shows that chimpanzees are not needed in HIV/AIDS, cancer, hepatitis C, comparative genomics, malaria, drug development/pharmacokinetics, biodefense, and monoclonal antibodies studies.

(2) Chimpanzees who have not been assigned to a research protocol in ten years

The majority of federally owned and/or supported chimpanzees have been held in laboratories for decades. Yet, the vast majority of them are inactive—i.e. not assigned to research or testing protocols. It is fiscally and administratively untenable to continue to house and maintain up to ten times the number of chimpanzees currently being used for research or testing. A significant impetus for the CHIMP Act was saving taxpayer dollars. Growing costs and resulting exorbitant NIH expenditures of limited research dollars resulted from what was deemed a "surplus" of chimpanzees for existing research needs. As demonstrated in this Petition in Section D.2, sanctuaries provide high quality care at a lower cost than laboratories provide. Further, a public opinion survey showed that 71% of the American public believed that a chimpanzee held in a laboratory for ten years or more should be retired. This result came prior to the ever increasing public concern for chimpanzees in research that has come from the last six years of growing socio-political and scientific debate about their use. The survey and public concern is further discussed in Section D.2.

(3) Chimpanzees who are unfit research models

As discussed in detail in Section D.3 of the Petition, chimpanzees in laboratories are unfit research models for myriad reasons, including:

Inadequate medical records: Severe inadequacies in chimpanzee records limit researchers' abilities to have a complete understanding of laboratory chimpanzees' histories and limit their ability to adequately interpret data from any research in which the chimpanzees are used.

History of use in multiple research protocols: Many chimpanzees have been infected with multiple viruses and used in various areas of disease research, sometimes in multiple laboratories, further confounding any research data and casting further doubt on the scientific validity of the research in which they are used.

Age: According to available information, over one-third of the approximately 937 chimpanzees held in U.S. laboratories are elderly (i.e., a male chimpanzee 25 years or older or a female 30 years or older). The aging chimpanzees that some would argue need to be available as models of human aging have spent all of their lives in an unnatural environment as research subjects and have been exposed to many different biomedical protocols and pathogens and subjected to a multitude of stressful procedures, routine and otherwise. It has been unequivocally demonstrated that cellular insults caused by stress, illness, and exposure to certain chemicals adversely affect the aging process. Therefore, it is likely that any results gained from chimpanzee aging studies would be both difficult to interpret and impossible to extrapolate to the average human being. Further, as discussed in Section D.3.2, there are increased physical risks for elderly chimpanzees who are used in experiments.

Physiological Diseases: Autopsy reports, medical records, and the health statuses of chimpanzees who died in laboratories or died after having been rescued from research over the

last ten years indicate the high probability that many chimpanzees currently in laboratories could be suffering from incurable physiological diseases or multi-organ diseases (see Section D.3.3). A recent review of autopsies performed on chimpanzees who died in laboratories, or after transfer from laboratory to sanctuary, revealed that the majority of chimpanzees from laboratories had been suffering from significant chronic or incurable illnesses and often multi-system diseases that should have made them ineligible for future research on scientific, as well as ethical, grounds. Chimpanzees remained in laboratories even though their autopsy records indicated that they had been suffering from multi-organ diseases, they had "Do Not Resuscitate" orders in their medical records, or they had been diagnosed with terminal illnesses prior to death, in some cases months and years prior to death.

Psychological Stress: Further, as documented in this Petition (Section D.3.4), chimpanzees suffer extreme psychological stress in laboratories, and the physical manifestations of stress adversely affect their suitability as subjects and research results. Stressors include: separation from biological and cultural context (i.e., separation from their natural physical, cognitive, emotional, social, and cultural environment); inadequate care-giving; social and other deprivations; invasive psychophysiological protocols; anticipatory stress of pending use; witnessing others being "knocked down" by darting or being knocked down oneself; separation and isolation prior, during, or after procedures; restraint via "squeeze cages;" confusion and fear associated with sedation recovery; pain and nausea from procedures; and housing conditions that impose unnatural levels of confinement and alteration of opportunities to engage in essential, varied, and self-determined behaviors. Resulting psychological symptoms include self-mutilation, stereotypic behavior, learned helplessness, inappropriate aggression, fear or withdrawal, diarrhea, anorexia, high infant mortality, post-traumatic stress disorder, anxiety, and other abnormal behaviors.

Laboratory stressors unavoidably lead to associated physiological harm via established trans-species biological mechanisms (outlined in Sec. D.3.4.d). While the minutiae of the genes and biochemical pathways responsible and their manifestations may be different in different species to some degree, there are common and central mechanisms and adverse effects that have been observed in all species examined to date. Sequelae (abnormal conditions resulting from a disease, injury, or other trauma) include cardiovascular diseases, attenuated immune function and autoimmune disorders, premature aging and mortality, developmental abnormalities, elevated tumor initiation and progression, musculoskeletal atrophy, and more. The adverse consequences of stress are multigenerational.

Chimpanzees share the same biomarkers of stress and stress-related biological mechanisms as other species, and are affected by stress-related oxidative damage in similar ways to other species. The weight of evidence indicates that it would be extremely unlikely if chimpanzees were <u>not</u> adversely physiologically affected by stress in similar ways to other species, and that such effects would render them inappropriate biomedical research subjects.

Action Requested

Congress enacted the CHIMP Act to ensure that chimpanzees who are "not needed" in federally funded and supported research would be retired to more cost-effective and ethologically appropriate sanctuaries. The North American Primate Sanctuary Alliance is willing and ready to accept all federally owned and supported chimpanzees with appropriate funding. Sanctuaries not only provide for the chimpanzees' physiological well-being, but also psychological well-being. As demonstrated in this Petition, and particularly because the IOM has determined that most current uses of chimpanzees for biomedical research are unnecessary, it is essential that the Secretary exercise its authority under the CHIMP Act to "determine" when chimpanzees are "not needed" for research and retire chimpanzees who meet such criteria.

Glossary and Acronyms

IOM:
Institute of Medicine of the National Academies of Science; At the request of the National Institutes of Health (NIH), and in response to congressional inquiry, the IOM in collaboration with the National Research Council (NRC) convened the Committee on the Use of Chimpanzees in Biomedical and Behavioral Research to consider the necessity of the use of chimpanzees in NIH-funded research. The Committee completed its report, Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity, in December 2011.

FOIA:
Freedom of Information Act

Knockdown:
Because of chimpanzees' tremendous strength, they must often be shot with dart guns to be anesthetized in a process that is referred to as a "knockdown." It is not unusual for a chimpanzee to be darted multiple times to administer an effective dose and to suffer injuries from falls after sedation.

Keeling Center:
Michale E. Keeling Center for Comparative Medicine and Research of the University of Texas MD Anderson Cancer Center

NCRR:
National Center for Research Resources, a government agency that provided funding to laboratories. It was dissolved and its programs transferred to other agencies in 2011.

NIRC:
New Iberia Research Center at the University of Louisiana-Lafayette

SNPRC:
Southwest National Primate Research Center

STC:
Save the Chimps Sanctuary

YNPRC:
Yerkes National Primate Research Center at Emory University

Introduction

Since 2000, when the Chimpanzee Health Improvement, Maintenance, and Protection Act (CHIMP Act, Pub. L. No. 106-551) (42 U.S.C. §283m [formerly 42 U.S.C. §287a - 3a]) was signed into law, only 161 chimpanzees have been retired under the Act to Chimp Haven, at this time the only sanctuary that is part of the federally-supported chimpanzee sanctuary system defined by the statute.[1] The majority of the nearly 600 chimpanzees now living in U.S. sanctuaries and one Canadian sanctuary (home to chimpanzees from U.S. research, see Appendices A and B), were rescued from private laboratories. The total number of chimpanzees held in laboratories is approximately 937 (Institute of Medicine 2011a).[2] According to IOM, the government supported 612 chimpanzees as of April 15, 2011 (Institute of Medicine 2011a).[3] This Petition demonstrates that the current system for retiring chimpanzees is not working. According to Jennifer Feuerstein, a former employee of Yerkes National Primate Research Center (YNPRC) and current Sanctuary Director for Save the Chimps, Inc (STC), "the retirement of chimpanzees from research has been haphazard at best, and has resulted in far fewer chimpanzees being retired under the CHIMP Act than anticipated at the time the law was passed" (Declaration of Jennifer Feuerstein).

Chimpanzee use in biomedical research has decreased dramatically and is at an historic low (Bailey, Balcombe, and Capaldo 2007). In fiscal year 2011, of the more than 94,000 active projects sponsored by the National Institutes of Health (NIH), only 53 used the chimpanzee (0.056 percent) (Institute of Medicine 2011a). Even the two areas of historic wide use have rapidly and significantly declined: the number of chimpanzees used in HIV/AIDS studies is down nearly 90%, and in hepatitis C research, chimpanzee use is down 50-60%, while the use of alternatives over the same time period shows an 80-fold increase (Bailey, Balcombe, and Capaldo 2007). Therefore, most of the chimpanzees currently in laboratories are not presently part of an active research protocol, and most will never be used in a research protocol (Abee et al. 2011).

Chimpanzees are languishing in federally-supported laboratories despite evidence that: an estimated 80-90% of federally owned/supported chimpanzees are not in active research protocols;[4] according to the IOM, "most current use of chimpanzees for biomedical research is unnecessary" (Institute of Medicine 2011a); many chimpanzees in laboratories are elderly and unfit for research; retiring these chimpanzees would be economically beneficial to the American

[1] Karen Allen, Director of Organizational Advancement at Chimp Haven, personal communication: "Of 161 chimpanzees retired to Chimp Haven under CHIMP Act, 119 were alive as of January 6, 2012."
[2] This estimated number could be higher. The IOM states in its December 2011 report, "Committee analysis of the use of chimpanzees in the private sector was hindered by the proprietary nature of the information…."
[3] Based on April and May 2011 emails from laboratory directors to the IOM (April 26, 2011 email from Janet Landry to Diana Pankevich "RE: IOM Chimp Study;" April 28, 2011 email from John VandeBerg to Diana Pankevich "RE: IOM Chimp Study;" May 9, 2011 email from Christian Abee to Diana Pankevich "RE: IOM Chimp Study"), the estimated number of government owned and/or supported chimpanzees could be as high as 737.
[4] As per John VandeBerg Panel Presentation at The International Primatological Society XXII Congress August 3-8, 2008 Edinborough, Scotland.

public—in tax dollar savings and reallocation of remaining federal funds to more promising areas of biomedical research; and retirement would also be beneficial for the chimpanzees' psychological and physical well-being. All of this evidence supports the position that the time is long overdue for the Secretary to exercise its authority under the 2000 CHIMP Act to "determine" which animals are "not needed" for research, and thus are eligible for retirement and must be sent to sanctuary. As Dr. Theodora Capaldo, President and Executive Director of the New England Anti-Vivisection Society, explains in her Declaration, "[i]n establishing such criteria and overseeing its enforcement and the resulting retirement of large numbers of chimpanzees, the spirit and mandates of the CHIMP Act can finally be realized.."

However, the U.S. Department of Health and Human Services (HHS) through NIH appears to be: allowing labs to decide for themselves which, if any, chimpanzees to retire; awarding extensive housing and maintenance grants for hundreds of chimpanzees without any assessment of the need or scientific appropriateness to keep them in the laboratory environment; funding projects for the public promotion of chimpanzee research in laboratories; funding questionable studies on aging chimpanzees as a justification for keeping chimpanzees in laboratories for decades; and supporting laboratory facility construction but not sanctuary facility construction (see Appendix C for supporting evidence). Indeed, NIH's 2001 Request for Proposals to construct and operate the National Chimpanzee Sanctuary System (Exhibit 1) called for immediate construction to house a minimum of 200 chimpanzees already identified for retirement, and included language for expansion to 900 chimpanzees possibly using subcontractors or multiple sites. Although Chimp Haven, Inc. was awarded the contract by NIH, the housing has yet to be completed and the facility is currently housing only about 130 chimpanzees.

A. Statutory Basis for the Requested Action

Congress enacted the CHIMP Act in 2000 to provide a "system for the lifetime care of chimpanzees" that were bred for use or used in federally funded research who are "not needed" for such research (42 U.S.C. § 283m(a)). As explained by the Senate Report accompanying the legislation, "[e]ach year, millions of Federal tax dollars pay for the care of federally-sponsored research chimpanzees through funding to the NIH and other federal agencies" (Senate Committee on Health, Education, Labor, and Pensions 2000) (emphasis added). As the Report further explains, the need for the legislation was prompted by the fact that in 1986, NIH launched an initiative to breed chimpanzees that were thought to be useful models for AIDS research, but which turned out not to be "suitable" models for such research, leaving the federal government with "a surplus of several hundred chimpanzees that are no longer useful in medical research" and that were being "warehoused in expensive federally funded research laboratory facilities" (Senate Committee on Health, Education, Labor, and Pensions 2000 at 1-2). Further, their use in HIV/AIDS research was expected to carry with it high mortality rates, which it did not.

To deal with this problem, NIH commissioned a report by the National Research Council, which concluded that:

> The concept of sanctuaries capable of providing for the long-term care and well-being of chimpanzees that are no longer needed for research and breeding should become an integral component of the strategic plan to achieve the best and most cost-effective solutions to the current dilemma.

(Senate Committee on Health, Education, Labor, and Pensions 2000), quoting (Institute for Laboratory Animal Research Committee on Long-Term Care of Chimpanzees 1997) (emphasis added). Acknowledging that it "fully recognized the financial implication" of placing these chimpanzees in long-term care facilities at taxpayer expense, the NRC based its decision on "the close similarities between chimpanzees and humans," and the "practical as well as theoretical reasons to reject euthanasia" as an alternative (Senate Committee on Health, Education, Labor, and Pensions 2000 at 2). In addition, the NRC noted that NIH was spending between $20-$30 per day per chimpanzee (2000 figures) on care in laboratory facilities, when sanctuary care would cost between $8-$15 per day for each such animal (2000 figures)—"a considerable savings to taxpayers" (Senate Committee on Health, Education, Labor, and Pensions 2000 at 3) (emphasis added).

In response to these concerns, the CHIMP Act provides that the Secretary of Health and Human Services "shall provide for the establishment and operation…of a system to provide for the lifetime care of chimpanzees that have been used, or were bred or purchased for use, in research conducted or supported by the National Institutes of Health, the Food and Drug Administration, or other agencies of the Federal Government, and with respect to which it has been determined

by the Secretary that the chimpanzees are not needed for such research" (42 U.S.C. § 283m(a)) (emphasis added).

The Act further provides that "[a]ll surplus chimpanzees owned by the Federal Government shall be accepted into the sanctuary system" and that laboratory chimpanzees not owned by the Federal Government "can be accepted into the system if the owner transfers to the sanctuary system title to the chimpanzee." *Id.* at § 283m(c) (emphasis added). *See also* Pub. L. No. 110-170 (the "Chimp Haven is Home Act"); 153 Cong. Rec. E2670-02 ("The system envisioned by the CHIMP Act is now a reality in Keithville, Louisiana. It is called Chimp Haven.").

Therefore, in order for the Secretary to effectuate Congressional intent that laboratory chimpanzees not needed for federally funded research be identified and sent to the federal sanctuary system, the Secretary must issue criteria for "determining" whether a chimpanzee is "not needed." Presented below are clear scientifically and factually based standards by which the Secretary should make such determinations, instead of the existing policy by which laboratories are allowed to hold onto chimpanzees in perpetuity without any evidence-based evaluation of necessity. Indeed, this existing policy is in direct conflict with the statutory mandate that determinations of necessity be made by the Secretary.

The purpose of this Petition for rulemaking is to implement these statutory provisions—i.e. by having the Secretary issue criteria for "determining" whether a chimpanzee is "not needed" for such federally funded research and hence must be retired. As demonstrated below, petitioners suggest scientifically and factually based standards by which such determinations can be made as a means to end the existing policy by which laboratories are allowed to make this determination for themselves without directed criteria of any kind.

B. Action Requested

The purpose of this Petition is to request that the Secretary exercise its authority under the CHIMP Act to adopt new regulations to specify that any chimpanzee who the Secretary determines meets one or more of these criteria shall be formally identified as "not needed" for research within the meaning of the CHIMP Act. Because The law also acknowledges that non-federally owned chimpanzees may be accepted into the federal sanctuary system if they are not needed for research, In the event a non-federally owned chimpanzee is deemed not needed for research, the Secretary should only provide further maintenance funding for that chimpanzee to be held in a facility that meets the standards of care in 42 C.F.R. Part 9. .

Any federally-owned chimpanzees so identified shall be sent to sanctuary not sooner than 90 days and not later than 120 days (adjusted to allow the receiving sanctuary appropriate time as needed to accommodate the retiring individuals and/or groups and to receive all medical records and other documentation) of the Secretary's determination. As noted above, the CHIMP Act compels the retirement of federally-owned chimpanzees not needed for research. Because the federal government financially supports most of the chimpanzees in laboratories (IOM 2011), including private and university-owned chimpanzees, the Secretary must evaluate the necessity of all chimpanzees in laboratories, regardless of ownership.

To insure compliance with the new criteria and retirement obligation the Secretary must inspect each federally funded laboratory with chimpanzees, both initially upon promulgation of the new requirements and periodically thereafter to insure that these requirements are met. Further, before awarding funding for maintenance of a chimpanzee colony, the Secretary must conduct an evaluation of necessity for each chimpanzee to be supported, based on the criteria established.

The criteria should not be left to the discretion of the laboratory receiving federal funding, which has a financial motivation to receive federally funded housing and maintenance grants. In fact, a review of available federal housing and maintenance grants involving chimpanzees revealed that institutional grant recipients were allocated anywhere from 39% to 71%, or on average 51%, of their total awards for "indirect expenses" alone (meaning the recipient can allocate this money to expenses extraneous to the research or the care of chimpanzees, i.e., to university salaries, administration, and/or other operating costs)—a likely motivation to not retire chimpanzees in spite of their unsuitability for research (Capaldo, Owens, and Lary 2010).

According to Gloria Grow, founder and director of Fauna Foundation Sanctuary, "When [the Laboratory for Experimental Medicine and Surgery In Primates] closed, the veterinarian had essentially established triaged criteria as to who would be transferred into further research and who would be retired…an individual chimpanzee is not an infinite "research resource" but rather a living being with physical and psychological limitations regarding how much hardship he/she can endure prior to being physically and/or psychologically in collapse" (Declaration of Gloria Grow).

We respectfully request that the criteria for a chimpanzee to be considered "not needed" for research should include but not be limited to:

Criterion 1:

(a) There are non-animal alternatives to the research being conducted on him/her; or

(b) Chimpanzees have been shown to be an unsuitable model or unnecessary for the research the chimpanzee is being used or held for.

Criterion 2: The chimpanzee has not been assigned to a research protocol[5] in ten years.

Criterion 3: The chimpanzee is an unfit research model because he/she

(a) lacks an accurate or complete medical or veterinary history;

(b) is an elderly chimpanzee (i.e. if a male chimpanzee is 25 years or older or a female 30 years or older);

(c) exhibits indications of chronic, severe, or multiple physical illness(es), including but not limited to the following: significant cardiac, renal, or liver disease unrelated to a current research protocol; recurrent infections or other such indicators of a poorly responsive immune system; epilepsy; any chronic gastrointestinal diseases; any other chronic disease; any terminal disease; or any congenital or anatomic abnormality;

(d) has multi-organ disease whether terminal or not;

(e) has a previous use history or multi-use history, including in biomedical research or testing or in cognitive behavioral studies involving invasive procedures or knockdowns. Previous use history may include cross-fostering studies or other areas where identity with and prior close relationship with humans made the chimpanzee a poor candidate for laboratory life and use; or

(f) is suffering from chronic psychological suffering or other indications of stress, a situational disorder that is not being resolved and has the likelihood of leading to post-traumatic stress disorder (PTSD), and/or other psychological maladies including on-going anxiety, depressions, withdrawal, etc., even in the absence of a full PTSD syndrome.

[5] As defined by NIH's Glossary & Acronym List (http://grants.nih.gov/grants/glossary.htm), "research" means "[a] systematic, intensive study intended to increase knowledge or understanding of the subject studied, a systematic study specifically directed toward applying new knowledge to meet a recognized need, or a systematic application of knowledge to the production of useful materials, devices, and systems or methods, including design, development, and improvement of prototypes and new processes to meet specific requirements," and protocol means "[a] formal description and design for a specific research project."

The regulations should also provide as follows:

(A) Immediately following the effective date of these regulations, the Secretary shall determine whether any chimpanzees residing in federally-funded facilities meet any of the criteria set forth above. If a federally-owned chimpanzee meets any of the criteria, not sooner than 90 days and not later than 120 days (adjusted to allow the receiving sanctuary appropriate time as needed to accommodate the retiring individuals and/or groups and to receive all medical records and other documentation) the chimpanzee shall be sent to a sanctuary that meets or exceeds the "Standards of Care for Chimpanzees Held in the Federally Supported Chimpanzee Sanctuary System," 42 CFR Part 9. If a chimpanzee not owned by the federal government is determined to meet any of the criteria, the Secretary shall notify the facility that federal funding for the chimpanzee will only be awarded if the chimpanzee is maintained in compliance with the standards of care established in 42 C.F.R. Part 9.

(B) To insure that the above criteria are being implemented, within 90 days of the effective date of this regulation, and on each quarterly basis thereafter, NIH will inspect all federally funded laboratories housing chimpanzees, and shall have access to all records bearing on these issues, to determine (a) whether any chimpanzees meet any of the criteria enumerated above; and, if so (b) whether the facility has made sufficient plans to insure that each such chimpanzee is being retired to a sanctuary that meets or exceeds the standards of care for chimpanzees held in the federally supported sanctuary system, as defined in part 9 of title 42, Code of Federal Regulations.

(C) Each federally funded facility housing chimpanzees shall submit annual reports to NIH specifying (1) the number of chimpanzees in its possession; (2) whether upon application of the criteria, the laboratory determines that any such chimpanzees meet any of the retirement criteria specified herein; (3) the identity of each such chimpanzee, an explanation of which criterion the laboratory determines applies to that chimpanzee, the date such determination was made, and the plans that have been made to insure that each such chimpanzee is retired; and (4) the number of chimpanzees that have been retired by such facility within the year, and the identity and current location of each such chimpanzee.

(D) All records generated as part of these regulatory requirements shall be maintained by NIH and shall be made available to the public under the Freedom of Information Act (FOIA), except for personal information that is exempt for disclosure under Exemption 6 or 7(C) of that Act, 5 U.S.C. §§ 552(b)(6), (7)(C).

(E) Non-compliance with any of these requirements will result in immediate termination of all federal funding for housing, maintenance, and/or research for chimpanzees at such facility.

The regulation should further specify that if a chimpanzee is determined to be "not needed" in research and sent to sanctuary, a family or significant group member should accompany him/her

to live at the sanctuary, even if the family or group member has not been determined to be "not needed" him/herself.[6] As Jennifer Feuerstein explains in her Declaration, "[f]rom my first hand and professional experience and given the Animal Welfare Act's requirement to provide for the psychological well being of primates, retirement criteria must include respect for family and social bonds and allow for cage mates/friends or family to be retired with given individuals deemed "no longer needed" for research." NIH has also acknowledged the importance of social groups staying together, for both the chimpanzees' psychological and physical well-being.[7]

Hunter and Lyons, Yerkes Field Station
Photo courtesy of N. Megna

[6] Chimpanzees are known to form and maintain long-lasting relationships with other chimpanzees (Mitani 2009). NIH has stated that "Chimpanzees that have completed their research service are eligible for transfer to the federal sanctuary," and "As always, careful consideration is given to the best interests of the animals" (Correspondence between NIH/NCRR personnel July 14, 2010) (Exhibit 2). Forcibly separating chimpanzee partners, family, or friends harms their psychological well-being and would not be in "the best interests of the animals." This is graphically demonstrated by the case of the chimpanzees named Hunter and Lyons: In 2006 twin chimpanzee brothers Hunter and Lyons, who were constant companions for 21 years at YNPRC, were forcibly separated. Lyons was retired and transferred to Chimp Haven likely because he was in acute renal failure. Hunter was sent to SNPRC. Chimp Haven offered a permanent home to Hunter, but the chimpanzees were never reunited. Lyons only spent a short time at Chimp Haven before his death and Hunter did not live long at SNPRC before he too, died. (See Declaration of Jennifer Feuerstein)

[7] A May 14, 2010 letter to U.S. Rep. Edolphus Towns from Sally Rockey, Ph.D., Acting Deputy Director at NIH, stated, "Chimpanzees establish very close social groups with a very strict hierarchy recognized among group members. Disruption of established groups, through removal or addition of animals, frequently results in significant fighting and subsequent injuries. Therefore, animals are best kept within their social groups; this is both for their individual benefit and the benefit of the other members in the social group" (Exhibit 3); An August 16, 2010 email from Pat White (NIH/OD) stated, "…it is difficult or impossible to move an animal without disrupting a social group and animals entering a research study need to be stably associated with their social groups to avoid stress related research complications" (Exhibit 4); and a July 15, 2010 email from Cindy McConnell (NIH/NCRR) stated, "To not return them to the APF would create permanent disruption of their social groups and increase stress to the animals, which could affect their health and would delay their entry into research projects." (Exhibit 5)

C. Background

Chimpanzee Numbers, Demographics, and Histories

The total number of chimpanzees held in all U.S. laboratories remains an estimated 937, and, as of April 2011, the U.S. government owned or financially supported 612 of these animals (Institute of Medicine 2011a). According to available information, over one-third—an estimated 350 chimpanzees held in U.S. laboratories—are elderly,[8] i.e. males 25 years or older and females 30 years or older (Videan, Fritz, and Murphy 2008). Ongoing biomedical and behavioral research on chimpanzees is largely conducted at four facilities: the Southwest National Primate Research Center (SNPRC), the New Iberia Research Center at the University of Louisiana-Lafayette (NIRC), the Michale E. Keeling Center for Comparative Medicine and Research of the University of Texas MD Anderson Cancer Center (Keeling Center), and the Yerkes National Primate Research Center at Emory University (YNPRC).

Chimpanzees in laboratories do not comprise a homogenous population. They derive from diverse developmental contexts (e.g., captive-bred, cross-fostered, conspecific crèches in laboratories, wild-caught), and experiential contexts (e.g., various, and often multiple laboratory histories; survivors of maternal deprivation and social isolation studies; used in "hard research" or decades of breeding; former "pet," zoo, entertainment, or other histories), and they have diverse personalities and a range of cognitive, social, and emotional capacities. Many have histories of intensive use in biomedical research and testing and/or observational behavioral studies that took place at one or more laboratories. Many older chimpanzees were singly housed for years in 5'x5'x7' cages at the Laboratory for Experimental Medicine and Surgery in Primates (LEMSIP), the Coulston Foundation (Coulston) (see Appendices D and E), and other facilities.

[8] 2011 - 2012 from NIH FOIA requests, correspondence with facilities, and Chimpanzees in Biomedical and Behavioral Research: Assessing the necessity Institute of Medicine 2011 report.

D. Basis for Proposed Criteria

D.1. Criterion 1: A chimpanzee is determined to not be needed for research if:

(a) There are non-animal alternatives to the research being conducted on him/her; or

(b) Chimpanzees have been shown to be an unsuitable model or unnecessary for the research the chimpanzee is being used or held for.

Basis for Criterion:

Having concrete criteria for determining when chimpanzees are not needed for research, while always a salient part of the CHIMP Act's intent, is especially important in light of the Institute of Medicine's (IOM) 2011 recommendations adopted by NIH, which set strict parameters for when a chimpanzee may be considered "necessary" for research. The IOM Committee concluded that most current uses of chimpanzees for biomedical research are unnecessary (Institute of Medicine 2011a). Indeed, the chair of the committee and IOM staff concluded that, "*[G]iven the information available to the committee through its research and provided by relevant federal agencies, it will be very difficult to defend the necessity of nearly all current biomedical research on chimpanzees*" (Altevogt et al. 2012) (emphasis added). The IOM Committee further concluded that "the present trajectory indicates a decreasing scientific need for chimpanzee studies due to the emergence of non-chimpanzee models and technologies," and that further "development of non-chimpanzee models requires continued support by the NIH" (Institute of Medicine 2011a) (emphasis added). We provide below a précis of this evidence that chimpanzees are not needed in biomedical research, including in HIV/AIDS, cancer, hepatitis C, comparative genomics, malaria, drug development/pharmacokinetics, biodefense, and monoclonal antibodies studies, and also include the summaries of the associated publications. All studies referenced herein are attached as Exhibits.

HIV/AIDS

Bailey, J. (2008). An assessment of the role of chimpanzees in AIDS vaccine research. ATLA, 36(4), 381-428. (Exhibit 6)

As the Legislative History of the CHIMP Act acknowledges, HIV/AIDS is the reason why so many chimpanzees were bred for research and why there has been a "surplus" in American labs for decades. See (Senate Committee on Health, Education, Labor, and Pensions 2000), supra (explaining that the chimpanzee surplus was the result of a 1986 NIH initiative to breed chimpanzees "that, at the time, were thought to be useful models for AIDS research," that "chimpanzees have not proved as suitable a model as expected for AIDS research, and the Federal Government is now faced with a surplus of several hundred chimpanzees that are no longer useful in medical research," and that "[t]hese 'surplus' chimpanzees are being warehoused in expensive federally funded research laboratory facilities.")

This study assessed past and potential future contributions of chimpanzees to AIDS vaccine development by determining to what degree AIDS vaccine trials in chimpanzees were predictive of human response.

The analysis showed:

- The majority of HIV vaccines and vaccine types had been tested in chimpanzees prior to human clinical trials.
- Vaccine responses in chimpanzees and humans are highly different.
- Vaccine responses in chimpanzees are not predictive of responses in humans.

By 2008, 85 different vaccines had been tested in almost 200 clinical trials. However, none of the vaccines provided protection and/or significant therapeutic effects in humans, in spite of prior "successful" trials in chimpanzees.

Claims that chimpanzees are still important for testing HIV/AIDS vaccines have no scientific foundation:

- AIDS-related chimpanzee studies fell by nearly 90% from 1998 to 2005.
- Due to their differing genetics and biochemistry, chimpanzees do not get AIDS from HIV.
- VaxGen's AIDSVAX vaccine—perhaps the most promising vaccine—results published in 2005 and 2006 showed that the vaccines failed to protect almost 8,000 trial participants from HIV infection after being tested on chimpanzees.

During the IOM inquiry, Professor Nancy Haigwood, director of the Oregon National Primate Research Center, acknowledged that science had "started to get out of chimp HIV research in about 1997 due to 'gray' and 'differential' results," and that there had been a "general consensus that it was a good idea to move on" (Institute of Medicine 2011b).

Hepatitis C

Bailey, J. (2010). An assessment of the use of chimpanzees in hepatitis C research past, present and future: 1. Validity of the chimpanzee model. ATLA, 38(5), 387-418. (Exhibit 7)

Bailey, J. (2010). An assessment of the use of chimpanzees in hepatitis C research past, present and future: 2. Alternative replacement methods. ATLA, 38(6), 471-494. (Exhibit 8)

These studies showed how chimpanzees were used historically because researchers believed there were few if any other options, despite many admitting numerous and serious problems with the chimpanzee model and stressing the urgent need for *in vitro* systems to culture the virus and accelerate discoveries, as had occurred for viruses such as polio and measles.

Human-based research features heavily in the discovery of hepatitis C and early characterization of the virus. Human-based contributions include: demonstrating that non-A non-B hepatitis (NANBH) was the salient complication of transfusion therapy; defining NANBH's natural history; identifying surrogate markers of the disease; and lowering the incidence of transfusion-associated NANBH, even prior to the identification of the virus itself.

Chimpanzees were useful in the generation of serum samples with high titers of the infectious agent, which aided identification of HCV. However, advanced molecular techniques that now exist were not available then; and, in retrospect, it is likely that the use of uncharacterized ("standard" titer) samples not screened in chimpanzees would have been equally useful for complementary DNA (cDNA) library construction, and the eventual identification of HCV clones and the virus itself.

Chimpanzee use in hepatitis C research has declined markedly by nearly 60% over the past 30 years and is at an historic low. Non-animal hepatitis C research has increased 80-fold over the same period. This would not be the case if chimpanzee use were crucial for such research. Much of this pattern is due to the chimpanzee being a poor model, as HCV pathology in chimpanzees and humans is very different. For example: there is a much lower rate of chronic infection in chimps due to greater viral clearance; immune responses to HCV differ; resultant liver fibrosis and cirrhosis are milder in chimps; and hepatocellular carcinoma is rare.

Chimpanzees are used infrequently in the development of HCV antiviral drugs. Regulatory requirements for preclinical pharmacokinetic and toxicological data from two animal species have been fulfilled in the majority of cases without recourse to chimpanzees. There are, to date, no publicly available data to show that chimpanzee HCV-antiviral and vaccine data are predictive of human response. It is widely acknowledged, even among the pharmaceutical industry, that there is no need for chimpanzees in the future development of HCV antivirals (Institute of Medicine 2011a). With regard to HCV vaccines, informative therapeutic vaccine trials are taking place with no requirement for chimpanzee preclinical efficacy data that may or

may not have been predictive. For prophylactic vaccines, the IOM inquiry noted that similar field trials could be achieved (Institute of Medicine 2011a), especially in countries where blood transfusions are not screened (Institute of Medicine 2011b).

There are now robust and productive *in vitro* methods of hepatitis C research. It is possible—without chimpanzees—to investigate in a human-based, and therefore completely relevant, context the entire HCV life cycle from the moment the virus attaches itself to the cells it infects; to study immune responses to infection and the roles of host factors; and to identify and test new therapies and vaccines. While full life-cycle infectious cellular clones represent the long awaited and most comprehensive *in vitro* system for many aspects of HCV study, all the *in vitro* methods employed—including HCV-infected cultured primary and immortalized cells—infectious molecular clones, subgenomic and genomic replicons, and virus-like particles and pseudoparticles, have added greatly to the body of knowledge on the hepatitis C virus and hepatitis C pathology, and enhanced progress toward new treatments.

Full life-cycle infectious clones (HCVcc), which were urgently called for by the research community for decades, provide the necessary data to facilitate the development and testing of HCV therapies, when supported by clinical, epidemiological, *ex vivo* and *in silico* methods—in contrast to dependence on the chimpanzee. These approaches are augmented by human clinical studies of hepatitis C patients and those at risk of infection. Even studying pathological events early in HCV infection is not the preserve of the chimpanzee, despite claims to the contrary. Informative studies have been performed with sufferers of needle stick injuries, recipients of contaminated blood products, and the screening of new admissions, for example. HCV investigations have entailed the use of human liver biopsies, resulting in important discoveries.

While there are limitations to *in vitro* methods—like all scientific models—they must be compared and contrasted to the considerable downsides of using HCV-infected chimpanzees, with their different pathologies and viral responses. Further, while the performance and relevance of these *in vitro* methods are being improved, the benefits and limitations of the chimpanzee model remain stagnant.

It is appropriate to note the power of VaxDesign's MIMIC system ("Essentially a clinical trial in a test tube for human immunity" (VaxDesign)), which provides human relevant vaccine immunogenicity data (see papers cited above, and VaxDesign.com). This system uses white blood cells from volunteer donors, and allows immune responses induced by new vaccine candidates to be studied at the vaccination site and/or point of virus attack, as well as the assessment of immune cell activities and antibody production. Advantages include its capacity to test adjuvants, vaccine components and complete vaccines and assess the quality of established vaccines in different human immune systems—reflecting biological and immunological diversity. Stated goals are to obviate preclinical animal-based vaccine tests and to identify optimal human vaccine formulations. Given the performance of this system to date, there is robust evidence that it will reduce the risk of adverse events in clinical trials, elucidate why some

vaccines work in certain populations of people and not others, and address safety and immunogenicity issues.

As long ago as 1998, GlaxoSmithKline (GSK) decided it was unnecessary to use chimpanzees, including for hepatitis C drugs and vaccines. GSK's Director of HCV Biology, Robert Hamatake, testified to the IOM that they utilized *in vitro* alternatives a great deal, such as replicon systems, enzymatic assays, and the full life cycle infectious virus system, all of which had been valuable for drug discovery. A global pharmaceutical company the size of GSK having done without using chimpanzees for so long further discredits proponents of chimpanzee use. Dr. Hamatake opined that there was no resultant delay in the development of GSK's putative HCV vaccines because they do not use chimpanzees, nor did GSK's decision indicate a lack of interest in competitive vaccine development (Institute of Medicine 2011b).

Cancer

Bailey, J. (2009). An examination of chimpanzee use in human cancer research. *ATLA, 37*(4), 399-416. (Exhibit 9)

A study of cancer—one of the leading causes of human death and a major research focus—found that, between 1968 and 2008 inclusive (forty years):

- Chimpanzees were scarcely used in cancer research. Many of the few published papers were published over 25 years ago.
- Chimpanzees have a very low incidence of cancer, especially epithelial cancers that kill humans; and chimpanzee tumors are biologically different from human cancers in their causes and in apoptosis and metastasis.
- Evidence indicates chimpanzees are not essential in the development of therapeutic monoclonal antibodies for cancer treatment. No publications were identified that described chimpanzee use in the development or testing of these drugs.
- The few papers that described potential new cancer therapies tested in chimpanzees included warnings concerning species differences, acknowledged that the chimpanzee model performed no better than other animal models, and/or described interventions that had not been pursued, presumably due to adverse results.

The reasons for such differences are genetic. A recent structural genomics study, which compared the regulation of apoptosis (programmed cell-death) between humans and chimpanzees acknowledged that nutritional and ecological differences contributed to changes in cancer incidence between the species, but could not "coherently explain" an order of magnitude increase in cancers of the breast, ovary, lung, stomach, colon and rectum in humans. Instead, the authors implicated some of the estimated 40 million differences between the human and chimpanzee genomes, which determine susceptibility and tolerance.

The examination of around 500 proteins involved in cancer-related pathways showed many of the proteins analyzed were expressed from genes with significant differences between the two species, both in constitution and regulation. Such genetic differences are responsible for the wholesale changes in carcinogenicity between humans and chimpanzees.

Comparative Genomics Studies

Bailey, J. (2011). Lessons from chimpanzee-based research on human disease: The implications of genetic differences. *ATLA*, *39*(6), 527-540. (Exhibit 10)

This study examined genetic differences between humans and chimpanzees, which underpins all evidence that the chimpanzee is a poor model for human biology. It is claimed by advocates of chimpanzee use that humans and chimpanzees are 98-99% genetically identical, and that it follows that they are very similar biologically in the diseases they suffer, their responses to infectious agents and drugs, and so on.

This review showed that such claims are facile. Humans and chimpanzees are actually approximately 94% genetically similar. This in itself has significant implications, but when account is taken of other genetic factors and of the different systems that control gene function—even when genes are identical or almost identical between humans and chimpanzees—they are even greater.

Examples of differences include genes involved in:

- Tumor formation
- Immune system function
- Cancer, schizophrenia and other cognitive disorders, migraine, and autoimmune diseases like lupus and rheumatoid arthritis
- HIV infection
- Parts of the brain involved in thought and language—and in problem-solving, emotion, and complex thought that are linked to Alzheimer's, Parkinson's, and Huntington's diseases.

Further:

- Human-chimpanzee gene-expression differences occur throughout the body: 25% in the liver; 33% in the kidney; 34% in the brain; 35% in the heart; 62% in the testes.
- 80% of orthologous proteins differ in their amino acid sequences.

In summary, there are extensive and fundamental genetic reasons why chimpanzees, however closely related to humans, are not *and can never be* good models for human research. These intrinsic differences are further confounded by the significant effects of the environment of gene function and expression, which are just beginning to be appreciated. In biomedical animal research, the quality and richness of the environment is critical to experimental results. The stress

of laboratory life for a chimpanzee is known to impact gene function and expression, and has particular consequences for immune system function, crucial to infectious disease research.

Even if we accept that we need to use chimpanzees in comparative genomics studies to benefit human medicine, we do not need captive chimpanzees in laboratories to determine or analyze these differences. Chimpanzees in sanctuaries or zoos can provide biological samples without harm to them for genetic analysis during routine check-ups, medical interventions, post mortems, and so on.

Additional Research Areas

Other research areas where chimpanzees are unnecessary include:

Malaria

Ann-Marie Cruz of the PATH Malaria Vaccine Initiative informed the IOM Committee that chimpanzees were not essential for the development of malaria vaccines, that other species were used, and that the human challenge model, widely used, was best for accelerating clinical testing and development (Institute of Medicine 2011b).

Drug development/pharmacokinetics

As the U.S. drug regulatory agency, the FDA provided telling evidence for the lack of need for chimpanzee use in drug development and testing. The FDA recently informed the IOM that: its policy is not to request data from chimpanzee studies; it has received just seven applications that included chimpanzee data in the past five years, none of which the FDA asked for or recommended in its guidance; none of this data were toxicological; it discourages chimpanzee studies, if asked; and it believes that, if chimpanzee data were no longer available, this would have "no discernible effect" on adequate and timely review of applications (Jacobson-Kram 2011).

Monoclonal antibodies (mAbs)

The National Centre for the 3Rs (NC3Rs) in the UK published a review on the subject of species relevance in mAb testing, which concluded that, "the assumption that a shift from Old World primates towards the use of chimpanzees might overcome some of the issues associated with species relevance is not necessarily supported by experts or evidence…the chimpanzee might be of limited value in the development of mAbs" (Chapman 2006).

This was echoed at the IOM hearing by Theresa Reynolds, Ph.D., Director of Safety Assessment at Genentech. She informed the IOM that due to "advances in scientific engineering" there is no need to use chimpanzees in monoclonal antibody development, and that they haven't used them since the early 1990s. She spoke of her poll of mAb developers, who agreed there was no need. She described how, when chimpanzees were used, one in four mAbs failed to progress to clinical trials on the basis of chimpanzee data, and two of the remaining three that did progress were

discontinued based on adverse findings in humans not detected in chimpanzees (Institute of Medicine 2011b).

Health security of the U.S. and biodefense

Joseph Bielitzki (University of Central Florida) opined to the IOM that chimpanzees were "probably not" critical to U.S. health security. He cited the many years it takes to develop a vaccine, and that a health emergency would be over before anything could be developed, even with the use of chimpanzees. "Even for the H5N1 strain of avian influenza, the quickest to market took around 6 months, by which time the epidemic was over and the problem gone." He cited maintenance costs for chimpanzees, at approximately half a million dollars per chimpanzee for lifetime care. He balanced his argument with what too few have considered carefully: the management nightmare that trying to house chimpanzees in biosafety level 4 containment labs would be. Concerns include not only managing internal environments, but more importantly managing escapes of chimpanzees infected with a virus deadly to humans. The likelihood of chimpanzee use leading to an efficacious vaccine in viruses of this nature is slim and could not mitigate the disastrous effects of the escape of an infected chimp (Institute of Medicine 2011b).

Michael Kurilla, director of the NIH Office of Biodefense Research Affairs informed the IOM that chimpanzees offer "no advantage over other NHPs for product development for biodefense," citing existing protections for smallpox, botulism, bubonic plague, etc. (Institute of Medicine 2011b).

James Swearengen, the Director of the National Biodefense Analysis and Countermeasures Center, told the IOM that he was "not aware of any historical or current use of chimpanzees in the U.S. in biodefense/for the Department of Defense," and that he did not envision any future speculative need (Institute of Medicine 2011b).

D.2. Criterion 2: If a chimpanzee has not been assigned to a research protocol[9] in ten years, then he/she is "not needed."

Basis for Criterion:

Based on available information, over two-thirds of U.S. chimpanzees in the four main laboratories and Alamogordo Primate Facility (APF), a holding facility for federally-owned chimpanzees, have been confined there for decades.[10] Eighty to ninety percent of federally owned and/or supported chimpanzees currently in U.S. labs are inactive—i.e. not in protocols—at any one time.[11] According to Laura Bonar, Program Director for Animal Protection of New Mexico (APNM), "[t]he nearly 200 government-owned chimpanzees at the APF…have not been used in invasive research since at least 2001" (Declaration of Laura Bonar, RN). It is ethically and fiscally untenable to continue to house and maintain up to ten times the number of chimpanzees currently being used experimentally. Further, in a 2006 public opinion survey, 71% of the American public believed that a chimpanzee held in a laboratory for ten years or more should be retired.[12]

Given the mounting evidence against the scientific necessity or value of chimpanzee research, it is important to analyze the costs to taxpayers of continuing to use and house such a costly species in laboratories. The 1997 Institute for Laboratory Animal Research Report (ILAR) report *Chimpanzees in Research: Strategies for their Ethical Care, Management and Use*, which provided impetus for the CHIMP Act opined that "cost savings…could be achieved by transferring such animals to appropriate public (nongovernment) sanctuaries," "[s]anctuary animals…entail lower costs of daily care," and "sanctuaries offer an opportunity for substantially reducing costs of long-term maintenance of chimpanzees without compromising high standards of well-being." In addition, the report noted that "the larger the number of animals moved to a sanctuary…the lower the annual marginal costs of adding one chimpanzee to the facility" (Institute for Laboratory Animal Research Committee on Long-Term Care of Chimpanzees 1997). According to the North American Primate Sanctuary Alliance (formerly Alliance of North American Chimpanzee Sanctuaries):

[9] As defined by NIH's Glossary & Acronym List (http://grants.nih.gov/grants/glossary.htm), "research" means "[a] systematic, intensive study intended to increase knowledge or understanding of the subject studied, a systematic study specifically directed toward applying new knowledge to meet a recognized need, or a systematic application of knowledge to the production of useful materials, devices, and systems or methods, including design, development, and improvement of prototypes and new processes to meet specific requirements," and protocol means "[a] formal description and design for a specific research project."

[10] Based on chimpanzees' ages, a census provided to the IOM Committee by SNPRC in 2011, and censuses for NIRC, the Keeling Center, and YNPRC that were provided to NEAVS in 2012 in response to FOIA requests.

[11] As per John VandeBerg Panel Presentation at The International Primatological Society XXII Congress August 3-8, 2008 Edinborough, Scotland.

[12] 2006 poll conducted by the Humane Research Council. 1,678 U.S. adults (age 18 and over) completed the survey with valid responses, resulting in a margin of error of about +/- 2.4% [at a 95% confidence level]

> Based on experience at the two larger Alliance member sanctuaries who experience this economy of scale, annual costs per chimpanzee of $13,140-$16,790 (range $36-46 per day) for direct care and administrative costs are achieved. An average daily cost per chimpanzee of $41 is anticipated with expansion of sanctuaries to accept additional chimpanzees retired by the government…Comparing an average cost of $41 per day in a sanctuary with the comparable average laboratory per diem of $60 would result in savings of approximately $90 million over the lifespan of the chimpanzees for the approximately 500 government owned chimpanzees (Alliance of North American Chimpanzee Sanctuaries 2010) (emphasis added).

Thus, retiring the chimpanzees would be economically beneficial to the American public—in tax dollar savings and the ability to reallocate some funds to more promising areas of biomedical research—and would be enormously beneficial for the chimpanzees' psychological and physical well-being. It has been established from scientific studies (Bradshaw et al. 2008; Bradshaw et al. 2009; Capaldo and Bradshaw 2011; Brune et al. 2006; Ferdowsian et al. 2011; Brent, Lee, and Eichberg 1989) as well as from undercover investigations (The Humane Society of the United States 2009a; Kleiman 2004) that confinement and use of these animals seriously undermines their physical and psychological well-being (Capaldo and Peppercorn 2012). Thus, retiring chimpanzees to sanctuaries is a win/win situation: it provides much higher quality care at a lower overall cost as well as untold savings in opportunity costs.



L to R: Lou, Wes, and Dana, STC, each spent ± 35 years in laboratories.
Photos courtesy of STC



L to R: Tom, Annie, and Pepper, spent 30, 20+, and 27 years respectively in laboratories.
Photos courtesy of Fauna Foundation Sanctuary

D.3. Criterion 3: A chimpanzee is not needed for research if he/she is an unfit research model because he/she:

(a) lacks an accurate or complete medical or veterinary history;

(b) is an elderly chimpanzee (i.e. if a male chimpanzee is 25 years or older or a female 30 years or older);

(c) exhibits indications of chronic, severe, or multiple physical illness(es), including but not limited to the following: significant cardiac, renal, or liver disease unrelated to a current research protocol; recurrent infections or other such indicators of a poorly responsive immune system; epilepsy; any chronic gastrointestinal diseases; any other chronic disease; any terminal disease; or any congenital or anatomic abnormality;

(d) has multi-organ disease whether terminal or not;

(e) has a previous use history or multi-use history, including in biomedical research or testing or in cognitive behavioral studies involving invasive procedures or knockdowns. Previous use history may include cross-fostering studies or other areas where identity with and prior close relationship with humans made the chimpanzee a poor candidate for laboratory life and use (see Section D.3.4.c.); or

(f) is suffering from chronic psychological suffering or other indications of stress, a situational disorder that is not being resolved and has the likelihood of leading to post-traumatic stress disorder (PTSD), and/or other psychological maladies including on-going anxiety, depressions, withdrawal, etc., even in the absence of a full PTSD syndrome.

Basis for Criterion:

D.3.1. Many chimpanzees in laboratories lack adequate or accurate histories, have been used previously in multiple research protocols, and/or have been infected with different clades of HIV, HCV, etc., which confounds any data derived from them.

Researchers rely in part on medical records and chimpanzees' histories to choose which chimpanzees to use in a particular research protocol (MA Bloomsmith, Schapiro, and Strobert 2006). However, severe inadequacies in chimpanzee records limit researchers' abilities to have a complete understanding of laboratory chimpanzees' histories and, therefore, to adequately interpret data. In addition, many chimpanzees' have been infected with multiple diseases, further confounding any research data and casting doubt on the studies' scientific validity.

Laboratories often do not keep adequate chimpanzee medical records. Of 110 autopsies reviewed by dependent board certified pathologists, the reviewers considered a total of 46% "incomplete." For example, some reports lacked significant data such as "sex designation, age, [or] weight." One autopsy "reported only histology" and no gross findings, whereas others "[were] comprised only of gross dissection data…[with]…no histopathology, toxicology, [or] microbiology." Some described only selected organs, omitting possibly important others. In some cases, "tissues [were] described as autolyzed [i.e. delayed or improper fixation likely]" and most reports lacked clinical history. Another report offered conflicting information regarding date of death. The report described a 22 year old female chimpanzee as having been "diagnosed with systemic hypertension…on 10/28/06…[and]…pronounced dead…on June 21, 2006"—four months prior to being diagnosed. Another autopsy identified a chimpanzee as female included a uterus but noted, "[s]ections of testis, epididymis, and seminal vesicle were also included with tissues submitted for this animal," and that "the origin of these tissues is unknown" (Capaldo and Peppercorn 2012).

When chimpanzees are retired to sanctuary, they are accompanied by their medical records. The animal records demonstrate gaping holes in their histories. Records available to Fauna and Save the Chimps (STC)—sanctuaries that care for many retired laboratory chimpanzees—are lacking important information. For example, Jeannie's records do not indicate whether she was captive-born or wild-caught, or whether she was transferred to the laboratory from the entertainment trade or relinquished as a companion ("pet") animal (see Appendix D). Nor is her medical record complete; there is little available information on her use prior to LEMSIP. Another chimpanzee, Yoko, was transferred from the circus to LEMSIP at seven years old. From 1984 to 1991, Yoko had at least one punch liver biopsy per month, but there are no indications in his medical records as to what these biopsies were for and no references to the research that the biopsies were performed for (Fauna Foundation). The exact origins of another chimpanzee, Sinbad the 1st, are unknown. Nothing is known about Sinbad the 1st prior to 1984, when he arrived at the Coulston

as an adult, purchased from another lab. He may have been born anywhere between 1964-1969—making even his age unknown—possibly in Africa, possibly in captivity (Save the Chimps). Similarly, the origin of the chimpanzee Tanya is unknown, but it is estimated that she was born in 1970, perhaps in Africa. Tanya was used by more than one lab in her early years, and was used in multiple biomedical research studies (Save the Chimps). Another chimpanzee, O'Dell, was born at LEMSIP, and then transferred to Coulston, but it is unclear from her records if she was used in any experiments at Coulston, and, if so, which research (Save the Chimps). See Appendices F and G for further reports of inadequate record-keeping.

Further confounding inadequate records is the fact that chimpanzees are used in multiple research protocols and transferred among multiple laboratories.[13,14] Documents from the laboratories and sanctuary records of chimpanzees from research consistently demonstrate that chimpanzees held in laboratories were used in multiple protocols and are in failing health. For example, Katrina, a chimpanzee transferred from APF to SNPRC in 2010, has been infected with hepatitis A, hepatitis B, hepatitis C, and HIV viruses, and her records indicate a diseased liver, shigella, and severe weight loss.[15] (More examples of chimpanzees infected with multiple diseases are included in Appendix D.) In addition, "[t]he majority of the 288 chimps taken from Coulston had been used in infectious disease protocols, some in multiple studies at multiple labs over the years, but these chimps were not retired…The NIH has to date refused to retire the remaining chimps who are at APF, despite the fact that the contract with Charles River has expired, many of the chimps have multi-use histories, and the chimps have not been used (and therefore not needed for research) for more than ten years" (Declaration of Jennifer Feuerstein). Laura Bonar further explains that "many of the APF chimpanzees were used in research at multiple laboratories around the country" (Declaration of Laura Bonar, RN).

[13] For example, some chimpanzees used in the U.S. space program were transferred from laboratory to laboratory after their use by the Air Force (see Exhibit 11, One small step: The story of the space chimps).

[14] Standard laboratory practices contribute to the problems inherent in multiple use of the same chimpanzee and the difficulty of keeping accurate records on them. At one time the Coulston Foundation was the largest holding of chimpanzees for use in research. Coulston had a long history of poor and negligent care of its chimpanzees and monkeys. Despite numerous, serious, and on-going USDA citations for AWA violations (see Appendix G for examples), Coulston continued to receive millions of dollars in federal funding and to make their chimpanzees available for use. None of the chimpanzees at this facility were retired under the CHIMP Act despite their physical health and multi-use histories. Instead, they were retired only after Coulston went bankrupt and the facility was purchased by STC. Coulston is an important example because former Coulston chimpanzees are still alive and in the system. While most now reside at STC, others from Coulston now reside in other laboratories because of the practice of transferring chimpanzees between laboratories.

[15] NEAVS received Katrina's medical records in April 2012 in a response to a FOIA request

Strapped for training

Propelled for crash testing

Chimpanzees used in research for the U.S. space program were later transferred between laboratories after their use by the Air Force. The Air Force retired 30 chimpanzees and sent 111 to Coulston. Despite that the chimpanzees could have sustained multiple physical and psychological injuries in the air and space program that should have made them ineligible for future use, they continued to be used in biomedical research. Photos courtesy of U.S. Air Force.

D.3.2. A third of chimpanzees in laboratories are elderly

According to available information, over one-third—an estimated 350 of the approximately 937 chimpanzees held in U.S. laboratories are considered elderly,[16] i.e. males are 25 years or older and females are 30 years or older (Videan, Fritz, and Murphy 2008). The lack of demand for chimpanzee aging studies in the past, even with ample aged chimpanzees available at the time, demonstrated that this type of research is unnecessary. In 1998, the National Advisory Council on Aging stated "there is no scientific demand for a center for aging chimpanzees" (National Institute on Aging 1998). Prior to this, of 1,600 NIH grantees who were surveyed regarding their interest in using chimpanzees in aging research, three said that they would be interested in using *post mortem* brain tissue and only one indicated a positive interest in using live subjects, i.e. a 0.0006% expressed need (National Institute on Aging 1998). Additionally, chimpanzees are not affected by Mild Cognitive Impairment or Alzheimer's or Parkinson's diseases, which makes their use in these areas of research difficult to rationalize and certainly much less relevant than research utilizing human cells and tissues. Again, at an October 2006 meeting at Yerkes, researchers noted that older chimpanzees were not useful in some brain and behavioral research (Cohen 2007). However, as a pending threat to the end of all chimpanzee research evolves, some laboratory directors are attempting to make a case, in the face of a lack of need for chimpanzees in all other biomedical research, for chimpanzee need in aging studies. In her Declaration, Jennifer Feuerstein recalls elderly chimpanzees needlessly languishing at YNPRC:

> Jorg, a gentle elderly male who lived with an equally amiable companion, Duncan, was not chosen [for retirement]. Jorg was old, thin, and had chronic air sacculitis and polyps in his nasal passages. But when I knew him, he still had energy and interest in life. He and Duncan lived in a small concrete and steel indoor/outdoor run. They were not assigned to research protocols, and Jorg would not have been a candidate for research in any case given his health condition. Yet they were not retired, and both Jorg and Duncan died at Yerkes in their barren cage, when they could have spent their final years in retirement at a sanctuary. (See Declaration of Jennifer Feuerstein)

Moreover, the aging chimpanzees that would be available as models of human aging have spent all of their lives in an unnatural environment as research subjects, and have been exposed to numerous different substances and subjected to a multitude of stressful procedures—conditions that are known to adversely affect research results (Würbel and Garner 2007; Richter 2012; Chance and Russell 1997). Further, it has been demonstrated that cellular insults caused by stress and exposure to certain chemicals negatively impact the aging process (Kregel and Zhang 2007; Hawkley and Cacioppo 2004; Stadtman 2002; Jones 2006)—all of which means that any results

[16] 2011 - 2012 from NIH FOIA requests, correspondence with facilities, and Chimpanzees in Biomedical and Behavioral Research: Assessing the necessity Institute of Medicine 2011 report.

gained from chimpanzee aging studies are difficult to interpret and impossible to extrapolate to human beings (Bailey 2006).

There are also unique physical risks for elderly chimpanzees used in experiments. For example, for chimpanzees, being anesthetized is a dramatic and traumatic process. Because of their tremendous strength, they must often be taken forcibly or shot with dart guns in a process that is referred to as a "knockdown," which can be much more dehabilitating for elderly chimpanzees (Bailey 2006). According to Jocelyn Bezner, VMD, senior veterinarian at Save the Chimps Sanctuary:

> In addition to the physiological deterioration and the symptoms that accompany age related, progressive disease come the added risks of sedation for chimpanzees who are elderly. Sedations for protocols or diagnostics become a high risk issue in this age group. Anesthesia predisposes elderly individuals to greater cardiac instability and blood pressure issues, both hypertension and hypotension. (See Declaration of Jocelyn Bezner, VMD)

A study published in 2007 reported that the risk of anesthesia-related death for chimpanzees over the age of 30 was about 30 times higher than the risk for younger individuals (Masters, Burns, and Lewis 2007). Clearly, the prospect of repeatedly anesthetizing older chimpanzees dramatically increases their chances of severe complications and even an iatrogenic death. In addition, elderly chimpanzees are more likely to experience cardiac disease. In a study of 34 Alamogordo Primate Facility (APF) chimpanzees, researchers found that the incidence of cardiac arrhythmia increased significantly at 20 years and older (Doane, Lee, and Sleeper 2006).

Flo, 55 years old, is believed to be the oldest living chimpanzee in a U.S. laboratory. Captured in the wild, her date of birth is estimated to be 9/29/57.
Photo received by NEAVS from a NIH FOIA request.

D.3.3. Chimpanzees in laboratories suffer from physiological diseases and from the effects of continual knockdowns:

Autopsy reports, medical records, and the health status of chimpanzees retired or rescued from research indicate that many chimpanzees currently in laboratories may be suffering from incurable physiological diseases. An October 2011 letter to IOM from Chimp Haven—currently the only facility that must comply with the very strict and rigorous federal standards for sanctuaries promulgated by the Secretary of HHS pursuant to the CHIMP Act, "Standards of Care for Chimpanzees Held in the Federally Supported Chimpanzee Sanctuary System" 73 Fed. Reg. 60423 (October 10, 2008) 42 CFR §9.1—demonstrates that chimpanzees who had been living in laboratories had been suffering from severe physiological diseases:

> Chimp Haven receives mostly old or chronically ill chimpanzees, who often require extensive diagnostics upon arrival to treat chronic problems. For example, many chimpanzees arrive with severe dental disease, including active infection and rotten teeth. Our veterinary team must often pull teeth and aggressively treat dental infection. (We follow with regular dental care and dental prophylaxis to maintain dental hygiene.) Many chimpanzees also arrive with heart, liver or kidney disease and are placed on appropriate medication to ensure their quality of life. As a final example, two chimpanzees arrived from a lab to Chimp Haven with large bony tumors on their maxilla, making it difficult for them to eat. They had had the tumors for about 15 years in the lab. These tumors were easily removed by our consulting oral and maxillofacial surgeon under the guidance of our veterinarian, and the chimpanzees recovered well (Butler 2011) (emphasis added).

The sanctuary further emphasized that

> Chimp Haven prides itself on acceptance of all chimpanzees offered for retirement to the facility, including many that were seriously ill, had been exposed to multiple infectious diseases and have chronic conditions (including behavioral pathologies). Chimp Haven provides sanctuary to chimpanzees found to have AIDS-like symptoms from repeated HIV exposure, and three diabetic chimpanzees (Butler 2011).

Other sanctuaries, including Fauna Foundation Sanctuary and Save the Chimps Sanctuary, reported similar findings.

> Among the 100 LEMSIP chimpanzees retired were those who, like the ones who arrived at Fauna: had reached the end of their ability to tolerate research protocols as assessed by the resident veterinarian and care staff; had serious and multiple physical symptoms such as involuntary and un-resolvable gagging, diarrhea, anorexia, liver, kidney or heart compromise, and/or bodily damage including injury which limited mobility or balance; had been used "hard" in multiple labs; and/or who had psychological damage that led to chronic anxiety, withdrawal and self-injurious or dissociative behavior (Declaration of Gloria Grow).
>
> When Save the Chimps took over [The Coulston Foundation], we found chimps who could have and should have already been retired due to chronic health problems multi-use history, and psychological disorders. (Declaration of Jennifer Feuerstein).

One document that exemplifies the multiple protocols to which chimpanzees in laboratories are subjected, and the concomitant health deterioration is the April 28, 2010 "Do Not Resuscitate Order" of a chimpanzee named Ken who was housed at APF before being transferred to SNPRC the same year as the DNR document referenced below was issued.

The Do Not Resuscitate Order states:

> Ken (1216) is a 28 year old hepatitis C infected, HIV positive male chimpanzee that has been diagnosed with multiple chronic clinical disease processes by the veterinary staff at APF. The clinical disease processes that 1216 is afflicted with includes: scrotal edema, hypoalbuminemia, hypocalcemia, multiform ventricular premature contractions, and congestive heart failure. The current differential diagnosis includes congestive heart failure or dilated cardiomyopathy.
>
> 1216 has been evaluated by each member of the Alamogordo Primate Facility veterinary staff. Ken's condition is stable. He is being provided with supportive care, his conditions are medically managed and he is being intensively monitored. However, none of these treatments are curative and acute decompensation may occur.
>
> It is the consensus of the Alamogordo Primate Facility veterinary staff that due to the grave prognosis associated with these diseases, 1216 will not be resuscitated in the event of acute decompensation. This does not preclude providing supportive therapy as needed, so long as the outcome will involve the return of 1216 to an acceptable quality of life in a reasonable amount of time. Humane euthanasia will be performed by the veterinarian in attendance. See Exhibit 12 (emphasis added).

Despite multiple diseases, Ken was not retired. In her Declaration, Margaret Peppercorn, M.D., a pediatrician with over 30 years of experience, states that, "[a]s a scientist and physician this makes no sense—lab animal models cannot already have multi-system disease and still be appropriate research models." More examples of chimpanzees who suffered from incurable physiological diseases in laboratories are included in Appendix D.

In fact, a recent review of autopsies performed on chimpanzees who died in laboratories, or after transfer from laboratory to sanctuary, revealed that the majority of chimpanzees from laboratories (of a broad age range with the average age 29 years old) had been suffering from significant chronic or incurable illnesses and often multi-system diseases that should have made them ineligible for future research on both scientific and ethical grounds (see Exhibit 13). One of the physicians who reviewed the autopsy reports, Dr. Margaret Peppercorn, recounts that "[t]he most disturbing finding was the fact that the vast majority of the chimpanzees had been extremely ill…yet had continued to be held in a laboratory setting presumably to be available for possible future research. To me this was unscientific and cruel" (Declaration of Margaret Peppercorn, M.D.) It was clear from the autopsy reports that many of those who died had been known to be seriously ill for quite some time: a large number of chimpanzees were known by the laboratory to have been chronically ill for more than 8 months prior to their deaths, and in some

cases for more than 4 years. Some autopsy reports included phrases like "on high risk list due to advanced heart disease, systemic hypertension, and chronic renal failure," "diagnosed with multiple chronic disease processes by veterinary staff, DNR (Do Not Resuscitate)," "on high risk list, DNR," or "at high risk for sudden cardiac death" recorded often many months, or even years, before the chimpanzee died. Yet, remarkably, those chimpanzees had been kept in the laboratory, either for possible future research use or simply so that the laboratories could continue to receive federally funded maintenance grants (Capaldo and Peppercorn 2012). According to Gloria Grow, founder and director of Fauna Foundation Sanctuary, which provided some autopsy reports for the study, "[t]he autopsies we have done on our deceased chimpanzees present compelling evidence of how decades of research simply cannot be endured without a price paid by even the strongest of chimps." (Declaration of Gloria Grow).

These autopsy reports showed:

- Significant cardiac disease present in 77% of chimpanzees autopsied, 57% of which was some form of cardiomyopathy.
- 48% had significant renal disease.
- 53% had significant liver disease—22% described as some form of hepatitis, while another 24% fibrotic livers.
- 22% had significant infections such as pneumonia, peritonitis, or abscess.
- 31% had enlarged or "congested" adrenal glands, possibly associated with chronic stress.
- 33% had significant abdominal adhesions.
- 16% had intestinal or gastric ulcerations and/or peticheal hemorrhages. Six had tracheal hemorrhages.
- 39% had been identified as having been known to have had severe chronic illnesses (25% for eight months or more and, in some cases, for four or more years) prior to their death.
- 25% were found to have chronic disease on autopsy which was likely to have been present for a significant length of time but had not been recognized before death.
- Overall, roughly 69% of all the chimpanzees autopsied had significant multiple organ disease.

- Moreover, because of the incompleteness of some of the records, it is probable that the presence of multi-organ and other disease was higher.

Dr. Jocelyn Bezner has explained that "[a]ny chimpanzee with changes in the blood chemistry or CBC is not a good candidate for a research study" (Declaration of Jocelyn, Bezner, VMD).

Cardiac disease, and in particular cardiomyopathy, is a common feature in chimpanzees in laboratories.[17] According to Dr. Jocelyn Bezner, "[c]ardiac disease is the most common cause of death in captive chimpanzees" (Declaration of Jocelyn Bezner, VMD). Thirty-five percent of chimpanzees at SNPRC (between 1982-2006), 36% at APF (between 2001-2006), and 36% at YNPRC (between 1992-2008) died from heart disease (N. Varki et al. 2009). The autopsy investigation further revealed that 77% of chimpanzees in labs had significant cardiac disease, of which 57% was some form of cardiomyopathy (Capaldo and Peppercorn 2012). This figure may have been higher—as in some cases gross findings were suggestive of cardiomyopathy but there was either no histologic examination to confirm it or no specific diagnosis given. However, heart disease in chimpanzees is different than in humans due to different underlying pathological processes (Doane, Lee, and Sleeper 2006; N. Varki et al. 2009), and therefore chimpanzees would not be a good model for studying human heart disease.

Studies have shown that chronic and/or social stress has severe negative effects on the heart (Seiler et al. 2009; Hansen, Alford, and Keeling 1984), and results in heart disease in monkeys (Hansen, Alford, and Keeling 1984). Thus, it has been postulated that this high occurrence of cardiomyopathy in captive chimpanzees—uncommon in the wild (Terio et al. 2011)—may be due to the chronic stresses experienced by chimpanzees in laboratories. There is unequivocal evidence of this link between psychological stresses and cardiovascular dysfunction in humans, from fifty years of epidemiological and clinical data (Nalivaiko 2011) which includes stress-induced sudden death via ventricular arrhythmia/tachycardia, and stress cardiomyopathy, also known as apical ballooning, "takotsubo" cardiomyopathy, or "broken heart syndrome."

Cardiomyopathy has been reported across species and its causation by potent emotional stressors has been an established concept in western medicine since 2005. A wide variety of physical and

[17] Studies have demonstrated the prevalence of cardiomyopathy in chimpanzees in laboratories. For example, (1) In a 2009 study of 87 necropsies at SNPRC, researchers identified an overall heart disease prevalence of 68 percent (73 percent for males), 76% of which was cardiomyopathy and 69% of which resulted in heart failure (Seiler et al. 2009); and (2) In a 2006 study at APF, 34 out of 265 (nearly 13%) chimpanzees had cardiac arrhythmias, 22 arrhythmias were of ventricular origin and consisted of uniform ventricular premature complexes (VPCs), bigeminy, trigeminy, multiform VPCs, and accelerated idioventricular rhythm. "Structural heart disease was diagnosed by echocardiography in 8 male chimps . . . Systemic hypertension was diagnosed in 4 male chimps, 1 of which also had left ventricular hypertrophy and mild renal insuficiency. Hyperlipidemia was diagnosed in 2 male animals. Noncardiovascular disease was diagnosed in 3 chimps and consisted of nephrotic syndrome, renal insuficiency, and hepatocellular carcinoma." Five of 13 chimpanzees with multiform PVCs experienced sudden cardiac death. During the two year study period, seven animals with cardiac arrhythmias died or were euthanized, representing a majority (54%) of the deaths during this time period. The incidence of cardiac rhythm disturbances was 4% of the studied chimpanzees between the ages of 10 and 19 years old, 18% of the 20 to 29 years olds, 20% of the 30 to 39 year olds, and 33% of the chimpanzees older than 40 years (Doane, Lee, and Sleeper 2006).

emotional stressors have been indentified that are present in up to 100% of patients, including those that may affect chimpanzees in laboratories such as social stressors, death and illness of those in the social group, surgical procedures, pain, recovery from anesthesia, etc. (Akashi et al. 2010; Castillo Rivera, Ruiz-Bailén, and Rucabado Aguilar 2011). Elevated levels of catecholamines (stress hormones), and associated histological changes, have been directly implicated in the pathology of stress cardiomyopathy via the direct lesion of myocytes and vasoconstriction through catecholamine-mediated calcium release, leading to cAMP-activation and "cardiac stunning" (Akashi et al. 2010; Castillo Rivera, Ruiz-Bailén, and Rucabado Aguilar 2011).

Due to the prevalence of heart problems, Dr. Jocelyn Bezner advises that "[i]t could be argued that any male chimp over 15 years of age is at risk of sudden death and therefore should not be used in any research protocol. At a minimum, all male chimpanzees should have echocardiograms beginning at 15 years old and removed from research if there are any abnormal findings. Other cardiac problems that should preclude the use of chimp are arrhythmias and murmurs." (Declaration of Jocelyn Bezner, VMD).

D.3.3.a. Effects of Anesthesia

The administration of dissociative anesthetics is also an acknowledged stressor for chimpanzees in laboratories, and can adversely affect chimpanzees' health. This is directly due to the disorientating effects accompanying entry into, and emergence from, anesthesia, coupled with the involuntary nature of its administration (Anestis 2009). This is evidenced by a doubling of plasma cortisol, and six-fold elevations in urinary cortisol (Whitten et al. 1998; Anestis, Bribiescas, and Hasselschwert 2006). These elevations indicate "a major disruption of homeostasis and an allostatic load" (Anestis 2009). In rats, repeated anesthesia elicits an increased stress response to subsequent stressors such as handling and changes in environment (de Haan et al. 2002). Chimpanzees have similar reactions (see Declaration of Jocelyn Bezner, VMD). (Stress resulting from knockdowns and anesthesia is further discussed in Section D.3.4.c.)

Adverse effects of repeated anesthesia in chimpanzees may not be limited to those associated with stress. It is known that repeated anesthesia also causes cognitive deficits—an inclusive term used to describe deficits in intellectual functioning in global disorders (e.g., mental retardation) or specific deficits in cognitive abilities (e.g., certain learning disabilities such as dyslexia) (Medscape 2012). For example, for human patients, post-anesthesia cognitive deficits tend to last a few weeks at most, but 5-10% of elderly patients show deficits that may persist for several months, or even be permanent (Blokland, Honig, and Jolles 2001). In rats, repeated anesthesia may reduce cholinergic function in the cerebral cortex (Hanning et al. 2003).

Adverse consequences of ketamine anesthesia—widely and frequently used in chimpanzee research protocols—have also been documented (see Declaration of Jocelyn Bezner, VMD). For example, heavy exposure to ketamine in humans results in harm to cognitive function and psychological well-being (C. Morgan, Muetzelfeldt, and Curran 2010). Ketamine elicits adverse effects on cortical neuronal morphology in rats (Hargreaves, Hill, and Iversen 1994) and neurodegeneration in the developing rhesus macaque brain, even at brief exposures, which may result in long-term neurobehavioral impairment (Brambrink et al. 2012). This evidence augments other cross-species studies illustrating that clinical doses of many commonly used anesthetics, such as midazolam, propofol, isoflurane, sevoflurane, and chloral hydrate (in addition to ketamine), could cause similar harm in humans and non-human primates (Brambrink et al. 2012).

Ketamine is also known to alter neural architecture from observations in human clinical studies and *in vitro* (Vutskits et al. 2007), and to impair a wide range of memory functions in both acute and chronic doses, including episodic memory, recollective processes, and semantic processing (C. Morgan and Curran 2006); ((Krystal et al. 1994) from (Okon 2007)). It also causes frequent adverse cardiovascular effects, including increased blood pressure and tachyarrhythmias (Okon 2007), and may be hepatotoxic, leading to liver enzyme abnormalities in greater than 16% of patients (Sear 2011).

Further, ketamine causes seizures in some chimpanzees. For example, when in the laboratory, a chimpanzee named Vanna seized under ketamine, yet she was continued to be anesthetized using it. “She was also observed to have seizures while awake on multiple occasions. She was not prescribed regular anti-seizure medication.” After retirement to STC, “Save the Chimps’ veterinarian prescribed anti-seizure medication to Vanna, with remarkable results. Vanna did not have a seizure for four years, allowing her and Nadia to join a social group… In fact, Vanna has never experienced a seizure while under anesthesia at Save the Chimps” (Declaration of Jennifer Feuerstein). Another chimpanzee, Rosie, began suffering from seizures induced by ketamine as early as eight years old. Despite repeated notes regarding her reaction to ketamine in her medical records, researchers continued to jeopardize her health and well-being by using it. Over the next 11 years, she continued to suffer from seizures induced by ketamine, sometimes multiple times a year. One seizure caused her to regurgitate and aspirate material into her lungs, which led to aspiration pneumonia being a concern.[18]

Pre-anesthetic protocols also cause harm to chimpanzees—including food and water deprivation and isolation from their social group. Pending “knockdowns,” as well as the knockdown itself, are causes of anticipatory anxiety and stress to chimpanzees in labs as they learn to recognize that food and water being withheld heralds being anesthetized some time the next day. Further, many develop anesthetic tolerance and the need to administer greater amounts of the agent to achieve anesthesia; stereotypical behaviors such as (but not limited to) pica (the consumption of

[18] NEAVS received Rosie’s medical records in April 2012 in a response to a FOIA request.

nonfood items) and coprophagy (the consumption of feces); and gastrointestinal problems such as sepsis, decreased motility, and increased gastroesophageal reflux with associated risk of aspiration and duodenal damage (Ardente et al. 2011).

Great ape anesthesia also carries a high risk of mortality—significantly greater than that of other species, including humans and horses (Masters, Burns, and Lewis 2007). For example, compared to human perioperative mortality risk of 0.2%, and equine risk of 0.9%, the risk for great apes has been determined to be 1.35%—almost seven times the risk for humans. Notably, with regard to the chimpanzee population in laboratories—comprised of old and unhealthy animals—this risk is significantly greater for those individuals with a poor health status and/or greater than 30 years of age (Masters, Burns, and Lewis 2007). Thus, many chimpanzees have been injured or have died due to complications with knockdowns or the anesthetics. (Complications with knockdowns are further detailed in Section D.3.4.c.)

The adverse biological impact of repeated anesthesia is established (see Declaration of Jocelyn Bezner, VMD). Given that chimpanzees may be subjected to dozens of knockdowns in any one investigation, each of which may require up to five darts, and that some individuals' lab records confirm that they have experienced more than 300 knockdowns during their use in just one of the several laboratories they have been in (NEAVS), the potential for serious and long-lasting neurological, cardiovascular, gastrointestinal, and/or hepatological damage to these chimpanzees is profound.

Anesthetized chimpanzee in a laboratory. Photo © M. Nichols

D.3.4. Chimpanzees in laboratories suffer psychologically and experience chronic stress, which has physiological implications that affect the well-being of the chimpanzee and his/her suitability for further use:

The IOM itself stressed that "any assessment of the necessity for using chimpanzees as an animal model in research raises ethical issues, and any analysis of necessity must take these ethical issues into account" (Institute of Medicine 2011a). These ethical issues encompass psychological harm imposed on chimpanzees in laboratories. "Chimpanzees for whom further laboratory confinement and use will cause, perpetuate or enhance symptoms of psychological stress and suffering must be considered inappropriate research subjects, "not needed," and therefore, must be retired" (Declaration of Theodora Capaldo, Ed.D.). In her Declaration, Laura Bonar explains,"[t]o date, all medical records of APF chimps examined by APNM show multiple documented examples of both physical and psychological suffering as a result of government-support research, including escape attempts ending in shooting, coprophagia, self-mutilation, amputation following injury and gangrene related to chronic disease, and death" (Declaration of Laura Bonar, RN).

Chimpanzees in laboratories exhibit multiple signs of chronic stress and psychological suffering which not only severely impacts their well-being, but also impairs their physiological suitability for further research. Even if chimpanzees were needed for biomedical research, the severe stress that laboratory life and use impose on chimpanzees and the physiological responses to such psychological, cognitive, and social stress would make them ineligible for future research. This section first discusses how the physical manifestations of stress could adversely affect research results, and hence, the implications of stress on research validity. It then describes the causes of stress in chimpanzees in laboratories and how this stress is manifested—including both psychological and physiological manifestations.

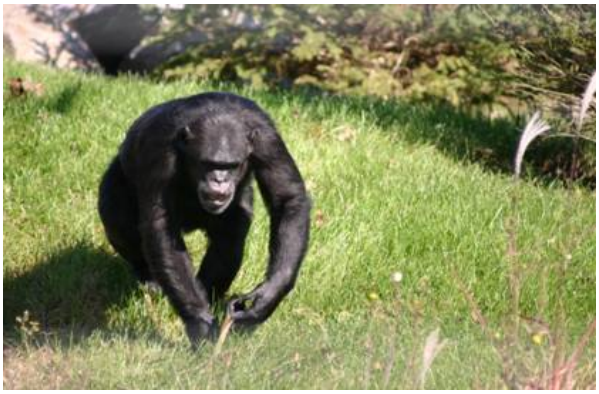
D.3.4.a. Adverse Impacts of Stress on Experimental Results

The stress experienced by chimpanzees has undeniably adverse and confounding effects on any experimental results derived from them, due to the associated modulation of many biochemical pathways and gene expression and resulting organ damage and or disease (Balcombe, Barnard, and Sandusky 2004). "A chimpanzee who exhibits chronic, re-occurring or severe psychological symptoms is an inappropriate model to study any disease as that level of psychological stress has major physiological consequences which confound research findings" (Declaration of Jocelyn Bezner, VMD).

With specific regard to chimpanzees, the impact of stress on immunological and inflammatory responses is critical, as these alterations exacerbate and compound crucial immune differences that already exist between humans and chimpanzees—particularly as most chimpanzee experimentation involves infectious agents (for a discussion and references see (Bailey 2011). For example, genomic duplication is one of the most significant causes of genetic variation

among primates (Armengol et al. 2010) and at the root of many aspects of intra-species and inter-species diversity. It differentially affects many human and chimpanzee genes involved in immune and inflammatory responses (Perry et al. 2008). Indels (genomic insertions and deletions) also affect major histocompatibility complex (MHC) genes which are critical to immune responses and are associated with differences in the handling of various infections including HIV, hepatitis B and C viruses, and the malarial parasite *Plasmodium falciparum*, as well as in differing susceptibility to autoimmune diseases. Additionally, the greater abundance of inhibitory Siglecs in chimpanzees dampens chimpanzee immune responses relative to humans and this may be further impaired as a result of psychological stress. This may explain species differences in diseases that involve immunopathology, including HIV, hepatitis C, asthma, psoriasis and rheumatoid arthritis (Soto et al. 2010).

Published literature warns, for example, that, "animals subjected to the environmental changes that occur during transportation…react with changes in their physiology, such as body weight, plasma hormonal levels, heart rate and blood pressure changes…When measurements of physiological parameters are performed using conventional measurement techniques, the results must be interpreted with caution as these conventional techniques also have effects on the animals" (Capdevila et al. 2007). Most importantly, "Suffering in animals can result in physiological changes which may increase the variability of experimental data" (Capdevila et al. 2007). Many scientists are well aware of these effects and considerations and have cautioned against disregarding them (Brenner et al. 1990; Mason et al. 1968; Roberts et al. 1995). Yet, while accepting the negative effects of pain, stress and distress, and their influence on study outcome, such effects are often not reported or underreported in published scientific papers (Reinhardt and Reinhardt 2000).

	
Pepper, LEMSIP	Pepper, Fauna Foundation Sanctuary
	
Jeannie, LEMSIP	Jeannie, Fauna Foundation Sanctuary
Pepper and Jeannie photos courtesy of Fauna Foundation Sanctuary.	

D.3.4.b. Overview of Stress and Stressors in Laboratories

All species experience stress and stressors, whether they are the result of natural or man-made environments. It is well established that great apes have psychological (mental, emotional, and other faculties of subjective experience) capacities comparable to humans (see Appendix H). These include maternal behavior, facial recognition, moral development, play, sexual behavior, fear, aggression, stress and emotion regulation, empathy, love, and grief, which are consistent across species (Narvaez et al. 2012; Panksepp 1998). Theoretical and empirical studies document that brain structures and processes governing consciousness, cognition, emotions, sense of self, and other faculties are shared among vertebrates (Bradshaw and Sapolsky 2006). Patterns of thinking, feeling, and behavior that are shaped through relationships and the associated brain structures affected by trauma (i.e., cortical and subcortical areas of the right brain, including the right orbitofrontal cortex, anterior cingulate, amygdala, hippocampus, and posterior areas of the right hemisphere) are also consistent across species (Capaldo and Bradshaw 2011). The most

obvious similarities exist among humans and great apes: our closest relatives are chimpanzees, with whom we share approximately 93.5-96% genetic similarity (Bailey 2011; Britten 2002; A. Varki and Altheide 2005; Wetterbom et al. 2006). The key issue is the now undeniable proposition that great apes suffer psychologically and physically when subjected to conditions that cause comparable suffering in humans (e.g., forced confinement, social and physical deprivation, being subjected to procedures without willing consent, torture).

Nonhuman primates have been used for decades to explore the effects of environmental stress on mind and behavior. Experiments and testing comprise not one, but multiple, physical and psychological stressors. In addition to vulnerability to malicious actions,[19] chimpanzees in captivity routinely sustain one or more traumatic events: premature separation from biological and cultural context (i.e., separation from their natural physical, cognitive, emotional, social, and cultural environment); attachment disruptions; inadequate care-giving; prolonged deprivation; and, in cases of biomedical experimentation, highly invasive psychophysiological insults. Laboratory confinement and experimentation are well known to cause severe stress and abnormal mental states and behaviors in animals used for research (Brune et al. 2006; K. Morgan and Tromborg 2007) (See also Appendix I). Stress is measurable in chimpanzees in laboratories: cortisol, produced by the body in response to stress, is a well-accepted measure of stress. Elevated cortisol levels can be measured in chimpanzees following many common laboratory routines. For example, significant increases in cortisol occur in chimpanzees following anesthesia (a known stressor) that may be measured in their urine and feces for up to two days (Anestis 2009; Whitten et al. 1998). Other common laboratory routines, such as handling, moving and cleaning cages, and blood collection, also cause rapid, pronounced, and statistically significant elevations of physiological stress indicators such as heart rate, blood pressure, and a variety of hormone levels (including cortisol), indicating significant fear, stress, and distress (Balcombe, Barnard, and Sandusky 2004; Meijer et al. 2007).

In addition, chimpanzees live in uncertainty about if and when they will be subjected to an experimental procedure. In the book *Why Zebras Don't Get Ulcers*, neuroscientist Robert M. Sapolsky discusses the "anticipatory stress response" for which there is evidence in a number of species such as humans, great apes, elephants, dogs, and others. Due to prior adverse experiences, individuals become hyper-vigilant, anticipating the reoccurrence of those experiences—much like, for example, adopted dogs who have suffered previous traumas flinch when they are approached. These individuals have evolved to learn from those experiences in order to identify risks of harm, and to facilitate their own safety, healing, and ability to get back to living their lives (Sapolsky 2004). Further, chimpanzees undergo capture from research

[19] Fear may be induced in the laboratory by personnel's' malicious actions, which may not be treated with concern by laboratory management, as demonstrated by the case of Narriman Fakier at NIRC. Dr. Goodall stated in March 2009 that she noticed a lack of concern for the psychological welfare of the chimpanzees in HSUS' NIRC undercover footage (The Humane Society of the United States 2009b).

cages[20] or "knockdown;" separation (if group housed) and isolation prior to procedure; restraint ("squeeze cage"); blood draws (these often require sedation); various organ (including brain) biopsies; injection of potentially allergenic dyes, viruses, and radioactive and other substances; and other invasive procedures. This is followed by post-procedure stress: confusion and fear associated with sedation recovery, pain and nausea from the procedure, isolation during this period of up to 18 hours or longer, and other debilitating stressors associated with serious surgeries and medical procedures.[21] This "direct" stress is compounded by other traumatic events and by standard laboratory housing conditions that impose unnatural levels of confinement, and commonly deprive, limit, or severely alter, the occupants' opportunities to engage in essential, varied, expansive, and self-determined natural behaviors.

Captivity comprises a fundamental stressor that undermines well-being because of the loss of agency, the ability to make choices surrounding one's life and needs (Herman 1992). In a 1998 report entitled *The Psychological Well-being of Nonhuman Primates*, the National Research Council (NRC) discussed the essential ingredients required for psychological well-being, including among other things, social companionship; opportunities to engage in species-typical behaviors, postures, and locomotion; freedom from pain or distress; and positive interactions with human caregivers (U.S. National Research Council 1998).

However, the physical conditions of laboratories are harsh and unyielding relative to the socio-ecological and psychological conditions to which chimpanzees have naturally evolved. Prime stressors include physical (e.g., small concrete or metal cages, overcrowding, limited types of nutritious, non-endemic food), social (e.g., lack of natural family groups, changing labs and loss of companions, isolation), and psychological (e.g., boredom and lack of appropriate stimulation; maternal deprivation; and uncertainty, pain, and fear when knocked down, anesthetized, and forcibly subjected experiments; cross-fostering—that is, taken from their biological mothers and raised by human mother substitutes). In many cases, social interaction with other members of their own species and the stress relieving comforts primates can and do provide each other are not possible (Hurst et al. 1999; Olsson and Dahlborn 2002). This irregular or lack of regular safe social support (i.e., intra- and inter-facility moving as well as moving from the pet or entertainment industry to laboratories), in situations where these traumas occurred, constitute additional stressors. Finally, "short feeding duration and lack of variety in the captive chimpanzee diet, among other characteristics of captive feeding routines, almost certainly contribute to chimpanzees' development and expression of numerous pathologic behaviors, particularly those in which a major component is orality, such as self-mutilation, coprophagy,

[20] For example, marmoset monkeys resolutely try to avoid capture from their research cages, during which they "easily become stressed and agitated and can cause harm to themselves." Such routine capture "has been associated with increased cortisol, signs of distress and decrease in other hormones in various nonhuman primate species" (Williams et al. 2008).

[21] Some brain, cognitive, and behavioral studies are also associated with some of the same steps and procedures. For example, in a study of ERP's (event related potentials) electrodes were attached to a fully conscious chimpanzee while s/he was taught to do tasks while wearing the electrodes. (The National Center for Biotechnology Information (NCBI) lists a sample of research diversity and various procedures at http://www.ncbi.nlm.nih.gov/pmc/?term=chimpanzee&TransSchema=title.)

repeated regurgitation, excessive grooming, and urophagy" (MA Bloomsmith, Alford, and Maple 1988). Specific laboratory stressors are discussed in more detail below.

D.3.4.c. Specific Laboratory Stressors

Social isolation and boredom

According to the 1997 Institute for Laboratory Animal Research (ILAR) report *Chimpanzees in Research: Strategies for Their Ethical Care, Management, and Use,* chimpanzee "well-being is most likely achieved when facilities provide for and promote a wide range of natural behaviors" (Institute for Laboratory Animal Research Committee on Long-Term Care of Chimpanzees 1997). This was further supported by the IOM, which stated that "[i]t is generally accepted that all species, including our own, experience a chronic stress response (comprising behavioral as well as physiological signs) when deprived of usual habitats, which for chimpanzees includes the presence of conspecifics and sufficient space and environmental complexity to exhibit species-typical behavior" (Institute of Medicine 2011a).

Like humans, chimpanzees are obligatorily social. They have an intrinsic need for "social interactions, for forming social relationships, both supportive and antagonistic, even for politicking (Brune et al. 2006)." Because their social lives are so complex, some researchers hypothesize that chimpanzees' intelligence may have evolved in response to social challenges (Brune et al. 2006). However, social enrichment and cage sizes fail to meet normative environmental conditions[22] for free-ranging chimpanzees (Goodall 1986). In many cases, social interaction with other members of their own species and the stress-relieving comforts primates provide each other are simply not possible (Hurst et al. 1999; Olsson and Dahlborn 2002). Regulations implementing the AWA's command for "minimum requirements" to insure "a physical environment adequate to promote the psychological well-being of primates" (7 U.S.C. § 2143(a)(2)(B)), do not require that primates always be housed in compatible social groups—they only specify that individually housed nonhuman primates must be able to see and hear nonhuman primates of their own or compatible species, unless the attending veterinarian determines that it would endanger their health, safety, or well-being (9 C.F.R. § 3.81(a)(3)).[23] This extremely lax requirement fails to address chimpanzees' social needs (Walsh, Bramblett, and Alford 1982).

[22] "The conditions appropriate for one species do not necessarily apply to another. Accordingly, these minimum specifications must be applied in accordance with the customary and generally accepted professional and husbandry practices considered appropriate for each species" (9 C.F.R. § 3.75(a)). Minimum size for primary enclosure for great apes is determined by height and weight. An adult female chimpanzee who averages 130 cm (51.2 inches) in height and weighs 45 kg (99 pounds), the floor size is only 8 square feet (less than 3 x 3 feet) and height of 36 inches. For a full grown male chimpanzee who averages 170 cm (66.9 inches) in height and 80 kg (176 pounds) minimum floorspace is 25 square feet and cage height is 84 inches. Since brachiating species such as chimpanzees are grouped together, additional space is provided to permit species-typical behavior: "great apes weighing over 110 lbs. (50 kg) and additional volume of space in excess of that required for Group 6 animals as set forth in paragraph (b)(2)(i) of this section, to allow for normal postural adjustments (9 C.F.R. § 3.80(b)(2))."

[23] See Exhibit 15, the PBS film Chimpanzees: An Unnatural History, for footage of chimpanzees in isolation at the Coulston Foundation.

While primates are known to bond through the cages if this is their only opportunity for social interaction, this inarguably unnatural world thwarts the animals' natural behaviors to comfort and protect each other. In addition, the cage size allowed to keep a full-grown chimpanzee (i.e., 5'x5'x7'), makes it impossible for a large male to even fully extend his arms and legs without hitting the bars. Nevertheless, given their ages and previous research histories, most if not all of the chimpanzees currently held in U.S. laboratories may have been singly housed for some part of their lives and some continue to be so housed today when required by the protocol or by the individual chimpanzee's health including an inability to be socialized, which is typically a sign of extreme psychological compromise in the individual.

Studies have examined behavioral change associated with single housing for infant and adult chimpanzees. Both negative psychological short-term and long-term effects have been documented, such as abnormal behaviors and self-mutilation, with more serious behavioral problems evident in the longer term (Brune et al. 2006). A 2009 investigation by the Humane Society of the United States revealed the conditions of some chimpanzees at NIRC (see Exhibit 14).

> The chimpanzees used in contract drug studies at NIRC endure the bleakest of conditions. Isolated in 30 square foot barren stainless steel cages, they languish in absolute boredom for months in between bouts of fear-inducing procedures. What passes for enrichment in this context are pictures of chimpanzees, islands, and cartoon characters taped to the cinderblock walls, a metal perch to sit on, and a kong-like toy (The Humane Society of the United States 2009a).

Because primates possess inquisitive brains and a strong need for stimulation and investigation, sensory and motor deprivation in barren and uncontrollable laboratory environments constitutes a major stressor (Brune et al. 2006). A single tire hanging from the center of an otherwise barren cage currently meets the law's requirement that an "enrichment" plan be in place. The resulting boredom also creates bizarre abnormal behaviors and self-mutilation as well as apathy (Brune et al. 2006). A 2004 USDA inspection report at NIRC calls its enrichment for singly-housed primates "mundane" (Appendix F). Years later, during the HSUS investigation, HSUS reported that the chimpanzees had the same mundane toys as were seen in 2004, such as balls and kong toys. As in other facilities, chimpanzees were denied any bedding materials, an extremely important enrichment item. Not even pregnant chimpanzees, who were kept in stainless steel isolation cages, were provided bedding or blankets at NIRC (The Humane Society of the United States 2009a).

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<tr><td colspan="2">Chimpanzees, Coulston Foundation. Photos courtesy of STC</td></tr>
<tr><td>  </td><td>  </td></tr>
<tr><td>A young woman’s height and weight demonstrates the size of the cages at Coulston.
Photo courtesy of STC</td><td>Interior view of LEMSIP’s suspended, singly housed chimpanzees.
Photo courtesy of Fauna Foundation Sanctuary</td></tr>
<tr><td>  </td><td>  </td></tr>
<tr><td>A 5 ft x 5 ft x 7 ft cage for an adult chimpanzee is still legal if required if required by protocol or health.
Photo courtesy of N. Megna.</td><td>Laboratory enrichment.
Photo © M. Nichols</td></tr>
</table>

Overcrowding

Overcrowding can cause psychological distress for chimpanzees (Aureli and De Waal 1997). By analogy, in human prisons, overcrowding is associated with negative health impacts and increased stress levels and violence (Gaes 1985). It has also been shown to have deleterious effects in other animals, such as increased aggression in monkeys (Alexander and Roth 1971) and chronic stress in mice (Reber 2006). Laboratories keep chimpanzees in small, ethologically-inappropriate cages. In addition, in 2004 and 2005, the USDA cited NIRC for overcrowding chimpanzees, but twice extended the date by which the facility had to come into compliance with the minimum standards of the AWA. In the 2004 inspection, the USDA cited NIRC for keeping two chimpanzees in a ten-square-foot baboon cage. In 2008, an HSUS investigator videotaped interior cement cages at NIRC that appeared overcrowded with both adults and juveniles (The Humane Society of the United States 2009a).

Knockdowns and Anesthesia

Laboratory procedures typically "involve immobilization by force (e.g., grasping their upper arms behind their backs [during studies on young chimpanzee]), sedative or other chemical immobilization, or other restraint, stretching the individual out across a table, head grasped tightly" (Gluck 2012). Chimpanzees are anesthetized not only for experimental procedures, but for routine procedures, including even changing cages.[24] While laboratories claim that some chimpanzees are trained to accept an injection, sanctuary directors estimate this to be a small number given their first-hand experiences.[25] Sometimes chimpanzees are put into squeeze cages—a highly stressful situation where the back wall of the cage squeezes the chimpanzee forward towards the front wall so that he or she can be anesthetized. Chimpanzees may scream, urinate, and defecate in panic and fear during this process. A third and common way a chimpanzee is anesthetized in a laboratory is through darting. As discussed in Section D.3.3.a, a chimpanzee in a laboratory may be sedated multiple times a week and hundreds of times over years in a laboratory.[26] Records indicate that chimpanzees are commonly anesthetized hundreds of times—a chimpanzee named Tom was knocked down over 369 times in 15 years at one facility alone and Billy was knocked down over 289 times.[27] The dart needles measure approximately 1 to 1 ½ inches long and are fired into the chimpanzee with a force of roughly 50 psi. A darted chimpanzee falls onto cement or steel barred floors sometimes from a high perch.

In addition to being physically harmful,[28] darting and sedation are particularly frightening experiences. Even "routine" blood draws or injections are magnified because they often require

[24] As per correspondence with Fauna Foundation and review of medical records received in response to FOIA requests.
[25] As per 2008 correspondence with Gloria Grow.
[26] As per medical records received by NEAVS in response to FOIA requests.
[27] As per correspondence with Fauna Foundation.
[28] Another adverse effect of dart-mediated anaesthesia may be the possibility of infection at the dart site. Complications can result from (unsterile or sterile) darts entering unprepared skin, inoculating the injection site with bacteria that grow well in the traumatized tissues associated with the dart site and leading to wounds that could develop into clinical infections (West, Heard, and Caulkett 2008). The question has been raised that the inadvertent introduction of bacteria and/or chemicals into the abdomen via darting could be a contributing factor to so many chimpanzees being found to have abdominal adhesions on autopsy (Capaldo

that the chimpanzee be anesthetized. The isolation prior to sedation, the effects of sedation, and the foreknowledge of the effects of sedation cause immense fear in chimpanzees. Former caregivers explain that chimpanzees know when a knockdown is about to occur because their food and water is withheld—leaving them in anxious anticipation. Highly stressed, chimpanzees attempt to evade the darts by thrashing, running around the cage, and making alarm calls. Chimpanzees may be darted several times to administer an effective dose. As a result, the laboratory records of chimpanzees now in sanctuary document how they were often hit in every conceivable body part—scrotum, corner of an eye, lip, back, stomach, foot. It has been known for several laboratory personnel to surround the cage to knockdown a chimpanzee (see Declaration of Gloria Grow).

A March 27, 2009 USDA inspection report of NIRC also discussed fear due to darting. It stated:

> "[M]ethods used to sedate chimpanzees that are housed in social groups may cause more than momentary or slight pain and distress…The act of sedating a non human[ ] primate with darts while in social groups may cause distress because the animals are fearful of the darting apparatus[ ] used. The primates recognize the darting apparatus[ ] and the entire social group may behave in an exaggerated distressful manner as a result. There is also a possibility of an animal falling from perches, benches, or other overhead structures causing injury as a result of an uncontrolled fall" (See Appendix F).[29]

Drugs used in sedation sometimes cause hallucinogenic effects, which can be terrifying experiences for chimpanzees. For example, ketamine, a commonly used drug in chimpanzees in laboratories, "has…psychological adverse effects" including "vivid dreaming, extracorporeal experiences (sense of floating out of body), and illusions (the misinterpretation of a real, external sensory experience" (Kronenberg 2002). In her Declaration, Dr. Jocelyn Bezner states that "[e]ven in young healthy chimpanzees, ketamine alone causes muscle rigidity, laryngospasm and hallucinations on recovery." The use of ketamine also causes some chimpanzees to bite themselves as they are experiencing the hallucinogen effects as they wake up.[30]

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and Peppercorn 2012). Though the authors of this study did not cite any investigations describing chimpanzee skin flora (microorganisms living on the skin), it was assumed to likely be similar to human flora. Vaginal flora is similar in humans and chimpanzees, for instance (Noguchi et al. 2004). Bacterial species that constitute normal human skin flora, but which may cause significant and even serious infections in certain circumstances, are known to be present in, and cause infections in, chimpanzees. These include: Staphylococci, which can be associated with skin infections, pneumonia, and bacteremia (U.S. National Library of Medicine at NIH); Streptococci, which can cause severe sore throats, scarlet fever, impetigo, toxic shock syndrome, cellulitis, necrotizing fasciitis, bacteremia, urinary tract infections (UTIs) and pneumonia (U.S. National Library of Medicine Medline Plus); Pseudomonas aeruginosa, an acknowledged prevalent and opportunistic pathogen involved in many nosocomial infections such as pneumonia, UTIs, surgical wound infections, bacteremias, and septicaemias (Van Delden and Iglewski 1998; Centers for Disease Control and Prevention); and Acinetobacter, which may cause similar problems (Centers for Disease Control and Prevention). Streptococci have been isolated from the chimpanzee oral cavity (Okamoto et al. 2012) and chimpanzee abscesses (Zhang et al. 2012), for example.

[29] For example, Katrina's July 22, 1992 medical records appear to indicate that a "cagemate fell on top of her head" during the administration of ketamine anesthesia. In addition, HSUS' investigation at New Iberia documented injury from darting.

[30] For example, on Nov. 29, 1994, during recovery from ketamine, a chimpanzee at LEMSIP, Katrina, "self-mutilated her left thumb." Billy also chewed off his thumb while the hallucinogenic effect of a tranquilizing and pain killing drug wore off.

After the procedure, waking up from anesthesia and reintroduction into the group, if socially housed, is stressful. According to John Gluck, PhD, Emeritus Professor of Psychology and Psychiatry, University of New Mexico and Georgetown University, “the individual is weighed and then released and left to recover” and “stumble around.” “Reintroduction to the group sometimes was a ‘touch and go’ proposition with more potential injuries from attack. Outbreaks of shigella were common, indicating the level of stress when dominance hierarchies changed” (Gluck 2012).

(L) Darting to anesthetize a chimpanzee, LEMSIP. (R) Chimpanzee being removed after a knockdown.
Photos courtesy of the Fauna Foundation Sanctuary

Chimpanzee subjected to a procedure
Photo © M. Nichols

Cross-fostering

It is not unusual for chimpanzees to be raised as human children and then left in laboratories after becoming older, stronger, larger, and no longer manageable (see Appendix D). Cross-fostered (that is, taken from their biological mothers and raised by human mother substitutes) chimpanzees are particularly vulnerable to the stresses of a laboratory environment.[31] Chimpanzees cross-fostered and then sent to laboratories suffer a series of traumatic events: premature separation from biological and cultural context—which has been repeatedly shown to result in severe psychological harm (Berkson 1968; Dienske and Griffin 1978; Kalcher et al. 2008; Reimers, Schwarzenberger, and Preuschoft 2007); attachment disruptions; inadequate caregiving; prolonged deprivation; and, in cases of biomedical experimentation, highly invasive psychophysiological insults. Symptoms of trauma are diverse, but Fabrega's criterion, significant behavioral alterations relative to an understood social and cultural space, is pivotal to the evaluation of cross-fostered individuals: Primary psychosocial issues were grounded in the nature of developmental context experience (Fabrega 2006). These impacts cannot be underestimated. Further, current research findings on mood and anxiety disorders report that "there is now compelling evidence that early life stress constitutes a major risk factor for the subsequent development of depression" (Bradshaw et al. 2009) (emphasis added). According to Gloria Grow, "There are chimpanzees in the U.S. laboratory population whose histories, like Billy's, make the psychological toll taken on them in research more chilling, more devastating." Billy had been cross-fostered for nearly 15 years prior to being turned over to LEMSIP, where he lived in a solitary, barren cage for 14 years until his rescue by Grow's Fauna Foundation Sanctuary (Declaration of Gloria Grow).

[31] Jaybee's years in multiple labs were confounded by the fact that he may have once known comfort as a "pet." Being a castrated chimpanzee is one clue to his possible past. Chimpanzees raised in a human environment struggle in their newfound captivity. Former employees at LEMSIP noted that Jaybee had a difficult time adjusting when he arrived at the lab. Another cross-fostered chimpanzee, Billie was observed regularly banging and shaking his cage violently in the laboratory, particularly when approached. He was considered "hostile," "uncooperative," "aggressive," and depressive (LEMSIP personnel personal communication May 2007). More accounts of cross-fostered chimpanzees are included in Appendix D and Exhibit 16. (Exhibit 16 contains commentary about cross-fostered chimpanzees by Roger Fouts, PhD, a psychologist who studied American Sign Language with chimpanzee Washoe and her family and a former co-director of the Chimpanzee and Human Communication Institute at Central Washington University.)

	
Billy, cross-fostered for 15 years, was walked into a LEMSIP cage by his owner where he spent the next 14 years.	Billy became friends with Dr. Jane Goodall and recognized her with excited pant hoots when he saw her on TV.
Photos courtesy of Fauna Foundation Sanctuary	

D.3.4.d. Manifestations of Stress

Laboratory conditions and experiences involving diverse experimental procedures and frequent anesthetics commonly lead to acute and long-term mental and physical breakdown. As such, stress can result in both psychological damage as well as severe physiological consequences for an individual. Different species and individuals of any species have different stressors, variable ranges of stress to which they are able to adapt, diverse spectra of tolerance, and dissimilar manifestations and sequelae of excessive stress. There are, however, commonalities that transcend species, much as many mammalian species have similar organs with similar functions, and the inability of an individual to adapt to repeated and/or chronic stress leads to allostatic overload (excessive wear and tear on the body). In her Declaration, Dr. Capaldo recalls, " I met and spent a great deal of time with the chimpanzees who...sanctuary directors felt were 'always depressed,' 'couldn't be comforted,' 'went into trance like states,' 'seemed to be reacting to something that wasn't there,' 'treated a hand or arm like it didn't belong to them'…and myriad other symptoms which indicated that the chimpanzee's ability to cope with the reality of their laboratory life and use had been depleted, leaving them in a progressively deteriorating state." The adverse psychological and physiological consequences of the inherent and unavoidably stressful aspects of laboratory life for chimpanzees are documented below (also see (Capaldo and Bradshaw 2011; Bradshaw et al. 2008; Bradshaw et al. 2009; Ferdowsian et al. 2011) (Exhibits 17-20)).

D.3.4.d.i. Psychological Effects of Laboratory Confinement and Use

As demonstrated below, laboratory conditions cause extreme psychological and negative physical damage to chimpanzees—such inherent consequences of laboratory use not only call into question our ethical obligation to our closest relative but also impair the value of any research in which they are used. Symptoms of such psychological trauma are diverse, including self-mutilation; stereotypic behavior; learned helplessness; inappropriate aggression; fear or withdrawal; diarrhea; high infant mortality; post-traumatic stress disorder; anxiety; and abnormal behaviors, such as spitting, feces throwing, over grooming of self or others, and playing with feces (Brune et al. 2006).

Self-mutilation and self-aggression

Chimpanzees in laboratories are known to develop self-injurious behaviors in response to laboratory conditions and experimentation—including over-grooming to the point of injury, hitting and/or biting one's self, or banging one's self against the cage (Bourgeois, Vazquez, and Brasky 2007; Brune et al. 2006). These are indicators of frustration, uncertainty, anxiety, and psychological stress (Baker and Aureli 1997), and can result in severe tissue and muscle damage, lacerations, and dismemberment—sometimes requiring amputation (Bourgeois, Vazquez, and Brasky 2007). According to Jocelyn Bezner, VMD:

> Many of the records I've read from the laboratories using these chimps [under psychological stress] before retirement have a documented and often long standing history of self-trauma during their time in the research labs…Pumpkin repeatedly traumatized his surgery site for years, yet was continued to be used in research. He had parts of his liver and lymph nodes removed and consistently traumatized the surgery sites. Someone who is stressed and prone to self-mutilating behaviors should be removed from any current and all future studies (Declaration of Jocelyn Bezner, VMD).

Examples of self-aggression are numerous[32]—HSUS's 2008 investigation at NIRC documented a chimpanzee with severe self-injurious behavior[33] and Norman Fakier, a former NIRC

[32] NEAVS received FOIA records in April 2012 for three chimpanzees transferred from APF to SNPRC in 2010. Two of their medical records indicate self-mutilation. Katrina's report over-grooming, and Ken's indicate abrasions on his trachea and tongue were self-inflicted wounds. Appendix D includes more examples of self-mutilation.

[33] "Sterling, a 21-year-old male chimpanzee infected with Hepatitis C, represented the worst case of psychological distress in any of the chimpanzees observed by the HSUS investigator at NIRC. Sterling lived in an isolation cage in a room without any natural light that also housed two pregnant female chimpanzees. The investigator's supervisor described Sterling as having "mental problems." The investigator noticed that the chimpanzee had a large wound on his face and later learned that Sterling had been removed from studies permanently due to 'severe self-injurious behavior.' The investigator videotaped Sterling engaging in aberrant behaviors that could qualify him as suffering from PTSD – appearing calm and then suddenly and viciously grabbing and attacking himself, sitting in a far corner of the cage and staring blankly out or turning his face to the wall, and prolonged and terrifying screams" (HSUS 2009a).

chimpanzee manager, recounted the self-injurious behavior of several chimpanzees at the facility.[34] Other examples are included in Appendix D.

	
Chimpanzee with injury and scars from self-mutilation.	Chimpanzee with severe hair loss from poor diet, high stress, or over-grooming.
Photos courtesy of STC	

[34] Fakier "complained for four months that Wilma, born in 1993, and owned by the federal government, was self-mutilating. Finally, Wilma was put on a low dose of Prozac, but she was still mutilating herself when Fakier left NIRC. Wilma was still at NIRC when the HSUS investigator left . . . Fakier's 2005 affidavit also refers to NIRC ignoring her repeated complaints and requests for help concerning Jack, who was 'pulling his hair out on his lower legs' and 'Chimp Bud who was being badly beaten by his cagemates.' On May 2, 2008, the HSUS investigator filmed a terrified Jack, with huge patches of his hair still missing throughout his body, being threatened by a dart gun" (HSUS 2009a).

When recovering from anesthesia, Billy chewed off his thumb.
Photo courtesy of the Fauna Foundation Sanctuary

Dana's severe hair loss and pale skin when she first arrived at sanctuary.

Dana years later at STC.

Photos courtesy of STC

(L) Eboni with hair loss resulting during laboratory confinement and use (R) Eboni at STC
Photo courtesy of STC

Abnormal/Stereotypic behaviors

Walsh et al. have listed over 20 behavioral patterns in captive chimpanzees deemed (statistically) abnormal for their unusual frequency, severity, or gross anomaly (Walsh, Bramblett, and Alford 1982). These behaviors are described in Appendix J. The list includes bizarre postures; hand clapping; coprophagy; eye poking; spreading of feces; patting of own genitals; hair pulling; head banging; head shaking; head wiping; flipping of the lower lip; ‘‘raspberry’’ vocalization (lip pursing and spitting air); rocking; self-clasping; self-mutilation; self-slapping; sticking out the tongue; sucking of objects, such as own body, skin, tongue or penis; urine drinking; wetting of the head with water; and regurgitation and reingestion of food. Many of these abnormal patterns of behavior have never been seen in wild populations, and none is habitual or customary for any group in nature (Brune et al. 2006). According to Walsh, the behaviors “present[ ] a pattern of chimpanzee behavior radically different from that described for wild chimpanzees by van Lawick-Goodall [1968]…Abnormal behavior may thus be the result of pushing the chimpanzee’s species-typical behavioral plasticity beyond the limits of what can be accommodated without the development of psychopathology” (Walsh, Bramblett, and Alford 1982).

Stereotypies (captivity-induced excessive repetitive movements) (Brüne, Brüne-Cohrs, and McGrew 2004) are generally considered pathological (maladaptive) and “are the desire for stimulation, which is pronounced in the highly intelligent and investigative apes, and the desire for security, which apes usually find in their ability to control situations, or with bonded companions…A variety of stereotypies may develop to counter boredom by providing some kind of controllable stimulation in an otherwise barren and uncontrollable environment” (Brune et al. 2006).[35] Stereotypies have been compared to “obsessive–compulsive disorder (OCD) spectrum of disorders in humans, particularly those involving stereotypic motor symptoms (such as stereotypic movement disorder)…Insofar as they may represent a response to the traumatic stress of captivity…they arguably fall on the spectrum of posttraumatic stress responses” (Hugo et al. 2003). Further, abnormal behaviors such as self-mutilation, coprophagy, repeated regurgitation, excessive grooming, and urophagy can be harmful to physical health. Abnormal behaviors can also be detrimental to a chimpanzee’s ability to socially integrate (MA Bloomsmith, Alford, and Maple 1988). According to Dr. Capaldo, “from conversations with veterinarians and other staff previously or still working in chimpanzee labs, I came to understand that there is an apparent tolerance for and acceptance of aberrant chimpanzee behavior as normative for the lab” (Declaration of Theodora Capaldo, EdD).

[35] Exhibit 21 (Breaking Barriers, An investigation of an SEMA, an AIDS research facility) demonstrates chimpanzees engaged in stereotypic behavior. While this film was taken in 1986, none of the practices are illegal if the Institutional Animal Care and Use Committee (IACUC) approved the practice as necessary to the research protocol. See also Exhibit 22, 2009 footage from NIRC, demonstrating stereotypic behavior (from http://www.humanesociety.org/news/news/2009/03/undercover_investigation_chimpanzee_abuse.html).

Multiple studies and first-hand accounts attest to the prevalence of abnormal behaviors:

- A 2003 note in the medical records of Ken, who was transferred from APF to SNPRC in 2010, indicates that pacing, beating the wall and door of his cage, and looking "agitated" was normal for him. An earlier medical record entry notes that Ken was "crying to himself a lot."[36]

- In a 2002 study of 80 chimpanzees, abnormal behaviors, such as consuming their own feces, feces smearing, regurgitation, and compulsively rocking, were common (Hook et al. 2002). Notably, these results are from the Keeling Center, which holds some 79 elderly chimpanzees according to available records.

- A 2012 study states "We have made similar observations of this type of the so-called planning behavior in the chimpanzees housed at the Yerkes National Primate Research Centre (YNPRC) and the University of Texas M. D. Anderson Cancer Centre. Some of the chimpanzees will pile feces or wet chow in their cage and wait for visitors to pass by before throwing this at them . . ." (Hopkins, Russell, and Schaeffer 2011).

- According to a 1996 study, "Regurgitation and reingestion (R/R) is a potentially self injurious behavior in nonhuman primates…R/R represents a common behavioral problem among captive primates. Since it is species-atypical (seen in the wild only in vervet monkeys *(Cercopithecus aethiops:* Struhsaker, 1977), and since it is observed under restricted conditions in non-human primates and in psychotic, disturbed, or retarded humans, R/R can be considered an "abnormal" behavior…Yerkes (1943)…suggests both alleviation from boredom and tension-relief as primary functions of R/R…Regurgitation/reingestion is a prevalent form of abnormal behavior among some chimpanzees, although it may be more difficult to detect than other abnormal behaviors" (Baker and Easley 1996).

- HSUS' NIRC investigation report notes "The baby chimpanzees at NIRC, who are torn from their mothers—some of them immediately after birth—are abandoned in NIRC's barren "nursery" at a time of life when they should be clinging to their mothers' backs and being comforted by their touch. Even as the HSUS investigator watched the antics of two youngsters through the nursery window, the psychological devastation was evident—the infants interrupted their play and began rocking—a self-comforting behavior associated with maternal deprivation and fear" (The Humane Society of the United States 2009a) (Exhibit 22[37]).

[36] Medical records received by NEAVS in April 2012 in response to a FOIA request.
[37] Footage is also available at http://www.humanesociety.org/news/news/2009/03/undercover_investigation_chimpanzee_abuse.html.

- Rocking is a common stereotypic behavior seen in chimpanzees. For example, according to one lab caregiver, Wenka has "spent plenty of time rocking in the back corner of her cage" (an abnormal behavior associated with the stress of laboratory institutionalization).[38] For more examples of abnormal behaviors, see the case studies in Appendix D.

Chimpanzee engaged in copraphasia.
Photo courtesy of N. Megna.

Frannie, Yerkes National Primate Center.
Photo courtesy of The Humane Society of the United States.

Learned helplessness

Conditions in laboratories, including confinement and chimpanzees' lack of autonomy, can also lead to a phenomenon known as "learned helplessness"—the extreme passive reaction of an individual who has come to learn that he or she cannot change the environment and, therefore, must endure an aversive situation because avoidance attempts are futile (Solomon et al. 1998; Brune et al. 2006; Wortman and Brehm 1975). "Repeated exposure especially to unpredictable and inescapable stress can lead to learned helplessness in humans and nonhuman species, a state that is characterized by anxiety, inactivity and neophobia, as well as chronically increased cortisol values" (Reimers, Schwarzenberger, and Preuschoft 2007). Examples in laboratories of learned helplessness include mothers freely handing over their babies and an unnatural over-dependence on laboratory staff. Chimpanzee mothers typically will fight against giving up their newborns. In the wild, they may die rather than give up the fight to protect their young. In captivity, they have to be knocked down to accomplish this. But when offspring are continually taken away in the lab, some mothers are said to eventually recognize their powerlessness and begin not to struggle.[39] Other mothers—having themselves been taken from their mothers at birth—do not know how to properly care for their infants. These mothers give up their infants out of ignorance of who the infant is to them and what their instinctive and learned role toward him or her should entail (Brune et al. 2006; M Bloomsmith et al. 2003).

[38] Personal account from anonymous former primate lab caregiver to NEAVS
[39] Personal correspondence with former laboratory caregiver Nancy Megna, 2007

According to a former laboratory worker, "Captive chimpanzees often develop an over-dependence on their caregivers, it seems to me. Not illogically so, since every aspect of their lives is dictated. Some chimpanzees develop this neediness. Many of the worst treated chimpanzees develop the most dependence, much like abused humans."[40] Learned helplessness and dependency has been demonstrated in humans (Gatchel, Paulus, and Maples 1975; Gatchel and Proctor 1976; Thornton and Jacobs 1971), including in prisoner of war research (e.g., (Solomon et al. 1998)) and in research on victims of physical and psychological assault (e.g., (Peterson and Seligman 1983)). Helplessness has been proposed to be part of a vicious cycle that disturbs coping mechanisms in a variety of situations because it inhibits responding to an aversive environment and, therefore, produces emotional disturbances (Solomon et al. 1998).

High infant mortality

The high infant mortality rate and the number of chimpanzee mothers who reject their offspring reflect a culture suffering from psychological damage. In the wild, chimpanzees typically give birth once every five years. Young chimpanzees stay very close to their mothers for several years (Bradshaw et al. 2009). Mothers in the wild learn child-rearing skills from their mothers and group members (Latham and Mason 2008). Laboratory captive-bred chimpanzees are variably reared, but are often prematurely weaned or taken from their mothers by coercion or force at infancy, bottle fed by one or more humans, and experience irregular peer socialization and little to no adult chimpanzee interaction during infancy/childhood (Bradshaw et al. 2009). Naturally protective, chimpanzee mothers suffer anxiety and depression when their babies are taken. Some mothers eventually lose the ability to care for their newborns.

Studies have shown that "Infant mortality can be related to parenting behavior in many primate species" (M Bloomsmith et al. 2003). In an eight year time-span (August 2000—July 2008), 14 chimpanzees from newborns to eight months died at NIRC (all autopsies available upon request). Their autopsies all showed the infant deaths to have been from severe trauma, multiple fractures, bites, and abrasions inflicted by cage mates. In response to the infant autopsy reports she reviewed, Dr. Margaret Peppercorn stated that "helpless infant chimpanzees were time and again noted to have been torn apart by older chimpanzees with no indication of the laboratories having made any attempts to better protect them" (Declaration of Margaret Peppercorn, M.D.). Infanticide has been seen in the wild at times of socio-ecological stress. In the laboratories, the stress of captivity could also be a factor (Capaldo and Peppercorn 2012). To evaluate the causes of high infant mortality, such as overcrowding or the poor monitoring of social dynamics, more information would be needed from the laboratories. However, laboratories are unwilling to provide the necessary information.

[40] Personal account from anonymous former primate lab caregiver to NEAVS

Infant deaths in laboratories also can be caused by the rejection of offspring by mothers in laboratories, which is relatively common.[41] One result of inappropriate living conditions in laboratories is maternal incompetence (Brune et al. 2006). In a 2003 study, 30% of mothers demonstrated inadequate maternal behavior, and the baby was removed from the mother (M Bloomsmith et al. 2003). In another study, "Of the wild-born females, 82% (18/22) were competent mothers. For females that had been reared in captivity with their mothers for 1 to 12 months, 71% (5/7) were competent. For females that had been removed from their mothers immediately and reared in a nursery by humans, only 14% (1/7) were competent (Brent, Williams-Blangero, and Stone 1996)." Given the historically typical policies of labs, the large majority of chimpanzees currently held in labs were taken from their mothers or, some of the earlier ones, captured in the most traumatic way imaginable, helplessly clinging on while their mothers and much of their families were killed as they tried to protect them.

Chimp captured to be sent to Lindi Camp research station, Belgian Congo, circa 1958.
Photographer: G. Rollais
Courtesy of E. Hooper

Bucky, raised in a laboratory.
Photo © PETA

A laboratory nursery.
Photo © M. Nichols

Diarrhea

Gastrointestinal problems are common in chimpanzees in labs, and can be chronic, severe, and intractable. This is evidenced by anecdotal evidence from laboratory caregivers and in the chimpanzees' medical records,[42] and the fact that 16% of chimpanzee autopsies (an underestimate, given the poor quality and incomplete nature of many of those procedures) indicated intestinal and/or gastric ulcerations (Capaldo and Peppercorn 2012). Chronic diarrhea

[41] For example, Dr. Roger Fouts has stated "It is well known that abandonment or loss of a parent can have devastating, if not lethal effects on the infants . . . Jane Goodall provides one of the more dramatic accounts of this when 8 year old Flint mourned himself to death after his mother Flo died. Also, it is quite common for free-living chimpanzee infants to die when they have lost their mothers, even when they are adopted by other chimpanzees. Over the past 33 years I have experienced a similar phenomenon with regard to separation and loss among young captive chimpanzees" (Fouts 2000).

[42] For example, see http://www.releasechimps.org/research/rachel (and) http://www.releasechimps.org/chimpanzees/their-stories/tom

may cause significant pain, dehydration and associated problems, and even death if not treated properly.

Studies have shown chronic diarrhea to be significantly associated with stress (Chang 2011), which may act via the disruption of intestinal permeability (Chang 2011; Yang et al. 2006). Co-morbidity with mood disorders such as anxiety and depression is common, with accumulating evidence indicating a role for a maladaptive stress response in irritable bowel syndrome (IBS) (O'Malley et al. 2011). Further, it is known that changes in gastrointestinal function are mediated by stress-induced secretion of corticotropin-releasing factor, and associated inflammation and immune activation are implicated in the generation of IBS symptoms (O'Malley et al. 2011), and also in significant increases in visceral sensitivity (Kanazawa, Hongo, and Fukudo 2011). Other manifestations of gastro-intestinal problems include anorexia and weight loss.

PTSD and Complex PTSD

Post-Traumatic Stress Disorder (PTSD) refers to a traumatic event where a "person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others" and/or experienced "intense fear, helplessness, or horror" (American Psychiatric Association and American Psychiatric Association. Task Force on DSM-IV. 2000). Clinical observations correlate with neural substrates (e.g., hippocampus) (Yehuda and LeDoux 2007; Tarr et al. 2009). As Dr. Capaldo explains, "[i]t has been established that chimpanzees' cognitive function, social needs, emotional needs, and ability to suffer not just physically but psychologically are similar to that in human primates. Why then would it not also be the case that their psychological and cognitive dysfunctioning could progress to the same level of disturbance that would make their disorder diagnosable, just as blood sugar level dysfunction, thyroid over or under activity, or other physiological maladies?" (Declaration of Theodora Capaldo, EdD.)

Chimpanzees in laboratories often suffer from psychological disorders (see Appendix K for methods of diagnosis). Relational trauma is common in chimpanzees in captivity. A baseline level of stress to which these chimpanzees have been subjected can be estimated by comparing differences between wild and captive conditions. For example, in captivity, differences in such variables as attachment and social processes; food type, variety, and availability; and habitat, significantly exceed the evolutionary and ecological conditions to which chimpanzees have adapted (Goodall 1986). Beyond the stress associated with the differential between free living and captive conditions, chimpanzee stress in confinement is exacerbated by a series of traumatic assaults and sustained trauma: biomedical procedures, the deprivation of captivity, and initial psychological ruptures from being taken from their mothers.[43] Further, studies have documented

[43] Many symptoms and vulnerability to later trauma are grounded in how an individual has been raised: "there is now compelling evidence that early life stress constitutes a major risk factor for the subsequent development of depression" (Charney and Manji 2004) and for one's ability to recover from trauma and other psychological assaults (Bradshaw et al. 2009).

humans becoming distressed from witnessing traumatic situations of others (Badger 2001; Argentero and Setti 2010; Figley 1995). Chimpanzees, as a socially aware and socially dependent species, also become distressed when they hear or see another chimpanzee experiencing a traumatic situation.

A second category of PTSD, Complex PTSD (C-PTSD) was created to accommodate the experiences of human prisoners and others who have sustained trauma over extended periods of time (Herman 1992). The physiological effects of biomedical experimentation and the accompanying sedatives or anesthetics that contribute to acute and long-term psychophysiological breakdown cannot be underestimated. Not only do both routine and experimental procedures impair health but they add to the chimpanzees' extreme fear and stressful anticipation associated with not knowing whether the approaching lab personnel would hurt or help them, or other chimpanzees, in any given moment.

Laboratory protocol and routine requires total compliance, which has profound effects on chimpanzees. For example, two chimpanzees described in Appendix D, Jeannie and Rachel, lived under persistent environmental stress in an atmosphere of fear, unpredictability, and a nearly total lack of control over their world, with a perceived omnipresent threat of violence. Herman and others make clear it that it is the victim's total dependence on the person in power that undermines their sense of agency—a sense of self as an instrument of change in one's life (Herman 2004). Each spent approximately one decade in solo caging under traumatic social and environmental stress (i.e., steel cages, artificial lights, lack of fresh air, social isolation and disruptions, restricted movement, depauperate nutrition). Each experienced a series of traumatic events during their early development. Whether wild-caught or captive-born, Jeannie experienced some form of early social disruption since she was already being used in laboratory experiments by five years old. Free-living chimpanzee young remain nearly inseparable from their mothers and are not weaned before this age (Bradshaw et al. 2008). Further, they had no way to control or assess their subjection to darting and experimental procedures, which resulted in severe stress (see case study in Appendix D and Declaration of Gloria Grow where Jeannie and others would begin screaming and rocking their cages when approached or when someone new entered the area, suggesting that, like the testimony of human hostage survivors, they were in fear of their lives.)

Both Jeannie and Rachel showed a constellation of symptoms that included disturbances in personality, social skills, and identity formation; persistent distress; and a high vulnerability to self-injury. Their behaviors were characterized by dissociation (e.g., Jeannie's rituals of "building an inner sanctuary") as well as chronic somatic ailments and overall ill health. Although their presentations varied, Jeannie and Rachel both exhibited the hypervigilance, anxiety, and affect dysregulation associated with the chronic stress of recurrent danger (Bradshaw et al. 2008). Their symptoms were pathognomonic for dissociative and attachment disorders and for Complex PTSD.

Severely stressed chimpanzee in a laboratory.
Photo courtesy of N. Megna

D.3.4.d.ii. Physiological Consequences of Stress

Stress manifests itself physiologically in numerous ways—including cellular process, impairment of immune system functioning, increased risk of disease, and onset and exacerbation of a range of somatic disorders. Further, the biological mechanisms of stress outlined below explain why stress has ramifications beyond its impact on any particular individual: successive generations, and individuals who have experienced prenatal and/or early-life stress, are destined to suffer negative consequences in adulthood.

Biological Basis of the Adverse Effects of Excessive Stress

A number of in vitro studies have shown that physical and chemical stresses generally block every important cellular process, including DNA replication, transcription, pre-mRNA processing, mRNA export, and translation, until the cells recover (Kurokawa et al. 2010). Stress, therefore, exerts its biological effects via an array of molecular mechanisms that have far reaching consequences. The principal molecular mechanisms that mediate psychological stress and affect its physiological sequelae are as follows:

Epigenetic Mechanisms: Histone Acetylation and DNA Methylation

(for references, see (Champagne 2010; Murgatroyd and Spengler 2011; R Wright 2011))

Laboratory conditions can also have adverse impacts on the genetic make-up of future generations of chimpanzees. While many heritable genetic variations are based on actual differences in genetic sequence, epigenetics is a concept whereby heritable changes in gene expression and phenotype occur by mechanisms that do not entail alterations in DNA sequences. Epigenetic mechanisms exist not just to mediate constitutive gene expression, but also to modify gene expression in response to environmental factors such as stress. A number of different mechanisms are involved. Two in particular are associated with alterations in gene expression due to psychological stress: histone acetylation and DNA methylation. Both involve modulation of the accessibility of a particular gene to the cell's transcriptional machinery, which facilitate or inhibit gene expression by physically opening up or blocking the DNA for access by it.

Many methylation "marks" on DNA are established early in life (Feinberg 2007), in order to ensure appropriate changes in gene expression and phenotype, suitable to the environment, and are stable throughout the life of the organism. Much of this methylation occurs in response to environmental triggers and exposures, such as diet, drugs, toxins—and psychological stress, as evidenced by epigenetic changes resulting from fear conditioning and maternal care (for references, see (R Wright 2011)). Genes involved in the functioning of the HPA axis are especially susceptible to stress-related epigenetic effects (RJ Wright and Enlow 2008), including the GC receptor gene, which shows increased methylation and decreased expression in suicide victims with a history of child abuse, for example (McGowan et al. 2009). Also, PTSD has been strongly associated with differential methylation of genes involved in immune function and inflammation (Uddin et al. 2010).

Alternative Splicing

The alternative splicing of gene transcripts is a powerful means of altering gene expression, and can be significantly affected by stress (Biamonti and Caceres 2009). For example, acute stress in humans has been shown to alter the splicing of 27 genes in peripheral leukocytes (Kurokawa et al. 2010).

Oxidative Damage & Aging

Mental stress also contributes to oxidative stress—and therefore oxidative damage—in the body (Hapuarachchi et al. 2003). This has been identified in students undergoing examinations, in whom DNA damage and lipid oxidation were increased (Sivonova et al. 2004), and is also observable in the lymphocytes of stressed individuals (Knickelbein et al. 2008). Psychological stress and oxidative stress and damage are strongly linked: PTSD and depression are closely associated with increased inflammation and oxidative stress (Maes 2001). Oxidative stress and damage contribute to the aging process, via reactive oxygen species (ROS) (for references, see (Videan et al. 2009)). These ROS, which are present in the body as a result of normal metabolic processes, cause damage to proteins, lipids and DNA, which may be counteracted by antioxidant defenses. Imbalance in these systems may result in higher oxidative damage and accelerated aging, resulting in age-related diseases such as neurodegenerative diseases, ophthalmologic diseases, cancer, and cardiovascular diseases including atherosclerosis, hypertension, cardiomyopathy, chronic heart failure, myocardial ischemia, and ventricular arrhythmias (for references, see (Videan et al. 2009) and (Wang et al. 2007)).

With specific regard to chimpanzees, oxidative stress and damage caused by psychological stress is of paramount importance for their welfare (for references, see (Videan et al. 2009)). This is because oxidative stress and damage are a fundamental cause of aging, and therefore of age-related health disorders and diseases. A compelling correlation between rates of aging and oxidative stress/damage is seen across many species, and mammalian lifespan is positively correlated with antioxidant levels and negatively correlated with oxidative damage. Chimpanzee lifespan is approximately half that of humans, despite many other biological similarities, and evidence was recently obtained to support the hypothesis that this was due to accelerated aging of chimpanzees as a result of greater oxidative damage and lower antioxidant capacity. It has been demonstrated that chimpanzees have significantly higher levels of biological markers of oxidative stress, a higher peroxidizability index, higher levels of pro-oxidants, and decreased levels of antioxidants. Not only does this lead to increased aging, but also to associated age-related health problems such as cardiovascular disease/cardiomyopathy (for references, see (Videan et al. 2009)) although, as described earlier, of a different sort than found in humans.

Chimpanzees, therefore, are by default at a significantly higher risk of age-related problems compared to humans. Psychological stress—inherent and unavoidable in the laboratory

environment—leads to even greater oxidative stress and oxidative damage. These exacerbate the already high rates of these phenomena in chimpanzees, leading to greater adverse physiological and health effects. While the consequences for all chimpanzees in laboratories are serious, they may be particularly so for those individuals who have been used in HIV and hepatitis C research (the greatest areas of chimpanzee research in recent years). Exposure to these viruses has been associated with cardiomyopathies in humans, as has exposure to SIV (Simian Immunodeficiency Virus—a virus similar to HIV that causes AIDS-like pathology in nonhuman primates) in nonhuman primates. Further, interstitial myocardial fibrosis, the major cause of cardiac arrest and progressive heart failure in chimpanzees (N. Varki et al. 2009), may be associated with an inflammatory response that would be exacerbated by an elevation of inflammatory cytokines and influx of inflammatory cells caused by psychological stress (Lammey et al. 2008); and chronic stress has been shown to cause potentially deleterious alterations in cardiac gene expression, and of catecholamine biosynthetic enzymes. The latter is of importance as high catecholamine levels in the myocardial interstitium may cause progressive damage, be toxic to cardiac myocytes, and be associated with heart failure (for references, see (Gavrilovic, Spasojevic, and Dronjak 2010)).

Stress-related Diseases

In addition to an array of altered behavioral states with adverse consequences, psychological stress leads to enduring adverse physiological effects, including increased risk of disease, and onset and exacerbation of a range of somatic disorders (for references, see (Kurokawa et al. 2010; R Wright 2011)). When stress is excessive, repetitive, and on-going without periods of relief, it adversely affects all species through common biological pathways and mechanisms. This seems axiomatic when one considers that, in humans for example, symptoms of stress include: anger, depression, anxiety, behavioral changes, food cravings, lack of appetite, frequent crying, difficulty sleeping, tiredness, lack of concentration, chest pains, constipation, diarrhea, cramps and muscle spasms, dizziness, fainting, nervous twitches, restlessness, sexual dysfunctions, breathlessness, and a host of diseases and illnesses believed to have an associated psychogenic (as well as biological) cause that either actually leads to disease, accelerates the disease process, or intensifies its symptoms. For example, studies in human PTSD patients have shown acute stress to affect glucose metabolism, inflammation, and various components of the immune system that are associated with type 2 diabetes (Nowotny et al. 2010). Serious long-term symptoms include hypertension, heart attacks, and stroke, as well as increased risk of obesity, Alzheimer's disease, AIDS, dementia (Raber 1998), and many other grave indications (see below). Examples of the many manifestations of stress reported in peer-reviewed literature in the last two years (2010 and 2011) are summarized in Appendix L.[44]

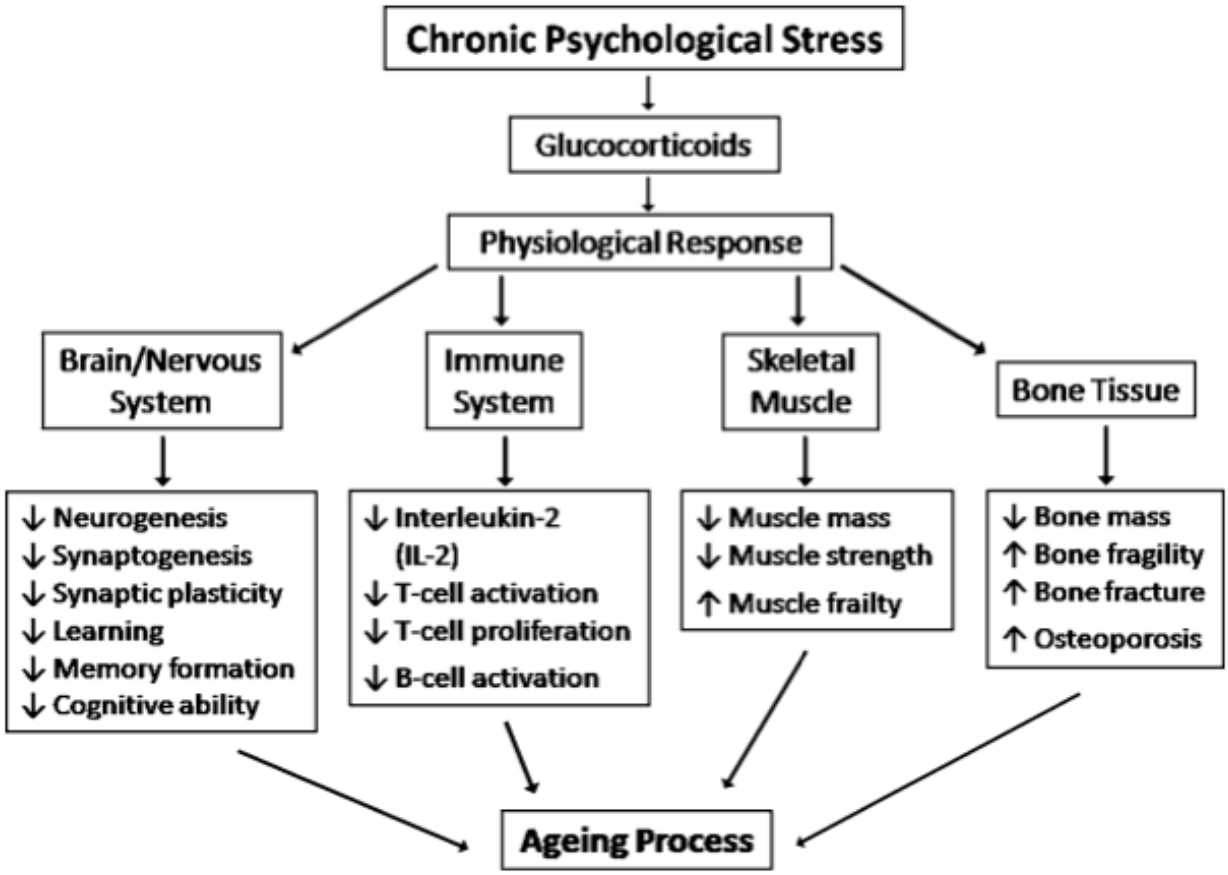
As Appendix L amply demonstrates, the adverse health outcomes of stress across many species are myriad: there is increased risk of cardiovascular events such as heart attack, stroke,

[44] In addition, many aspects of the effects of stress are discussed in detail in, "Why Zebras Don't Get Ulcers" (Sapolsky 2004). The book describes how stress kills slowly, suppressing the immune system, shutting down growth, and eroding memory and the ability to learn.

atherosclerosis and hypertension (Dimsdale 2008; Figueredo 2009; Huang et al. 2011; Olinski et al. 2002), and a greater propensity to cancer and increased risk of dying from it (Godbout and Glaser 2006; Schuller et al. 2012; Thaker, Lutgendorf, and Sood 2007). There is a higher risk of some autoimmune diseases, such as multiple sclerosis (Sorenson, Janusek, and Mathews 2011), and of gastrointestinal problems and inflammation, such as irritable bowel syndrome (IBS) (Rampton 2011). Impaired wound healing is a consequence not just of chronic stress, but also of mild and episodic stress and anxiety (for references, see (Christian 2012)). Stress causes a decrease in lean body mass, which increases susceptibility to musculoskeletal injuries. In concert with stress-induced increased visceral adiposity, this leads to an adverse metabolic profile in which levels of circulating hormones, fatty acids, cytokines, and glucose are affected, negatively affecting health and increasing risk of cardiovascular disease (for references, see (Allen et al. 2010)).

Stress activation of the hypothalamic-pituitary-adrenal (HPA) axis also accelerates the aging process in general, which contributes to adverse effects on the brain/central nervous system, the immune system, skeletal muscle, and bone tissue (see Figure 1 (Hasan et al. 2011; Kitajima et al. 1996; Porter and Landfield 1998)):

Figure 1: Stress-related acceleration of the aging process, and adverse effects on physiological function and health. *Credit: Hasan, K.M., Rahman, M.S., Arif, K.M. & Sobhani, M.E. (2011). Psychological stress and aging: role of glucocorticoids (GCs). Age (Dordr)*



Impairment of immune system function

Close interaction of the HPA axis, which is pivotal to biological systems in many species that respond to stress and regulate responses to stress,45 with the immune system is necessary for the maintenance of stress-related allostasis. For example, the psychosocial stress that is experienced chronically and to excess by chimpanzees in laboratories and in many other species may be illustrated in an example from individuals who have experienced the phenomenon known as "social defeat (Champagne 2010)." Socially defeated males display numerous behavioral and neuroendocrine changes, including reduced movement, less social interaction, greater self-administration of drugs, and increased activity of the HPA axis. Consequently, the HPA axis' impairment may lead to excessive inflammation via increases in levels of circulatory inflammatory cytokines, concomitant decreases in anti-inflammatory cytokines, and alterations in the expression of genes involved in immune activation of peripheral blood cells (for references, see ((Smith et al. 2011)). Several publications that more generally describe the adverse effects of stress on immune function, and the attendant increased susceptibility to infectious and autoimmune diseases, are listed in Table 1.

[45] The biological mechanisms of stress are complex, but in brief: stress induces the hypothalamus to release corticotropin-releasing hormone (CRH), which in turn acts upon the anterior pituitary gland to stimulate the synthesis of adrenocorticotropic hormone (ACTH). ACTH then acts upon the adrenal cortex to stimulate the production of glucocorticoids (GC) such as cortisol and corticosterone, "stress hormones," which mediate many of the biological effects of stress. The HPA acts together with the sympathetic-adrenal-medullary system (SAM). The SAM involves stress-activation of the autonomic nervous system, stimulating and inhibiting the sympathetic and parasympathetic nervous systems respectively to prepare the body for "fight or flight" (for references, see (Chang 2011; Murgatroyd and Spengler 2011; Pace and Heim 2011; Rampton 2011)).

Table 1: Examples of publications highlighting the general effects of stress on immune function and disease susceptibility.

Impact on/attenuation of immune system function
Beaulieu JM et al. (2008). A beta-arrestin 2 signaling complex mediates lithium action on behavior. Cell 132, 125–136.
Dhabhar FS & McEwen BS (1999). Enhancing versus suppressive effects of stress hormones on skin immune function. Proc. Natl. Acad. Sci. U. S. A. 96, 1059–1064.
Frieri M (2003). Neuroimmunology and inflammation: implications for therapy of allergic and autoimmune diseases. Ann. Allergy Asthma Immunol. 90, 34–40.
Hawkley LC & Cacioppo JT (2004). Stress and the aging immune system. Brain Behav. Immun. 18, 114–119.
Quan N et al. (2001). Social stress increases the susceptibility to endotoxic shock. J. Neuroimmunol. 115, 36–45.
Yang EV & Glaser R (2002). Stress-associated immunomodulation and its implications for responses to vaccination. Expert Rev. Vaccines 1, 453–459.
Yin D et al. (2000). Chronic restraint stress promotes lymphocyte apoptosis by modulating CD95 expression. J. Exp. Med. 191, 1423–1428.
Yin D et al. (2006). Chronic restraint stress modulates expression of genes in murine spleen. J. Neuroimmunol. 177, 11–17.
Zhang Y et al. (2008). Restraint stress induces lymphocyte reduction through p53 and PI3K/NF-kappaB pathways. J. Neuroimmunol. 200, 71–76.
Zorrilla EP et al. (2001). The relationship of depression and stressors to immunological assays: a meta-analytic review. Brain Behav. Immun. 15, 199–226.
Increased susceptibility to infectious & autoimmune disease
Cao L et al. (2007). Chronic foot shock induces hyperactive behaviors and accompanying pro- and anti-inflammatory responses in mice. J. Neuroimmunol. 186, 63–74.
Reiche EM et al. (2004). Stress, depression, the immune system, and cancer. Lancet Oncol. 5, 617–625.
Shi Y et al. (2003). Stressed to death: implication of lymphocyte apoptosis for psychoneuroimmunology. Brain Behav. Immun. 17 (Suppl 1), S18–S26.

In many, if not all, mammalian species, stress and distress (such as symptoms of depression, hyper- vigilance, anxiety, etc.) induce impairment of immune function and inflammatory responses, notably the production and secretion of cytokines—small proteins that communicate between different cells to regulate biological processes, such as immune function (for references, see (Christian 2012) and (Sorenson, Janusek, and Mathews 2011)). Humans who suffer from post-traumatic stress disorders (PTSD, Complex PTSD) have long been known to have increased cytokine levels, both in the plasma and in the central nervous system; to have impaired Natural Killer Cell activity; to have lower total T lymphocyte counts; and also to harbor epigenetic changes that exert a lifelong impact on immune and inflammatory function (for references, see (Pace and Heim 2011)). Adults with depression also show greater inflammatory responses to vaccinations (Glaser et al. 2003); neuropeptides involved in the stress response are thought to accentuate pathophysiological sequelae in critically ill individuals (Papathanassoglou et al. 2010); and in healthy humans, 49 different genetic pathways are affected by stress including genes associated with the immune system (Nater et al. 2009). Further studies intend to detail such effects on specific tissues and organs (Cole 2010).

Adverse Physiological Sequelae of Psychological Stress are Initiated Prenatally/in Early Life, and are Heritable

The adverse psychological and physiological effects of stress thus far described are of great concern for the welfare of chimpanzees currently residing in laboratories. They also raise concerns over their appropriateness as models for research, given the wide and significant likely impact of stress on their health, as described above. However, there are other crucial ramifications of stress that further confound the prospect of using chimpanzees in research protocols now or in the future, whether they have been born/bred/reared in a laboratory environment, or are the offspring of wild caught chimpanzees—or both.

Laboratory-born chimpanzees have been exposed to excessive stress prenatally via their mothers, and then subsequently as infants in a lab environment, often without adequate and appropriate maternal contact and care. If their parents or their grandparents lived in laboratories, and/or were born of parents who lived in laboratories and/or endured being wild-caught, then their ancestors experienced highly stressful lives and will have been psychologically and physiologically affected by the adverse consequences described earlier. Even if a chimpanzee that meets these criteria is subsequently afforded as stress-free a life as possible—which evidence shows is not possible in a laboratory environment—the consequences of the nature of their early lives, and of the lives of their ancestors, inherently and unavoidably lead to the same adverse effects as if they had continued to experience excessive stress in their adult lives.

The effect of adverse experiences in early life on adult psychopathology is widely accepted. As philosopher Jean-Paul Sartre opined, “Childhood decides” (for references, see (Murgatroyd and Spengler 2011)). Underlying this is the principle that the development of biological systems that respond to stress—notably the HPA axis—is adversely affected before birth and during infancy,

and that these effects persist into later life. It is known that early-life/prenatal exposure to maternal stress leads to altered ACTH responsiveness; dysfunction of feedback regulation of the HPA axis (Heim et al. 2002; Heim et al. 2008); and altered autonomic nervous system activity that leads to modulation of immune function that may begin *in utero* (for references, see (R Wright 2011)). Social isolation in several species leads to neuroendocrine changes, increased cortisol, and ensuing behavioral problems (for references, see (Champagne 2010)). Maternal inflammation during pregnancy (as a result of infection, though it is hypothesized stress-related inflammation could induce similar outcomes) may lead to increased risk of neurodevelopmental disorders such as schizophrenia and cerebral palsy (for references, see (Christian 2012)). Physiological sequelae include cardiovascular disease and metabolic disorders such as diabetes (for references, see (Kinnally et al. 2011)); compromised immune function, including poor lymphocyte proliferation upon infection and reduced placental transfer of antibodies during pregnancy (for references, see (Christian 2012)); autoimmune disorders, chronic obstructive lung disease, asthma, and obesity (for references, see (Chang 2011)). Pivotal to these adverse health outcomes are the aforementioned stress-related epigenetic processes and oxidative damage.

It has been known for some time that the adverse effects of early-life stress on later-life stress adaptation are mediated via DNA methylation of gene regulatory regions (Bird 1986). Some methylation patterns of DNA may be partially inherited, while some may be set during prenatal development (for references, see (Kinnally et al. 2011)). Cord blood samples of infants of mothers with late-pregnancy depression show altered methylation of the GC receptor promoter, which also predicts elevated salivary cortisol in early life (Oberlander et al. 2008).

Transgenerational effects of stress—as well as of other environmental factors—are a result of daughter cells inheriting DNA methylation patterns (and resulting phenotypes) during cell division in development (Fukuda and Taga 2005). Examples include the transgenerational impact of nutrition, in which prenatal protein restriction affects the methylation status of the GC receptor, in turn affecting the growth and metabolism of first and second-generation offspring (Zambrano et al. 2005). Matrilineal transmission of the effects of diethylstilbestrol (DES) occurs via hypomethylation, causing increased risk of cancer through two generations (Newbold, Padilla-Banks, and Jefferson 2006). In many species, the transmission of differences in maternal behavior occurs through successive generations (for references, see (Champagne 2010)).

E. Benefits of and Capacity for Retirement

Ensuring the swift and timely retirement of chimpanzees who are not needed in research is critical to carrying out the CHIMP Act's overall purpose "to provide for the lifetime care" of such animals (42 U.S.C. §283m). *See also* Pub. L. No. 110-170 (the "Chimp Haven is Home Act"); 153 Cong. Rec. E2670-02 ("The system envisioned by the CHIMP Act is now a reality in Keithville, Louisiana. It is called Chimp Haven."). As demonstrated below, sanctuaries are the only way these chimpanzees have of obtaining any semblance of psychological and physical well-being. Sanctuaries not only provide for the chimpanzees' physiological well-being, but also psychological well-being. For example, in addition to an environment without the stress of experimentation, they provide:

- more indoor and outdoor space (Butler 2011),
- daily access to fresh air,
- nesting material and other environmental modulations (such as the provision of various activities, objects, and foods to explore), which give the chimpanzees a sense of physical safety while being allowed to exercise a greater degree of choice and freedom even within the confines of captivity (Butler 2011),
- greater opportunities for mental and social stimulation that challenges and energizes cognitive functioning,
- socially compatible housing with informed oversight of the fission-fusion social rhythm of chimpanzees as well as carefully monitored re-socialization and social interactions to allow individuals to learn how to regulate affective responses to stress,
- a more individualized approach to rehabilitating chimpanzees suffering from post-traumatic stress disorder as a result of years or decades in laboratories,
- an environment free of threat—or, as in the wild, encompassing the spatial opportunity to escape such threat, and
- the ability to make choices (even within the confines of captivity) regarding who to live with, where to go, what to eat, and in which activities to participate in.

Thus, sanctuaries provide chimpanzees an opportunity to heal from past physical harm and trauma and recover from social and mental deprivation to the extent possible (Reimers, Schwarzenberger, and Preuschoft 2007). They provide an adaptive medium in which renewed confidence and identity can emerge. For examples of chimpanzees' recovery experiences, see Appendix D.

Sanctuaries have outdoor protected acreage and indoor night rooms. Some have indoor day rooms as well. At STC, one of two U.S. sanctuaries with populations comparable in size to those of laboratories, each chimpanzee group has access to an entire moated island that ranges from 3-5 acres for each group. The maximum group size is 26 members. This averages 5,050 square feet per chimpanzee and larger for the smaller groups. To meet individual needs, the sanctuary is

currently constructing cubic space for chimpanzees needing to be individually housed that equals 1,100 sq ft/24,900 cubic ft. Outdoor forested woods are available to residents of Chimp Haven, which average 14,533 ft.^{2} for groups that average 15 members. Smaller play yards allow roughly 5,776 ft.^{2} for groups that average 12 chimpanzees. Indoor bedrooms offer roughly 202 ft.^{2} for, on average, up to 3 chimpanzees. In all cases, square footage available to the chimpanzees at these sanctuaries vary depending on the types of enclosures, needs of an individual or a group, and what space a given chimpanzee wishes to use (NEAVS correspondence with NAPSA sanctuaries).[46]

In addition to enhancing chimpanzees' generic needs as a species, sanctuaries also address their needs as individuals. Since psychological damage occurs at the individual level, an institutional approach to chimpanzee care is by definition insufficient. For example, some chimpanzees allowed a single object in a lab, such as a tire, may want to continue to use a similar object to provide a sense of security. Once such security is achieved they may give up that object never to return to it again. However, others may find such reminders highly re-traumatizing. Hence, this is another example of how crucial it is that the intervention and rehabilitative approach is individually-based and care tailored to specific strategies that serve a given individual at a given time in her/his life. At existing chimpanzee sanctuaries, through sessions with the caregiver and/or other chimpanzees, there is an effort to help rebuild confidence and competence physically and socially, revitalizing psychological coping strategies, environmental control, and positive anticipation.

All members of the North American Primate Sanctuary Alliance (NAPSA, formerly the Alliance of North American Chimpanzee Sanctuaries) far exceed the standards of the Animal Welfare Act (AWA), while, as demonstrated supra, laboratories are often unable to meet these already inadequate standards (The Humane Society of the United States and Project R&R: Release and Restitution for Chimpanzees in US Laboratories/NEAVS 2010) (see Appendix F for examples of recent laboratory AWA violations). However, there is space for all federally owned and supported chimpanzees in NAPSA facilities, which meet the high standards set by the Global Federation of Animal Sanctuaries. NAPSA membership includes Chimp Haven, currently the only federally-approved chimpanzee sanctuary. Thus, as stated below, if given adequate funding, NAPSA is willing and ready to accept all federally owned and supported chimpanzees. As stated to the NCRR on April 14, 2010 (Alliance of North American Chimpanzee Sanctuaries 2010) (Exhibit 23):

1) With appropriate financial commitment for lifetime care, logistical arrangements and construction/renovation of housing, our alliance has the expertise to maintain not just 80-120 chimpanzees, but the entire community of government owned chimpanzees currently in U.S. laboratories (approx. 500).

[46] See Exhibit 15, the PBS film Chimpanzees: An Unnatural History, for sanctuary footage.

2) Seven of the eight member sanctuaries currently care for former research chimpanzees. Three of the sanctuaries care for chimpanzees experimentally exposed to infectious agents.

3) The Alliance member sanctuaries provide a level of care exceeding the minimum requirements of the Animal Welfare Act. The goal for each sanctuary is not to meet the legal requirements but to surpass those standards in keeping with the care appropriate for chimpanzee welfare. The chimpanzees live in large enclosures with both indoor and outdoor spaces, in appropriate social groups and with extensive environmental enrichment programs. Sanctuaries offer increased welfare at lower cost than the research environment.

4) Each member sanctuary provides emergency and preventive veterinary care to their chimpanzees, either through experienced consulting veterinary agreements or staff veterinarians.

5) All chimpanzees would be housed in indoor/outdoor areas in social groups appropriate to their needs. Transfer of chimpanzees to individual sanctuaries would be coordinated with the Alliance to determine the best placement and provide a central point of contact for NCRR and the laboratories. Chimpanzees would be transferred from the laboratories with social partners whenever possible. Given the experience of Chimp Haven and other Alliance member sanctuaries, former research chimpanzees can be successfully relocated from a laboratory to a sanctuary and integrated into large social groups with little disturbance. With the appropriate planning, a caring and experienced staff, and space for group formation at the sanctuary, the chimpanzees usually acclimate within a few weeks.

(6) All records (medical, behavioral, housing, history) would be transferred to the receiving sanctuary at least three months prior to the scheduled transfer. Proprietary research information may be redacted.

A collage of life in sanctuary at Fauna.
Photos courtesy of Fauna Foundation Sanctuary

Aerial view of multi island STC sanctuary in Florida.
Photo courtesy of STC

Chimpanzees in sanctuaries are given blankets to build night nests.
Photo courtesy of Chimpanzee Sanctuary Northwest

Natural setting and social bonding at STC.
Photo courtesy of STC

Environmental enrichment at Chimp Haven.
Photo courtesy of Chimp Haven

Environmental enrichment at STC.
Photos courtesy of STC

Environmental enrichment at Fauna.
Photo courtesy of Fauna Foundation Sanctuary

Natural setting at Chimp Haven.
Photo courtesy of Chimp Haven

Natural setting at Primate Rescue Center.
Photo courtesy of Primate Rescue Center

Environmental enrichment at the Center for Great Apes.
Photo courtesy of the Center for Great Apes

F. The Proposed Regulation is Cost-Effective

The clear economic advantages of retiring chimpanzees to sanctuary are discussed above in Section D.2. As demonstrated, retiring unneeded chimpanzees to sanctuary would save taxpayers tens of millions of dollars over the lifespan of the chimpanzees currently languishing in federally-funded laboratories.

Conclusion

Congress enacted the CHIMP Act in 2000 to provide for the retirement of chimpanzees who are "not needed" in research to more cost-effective and ethologically appropriate sanctuaries in order to provide for their "lifetime care." To accomplish this objective, the legislation authorized the Secretary to "determine" when chimpanzees are "not needed" and hence eligible to be retired. However, over twelve years later, many chimpanzees continue to languish in laboratories, even though the vast majority are not being used in active research protocols; elderly, sick, and psychologically ill chimpanzees continue to be held; and many have been in laboratories for over a decade. Thus, the goal of the CHIMP Act has yet to be realized, in large part because of the lack of defined criteria for when a chimpanzee is "not needed" and because the laboratories have financial incentives for continuing to hold onto chimpanzees for whose maintenance they continue to receive federal grant money. Promulgation of criteria for determining when chimpanzees are "not needed" for research, including clear, specific, and enforceable criteria, would go a long way to implementing the important goals of this legislation and help ensure that chimpanzees who are eligible for retirement do not continue to languish in laboratories—at the expense of their psychological and physical well-being and millions of taxpayer dollars.

We urge the Secretary to promulgate the proposed regulation, including criteria for making this statutorily authorized determination—the all important gateway to insuring that hundreds of chimpanzees who have been subjected to years of trauma, confinement, and research, can live out the remainder of their lives in sanctuaries capable of providing for their physical and psychological well-being.

Respectfully submitted,

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Senator Bob Smith
Lead Senate Sponsor of the CHIMP Act

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