Physiological and Welfare Concerns of the At-Risk Chimpanzee Population—A Literature Review

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Executive Summary

BACKGROUND

Chimpanzees (*Pan troglodytes*) are our closest relatives in the animal kingdom and their use in NIH-supported behavioral and biomedical research has over the decades provided significant insights into the causes and treatments of a range of devastating human diseases. Much of what scientists know regarding the pathogenesis and the correlates of immunity against hepatitis A, B, C, D, and E viruses stem from studies using chimpanzees. Research on these animals has led to the development of diagnostic tests and vaccines against hepatitis A and B, along with monoclonal antibody therapies. These animals served as experimental models for several other diseases and recently have been shown to display markers of Alzheimer's disease. Despite these scientific advancements, there are important factors to consider when using chimpanzees for research purposes that create uncertainty or difference in opinions regarding the justification for using chimpanzees. To address this, the National Institutes of Health (NIH) enforced a moratorium on chimpanzee breeding in 2007 resulting in a decline of laboratory research using these animals. In 2013, the NIH declared its decision to reduce significantly the use of these animals in NIH-supported research and to retain only a small number of animals for projects that meet certain animal welfare and bioethical criteria. Subsequent to this, NIH Director Dr. Francis Collins announced in November 2015 that the NIH had "phased out all previously active biomedical research protocols using chimpanzees…no new biomedical research projects have been approved." Therefore, all NIH-owned chimpanzees are eligible for retirement in accordance with the Chimpanzee Health Improvement, Maintenance, and Protection Act (CHIMP Act). The discontinuation of biomedical research protocols using chimpanzees, and in particular a ban on breeding these animals, has created an increasingly aging population of chimpanzees.

The population of captive, federally owned chimpanzees residing at non-sanctuary facilities requires relocation to the NIH-supported federal sanctuary operated by Chimp Haven. The NIH has devised a plan (1) for the safe relocation of retirement-eligible chimpanzees into the sanctuary system, while ensuring their long-term welfare. Many of these animals experience age-related ailments, which will complicate the transport and relocation process. Aging chimpanzees experience among other conditions cardiovascular and renal disease, obesity, diabetes and arthritis, which may be exacerbated by relocation. Conducive measures for managing stress, weight, and overall health are needed for successful relocation, acclimation to novel surroundings, and long-term care. As the chimpanzee population ages, the successful diagnosis and management of diseases are necessary. An important focus of the NIH is to provide direction for the relocation and overall welfare for the retirement-eligible chimpanzees.

NIH will create a Working Group of the Council of Councils to assess factors that put chimpanzees at risk during relocation to the Federal Sanctuary. The Council of Councils provides advice to the Division of Program Coordination, Planning, and Strategic Initiatives which includes the Office of Research Infrastructure Program which is responsible for management of the chimpanzee program and relocation of chimps to the Sanctuary. An essential part of this process requires a review of literature related to the physiological and general health considerations for chimpanzees that might put them at–risk during relocation. At-risk chimpanzees have a greater risk of experiencing severe adverse events during the transfer and relocation process. If safety factors are not considered, the relocation process may take a fatal toll on older frail animals. Trained staff at each facility are available to address the health

concerns of each animal, therefore minimizing the incidence of mortality and ensuring the success of quarantine and socialization with other animals at the sanctuary. The goal of this literature review is to facilitate discussion among scientific experts with knowledge in veterinary medicine and animal welfare to inform the scientific community on how to relocate these retirement-eligible chimpanzees and maintain their long-term care. Based on the literature, it is important to develop (i) a risk assessment of the various medical conditions for transfers and introductions of aging populations of chimpanzees to another facility and (ii) general guidelines addressing the types of medical conditions that warrant more careful consideration for transfer.

EXECUTIVE SUMMARY

Chimpanzees are phylogenetically the closest living relative to human beings and they experience similar age-related ailments in the wild and in captivity (2). Scientists have long studied behavioral and biological changes in captive chimpanzees however not much has been comprehensively reported regarding guidelines for and the consequences of relocating these animals to new facilities. Within the last few years, increased reporting about chimpanzees has helped scientists to not only understand human disease, but also identify physiological and welfare considerations for these animals. A systematic review of relevant chimpanzee literature from the last 20 years highlights *cardiovascular and renal diseases, stress, obesity, osteoarthritis, and immune status* as important considerations for the relocation of retirement-eligible chimpanzees into sanctuary facilities.

Scientists agree that cardiovascular disease (CVD) is the leading cause of death in captive chimpanzees (3–10). The primary etiological agent for CVD in chimpanzees is believed to be the formation of diffuse interstitial myocardial fibrosis (4). Death in chimpanzees as a result of CVD often occurs without warning, and is believed to be caused by sudden cardiac arrhythmias (10, 11). Several cases of arrhythmia in captive chimpanzees have been reported and are linked to the progression of myocardial fibrosis. In one article (9), cardiac arrhythmias and myocardial fibrosis were observed in 42 and 81 percent of captive adult chimpanzees, respectively. This along with other studies demonstrates that there is a high prevalence of these conditions in captive chimpanzees. It has been discovered that age is a major risk factor for the development of arrhythmias. Also, the risk of CVD in chimpanzees may be determined in part by using reference blood pressure values (12). Therefore, prophylactic cardiac monitoring may help manage CVD and reduce the incidences of sudden death in aging captive chimpanzees before and after transfer.

C-reactive protein is an important biological marker for cardiac-related diseases in humans. It has been shown that this protein is not a predictor of CVD in adult captive chimpanzees (13). This supports the idea that there are different mechanisms causing CVD in chimpanzees. Also, pathogen-related co-infections (i.e., hepatitis, human immunodeficiency virus) that are present in these animals do not influence the incidences of cardiac diseases (11). These data suggest that there are other factors predicting CVD in captive chimpanzees.

Because of the prevalence of CVD in captive chimpanzees, scientists have established efforts toward the antemortem diagnosis of cardiac dysfunction. Scientists have created cardiographic reference ranges for normal adult chimpanzees to serve as a recommended baseline for monitoring cardiac function in these animals (14, 6). Electrocardiogram (ECG) readings outside of these reference ranges can provide a basis for long-term treatment of captive chimpanzees. To support this idea, scientists discovered that ECG can diagnose certain forms of CVD (pulmonary arterial hypertension and atrial fibrillation) in an adult captive chimpanzee (15). This diagnosis led to treatment with therapeutic drugs that at least, temporarily improved the quality of life. In another study (16), the congestive heart failure discovered in an adult captive chimpanzee was successfully managed for at least 2 years by the administration of a triple diuretic therapy that included *hydrochlorothiazide*, spironolactone, and furosemide. The early evaluation, diagnosis,

and intervention for animals perceived or confirmed to have heart arrhythmias are needed. Using published reference values for cardiac function (14, 6) is an integral part of this process.

Because of the confounding factors associated with using anesthesia for traditional ECG testing, some scientists recommend the use of an implantable form of an EKG monitor to measure cardiac function in captive chimpanzees (4, 8). The use of an implantable loop recorder (ILR) has enabled researchers to evaluate and diagnose arrhythmias in non-anesthetized adult captive chimpanzees that were considered high risk because of previous cardiac related-events (8). These cardiac events included the formation of *ventricular premature complexes*. An advantage of an ILR is the capture of intermittent arrhythmias, which are rarely measured by standard EKG methods. However, ILRs are unable to store long-spans of continuous data (e.g., limited to 24 hours).

Although it is unclear whether ECG and related cardiac testing (i.e., echocardiography) will improve the relocation process, it is recommended that cardiac monitoring should be a compulsory part of the routine care of captive chimpanzees. Presumably, CVD-related mortality may be avoided if animals are diagnosed and medically treated prior to transport. However, animals with end-stage CVD may be at too great of a risk for transport. This suggests that the severity of CVD may be a criterion to determine whether relocation is feasible. The CVD disorder along with other conditions should be considered for the relocation process. It is predicted that veterinary staff at non-sanctuary facilities will approve or disallow transport based on the severity of cardiac disease and/or the possible presence of co-morbidities. Because of the complex nature of CVD and other diseases that differ between animals, veterinarians must decide on transport based on each individual animal's health status.

Stress management also should be considered for the transport and relocation of chimpanzees. Deciphering the environmental and social factors that are linked with long-term stress levels is crucial for managing stress and improving overall animal welfare. Social housing structures and hierarchal status, sex, and rearing history are all factors that affect stress levels. In the wild, chimpanzees have a predilection toward multiple female and male social groups and the disruption of this structure results in diverse abnormal behaviors, such as self-injury (17). Modeling wild-type social conditions for captive animals may cause elevated levels of male aggression and surplus (isolated) males. Therefore, selecting the right type of social group for relocation of animals is significant. How the animals were reared also is significant. The time of separation from the mother (late or early) and the location of rearing (captivity vs. wild) greatly influences stress levels in chimpanzees. The social dynamic between chimpanzee and human is noteworthy. Human to animal interaction, depending on the circumstances, may be quite unpredictable and contribute to stress. The relocation of captive chimpanzees to a new environment causes inherent stress that is coupled with human-derived alterations of social groups to minimize aggression. Quantifying stress levels in animals before and after relocation provides a marker for assessing welfare.

Circulating levels of glucocorticoids, steroid hormones produced by the adrenal gland, play an important role in the stress response of an organism and may serve as an indicator of both short- and long-term stress. Cortisol, the primary glucocorticoid in primates, is also present in many biological fluids and tissues, including hair. Hair cortisol (HC) is considered a marker for long-

term stress and overall animal welfare (17, 18, 19). Scientists have developed an *in vitro* assay to measure accumulated cortisol levels in the hair of captive chimpanzees (18, 19), which is an alternative method than fecal (20) or salivary measurements (21). In one study, anesthesia correlated with elevated fecal cortisol (20), suggesting that anesthesia administration is a stressful event. Interestingly, compared to the levels measured at the former institution, HC levels in captive chimpanzees change after relocation. Overall, males experience greater changes in stress cortisol than females. In one study (17), HC levels were elevated in a group of captive chimpanzees during the first year of relocation to a new environment and then decreased in the second year. In the same report, increased HC levels were associated with aggression from alpha males toward subordinate males. These results are similar to findings that show increased aggression in the form of wounding among all male groups (22). Regarding the influence of rearing history, late-deprived (separated from their biological mothers after 333 days and reared by humans) animals showed lower levels of HC than other groups of chimpanzees. The stress-related literature outlines important recommendations such as: (i) selecting correct social groups for initial transport and relocation, (ii) minimizing aggression incidences after relocation by periodically adjusting the membership of social groups, and (iii) performing routine behavior monitoring.

In addition to stress, obesity is another important parameter to consider for the long-term welfare of captive chimpanzees. Obesity is considered a major health concern for captive primates. Obesity can be defined by several parameters—body mass index (BMI), total body weight, waist-to-hip ratio, abdominal skin folds, and waist circumference in non-human primates (23, 24). Waist circumference can be used as an index for total body fat in these animals. Obesity increases the risk of developing CVD, type 2 diabetes mellitus, hepatic dysfunction, and hypertension. Therefore, it is important to understand the effect of and how to diagnose obesity in chimpanzees for their long-term welfare. In one report, scientists developed guidelines for defining obesity in chimpanzees by assessing weight and various metabolic parameters (24). They discovered that BMI and skin fold measurements positively correlated with elevated levels of blood glucose and triglycerides, which were predictors of obesity in the female animals. In the clinical setting, CVD is linked with increased triglycerides, blood glucose, and hypertension. Therefore, the animals tested in the aforementioned study (24) may have had undiagnosed compromised cardiac function.

Further supporting the idea that obesity is linked with alterations to metabolic markers is another finding that showed a positive association between triglyceride levels and waist circumference in male and female chimpanzees (23). Also in this study was an apparent link between body weight, systolic/diastolic blood pressure, and serum glucose in female animals. Some evidence suggests that these metabolic changes in overweight animals are chronic. In one study (7), approximately 43 percent of geriatric female chimpanzees experienced chronic metabolic syndrome (i.e., elevated blood glucose, obesity). Further highlighting the prevalence of obesity in female chimpanzees, captive females that were group-housed over a 5-year period and experienced strokes also were overweight (25). In another finding (26), obese females displayed elevated systolic blood pressure levels. Taken together, these reports demonstrate a strong link between obesity and metabolic conditions that can be chronic and predispose captive animals to serious diseases. Implementing an obesity monitoring system and intervention strategies (i.e., diet regimes, blood glucose testing, increased physical activity, and reducing high blood

pressure) by using published guidelines (26, 12, 27, 24) can reduce the risk for obesity and other related conditions for chimpanzees. Because status hierarchy is essential to maintaining chimpanzee social groups and affects access to food, obesity monitoring should include attention to status.

Aging is a risk factor for inflammatory-based diseases, which are identified as ailments that present with elevated levels of pro-inflammatory cells and proteins in the blood. Although inflammatory responses are a normal reaction to infection or injury, dysregulation of these responses can lead to chronic inflammation causing illnesses, such as rheumatoid arthritis, systemic lupus, and some forms of cancer. Chronic inflammation is a risk factor for developing aging-related diseases. It has been shown that various components of the immune system are altered in a population of older chimpanzees rescued from illegal trafficking and captivity. In one report (28), higher neutrophil cell counts and platelet microparticles were observed in older captive male chimpanzees. Interestingly, these animals had an elevated BMI. There is indication that the link between increased neutrophils and age in captive chimpanzees may occur in the absence of obesity. In one article (29), clinically normal older chimpanzees displayed higher levels of neutrophils, but had a reduced overall lymphocyte count compared to younger animals. These results suggest that there may be alterations in the immune system that are part of the normal aging process, but may be exacerbated by overweightness. Managing BMI in aging chimpanzees may be important for reducing inflammatory disease risk.

Assessing the immune status of chimpanzees before and after transport is important for their successful relocation. In one finding (30), clinically normal captive chimpanzees experienced increased total white blood cell counts, interferon gamma production, red blood cell numbers, and segmented neutrophils, along with a decrease in total lymphocytes and natural killer cells immediately after transport. These immune alterations lasted up to 12 weeks post transport. There are likely a variety of reasons why these physiological changes occurred, such as stress. Nonetheless, these data support the need for allowing sufficient periods of acclimation time. The observed differences in immunological profiles between studies may be a result of unidentifiable factors (e.g., testing methods). However, the studies do agree that there are several factors that may affect the blood chemistry and immunological profile of captive chimpanzees. These changes may affect the relocation process and have a long-term effect on animal welfare. Trained veterinary staff must determine the course of treatment, if necessary, for those animals with an altered immune status.

Based on the reviewed literature, the health status of captive chimpanzees is not only important for transfer and relocation, but also for the socialization and maintenance of social groups. Regarding animal health, it is necessary to implement an up-to-date evaluation of cardiac function, appropriately manage stress and total body weight, and conduct blood component measurements. These approaches, in combination with other intervention strategies, are important for the overall health and welfare of chimpanzees as well as forming and maintaining social groups at the sanctuary. Considerations for immediate transport and relocation include mitigating stress during the transport by housing animals in familiar groups. The NIH acknowledges that in some instances, the stress of relocation may be fatal for the more frail animals.

NIH-supported facilities have trained veterinary staff to implement the aforementioned recommendations. However, it is important to note that these recommendations are incumbent on the individual animal's health status, which will likely vary between animals. Health monitoring on a case-by-case basis is necessary to ensure the successful relocation and welfare, as well as reduced mortality of chimpanzees. Veterinarians will be consulted to perform a health assessment and issuance of a health certificate of individual chimpanzees to determine if relocation is possible or to ensure safe relocation.

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