DEPARTMENT OF HEALTH & HUMAN SERVICES

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DATE: December 23, 2014

TO: Michael M. Gottesman, M.D.
Deputy Director for Intramural Research, NIH

FROM: Director, Division of Compliance Oversight, OLAW

SUBJECT: Animal Welfare Investigation - Animal Welfare Assurance A4149-01 [Case 9Y]

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your December 22, 2014 submission of additional detailed information regarding the conclusions reached by the National Institute of Child Health and Development (NICHD) Animal Care and Use Committee (ACUC) following an investigation into allegations made by the People for the Ethical Treatment of Animals regarding studies involving infant macaques. The thorough response by the ACUC provides OLAW with additional knowledge, including descriptions of ongoing refinements to the study (i.e., amending the protocol to remove some neonatal clinical procedures, defining distress behaviors, soliciting protocol review from external unaffiliated scientists), but does not materially alter the explanations provided in the initial response from October 8, 2014. As such, OLAW's original assessment and acceptance also is not changed and there is no need for further action on our part other than adding this information to the case file. We commend the NICHD ACUC for conducting such a detailed, meticulous, and thoughtful review and response. Thank you for keeping OLAW apprised on this matter.

Axel Wolff

Axel Wolff, M.S., D.V.M.

cc: Dr. Terri Clark
Dr. Richard Wyatt
Dr. Karl Pfeifer

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

www.nih.gov

December 22, 2014

TO: Axel Wolff, D.V.M.
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare

FROM: Deputy Director for Intramural Research, NIH

SUBJECT: Animal Welfare Investigations - Assurance A4149-01 (Case 9Y); Second Response

This correspondence is the second and final response to the OLAW Case 9Y which was opened on September 9, 2014 regarding studies conducted by the National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH) using infant macaque monkeys; and the companion set of allegations sent by PETA directly to the NICHD ACUC regarding Dr. Suomi's Animal Study Proposal 14-043. In addition to the comments NICHD provided in our first response to answer OLAW's inquiry; the NICHD ACUC has now completed their investigation of the allegations presented by PETA and their comments are attached.

It is my opinion that the NICHD ACUC provided a thorough and thoughtful review of the allegations presented, and I agree with their conclusions and recommendations.

Please contact me or Dr. Terri R. Clark, Director, Office of Animal Care and Use, if additional information or clarifications are required.

Michael M. Gottesman, M.D.

Attachments

cc: Dr. Stratakis
Dr. Pfeifer
Dr. Clark
Dr. Wyatt

DEPARTMENT OF HEALTH & HUMAN SERVICES

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To: Dr. Michael Gottesman
Deputy Director for Intramural Research

From: Karl Pfeifer KP
Chair, NICHD ACUC

Date: December 17, 2014

Subject: Animal Welfare Investigation – Animal Welfare Assurance A4149-01
Case 9Y – Part 2

This report describes the NICHD response to the concerns raised by Dr. Katherine Roe of the People for the Ethical Treatment of Animals (PETA) in regard to nonhuman primate research described in NICHD ASP 14-043. The research program described in ASP 14-043 addresses the role of the social environment in social and cognitive development of juvenile rhesus monkeys and also looks at interactions between genes and the social environment. One of Dr. Roe's specific concerns was that these experiments were inappropriately designated as USDA pain/distress category C. Moreover, she maintained that the research goals could be successfully accomplished using non-animal models and also that the research was not sufficiently novel to warrant the use of animals. Essentially, Dr. Roe asked us to evaluate whether NICHD had sufficiently considered principles II, III, and IV of the *US Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training*. Dr. Roe's letter and supporting documents are attached.

At our meeting on September 17, 2014, we reviewed the information provided by PETA and agreed that it was appropriate and necessary to investigate the concerns described above for the following three reasons. First, we agreed on the great importance of being very careful in our oversight of nonhuman primate research. Second, as discussed in below, we have always understood that the correct assignment of the USDA pain/distress category is not entirely straightforward in regard to this research. In fact, some of the same issues raised by Dr. Roe are ones that we discussed during our original review of the protocol in April 2014. Third, we recognized that this was a particularly useful time to review this ASP. The renewed ASP included significant new procedures for animals born in 2014. Since the birthing season for 2014

was over, it was a good time to review how those new procedures worked in practice and then based on our experiences, to consider further refinements and to determine if new information might affect the USDA classification.

A subcommittee of five members directed our investigation which included the following: 3 visits to the Poolesville facility to inspect the animals and the facility and to conduct extensive talks with the research and the animal care staff; several phone and multiple email discussions with key research and animal care staff; and discussions with animal care staff at National Primate Centers. We prepared several formal questionnaires for the PI to address specific concerns raised by Dr. Roe and by ACUC members. Our facility veterinarian also responded to these queries. In addition to these completed questionnaires, we distributed the following documents to all committee members: the PETA letter with the accompanying summary report and collection of supporting letters; USDA Policy 11 – *Painful and Distressful Procedures*; NIH OACU *Guidelines for Preparing USDA Annual Reports and Assigning USDA Pain and Distress* Categories; National Research Council Discussion –*Stress or Distress*; and OLAW FAQs describing Institutional responsibilities for scientific review. The PI's peer-reviewed manuscripts are available through PubMed but we also directly provided each member with three key recent publications that addressed the impact of nursery rearing on long-term animal welfare (http://www.ncbi.nlm.nih.gov/pubmed/23184974; http://www.ncbi.nlm.nih.gov/pubmed/22615410; http://www.psych.utah.edu/people/people/fogel/jdp/journals/1/journal1-05.pdf). To supplement our understanding of the USDA requirements, I consulted by phone and email with a key staff veterinarian at that agency. Finally, we obtained and considered information from the Office of the Scientific Director regarding the scientific review of the research described in this ASP. Progress of our subcommittee was reviewed at our meeting on October 15, 2014 and the conclusions described here were obtained after extensive discussion at our meetings of November 19, 2014 and December 17, 2014.

In regard to Scientific Review and consideration of novelty and relevance to human health and the good of society (US Government Principle II): In addressing this concern, we used OLAW FAQs (http://grants.nih.gov/grants/olaw/faqs.htm) as our primary guide.

According to NIH Intramural policies, all intramural investigators must undergo a review of their scientific research program once every four years. In accordance with this policy, the program associated with ASP 14-043 was reviewed in November 2012 by a panel constituted by the NICHD Board of Scientific Counselors. (The Board of Scientific Counselors (or BSC) is the NICHD Intramural program's external formally constituted advisory body.) The November 2012 review panel consisted of 4 scientists: 2 BSC representatives as chair and co-chair and 2 ad hoc reviewers who are specialists in the field. NICHD external reviewers are specifically charged to evaluate research significance and also the appropriateness and likely success of the research plan. The panel reviewed the research favorably. At their semi-annual meeting in June 2013, the NICHD BSC reviewed and endorsed the site visit report and the research program. No concerns about vertebrate animal research were raised in the site visit report or by the BSC. The signature of our Scientific Director in Section O of the ASP attests that the research program was appropriately reviewed and verifies the congruence of the research plans described in the ASP with those reviewed by the external reviewers.

As noted above, scientific merit and research significance are primarily addressed through external review. However, the IACUC also plays a role through its evaluation of the responses to Section D of the ASP. During our review of the ASP this fall, we asked the PI to provide an expanded version of Section D that more precisely clarified the purposes of his research. This new information was provided in two documents that are attached to our December minutes and can be supplied upon your request.

We carefully read the supporting letters provided by Dr. Roe and PETA. We are aware that several letters, especially those from Dr. Gluck and Dr. Hansen provide specific and detailed arguments that the research work performed under ASP 14-043 is not of sufficient significance to merit support by the NIH. We appreciate that scientists can disagree as to the merits of specific research programs. Therefore we have forwarded the PETA letters to our Scientific Director and asked him to share these with the NICHD BSC. *However, the unanimous conclusion of our committee is that the external review is the primary method for determining research merit and the likelihood that the protocol will contribute to human health and the advancement of knowledge. We further conclude that the information provided in response to our questions about Section D is consistent with the report of the external reviewers and that the publication of multiple peer-reviewed manuscripts is consistent with the report of the external reviewers. Therefore it is appropriate for the ACUC to conclude that the research plan is consistent with U.S. Government Principle II.*

In regard to the consideration of alternative species (US Government Principle III):
Evaluation of the appropriateness of the species is an important part of every ASP review. According to OLAW FAQs, this responsibility for addressing this issue lies with both the ACUC and the external reviewers. In our past experience, the crucial question is usually whether simpler model systems can be effectively used to address the research questions. In ASP 14-043 and in supporting documents provided as part of our investigation, the PI provided compelling reasons that justifies why a rodent (or other animal) model will not work. That is, only by using NHPs can the investigators address behaviors and manipulate a social environment that might model human cognitive development and psychology.

We note, however, that the main PETA objection is not that simpler model systems will suffice. Rather, PETA suggests that this research can be supplanted with human studies. We asked the PI to respond specifically to these concerns and his answers are available in our November minutes. His response includes supporting letters from medical researchers whose area of expertise is human behavior and psychology. As with the overall evaluation of the research scientific merit, we put primary emphasis on the external review results. The expertise of the NICHD BSC in human development and medicine is exceptionally strong. *For these reasons, our unanimous conclusion is that this ASP was sufficiently reviewed in regard to species appropriateness.*

Having made that conclusion, during our review, we identified changes in our procedures that will improve future review of NICHD NHP research. We recognize that currently we are relying on the lack of any stated concern by the external review panels as demonstration that the issue of species appropriateness was sufficiently evaluated. We will improve on our current system by having the issue of species appropriateness directly addressed by the external

reviewers since they are the scientists with the expertise in human development. Therefore, our ACUC chair will work with our Scientific Director to provide a worksheet to be included as part of future external reviews of NHP research. This worksheet will be modeled on one used by extramural researchers (http://grants.nih.gov/grants/olaw/vaschecklist.pdf) and will ask the PI to justify the species and to specifically address whether past or ongoing human research studies better address the research questions. The external reviewers can then explicitly indicate whether the PI's explanation is acceptable. The next external review for this research team is scheduled for 2016.

Similarly we will require specific external review of animal numbers in order to make full use of the expertise of the ad hoc reviewers and the BSC and try to refine the study in every possible way to minimize the use of NHPs.

In regard to USDA classification of procedures in regards to pain and distress: Based on OLAW FAQs, we considered this area of review to be primarily the responsibility of the IACUC.

To help OLAW understand our extended discussion, we provide a brief synopsis of the experiments: Each year in spring and early summer, up to 45 rhesus monkeys are born and sorted into two groups. Up to 20 infants are permanently separated from their mothers within 24 hours after birth and raised in a nursery. The other infants are raised by their mothers but are removed periodically for brief testing periods as discussed below. In 2014, for example, 14 monkeys were born on this ASP and 10 were raised in the nursery. The general scheme is described on the attached charts, *ASP Procedures,* which denotes all the experimental procedures performed under this ASP. We evaluated the pain/distress for each of these groups (mother-reared and nursery-reared) separately and with separate attention to the mothers and to the juveniles in each cohort.

Re-evaluation of mothers participating in mother rearing experiments: Our review focused on a significant new procedure for this laboratory: at 3-4 months of age (when animals are beginning to self wean), juveniles are removed from their mothers and singly housed for 25 hours for behavioral testing. This procedure is modeled on testing done at the California National Primate Research Center (see Capitanio JP et al., 2006, *Nursery rearing and biobehavioral organization*. In: Gene P Sackett et al. (eds.) Nursery rearing of nonhuman primates in the 21st Century. Springer Science + Business Media Inc., NY, pp. 191-214.), one of the groups we consulted during our investigation.

Please note that this long separation follows 4 briefer separations (up to 1.5 hours). (See the *ASP Procedures* attachment for details). Thus there is prior adaptation training for both mothers and infants.

Consistent with information from other Primate Centers, our experience is that stress to the mothers appears to be minimal and discrete. Mothers do sometimes call for their infants, especially when they first notice human caretakers entering their area. However, this vocalization has always been limited in scope and the mothers continue to interact with their cohorts and they feed and groom normally.

We considered the possible use of drug therapy such as Valium to reduce potential stress to the mothers. Our veterinary staff assured us that this was not appropriate for our protocol. That is, given the lack of symptoms associated with these separations, even the very low risk associated with use of Valium could not be medically justified.

Instead, in collaboration with the veterinary staff, the research team has proposed several refinements to the ASP to ensure minimal stress to the mothers. These refinements will be formalized in an amendment to the ASP that must be approved by the ACUC prior to beginning these experiments next summer. Specifically, the amendment will define a mechanism for multiple behavioral observations using a checklist that describes behaviors that indicate distress to the mother. If these behaviors are noted, the experiment will be terminated by early reunion of the mother and infant. *Based on the laboratory's experience this past summer and given the ASP amendment to include clear experimental endpoints, our unanimous conclusion is that in regard to the mothers, this separation procedure is appropriately labeled as column C.*

As mentioned above, the 25-hour separation follows 4 shorter separations. For the safety of the research staff, each of these separations requires sedation of the mother. Thus the 1-1.5 hour separation period includes only about 30 minutes where the mother is aware of the separation of her infant. There are no behaviors, such as continuous vocalizations, that suggest distress. *Our unanimous conclusion is that in regard to the mothers, these separation procedures are appropriately labeled as column C*

Re-evaluation of infants participating in mother rearing experiments: Our review focused first on the 25-hour separation that was a new procedure to this ASP. We reviewed this procedure carefully with the research staff and inspected the standard operating procedures and also the rooms and equipment for this experiment. We discussed veterinary and research records for this summer's experiments.

We do presume that this procedure does result in some stress or discomfort to the infants. Their eager reunion with their mothers at the end of the 25-hour test demonstrates that the infants prefer to be with their mothers. Accepting this fact, our obligations as an ACUC are twofold. First, we need to determine whether the stress is sufficient so that it would be more accurate to refer to it as distress and therefore to re-label the experiment as USDA column E. Second, and regardless of the USDA classification, we are obligated to seek ways to refine the experiment so that we cause the minimal stress and discomfort that is consistent with obtaining data necessary to address the experimental question.

Consistent with reports from other primate centers performing similar studies, there is some stress for the separated infants. Specifically, our research and veterinary staff noted one infant (of 4 tested) that particularly showed significant agitation when he came into contact with humans during his time in the test. (This contact with humans would occur as he was moved back and forth from his home cage space to the testing procedure area, during the two 5 minute periods when saliva samples were collected, and also during one behavioral test where his reaction to a human visitor was recorded for 5 minutes.) On the other hand, when this infant was removed from human contact, he calmed down. (We know this because of the cameras in the testing rooms). Overall, our veterinarian and primatologists concluded that this animal should still be classified as a column C but his reactions gave us information about the sorts of negative response we might encounter and allowed the researchers to develop refinements to limit

discomfort and stress in future studies. Therefore the following refinements will be incorporated into the ASP before resumption of the experiments next spring: First, researchers will make changes to the home cage environment to provide the sorts of enrichment that have been already demonstrated to comfort nursery reared animals. Second, researchers will install cameras in the room that acts as the home base of the animals. This will allow us the ability to monitor animals for the full 25-hour period and not just during the several hours they are being actively tested. Third, the amendment will establish behavioral criteria that will act as endpoints requiring premature termination of the experimental procedures by unification of the infant with the mother. *In regard to the infants, the USDA classification of this procedure will depend upon the specific endpoints described in the amendment. We will look at those endpoints very critically before assigning USDA category. However, given the experiences this summer and the stated goal of the researchers to terminate the procedure (if necessary) before the animals are distressed, we think it is likely that this will remain a column C classification.*

As described above, mother-reared infants are also separated for four shorter periods of 1-1.5 hours. These separations allow for behavioral testing of the infants and for collection of biological samples (mothers and infants). During each separation the mother is sedated or emerging from sedation for the first half while the infant is sedated or emerging from sedation for the second half. Sedation in each case is used as a chemical restraint to allow safer handling of the animals and is not alleviate pain. *The experience of the research staff – verified by the veterinary staff – indicates that these short-term separations are appropriately considered USDA column C.*

We also note that the PI has already amended this ASP in regard to these shorter separations to remove the following three procedures: EEG analyses on neonates, one blood draw, one CSF tap. A second amendment to remove all CSF taps is now being prepared. These changes were possible because sufficient data had been collected this summer obtained to answer the experimental questions. During our annual reviews of this ASP, we will continue to work with the PI to identify areas for further refinement.

Re-evaluation of the nursery rearing. Perhaps the main issue raised by the PETA report concerns the possibility that animals raised in the nursery are experiencing distress. In support of this idea, the PETA report cites literature that notably includes manuscripts from this PI and describing data obtained from previous iterations of this ASP. The PETA arguments are straightforward and can be summarized as follows: "This study purports to investigate the effect of social deprivation. If the experimenters are truly succeeding in creating this deprivation and altering behavioral outcomes in the process, is it not correct to label the study as causing more than transient distress and pain?" This is a reasonable question and an important one.

The PETA report implicitly and explicitly compares the current ASP to early studies from Harlow et al. at the University of Wisconsin. In these early studies, infants were separated at birth and then raised under truly deprived conditions with minimal environmental stimulus and resulting in severe behavior defecits. This is not the case with this current ASP. Rather, as described in our OLAW memo of October 2014, infants are raised with an intense environmental enrichment program. The purpose of this study is not to cause distress but to isolate the effects of the social environment on infant development. Our program includes regularly rotated toys, handling sessions with human caretakers, and a regular rotation of various food items. Infants are

within visual, olfactory, and tactile contact with one another and receive no less than 2 hours per day of physical social interaction. Infants receive surrogate cloth mothers for the first 4-8 months of life (peers are weaned from surrogates at 4 months and surrogate-reared infants keep them until they leave the nursery). We have adapted the surrogate mother to include a fleece-lined pouch that provides a hiding place and additional comfort for the infant. Additionally, nursery infants undergo a battery of cognitive and social tasks/observations, which gives them numerous daily interactions with human caregivers, occurring between 25-50% of their waking hours (and often more). Our animal care staff routinely observes nursery animals. ACUC members inspect the nursery twice each year. The ACUC also regularly reviews SOPs for nursery care. It is relevant to note that our triennial AAALAC inspection has always occurred during the late spring or early summer when the nursery is in use and that our inspectors routinely commend the NICHD NHP facility with emphasis on the richness of our enrichment program. It is therefore our conclusion that the nursery care in this facility fulfills all the measureable requirements of the *Guide for the Care and Use of Laboratory Animals* (8th edition).

Of course, the effectiveness of an enrichment program must be determined not just by tallying the inputs but also by observing the output, i.e. the animal behavior. Clearly the researchers intend to impact behavior, otherwise this research program would be pointless. In fact, multiple publications now document differences between nursery-reared and mother-reared infants in the following areas: cognitive development, anxiety in novel situation, alcohol preference, position in the social hierarchy, and stereotypic behaviors. It would be disingenuous not to note that in each case, nursery rearing moves the average behavior of the monkey toward something that humans would consider less desirable. But it is equally important to note that these are all population effects. That is, nursery rearing is not inducing a novel behavior but is increasing the frequency of a behavior that is already often observed in a normal (i.e. mother-reared) population. Moreover, other factors, for example genetic background or innate sensitivity to cortisol, also increase the frequencies of these behaviors, sometimes even more so than nursery rearing.

In addition to these manuscripts generated by the researchers, we also considered data and conclusions generated by our animal care staff. Animal caretakers evaluate each animal twice daily for physical and for psychological health. Health records therefore include information about such issues as appetite, hair loss, lethargy, or any behavior that might be evidence of stress or distress or an inability of the NHP to adapt to its social environment. In addition to these twice-daily checks, an NICDH veterinarian performs weekly evaluations of each animal. These daily and weekly evaluations are used to prescribe additional environmental enrichments and/or alterations to promote the psychological health of each animal on the protocol. Finally, in addition to these health checks, trained specialists on our staff perform formal behavioral analyses twice yearly on each animal. These analyses form the bases for independently evaluating the effectiveness of our environmental enrichment program for each animal. We recognize that each NHP is an individual and our staff develops an enrichment and housing program that is appropriate and beneficial for that animal. The ACUC reviews the veterinary care and behavioral care as part of its semi-annual review when we visit the facility in Poolesville and also by organizing additional meetings in Bethesda where the entire ACUC meets with key personnel to review the environmental enrichment SOPs and the overall success of behavioral management for NICHD NHPs.

To address the issue of USDA classification, we put primary emphasis on understanding whether the behavioral changes interfered with normal biology or social function of the animals. We focused especially on two specific behaviors associated with adult animals that had been

nursery-reared – they tend to be lower in social hierarchy and they are much more likely to exhibit stereotypic behaviors. These behaviors are especially important for three reasons: 1) the differences between nursery- and mother-reared animals are statistically significant; 2) these behaviors did not always need to be induced by specific experimental conditions but can be apparent upon simple observation; and 3) these behaviors might conceivably interfere with normal life in the colony.

Although nursery-reared animals have lower status on average, they are not behaving differently than non-nursery reared animals of the same status. Thus whatever the impact of social status on animal welfare/happiness, there is no net change in the collective colony because of nursery rearing.

The frequency of stereotypic behaviors among nursery-reared animals is clearly increased, especially in stressful situations (e.g. during observation by a human visitor). However, it is important to note that the severity of the behaviors does not increase. There is not even anecdotal evidence that nursery-reared animals show self-injury behaviors or that stereotypy interferes with daily activities such as social interactions, infant-rearing, foraging, or grooming. Our observation is that these stereotypic behaviors are more accurately viewed as effective mechanisms for coping with increased anxiety than as pathological and preventing normal social relations. In fact, nursery-reared animals are able to interact normally with mother-reared peers and their reproductive health and ability to form family units is good and is comparable to mother-reared animals. *Altogether based on our analysis of the research literature and our Program's own inspection and observation of the animals while in the nursery and after reunion with their cohorts, we unanimously conclude that nursery rearing has been appropriately labeled as column C.*

Summary

--We thank PETA for their interest in the welfare of the NHPs at the NICHD and appreciate the reasoned and passionate report that instigated this investigation.

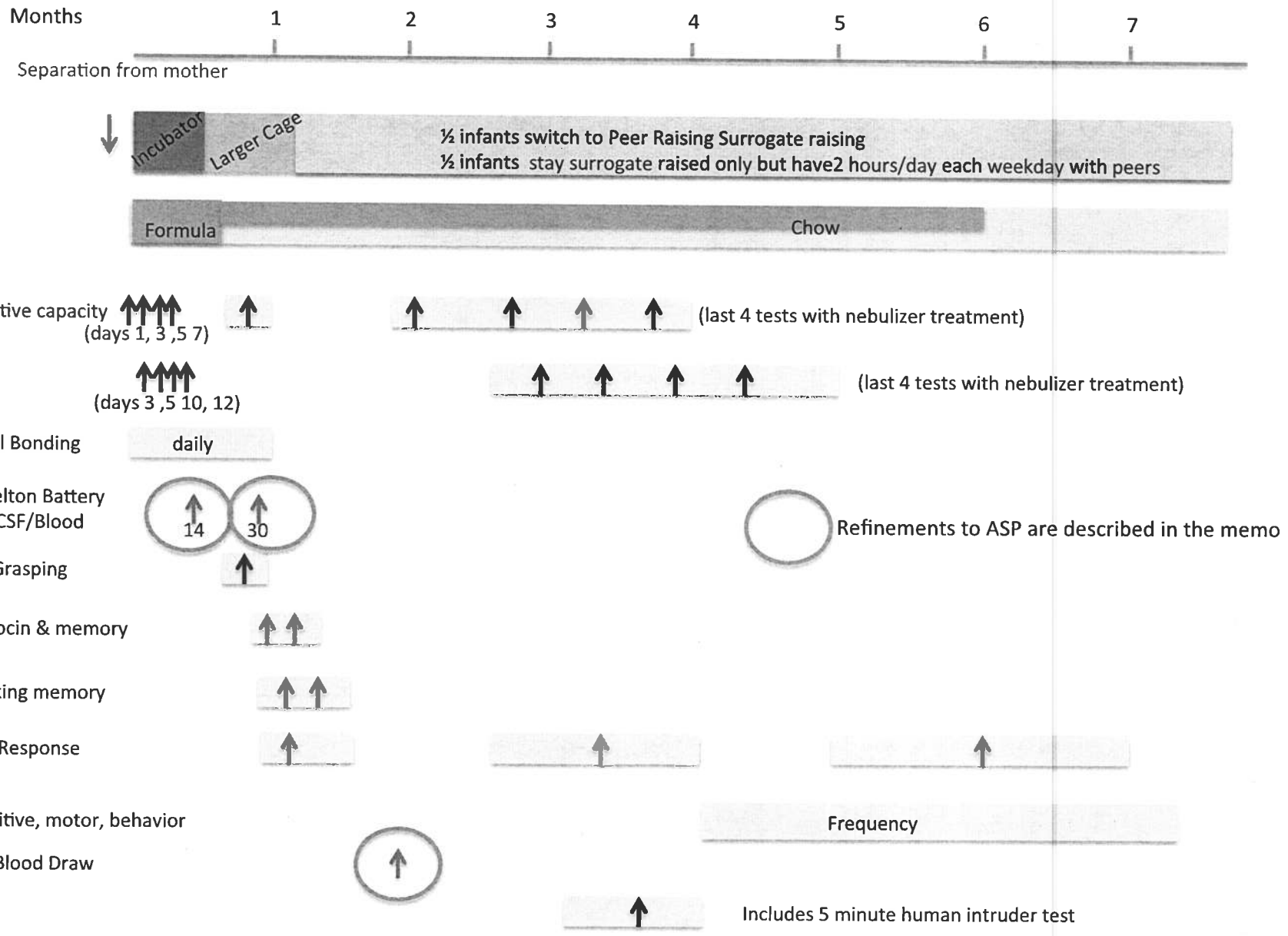
--As detailed in this report, our investigation has led to several important refinements that will protect and improve animal welfare. 1) Already, we have approved an amendment to the ASP to remove several procedures including neonatal EEG analyses, CSF taps, and one blood draw. 2) New ASP Amendments will define distress behaviors so that the 25 hour behavioral assessment performed on mother-reared infants will not have even a potential to cause distress to mothers or infants without premature termination of the behavioral assessments. 3) Changes in our external review process will make better use of the expertise of external, unaffiliated scientists. Thus we will obtain direct feedback on species appropriateness and animal numbers so that we can work aggressively to refine NHP experiments.

-- Finally, we want to emphasize that we do not consider the issues addressed in this report to be fully settled. Rather, as new data is generated regarding nursery reared NHPs and also as new standards for animal welfare emerge, we will continually re-evaluate both the USDA classification and also the enrichment program for NHPs in the nursery and otherwise. We have unanimously agreed that we will again review this ASP next October (after the completion of the

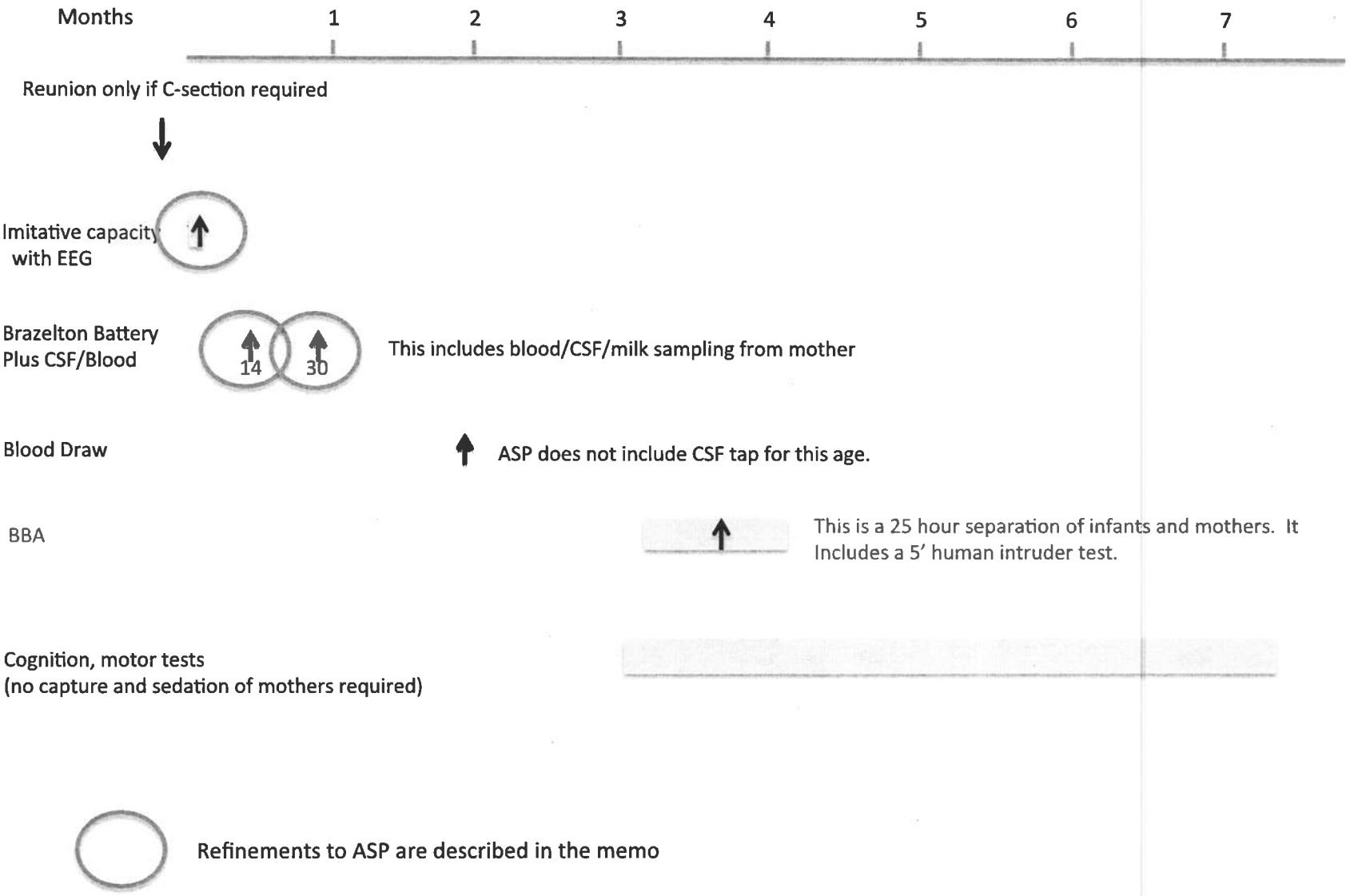
nursery study for 2015) to re-evaluate the USDA pain categorization and to consider new refinements. Our committee believes that the ethics of an animal study is never a settled issue but one that must be constantly reconsidered by evaluation of both the merits of the study and of the animal care.

We recognize that our conclusions regarding the USDA classification will likely not be satisfactory to Dr. Roe and to her PETA colleagues. We appreciate that PETA's guiding philosophy is that animal research can essentially never be justified. In contrast, however, the US Public Health Service considers that animals can be of great importance to biomedical research. We have concluded that the assigned USDA pain designations accurately and fairly portray the care and actual welfare of the NHPs on this protocol. We understand that reasonable people might disagree with our conclusions. However, we are confident that we have addressed this question appropriately, according to the Guidelines of the PHS and the USDA, and to the best of our ability. We took this issue to heart, spent considerable time and effort, and seriously considered the question, often arguing the PETA position in our debates. Our conclusions were not predetermined but followed full consideration and debate. Certainly, regardless of the USDA classification, we will continue to seek refinements to these experiments to minimize the numbers of animals used on this study and to reduce stress and discomfort.

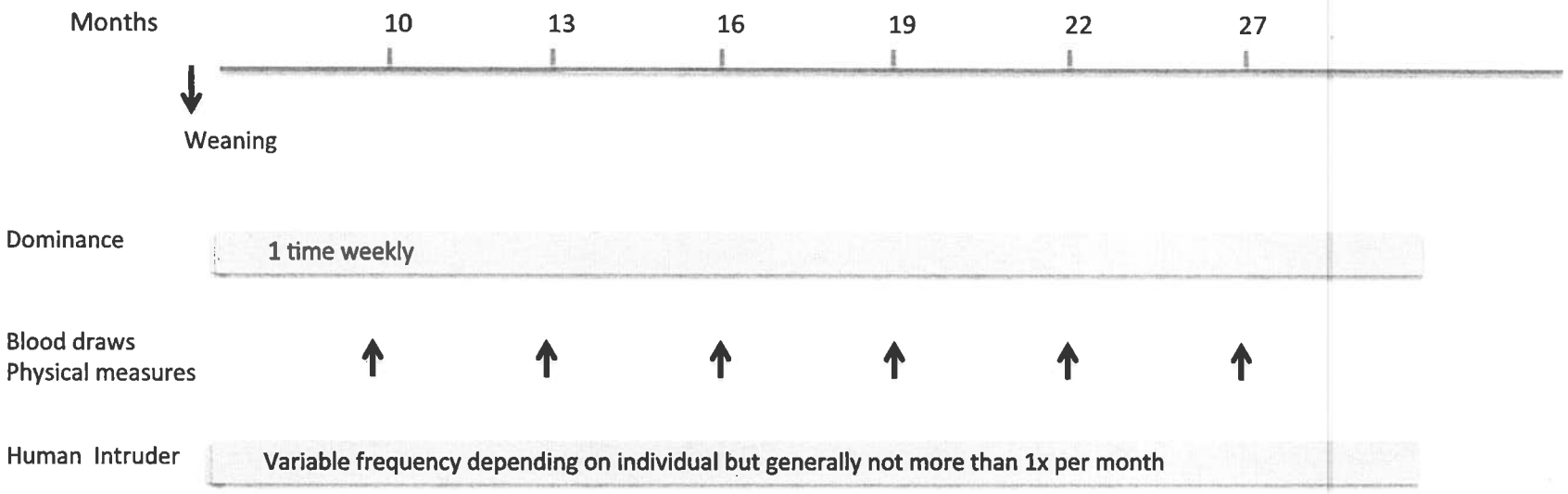
Experimental plan for nursery reared animals.



Experimental plan for mother reared animals.
Note: most procedures require capture of mother/infant and chemical restraint of the mother.



Experimental plan post-weaning.



September 08, 2014

Karl Pfeifer, Ph.D.
Chair, NICHD, ACUC
Animal Care and Use Committee Member
National Institute of Child Health and Human Development

Dear Dr. Pfeifer,

I am writing on behalf of People for the Ethical Treatment of Animals (PETA) and our more than 3 million members and supporters to express our concerns regarding the National Institute of Child Health and Human Development (NICHD) Animal Care and Use Committee's (ACUC) approval of a series of harmful psychological experiments on infant, juvenile, and adult monkeys conducted by Stephen Suomi and his colleagues at the Laboratory of Comparative Ethology (LCE). These experiments subject hundreds of monkeys to maternal deprivation, social isolation, frequent restraint, and numerous painful and stress-inducing tests in order to cause and study long-term symptoms of anxiety, depression, and social withdrawal. The NICHD ACUC, of which you are a member, reviewed and approved the Animal Study Proposal (ASP 14-043) for these procedures on April 16, 2014.

Attached is an overview and critical review of these studies prepared by PETA in consultation with specialists in the fields of bioethics, psychiatry, psychology, and primatology, based on an extensive review of animal study proposals, all relevant publications documenting the LCE studies, and more than 550 hours of video footage and hundreds of photographs taken by National Institutes of Health (NIH) experimenters. In this document, we outline our concerns about the continued ACUC approval of these studies despite the devastating psychological and physical harm that they cause to animals, their inapplicability to human health, and the availability of superior human-based

research methodologies that can identify the etiology of and treatments for mental illness in humans more effectively. We have also attached statements from independent consulting specialists outlining their scientific and ethical concerns about the project.

Additionally, we are disturbed by the fact that the substantial harm to animals in these experiments has been misrepresented in the ASPs submitted for your approval. Specifically, ASP 14-043 classifies all the procedures contained in the protocol under USDA Column C. As was clarified by the National Research Council's Committee on Recognition and Alleviation of Distress in Laboratory Animals, an animal who is unable to adapt or cope with stressors in his or her environment is in a state of distress. The experiments described in ASP 14-043 are designed to cause animals to experience both acute and chronic distress in response to stressors in their environment.

The maternal deprivation procedures described in ASP 14-043 are well known to cause long-term anxiety, depression, social withdrawal, increased vulnerability to addiction, increased susceptibility to physical illness, decreased immune response, and increased risk for self-injurious behavior. The National Research Council of the National Academies considers all these factors to be clinical evidence of chronic distress in the laboratory.

Several of the procedures in this protocol—and in the most recent past version—including the auditory reflex, response to novelty, and human intruder tests require infants to be restrained frequently and subjected to stress- and fear-inducing procedures for several hours a day, causing acute distress to the animals during the experimental trials and surely leading to residual fear and distress following the frightening sessions. Video footage of these trials taken by the experiments indicates very clearly that the animals are experiencing acute fear and acute distress that are absolutely more than "minimal" or "transient."

Given the available evidence about the nature of the procedures in ASP 14-043, we think that the experiments contained in this protocol would be more appropriately classified under USDA Column D ("Pain or Distress Relieved by Appropriate Measures") and/or Column E ("Unrelieved Pain or Distress").

This misclassification is particularly troubling because, as you know, experiments deemed to be in Column C entail less rigorous scrutiny than those in Columns D and E. In particular, at NIH, Column C studies do not require that experimenters seek out and consider alternatives to animal use or certify by signature that they are not available. Moreover, when a protocol calls for animals' exposure to stressful situations known to produce distress, as is the case in ASP 14-043, the NRC deems it crucial that the experimental protocol approved by the ACUC describe procedures for distress management.

Thus, classifying procedures as Column C downplays concerns about animal welfare, eliminates the need to describe and manage distress, and allows applicants to avoid having to defend to the ACUC why animals are needed in harmful studies in light of any non-animal alternatives that might be available. As we outline in the attached document, in the case of ASP 14-043, there are non-animal research methods already in use and readily available that could replace the use of primates in these experiments.

Having conducted research with human subjects under the guidance of the NIH Internal Review Board for seven years at the National Institute of Mental Health, I have always lauded the Intramural Research Program for having the best ethical oversight and using the most innovative and humane methodology available in the interests of science and human health. These experiments on monkeys do not meet this standard, scientifically or ethically.

We respectfully urge you to review these documents and re-evaluate these studies in light of their questionable relevance to humans and the superior non-animal research methodologies that are readily available. Such an analysis will reveal that the use of animals in these studies is not justifiable and should no longer be approved by the NICHD ACUC.

Thank you for your time. I am available to answer any questions that you may have.

Sincerely,

Katherine Roe, Ph.D.
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Expert statements regarding
NIH maternal deprivation experiments on monkeys

September 2014

the Jane Goodall Institute

I have studied the mother child bond in chimpanzees for many years in the wild (in the Gombe National Park in Tanzania) and in captivity through our ChimpanZoo program. My team has also studied infant development in baboons at Gombe. I am also familiar with a good deal of the literature on the subject.

Without doubt the mother infant bond in most primates is very strong, as it is in the human primate (and many other mammals as well). During the early months infants are totally dependent on their mothers for food, transport, contact and protection. Any disruption of this bond during the early months of life is extremely damaging to the psychological and often the physical well-being of the infant and sometimes the mother as well. Moreover, as is well known, trauma in infancy may negatively affect adult behavior.

Extensive experiments showing the damaging effects of maternal deprivation and isolation were carried out on rhesus monkeys by Harry Harlow and his students in the 1950s, 1960s and 1970s. And even after proof had been obtained, Harlow continued to devise ever more stressful situations, such as his "pit of despair." All these infants showed abnormal behavior when they grew up, sometimes self mutilating.

These experiments, getting more and more extreme, were unbelievably cruel. Indeed they are sometimes credited with having given rise to the animal rights movement in the United States. Nevertheless researchers continued working in this field after Harlow's death. And continue to do so today.

It is my understanding that monkeys are being subjected to what I consider inhumane experiments at a laboratory in Maryland that is funded by public money. I was shown a video in which infant monkeys were taking part in experiments which I considered extremely cruel and unacceptable. I understand some of these particular experiments in the video have stopped, but that part of this maternal deprivation project has recently been reapproved. I am shocked and saddened that this is so.

Jane Goodall

Jane Goodall, Ph.D., DBE
Founder, the Jane Goodall Institute
UN Messenger of Peace

UNIVERSITY OF
NOTRE DAME

DEPARTMENT OF ANTHROPOLOGY

June 9, 2014

To Whom It May Concern,

This is a response to the queries regarding the Maternal Deprivation and Psychopathology Experiments on Primates at the National Institutes of Health *via* Dr. Stephen J. Suomi and the Laboratory of Cognitive Ethology (LCE) at NICHD and affiliated researchers. My input was solicited by Alka Chandna, Ph.D., Senior Laboratory Oversight Specialist, Laboratory Investigations Department, People for the Ethical Treatment of Animals, and is based on my reading of published articles produced from the research, my experience, my knowledge of laboratory and field research, and the informational materials provided by PETA.

I am an anthropologist and primatologist with degrees in zoology and anthropology and more than 26 years working with captive and free-ranging primates (for details and CV, visit http://anthropology.nd.edu/faculty-and-staff/faculty-by-alpha/agustin-fuentes/). I am an active field worker (ongoing projects with free-raging primates and humans) and have worked (as both primary investigator and affiliated researcher) with primates in captive contexts. My work has largely been observational; however, multiple projects have involved trapping and sedating of primates, drawing of blood, collection of hair and fecal/saliva/urine samples and the attachment of telemetry devices to free-ranging monkeys. I am not opposed in principle to the use of primates in research, including a degree of invasive research. However, I do hold a strong belief that such research must be held to high ethical standards and justifications, must result in benefits for the specific individuals and/or populations of primates being studied, and must be discontinued when either of these elements are no longer valid.

Reponses to the specific queries:

While the work with the maternal deprivation model of psychopathology has provided some substantive advancement in our understanding of the behavioral, developmental, and even some genetic correlates of psychopathology in monkeys, it has not provided robust insight to human psychopathology. I do want to note that I believe important insight was provided by the early work of this primary investigator and lab in this area but that I have seen no significant addition to those early insights over the past decade. Given the current status and progress of the research (as assessed *via* the published literature), I can no longer see a potential benefit from such experimentation as is ongoing currently. I cannot consider the depicted experiments, designed to create and study psychopathology in monkeys, to be a valuable undertaking that will likely contribute to the health and well being of humans.

A colleague and I have recently argued (Ferdowsian and Fuentes 2014) that one assessment of the ethical experimentation on primates would be to set the level of acceptable risk for the use of nonhuman primates equal to that they would otherwise face in wild or similar environments, either in the course of daily life or during the course of medical treatment conducted for the benefit of the animal. Rare exceptions could involve contexts in which the nonhuman primates

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receive direct benefits of the research. I personally believe that there may be cases where the benefits to humans and other primates are immediately obvious and immense—in such cases, there may be a need to closely examine the potential impacts in the context of these ethical guidelines. However, as noted above, the current experiments of focus in this case do not fit any of these criteria in regards to benefits and levels of risk and, thus, are clearly not ethically sound, in my judgment.

Substantial research demonstrates the core importance of social bonding and multiple age-/sex-diverse social relationships during development and across the lifespan for primates. In the absence of such normative experiences, both psychological and physiological pathologies can emerge (as thoroughly documented by Suomi and colleagues for more than two decades). For primates, the socially constructed niche is intertwined with behavioral components of relationships, and it is the dynamics of these patterns and processes that affect the overall psychological and physiological health. Conditions of the experiments of interest here—radical manipulation of social contexts in developing monkeys, isolation, forcing of behavioral action *via* human manual manipulation of infants/juveniles, trauma and stress induced in infants by exposure to drugged unresponsive mothers, forced exposure to acute and deleterious auditory stimulus while nearly immobilized in small cages, and various other forms of deprivation from physical and social contact—do adversely influence the basal psychological and behavioral profiles and experiences of the subjects.

From the methodologies described in the proposals and articles and the written and visual documentation provided by PETA of actual laboratory procedures and activities, it is my assessment that the monkeys used in these experiments experience substantial psychological (and likely physiological) harm and that there is no current evidence that there will be any results from the studies that move our understanding of human psychopathology forward. It goes without saying that these experiments hold no benefits for either the individual monkeys or the populations from which they come.

Because of the harm done to the primates in these experiments and the lack of substantive contribution to the stated goals (providing insight into human health in regards to understanding the genetic and developmental contexts of psychopathology), I find them neither ethically justifiable nor defensible and urge the researchers to cease such undertakings.

Sincerely,

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July 30, 2014

In reviewing recent portions of the work emanating from the **Laboratory of Comparative Ethology** of the National Institutes of Health, headed by Dr. Stephen J. Suomi, I have focused primarily on the protocol (redacted) entitled: *Genetic and Environmental Determinants of Primate Biobehavioral Development* which was approved in March of 2011, and the 2013 Annual Report entitled *Genetic and Environmental Determinants of Primate Biobehavioral Development* of the Division of Intramural Research.

I recognize that limiting myself to those documents has drawbacks, but in defense I would say that I have been generally familiar with this line of research - the effects of early environments on biobehavioral development, for over 45 years. More than just familiar, I have in the past actively contributed to this area of research with studies on the impact of social isolation on learning and neurological substrates in rhesus monkeys (Macaca mulatta). Further, during my graduate education I was also directly mentored by Harry F. Harlow, an innovator in the use of nonhuman primate models of human psychopathology while a student at the Department of Psychology Primate Laboratory of the University of Wisconsin, Madison. I should also add that Stephen Suomi and I were students together in that program where we were both colleagues and friends.

I chose to close my primate laboratory and leave that area of research for three fundamental reasons. First, after completing my Postdoctoral Clinical Psychology Fellowship, at the Department of Psychiatry and Behavioral Sciences at the University of Washington, I lost considerable confidence in the ability of animal models to adequately represent the multi-level dynamics associated with the development of human psychopathology, particularly affective disorders, and to provide direction for successful clinical interventions. Second, as my knowledge of the impact of differential rearing conditions had on the cognitive-affective behaviors of nonhuman primates expanded, it seemed that the costs to the animals far outstripped the usefulness of the information produced. Third, as my familiarity with the area of biomedical and research ethics continued to develop, in part thanks to a Fellowship I had with the Department of Bioethics at the NIH Clinical Center and Georgetown University in 1994, I came to appreciate the complexities of the concept of moral standing and the principle of justice as it applies to the fair selection of research subjects.

In reviewing the goals and methods of the protocol and the achievements described in the Annual Report I offer the following impressions:

1. As I expected the scientific breadth of knowledge of Dr. Suomi, the laboratory Head, is quite extraordinary.

2. Despite the fact that the experimental methods described involve extravagantly harm-generating manipulations such as: mother-infant separations, socially deprived rearing, frequent Ketamine knock-downs, more than brief full-body immobilizations, deliberate provocation of fear, introduction to stranger monkeys in social contexts that involve a range of risk from minimal to severe aggression etc, the entire protocol has been placed on the USDA pain scale as Category C - that is a category appropriate for studies involving no more that momentary exposure to unrelieved pain and distress. Putting this protocol in that category would be like saying that the only significant harm for a human patient having their leg amputated would be the post surgical pain and not the cascade of blocked welfare interests and disabilities that will follow such a broadly impactful procedure.

3. While the general scientific concepts (e.g., gene/environment interactions) discussed are sophisticated and important, the ethical justification for the species used is unchanged from what one might have seen in 1965. That is, since the investigator is ethically prevented from doing the study with humans because of the harms involved, or the time and difficulty associated with valid human cross sectional and longitudinal studies of naturally occurring clinically important experiences, it is (automatically) considered ethical to do the work on nonhuman primates, who are of course selected exactly because they are sensitive to the same categories of harm.

The current investigators do not acknowledge or attempt to describe why human harms are morally relevant and animal harms ethically irrelevant. Is it the contention that nothing has changed about the ethical justification of primate research in the last decades? If this is the belief it is an unfortunate and fundamental weakness of this work.

4. I think these studies are to some extent the result of scientific momentum created by having over several decades established a large, well staffed, high level primate laboratory capable of breeding, nursery rearing, and a myriad of complex behavioral, neurological, and physiological analyses. As Jeffery Kahn, the Chair of the 2011 Institute of Medicine committee on the necessity of biomedical research on chimpanzees commented with regard the long standing chimp colonies owned or supported by the NIH "An available resource is a used resource" whether needed or not. It is important to note that a research group from the University of Wisconsin Department of Psychology recently published a study that investigated the neuroanatomical differences in brain structures concerned with emotional processing and regulation between three groups of human children with early life stress - abused, neglected, low socioeconomic status - and found smaller volumes in the hippocampus and amygdala.[1] Human studies can be done.

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[1] Jaime Hanson et al (2014). Behavioral problems following life stress: Contributions of the hippocampus and the amygdala. *Biological Psychiatry*.

5. Finally, In the end I found myself wishing that the researchers involved in this work could be convinced to use their high level of scientific, statistical, and theoretical skill toward developing animal alternatives and ways to conduct more directly meaningful human research in these areas.

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Statement from Lawrence Hansen, MD

As a neuroscience researcher for more than 30 years and a Professor in the Departments of Neurosciences and Pathology at the University of California, San Diego, for the past 26 years, I am writing to express my concern about the maternal deprivation and psychopathology experiments being performed on infant monkeys at the National Institutes of Health (NIH). In an attempt to model various human psychiatric diseases, investigators intentionally inflict severe psychological stressors upon developing infant primates, causing permanent psychopathology and/or alterations in brain structure and function. These studies raise profoundly disturbing issues about scientific and ethical "cost-to-benefit ratios" in research using our fellow primates. Both the *International Guiding Principles For Biomedical Research Involving Animals* and the *European Directive on the Protection of Animals Used for Scientific Purposes* dictate that animals should be used in research only when no alternatives are available, and that the benefits of those experiments must outweigh the cost or harm to those animals. The Guide for the Care and Use of Laboratory Animals specifies that "Using animals in research is a privilege granted by society to the research community with the expectation that such use will provide either significant new knowledge or lead to improvement in human and/or animal well-being."[3] This is certainly not the case for the maternal deprivation experiments being conducted at the NIH, for which numerous alternatives exist, and which inflict a cost upon the animals that far outweighs any theoretical scientific benefit.

The scientific objections to continuing this research are immediately obvious. If the goal is to model neuropathologic/neurophysiologic substrates of human psychiatric diseases, then these efforts are hopelessly crude and antiquated, having long been superseded by *in vivo* neuroimaging studies of human patients with the psychiatric diseases of interest. Simply conduct a search in PubMed on any psychiatric diagnosis, such as psychopathic personality disorder, depression, schizophrenia, and a host of others, and you will find dozens of current, sophisticated, state-of-the-art neuroimaging studies comparing brain structure and function in patients and controls, clearly delineating structural and functional abnormalities in human patients.[4,5,6,7,8] These patients, along with their early life experiences, genetic make-up, and medical histories, can be followed longitudinally to evaluate illness etiology and treatment efficacy.[9,10,11,12] Modern research methodology has also allowed investigators to measure the separate and interacting contribution of genes and early environmental stress in the development and neural substrates of mental illnesses in humans.[13,14,15,16,17] Postmortem studies of human brain tissue from individuals with mental illnesses or individuals carrying risk-alleles associated with psychiatric diseases are far better methods for clarifying the molecular etiologies of these complex ailments.[18,19,20] If the goal of the infant monkey psychological trauma experiments is not to eventually improve our understanding of human psychiatric diseases—as the above cited imaging, genetic, and epidemiological studies are already doing—then in the zero sum game of research funding, the National Institutes of Health (presumably referring to human health) should have nothing to do with them.

Ethical objections to continuing this research are also obvious. First impressions about what constitutes animal cruelty are almost always correct, and it is difficult even to merely read about what the investigators are doing to infant primates (baby monkeys, some might term them), without flinching. The profoundly negative effects of laboratory life on primates are well documented as are the devastating psychological consequences of maternal deprivation. It is obvious that the experimenters either lack the capacity to empathize with the primates they are traumatizing (ironically enough, its own form of psychopathology) or have hardened themselves to inflicting such suffering and long-term damage on infant primates. But the decision to engage in such systematic animal cruelty lacking commensurate human benefit cannot be left to the self-interested researchers. The money that pays for these experiments comes from taxpayers who, I am confident, would instinctively recoil in ethical revulsion from this abuse of baby monkeys, especially once they were informed of its irrelevance to human psychiatric diseases.

Lawrence A. Hansen

Lawrence A. Hansen, M.D.

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[1] Directives. Accessed on May 20 2014
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:276:0033:0079:EN:PDF
[2] International Guiding Principles for Biomedical Research Involving Animals. Accessed on May 20 2014.
http://grants.nih.gov/grants/olaw/Guiding_Principles_2012.pdf
[3] National Research Council. Guide for the Care and Use of Laboratory Animals: Eighth Edition. Washington, DC: The National Academies Press, 2011.
[4] Bora E, Fornito A, Christos P, Yucel M. (2012). Gray matter abnormalities in major depressive disorder: A meta-analysis of voxel based morphometry studies. Journal of Affective Disorders 138(1):9-18.
[5] Strakowski SM, Adler CM, Almeida J, Altshuler LL, Blumberg HP, Chang KD, DelBello MP, Frangou S, McIntosh A, Phillips ML, Sussman JE, Townsend JD. (2012). The functional neuroanatomy of bipolar disorder: a consensus model. Bipolar Disorders 14:313-325.
[6] Stiglera KA, McDonald BC, Anand A, Saykin AJ, McDougle CJ. (2011). Structural and functional magnetic resonance imaging of autism spectrum disorders. Brain Research 1380:146-161.
[7] Fitzsimmons J, Kubicki M, Shenton, ME. (2013). Review of functional and anatomical brain connectivity findings in schizophrenia. Current Opinion in Psychiatry 26(2):172-187.
[8] Frodl T, O'Keane V. (2013). *How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and* hippocampal structure in humans. Neurobiology of Disease 52:24-37.
[9] Frankle WG. (2009). Schizophrenia: Epidemiology, clinical features, course and outcome. Encyclopedia of Neuroscience. 2009, 453-458.
[10] Tottenham N. (2012). Risk and developmental heterogeneity in previously institutionalized children. J Adolesc Health 51(2 Suppl):S29-S33.
[11] Lyall K, Schmidt RJ, Hertz-Picciotto I. (2014). Maternal lifestyle and environmental risk factors for autism spectrum disorders. International Journal of Epidemiology 43(2):443-464.
[12] Helenius D, Jorgensen PM, Steinhausen HC. (2013). A three generations nation-wide population study of family load estimates in bipolar disorder with different age at onset. Journal of Affective Disorders 150(1):146-151.
[13] Grabe HJ, Schwahn C, Mahler J, Appel K, Schulz A, Spitzer C, Fenske K, Barnow S, Freyberger HJ, Teumer A, Petersmann A, Biffar R, Rosskopf D, John U, Völzke H. (2012). Genetic epistasis between the brain-derived neurotrophic factor Val66Met polymorphism and the 5-HTT promoter polymorphism moderates the susceptibility to depressive disorders after childhood abuse. Prog Neuropsychopharmacol Biol Psychiatry 36(2):264-270.
[14] Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, Pariante CM, Pace TW, Mercer KB, Mayberg HS, Bradley B, Nemeroff CB, Holsboer F, Heim CM, Ressler KJ, Rein T, Binder EB. (2013). Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. Nat Neurosci 16(1):33-41.
[15] McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonté B, Szyf M, Turecki G, Meaney MJ. (2009). Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci 12(3):342-348.
[16] Armbruster D, Muellera A, Strobela A, Lesch K-L, Brocke B, Kirschbaum C. (2012). Children under stress - COMT genotype and stressful life events predict cortisol increase in an acute social stress paradigm. The International Journal of Neuropsychopharmacology 15(9):1229-1239.
[17] Dempster E, Viana J, Pidsley R and Mill J. (2013). Epigenetic studies of schizophrenia: Progress, predicaments, and promises for the future. Schizophr Bull 39(1):11-16.
[18] Durie V, Banasr M, Stockmeier CA, Simen AA, Newton SS, Overholser JC, Dumun RS. (2013). Altered expression of synapse and glutamate related genes in post-mortem hippocampus of depressed subjects. The International Journal of Neuropsychopharmacology 16(01):69-82.
[19] Stoner R, Chow ML, Boyle MP, Sunkin SM, Mouton PR, Roy S, Courchesne E. (2014). Patches of Disorganization in the Neocortex of Children with Autism. New England Journal of Medicine 370(13):1209-1219.
[20] Kunii Y, Hyde TM, Ye T, Li C, Kolachana B, Dickinson D, Lipska BK. (2014). Revisiting DARPP-32 in postmortem human brain: changes in schizophrenia and bipolar disorder and genetic associations with t-DARPP-32 expression. Molecular Psychiatry 19(2):192-199.

NJ Johnson

Statement from Nora J. Johnson, M.B.A., M.S., Psy.D.

As a licensed psychologist specializing in clinical neuropsychology at the University of Pennsylvania, I found the videos of experiments on infant monkeys deeply disturbing for both ethical and scientific reasons. The infants were treated cruelly and forcefully, which violates this clinician's approach to research and brings into question the study's validity. If these experiments are meant to parallel or predict the psychopathy and mental illness of human infants in the care of negligent, absent, and/or abusive mothers, they fail profoundly. Contrived maternal deprivation, chronic exposure to stressful experimental paradigms, confinement, and social isolation in laboratory settings do not parallel the types of early stressors experienced by most human mental illness sufferers.[1] These laboratory versions of early-life adversity are too routinized and methodical to be representative of *any* real-world experiences faced by humans. The circumstances surrounding physical, social, emotional, and cognitive development in human beings is multifaceted and more complicated than those that can be imposed on infant monkeys reared in a laboratory. Good, creative research either cleverly sets up situations that allow behavioral and biological responses of interest to occur naturally, or it takes the form of field studies to observe real-world dynamics in a natural setting. The NIH experiments depicted on video include constraining infants in small cages and startling them with loud noises, trapping infants and then threatening them with human experimenters, or caging them with a drugged, unresponsive mother. These procedures do not accurately or creatively replicate the stressful situations believed to precipitate mental illness in humans.[2,3]

Moreover, the causes, manifestations, and treatments of mental illness can be and are successfully researched without the involvement of animals. For example, the famous and important work on prolonged exposure and post-traumatic stress disorder (PTSD) by Edna Foa, Ph.D., was conducted directly with PTSD victims. Foa is lauded for her work in PTSD and with rape victims. By working directly with patients, she has furthered the case of Prolonged Exposure as an effective mode of treating PTSD.[4,5] Neuroimaging studies with patients suffering from all forms of mental illness have already illuminated the brain mechanisms associated with these disorders.[6,7,8,9,10] Epidemiological studies that take into account the early-life experiences

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[1] McLaughlin, K. A., Green, J. G., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2010). Childhood Adversities and Adult Psychiatric Disorders in the National Comorbidity Survey Replication II: Associations With Persistence of DSM-IV Disorders. Arch Gen Psychiatry, 67(2), 124-132.

[2] McLaughlin, K. A., Gadermann, A. M., Hwang, I., Sampson, N. A., Al-Hamzawi, A., Andrade, L. H., ... & Kessler, R. C. (2012). Parent psychopathology and offspring mental disorders: results from the WHO World Mental Health Surveys. The British Journal of Psychiatry, 200(4), 290-299.

[3] Green, J. G., McLaughlin, K. A., Berglund, P. A., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., et al. (2010). Childhood Adversities and Adult Psychiatric Disorders in the National Comorbidity Survey Replication I Associations With First Onset of DSM-IV Disorders. Archives of General Psychiatry, 67(2), 113-123.

[4] Foa, E. B., Rothbaum, B. O., Riggs, D. S., & Murdock, T. B. (1991). Treatment of posttraumatic stress disorder in rape victims: a comparison between cognitive-behavioral procedures and counseling. Journal of Consulting and Clinical Psychology, 59(5), 715.

[5] Foa, E. B., Rothbaum, B. O., & Furr, J. M. (2003). Augmenting exposure therapy with other CBT procedures. Psychiatric Annals, 33(1), 47-53.

[6] Duff, B. J., Macritchie, K. A., Moorhead, T. W., Lawrie, S. M., & Blackwood, D. H. (2013). Human brain imaging studies of DISC1 in schizophrenia, bipolar disorder and depression: A systematic review. Schizophrenia Research, 147(1), 1-13.

[7] Sheridan, M. A., Fox, N. A., Zeanah, C. H., McLaughlin, K. A., & Nelson, C. A. (2012). Variation in neural development as a result of exposure to institutionalization early in childhood. Proceedings of the National Academy of Sciences, 109(32), 12927-12932.

and genetic make-up of patients with mental illness have made invaluable contributions to our understanding of illness etiology and have helped develop the most effective treatments.[11,12,13,14,15,16,17]

Conducting these studies with infant monkeys that are experimentally manipulated to exhibit symptoms of mental illness is not only cruel and invalid but unnecessary.

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[8] de Wit, S. J., Alonso, P., Schweren, L., Mataix-Cols, D., Lochner, C., Menchón, J. M., ... & van den Heuvel, O. A. (2013). Multicenter voxel-based morphometry mega-analysis of structural brain scans in obsessive-compulsive disorder. American Journal of Psychiatry, 171(3), 340-349.

[9] Mueller, S. C. (2013). Magnetic resonance imaging in paediatric psychoneuroendocrinology: a new frontier for understanding the impact of hormones on emotion and cognition. Journal of Neuroendocrinology, 25(8), 762-770.

[10] Kerestes, R., Davey, C. G., Stephanou, K., Whittle, S., & Harrison, B. J. (2014). Functional brain imaging studies of youth depression: A systematic review. NeuroImage: Clinical, 4, 209-231.

[11] Pedersen, C. B., Mors, O., Bertelsen, A., Waltoft, B. L., Agerbo, E., McGrath, J. J., ... & Eaton, W. W. (2014). A Comprehensive Nationwide Study of the Incidence Rate and Lifetime Risk for Treated Mental Disorders. JAMA Psychiatry, 71(5), 573-581.

[12] Stein MB, Schork NJ, Gelernter J. (2008) Gene-by-environment (serotonin transporter and childhood maltreatment) interaction for anxiety sensitivity, an intermediate phenotype for anxiety disorders. Neuropsychopharmacology, 33, 312–319.

[13] Arseneault, L., Cannon, M., Fisher, H. L., Polanczyk, G., Moffitt, T. E., & Caspi, A. (2011). Childhood Trauma and Children's Emerging Psychotic Symptoms: A Genetically Sensitive Longitudinal Cohort Study. American Journal of Psychiatry, 168(1), 65-72.

[14] Caspi, A., Hariri, A. R., Holmes, A., Uher, R., & Moffitt, T. E. (2010). Genetic Sensitivity to the Environment: The Case of the Serotonin Transporter Gene and Its Implications for Studying Complex Diseases and Traits. American Journal of Psychiatry, 167(5), 509-527.

[15] Bradley, R. G., Binder, E. B., Epstein, M. P., Tang, Y., Nair, H. P., Liu, W., et al. (2008). Influence of child abuse on adult depression - Moderation by the corticotropin-releasing hormone receptor gene. Archives of General Psychiatry, 65(2), 190-200.

[16] Sheikh, H. I., Kryski, K. R., Smith, H. J., Hayden, E. P., & Singh, S. M. (2013). Corticotropin-releasing hormone system polymorphisms are associated with children's cortisol reactivity. Neuroscience, 229, 1-11.

[17] Ng, C., Sarris, J., Singh, A., Bousman, C., Byron, K., Peh, L. H., ... & Schweitzer, I. (2013). Pharmacogenetic polymorphisms and response to escitalopram and venlafaxine over 8 weeks in major depression. Human Psychopharmacology: Clinical and Experimental, 28(5), 516-522.

NJ Johnson

Nora J. Johnson, M.B.A., M.S., Psy.D.

Dr. Johnson is a licensed psychologist who specializes in clinical neuropsychology at the Clinical Practices of the University of Pennsylvania in Philadelphia. She provides cognitive evaluations, and group and individual psychotherapy services to a wide range of medical inpatients and outpatients. Services include assessing patients' cognitive functioning, emotional status, and orientation; providing pain management; individual and family therapy; mediating staff and patient conflicts; and providing health psycho-education to patients. Dr. Johnson also educates hospital staff and patients about aspects of spinal cord injury, stroke, and psychosocial issues that accompany patient care. She was involved in a field research project administered collaboratively by the American Psychiatric Association and the University of Pennsylvania to revise the definitions and traits of mental disorders for the upcoming 5th edition of the *Diagnostic and Statistical Manual for Mental Disorders*. Dr. Johnson was recently elected as an ombudsman for the resident physiatrists at the Penn Institute for Rehabilitation Medicine. Past publications include workplace issues and how personality disorders affect others in the workplace.

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May 30, 2014

I viewed this video footage of infant rhesus monkeys used in psychological experiments at the National Institutes of Health (NIH) as a biological anthropologist who has spent hundreds of hours observing monkeys and apes and has written widely about patterns of thinking and feeling in animals generally. The video, provided by PETA, conveyed to me one overwhelming fact: these baby monkeys experience fear that at times escalates to terror and despair that is in no way ethically justifiable.

Over and over again in video taken by NIH experimenters, we see these little ones forced to cope with physical discomfort, confinement in cages so tiny that their bodies are pressed against the wire, and scary situations where there is no possibility of escape or comfort. Trapped in bare wire cages, they are purposefully startled, endure human intruders looming in front of them, and—worst of all for a primate with deep and enduring infant-mother bonds—forced to cope with a mother drugged by injection and strapped into an infant car seat who is suddenly completely unresponsive.

I have had the profound pleasure of spending long hours with baboon mothers and infants on the savannas of Kenya, where the monkeys are organized into matrilines (groups of related females), just as rhesus monkeys are. Knowing that the monkeys in the NIH experiments naturally occur in groups very similar to the baboons I observed, I found it excruciating to watch this video and, even worse, to know that behind the nine minutes are hundreds of hours during which these and other infants were put through these experiences repeatedly.

Consider what is evident on video. One baby monkey attempts with increasingly frenetic movements to revive his unresponsive mother during an experiment in which she was sedated to see how the baby would cope. Another baby monkey whose terrified eyes clearly indicate she cannot cope with the terrible things happening in an impossibly small cage screams during startle tests in which she is intentionally frightened by loud noises.

Primates like these monkeys don't just live in the present moment. We know to a certainty that they learn and they remember. The psychological distress that these infants were made to feel certainly would have carried forward into their lives (if indeed they were allowed by the NIH to live and not be killed).

Consider the 2012 published article by Amanda Dettmer, Melinda Novak, Stephen Suomi, and Jerrold Meyer in which physiological results of stress are shown to be reliably measurable via hair cortisol.[1] In this case, the stress was what the scientists called "relocation" stress (i.e., the young monkeys were put into a new environment with new peers). Keep in mind that while, yes, such social changes may cause distress, that particular challenge does not rise to the level of the stressors depicted in the video—and yet, the authors report the following:

[1] Dettmer AM, Novak MA, Suomi SJ, Meyer JS. (2012). Physiological and behavioral adaptation to relocation stress in differentially reared rhesus monkeys: hair cortisol as a biomarker for anxiety-related responses. **Psychoneuroendocrinology 37(2)**:191-199.

"A major finding of the present study is that peer-reared infants with higher hair cortisol levels measured early in life before relocation exhibited more anxious behaviors in the months immediately following relocation, a relationship that tended to persist for the subsequent 6 months." (p. 6)

The underlying idea in this particular experiment at the NIH is that the monkeys serve as an animal "model" for human anxiety. And in a publication by Bo Zhang and nine co-authors resulting from the sedated-mother experiment[2], the motivation is again stated to be better understanding of human anxiety. Yet, as the conclusions of a National Institutes of Mental Health workshop dedicated to animal models of anxiety disorder pointed out more than ten years ago, "The probability of developing comprehensive animal models that accurately reflect the relative influences of factors contributing to anxiety disorder syndromes is quite low" (p. 36).[3] If the benefits of these animal studies are inherently limited, and they are as much now as they were then, how can subjecting monkeys to a "prolonged reaction over many months" be justified?

It seems to me an inescapable conclusion that the "prolonged reaction over many months" resulting from the relocation experiment would be *far worse* in some of the more intensely stressful experiments, like the one featuring sedated and unresponsive mothers, that the video shows.

Taken as a group and without exception, these experiments are cruel, plunging infant monkeys into hellish conditions that they can neither control nor escape from. Ethically and morally, they have no place in science today. The cost to these animals is far too high. As we have seen, it is not as if the experiments lead to an earth-shattering breakthrough that could, in some moral calculus (though not PETA's and not mine), give us reason to think the cost was remotely worth it. This lack of justification is particularly true given the myriad of human-based research methodologies available to study the environmental, genetic, and social causes of mental illness as well as the fact that these experiments on monkeys often seek to replicate knowledge already ascertained in humans.

I cannot get the voices, eyes, and bodies of those little monkeys in the video out of my mind. There is no justification for observing small monkeys fall into terror once we have drugged their mothers—the most important beings in their whole small universe—into unconsciousness. We need to stop subjecting animals who deserve our protection and kindness to this experimental torture.

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[2] Zhang, B., Suarez- Jimenez, B., Hathaway, A., Waters, C., Vaughan, K., Noble, P. L., ... & Nelson, E. E. (2012). Developmental changes of rhesus monkeys in response to separation from the mother. **Developmental Psychobiology, 54(8),** 798-807.
[3] Shekhar A, McCann U, Meaney M, Blanchard D, Davis M, Frey K, Winsky L. (2001). Summary of a National Institute of Mental Health workshop: developing animal models of anxiety disorders. **Psychopharmacology 157(4)**:327-339.

Statement of Lori Marino, Ph.D.

I am a neuroscientist who has studied the brain and intelligence in mammals for close to 23 years—the last 19 as a faculty member at Emory University. I have published several empirical research papers on primate brains, intelligence, and behavior and am also a former research associate at Yerkes National Primate Research Center. Finally, I have been a faculty associate in the Emory University Center for Ethics for the past five years.

I have read a number of the scientific articles from the National Institutes of Health (NIH) Intramural Research Program on the effects of social deprivation on psychological development and health in rhesus macaques. Furthermore, I am quite familiar with many of the protocols utilized in these studies. Most of the studies in question are conducted by Stephen J. Suomi and his colleagues at the Laboratory of Cognitive Ethology (LCE) at National Institute of Child Health and Human Development.

Suomi's group employs a "monkey model" for a range of cognitive, emotional, social, and physical deficits, which are applied with the stated intention of understanding and mitigating human psychological problems. *The Guide for the Care and Use of Laboratory Animals* specifies that "[u]sing animals in research is a privilege granted by society to the research community with the expectation that such use will provide either significant new knowledge or lead to improvement in human and/or animal well-being."

The question at hand, therefore, is whether these criteria have been or are being met adequately by this research group. I contend that they have not, and moreover, for the past three decades, Suomi's group has operated unchecked by these important guidelines. This issue is not only an ethical one but also one that threatens the scientific validity of the work done by Suomi's group. Specifically, if these experiments are not generalizable to a human population, as is their ostensible purpose, then their external validity, specifically, and scientific validity in general are seriously compromised.

Furthermore, the *NIH Policy Manual for Animal Care and Use in the Intramural Research Program* clearly states that the principal/responsible investigator is accountable for assuring that the "proposed studies are not unnecessarily duplicative" (p .7). Here there is clear evidence that the research Suomi and his colleagues have conducted over the years is unnecessarily duplicative.

For the past three decades, Suomi's group has studied the effects of stress on rhesus monkeys by utilizing a maternal deprivation model of psychopathology, depriving hundreds of infant macaques of maternal contact and resulting in individuals with a range of severe and persistent cognitive, social, emotional, and physical deficits with no substantive evidence for applicability to human pathology. This line of research has, again, been allowed to proceed unchecked by the NIH and the scientific community.

As just one of many examples, the stated purpose of a 2012 study by Zhang *et al.* is to better understand human anxiety. Yet, after highly stressful manipulations on infant monkeys involving maternal separation and maternal sedation, the authors note: "Human studies, likewise,

have shown strong correlation between separation distress and proximity seeking behavior in infants and toddlers." (p. 805). They then go on to cite a list of studies of human children showing essentially the same effects of similar stresses at similar relative age periods. Needless to say, the effects of maternal separation on the measured behaviors are already known for humans and make tests on monkeys redundant.

At the same time, they conclude: "In sum, our data suggest that in infant rhesus monkeys, as in rodents, the motivation to maintain maternal proximity undergoes a gradual transition across development" (p. 806). Therefore, the authors engage in a "double speak" whereby their studies are "justified" by the fact that we already have similar findings for humans, while, at the same time, are too limited in external validity to be relevant to animals other than rodents. So, which is it? Do we already have these data for humans? Or, are the monkey data simply not generalizable to humans? These kinds of questions appear to continue to fly under the radar of the NIH or the scientific community.

A full 10 years before the Zhang *et al.* study, an NIMH workshop concluded: "The probability of developing comprehensive animal models that accurately reflect the relative influences of factors contributing to anxiety disorder syndromes is quite low" (p. 36). Again, the message from the NIH and the continuation of Suomi's work is nothing short of bewildering when it comes to whether this research program meets ethical and scientific standards.

As someone who has published over 100 papers in scientific journals, books, and magazines, I fully understand the way in which the language of peer-reviewed publications works. I am not "picking on" technicalities here or holding this group to a higher standard than others. I recognize what needs to be said—and how to say it—in order to keep funds flowing in one's direction. Suomi's group's papers are a good example of such rhetoric.

The study above is merely one recent example of a research program that NIH *does need to take a closer look at*. I contend that this line of research has become anachronistic and entirely insular in its methods and goals and is therefore contraindicated by ethical and scientific guidelines.

Citations

International Guiding Principles for Biomedical Research Involving Animals. Accessed on July 7, 2014. http://grants.nih.gov/grants/olaw/Guiding_Principles_2012.pdf.

National Research Council. Guide for the Care and Use of Laboratory Animals: Eighth Edition. Washington, D.C.: The National Academies Press, 2011.

Shekhar, A., McCann, U., Meaney, M., Blanchard, D., Davis, M., Frey, K., & Winsky, L. (2001). Summary of a National Institute of Mental Health workshop: developing animal models of anxiety disorders. *Psychopharmacology* 157(4):327-339.

Zhang, B., Suarez-Jimenez, B., Hathaway, A., Waters, C., Vaughan, K., Noble, P. L., Fox, N. A., Suomi, S. J., Pine, D. S., & Nelson, E. E. (2012). Developmental changes of rhesus monkeys in response to separation from the mother. *Developmental Psychobiology*, 54(8): 798-807.

Michael Radkowsky, Psy.D.

My name is Michael Radkowsky. I am a clinical psychologist, licensed in Washington, DC, and a member of the American Psychological Association. I received my doctorate in psychology in 1995 and treat individuals and couples. I have been proud to be a psychologist because I believe that our profession can contribute to the betterment of all life on our planet by promoting mental health, thoughtfulness, kindness, and empathy. If humanity is to survive not only physically but also as a moral species, we need to live in a way that respects our planet, other people, and the different species with whom we share our planet. Our conscious destruction of nature and of the complex ecosystems that support all life is putting our future existence in jeopardy; our conscious disregard of others' pain has caused vast, horrific suffering to our fellow humans and to other sentient beings.

As a psychologist, I was stunned and nauseated to read of psychologist Stephen Suomi's maternal deprivation and depression experiments done on baby monkeys and their mothers, both because these experiments are unnecessary and because I believe that they are cruel.

As a clinician, I can say that experiments that deprive baby monkeys of maternal care and prevent monkey mothers from being able to care for their young do not contribute at all to improving mental health treatment of humans. Given their lack of human health applicability and the numerous research alternatives available, these NIH maternal deprivation experiments seem merely exercises in cruelty.

The effects of maternal deprivation and depression on human infants and children are already well established; we do not need more experiments that inflict various forms of stress and adversity on infant monkeys to tell us what we already know. At birth, babies are unable to regulate their own stress and rely on a caregiver who must be attuned to their needs in order to keep them alive and feeling safe. It is through having this experience on an ongoing basis that small children learn, over time, to soothe themselves. When a caregiver is unable to be consistently present, responsive, and loving—for example, due to depression—the child never gets the message that he or she is safe. Such a child is likely to grow up fearful of the world and of others, with consequent difficulty forming relationships and functioning as a competent, capable adult. Significantly, without the experience of empathic attunement by a caregiver, children have difficulty developing empathy for others.

It is not surprising that monkeys reared under such adverse conditions at the NIH are physically, mentally, and emotionally unwell. However, despite the outcome being known, it is surprising that experiments in which these animals are deliberately subjected to extreme stress are allowed to continue. Moreover, monkeys are not humans, so any experimental findings that are true of monkeys would not necessarily be true of humans. If the researchers who are performing these experiments wish to argue that the monkeys are similar enough to humans in terms of emotional development that studies done on them can be applied to human development, then they must acknowledge that they are performing studies that cause intense pain and terror to their subjects, much as any human would experience intense pain and terror were these experiments performed on humans. How can this cruelty be justified? Simply because the experimenters have the power to do as they wish with these monkeys? I believe that it is highly unethical to inflict suffering on others simply because one can do so.

Michael Radkowsky, Psy.D.

The American Psychological Association should not permit these experiments, which I believe are in violation of several sections of the APA Guidelines for Ethical Conduct in the Care and Use of Nonhuman Animals in Research. Specifically, Guideline I (2) states that "[T]he scientific purpose of the research should be of sufficient potential significance to justify the use of nonhuman animals" and notes that "psychologists should act on the assumption that procedures that are likely to produce pain in humans may also do so in other animals." Yet, in a 2014 paper published in *The American Journal of Psychiatry*, the experimenters acknowledge that their anti-depressant experiments on monkeys cannot be applied to humans, that maternal deprivation studies on monkeys have never been confirmed as an effective way to test the efficacy of drug treatments for human mental illness, and that the only way to test treatments for human psychological disorders is in humans. Furthermore, Guideline III (C) states that "Laboratory animals are to be provided with humane care." These monkeys are certainly not being provided with humane care. Oxford Dictionary defines the verb "torture" as "to inflict severe pain on," and I believe that these monkeys are being tortured psychologically.

Importantly, many studies link the abuse of animals to violence against people, yet not much is known about what leads some people to abuse animals. Do they lack empathy, or are they able to suspend their empathy when abusing animals? Does being part of a group that is mistreating animals dilute an individual's moral compass, allowing the individual to perform actions that are not consistent with her or his sense of right and wrong? What could be done to help these individuals establish a consistent sense of empathy, which might prevent them from being cruel toward animals and perhaps also, ultimately, toward people? I believe that a useful study that could be done at the laboratory where these experiments are being performed would be to examine what factors have contributed to the experimenters being able to inflict suffering on these baby monkeys and their mothers without any demonstrable empathy. In one of the most horrifying moments, experimenters were laughing as a mother whom they had chemically sedated to be unresponsive attempted to stay awake in order to comfort her terrified child. This total lack of empathy is the true psychopathology we should be studying.

Jaymie Shanker, MD

Statement from Jaymie Shanker, M.D.

I received my undergraduate degree (Bachelor of Science) in Biological Psychology from the University of Michigan in 1988 and my MD degree from Case Western Reserve University in 1993 and completed my residency in general adult psychiatry at the Cleveland Clinic in 1997. I am licensed to practice medicine in Ohio and became Board Certified by the American Board of Psychiatry and Neurology in 1999 and was recertified in 2009.

Most of my work has been in community mental health centers. I also worked part time at the Cuyahoga County Jail for a year and at the Cleveland Veterans Administration Hospital for eight months.

My first thought about these experiments is that they are heartbreaking, and I wonder how the people who conducted these experiments overcame their inborn empathy in order to perform such cruel and pointless tests on clearly suffering animals.

But in my professional opinion, I can't imagine how these experiments could possibly relate to human mental illness. It is already well established that neglected children suffer more mental illness than their loved and supported counterparts, so I don't know what depriving an infant monkey of his or her mother (whether that means raising the infant without his or her mother or sedating the mother so that she cannot be a competent parent) could ever teach us. That these infant monkeys grow up depressed and anxious? That they have Reactive Attachment Disorder and Self-Inflicted Behaviors? That they are physically unwell? We already know that.

The head-orienting experiments are particularly puzzling. Why must a monkey be deprived of his or her mother in order to assess his or her handedness? And who cares which hand he or she prefers? How does that relate to mental illness?

The cruel experiments done to mother-reared infants are also pointless. Again, we already know that children who suffer trauma often (but not always) become mentally unstable adults. Adults who suffer trauma sometimes become mentally unstable as well. Bottom line: Trauma isn't good for anyone.

The cause of mental illness in humans is unknown, but it is clearly complex and multifactorial. Some genetic studies are promising. Abusing monkeys, however, won't get us any closer to that understanding.

I believe that the best treatments for mental illness in humans have been discovered serendipitously. For example, the first antipsychotic medication, chlorpromazine (Thorazine), was initially approved as an anesthetic agent. When schizophrenic patients woke from surgery using the new anesthetic, their psychotic symptoms had diminished. The remainder of the first generation antipsychotic drugs are "me-too" drugs, simply variations on Thorazine's chemical structure.

The very best antipsychotic drug we have (clozapine) was initially discarded because it didn't cause muscle stiffness in animals—as every other antipsychotic drug did. Thank goodness the

researchers did not entirely rely on animal experimentation data! They returned to clozapine and gave it a second chance. Millions of people with schizophrenia have been helped because researchers **did not** rely on animal data.

The best treatment we have for substance abuse is Alcoholics Anonymous, which was started by two people who began talking with each other about their struggles with alcoholism and supporting each others' sobriety. No animals were harmed in that experiment!

Human mental illness involves our brain's neocortex (in addition to other structures in the brain) and that is precisely how we differ from nonhuman animals. Our neocortices are so much larger and more complex than the animal counterpart that I cannot imagine how research on nonhuman animals can be of any value in mental illness.

In seven years, $30 million in taxpayer money has been spent. I imagine all that we in community mental health could do with $30 million. We could get people housing, medication, and substance abuse treatment—all of which are interventions known to reduce the symptoms of mental illness. It is laughable (and very sad) that so much taxpayer money is spent in cruel experiments that not only do not help humans but that cause terrible suffering to our fellow beings.

Finally, I absolutely do not consider these experiments to be ethically justifiable. Even if these experiments fully elucidated a cure for all human mental illness, I still would not consider them to be ethically justifiable. The ends do not justify the means. Intentionally inflicting suffering on sentient beings is entirely unethical. If the argument is that monkeys (or rats or mice or dogs or cats or apes) are less intelligent than humans, then by that logic we should be experimenting on intellectually challenged children and adults as they are in many cases less intelligent than cognitively intact animals—and that, of course, is patently absurd. I believe the concept of human exceptionalism is flawed. We cannot treat animals poorly in the name of potential human progress. We should do the science that we can, without causing harm. With more intelligence comes more responsibility, and I believe it is our responsibility to treat those around us well.

From 1995 to 2000, I was a doctoral student in the Clinical Psychology program at Stony Brook University. I completed all of the course work necessary for a doctorate in Clinical Psychology, and all of the required clinical hours, excluding the internship. In 2000, my interests changed, and I switched to the Social Psychology program, earning my Ph.D. in 2003.

I have taught a number of college-level courses in psychology, including Introduction to Psychology, Social Psychology, Small Group Processes, and Developmental Psychology. I also served as a teaching assistant for the undergraduate courses, Behavior Modification and Behavior Deviations in Children, and for the graduate level course, Research Methods, Correlation, and Regression.

I conducted research on substance abuse in both academic and applied settings, including an examination of the relation between the presence of alcohol problems in non-alcoholic men and family histories of alcoholism and mental illnesses (e.g., Finn et al., 1997), and the effectiveness of school-based substance abuse prevention programs (e.g., Williams, Griffin, West, Gronewold, & Macaulay, 2005).

Please see my attached curriculum vitae for further information.

In my opinion, the procedures that I witnessed on the video supplied by PETA are irrelevant to the causes and manifestations of psychopathology in humans. I see no realistic analogue for the procedure where the monkeys were isolated in medium-sized cages, subjected to the occasional staring human; nor for the procedure in which the monkeys were trapped in very tiny cages, subjected to loud noises and blasts of air. It was also difficult to envision a realistic analogue for the procedure that entailed sedation of the mother monkey, in the baby monkey's presence, aside from the relatively rare situation in which a child discovers his or her mother inexplicably passed out. However, mimicking such an occurrence did not seem to be the goal of Zhang et al. (2011), who were including the sedated mother as a "salient stimulus," unable to interfere with the infant's behaviors (p. 800). This was apparently to serve as a control condition, in comparison to an experimental condition in which the mother was absent, the purpose being to assess the infant's response to the separation. However, the presence of the unresponsive mother drew reactions of extreme distress from the monkeys, who appeared to be alarmed and frightened by her sedated state. Clearly, this is an improper control condition, as it added its own unique, unintended variable rather than simply removing a variable (e.g., separation). It is worth noting that the authors' discussion of the study's limitations revealed such obvious confounds as to render the results virtually meaningless. In an understatement, the authors acknowledge that, "[i]t is possible, therefore, that some of the significant effects in this manuscript are spurious" (p. 806).

I do not consider the depicted experiments, designed to create and study psychopathology in monkeys, to be a valuable undertaking that will likely contribute to the health and well-being of humans. Rather, the causes and manifestations of mental illness in humans are most effectively researched without the use of animals (e.g., Bouma, Ormel, Verhulst & Oldehinkel, 2008; Bornovalova, Hicks, Iacono & McGue, 2013; Brenner & Beauchaine, 2011; see also Ainsworth & Bell, 1970; Behrens, Hesse, & Main, 2007; Kobak, Cole, Ferenz-Gillies, Flemming, & Gamble, 1993; Knappe et al., 2009).

According to the American Psychological Association (2002), the *Humane Care and Use of Animals in Research* requires that "Psychologists use a procedure subjecting animals to pain, stress or privation only when an alternative procedure is unavailable and the goal is justified by its prospective scientific, educational or applied value" (8.09 [e]).

After reviewing the video provided by PETA, reading the fact sheet, "NIH Child Abuse: A PETA Investigation," and reviewing selected relevant research articles, I see no ethical justification for the experimental procedures that I witnessed in the video.

References

American Psychological Association (2002). Ethical principles of psychologists and code of conduct. *American Psychologist, 57*, 1060-1073. Retrieved May 14, 2014, from hhttp://www.apa.org/ethics/code/index.aspx?item=11

Ainsworth, M. D. & Bell, S. M. (1970), Attachment, exploration, and separation: Illustrated by the behavior of one-year-olds in a strange situation. *Child Development, 41*, 49-67.

Behrens, Kazuko Y.; Hesse, Erik; Main, Mary (2007). Mothers' attachment status as determined by the Adult Attachment Interview predicts their 6-year-olds' reunion responses: A study conducted in Japan. *Developmental Psychology, 43*(6): 1553–67. doi:10.1037/0012-1649.43.6.1553

Bouma EMC, Ormel J, Verhulst FC, Oldehinkel AJ. (2008). Stressful life events and depressive problems in early adolescent boys and girls: The influence of parental depression, temperament and family environment. *Journal of Affective Disorders 105*(1-3):185-193.

Bornovalova MA, Hicks BM, Iacono WG & McGue M (2013). Longitudinal Twin Study of Borderline Personality Disorder Traits and Substance Use in Adolescence: Developmental Change, Reciprocal Effects, and Genetic and Environmental Influences. *Personality Disorders: Theory, Research, and Treatment, 4*(1), 23-32.

Brenner, S. L., & Beauchaine, T. P. (2011). Pre-ejection period reactivity and psychiatric comorbidity prospectively predict substance use initiation among middle-schoolers: A pilot study. *Psychophysiology, 48*, 1587-1595.

Finn, P. R., Sharkansky, E. J., Viken, R., West, T. L., Sandy, J., & Bufferd, G. (1997). Heterogeneity in the families of sons of alcoholics: The impact of familial vulnerability type on offspring characteristics. *Journal of Abnormal Psychology,* 106(1), 26-36.

Kobak, R. R., Cole, H. E., Ferenz-Gillies, R., Flemming, W. S., & Gamble, W. (1993). Attachment and emotional regulation during mother-teen problem-solving. A control theory analysis. *Child Development*, 64, 231-245.

Knappe, S., Lieb, R., Beesdo, K., Fehm, L., Low, N. C. P., Gloster, A. T., & Wittchen, H.-U. (2009). The role of parental psychopathology and family environment for

social phobia in the first three decades of life. *Depression and Anxiety, 26*(4), 363–370.

Williams, C., Griffin, K.W., West, T., Gronewold, E., & Macaulay, A.P. (2005). Efficacy of a drug prevention CD-ROM intervention for adolescents. *Journal of Substance Use and Misuse, 40*, 869-877.

Zhang B., Suarez-Jimenez B., Hathaway A., Waters C,. Vaughan K., Noble P.L., Fox N.A., Suomi S.J., Pine D.S., Nelson E.E. (2002). Developmental changes of rhesus monkeys in response to separation from the mother. *Developmental Psychobiology, 54*(8), 798-807.

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Review of Maternal Deprivation Experiments on Primates at the National Institutes of Health

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This document provides a critical scientific review and assessment of continuing maternal deprivation and psychopathology studies on nonhuman primates conducted within the National Institutes of Health (NIH) Intramural Research Program. A careful analysis of Animal Study Proposals, Board of Scientific Counselors reviews, scientific publications, photographs, and videos related to these projects casts doubt on the worth of these experiments in light of advancements in the field, and offers several examples of human-based studies that successfully address precisely the questions asked by these NIH investigators. Moreover, after consulting numerous experts in the fields of anthropology, primatology, medicine, and mental health, we conclude **that given the harm caused to animals, the experiments' limited relevance to humans, the substantial financial cost, and the existence of superior nonanimal research methods that the continued use of animals in this work is scientifically and ethically unjustifiable.**

Project title: "Biobehavioral Reactivity in Monkeys"
Institute: National Institute of Child Health and Development (NICHD)
Principal Investigator: Stephen J. Suomi
Intramural Animal Study Proposals: 11-043, 14-043
Project Number: 1ZIAHD001106
Start/end: 2007–present
Funding: $907,723 in 2013 ($7,786,372 total)

At the foundation of all of the studies in question are maternal deprivation experiments conducted by Stephen J. Suomi and the Laboratory of Cognitive Ethology (LCE) at NICHD. For the past three decades, Suomi's group has utilized a maternal deprivation model of psychopathology, depriving hundreds of infant macaques of maternal contact and resulting in animals with an array of cognitive, social, emotional, and physical deficits that persist throughout their lifetimes. According to the approved Animal Study Proposal (ASP), approximately 45 macaques are selectively bred each year to carry different alleles of the 5H-TTT and MAO-1 genes, known to be risk factors for psychopathology in humans. Half of these captive-born infants are separated from their mothers within 24 hours of birth, causing great distress to mother and baby, and are hand-reared by humans in a nursery for one month and then put into a nursery with other like-reared peers, sometimes with a terrycloth-covered water bottle. Starting on their first day of birth, all infants are subject to numerous fear, stress, and pain-inducing tests. Day-old infants are forcibly restrained by experimenters for behavioral tests, such as facial imitation or head-orientation bias trials. Other experiments entail the infants being isolated in small cages, placed in unfamiliar locations, and deliberately startled by threatening human strangers, unfamiliar objects (including realistic-looking snakes, which are innately frightening to monkeys), and unfamiliar conspecifics. In one such procedure designed to measure infants' auditory startle response, newborn infants are restrained inside tiny mesh cages and placed in "startle chambers" where they are presented with unexpected loud noises. During their first few months of life, the infants are repeatedly subjected to blood draws and cerebral spinal fluid taps; hair and saliva samples are also taken. Additionally, in a project funded by the NICHD (Project 5P01HD064653; $877,229 of funding in 2013), Nathan A. Fox from the University of Maryland takes infants as young as one day old from Suomi's colony, shaves their heads, and physically restrains them for electroencephalogram testing.[1,2]

The approved ASPs for the breeding and experimentation regimen (11-043, 14-043) in Suomi's laboratory does not explain the scientific relevance of the single nucleotide polymorphisms that animals are bred to carry, their methods for selective breeding of these animals, the exact conditions they classify as "mother-rearing," the scientific purpose for numerous cognitive and biological tests

being conducted, or any risk factors associated with capture, restraint, and biological or behavioral testing that they perform repeatedly on the animals.

The NIH Policy Manual for Animal Care and Use in the Intramural Research Program clearly states that the Principal/Responsible Investigator is accountable for assuring that the "proposed studies are not unnecessarily duplicative" (p. 7).[3] Several of the experiments currently being conducted have already been performed using the same procedures and the results published.[4,5,6,7,8,9,10,11,12] The rearing procedures described have been in place for decades, and behavioral and biological data from these animals have also been collected for decades.[13,14,15,16] Repeating these test batteries and causing suffering to additional infant monkeys is required by law to be justified; however, given the limited information contained in the ASP, it is virtually impossible for a review committee to adequately evaluate the project's design or scientific merit. The LCE's approved ASP emphasizes that the purpose of the study is to model the genetic and environmental contributions to abnormal human behavior and to develop interventions for at-risk individuals. However, a comprehensive review shows that none of the aforementioned studies have resulted in the development or modification of treatments for the human mental illnesses they are purported to model.

In addition to the study designed to create and quantify mental illness in infant macaques, the LCE has also received $6,289,327 since 2007 to assess whether the laboratory-reared, mentally ill animals they created can adapt to a non-laboratory environment (Project 1ZIAHD001107). According to the approved ASPs associated with this project (11-105, 14-105), the purpose of the study is to understand "how humans of all ages and backgrounds adapt to new physical and social settings, as well as what aspects of their immediate environment might be affecting their psychological well-being." However, in their 2013 annual NIH Intramural Database report, the experimenters describe several findings related to infant-mother communication, facial processing in infants, the effect of oxytocin on monkey-human interactions, and cortisol levels in nursing mothers' milk. The discrepancy between the procedures and purposes outlined in the ASP and the reported findings from those procedures makes it difficult to evaluate the value of this study in understanding human health and behavior.

Though the ASPs for these projects claim the protocols are designed to elucidate genetic and environmental influences on pathological behavior unattainable with human participants, many resultant publications from these projects merely address whether macaques exhibit visual preferences, facial asymmetries, facial preferences, imitative behaviors, or similar hand- and head-orientation biases as those already well documented in human infants.[17,18,19,20,21] Given the wealth of knowledge about human behaviors of this sort—and the non-invasive research with humans available to further explore these same issues—these studies are gratuitous.

Project title: "Assessment of Neural and Behavioral Alterations Associated with Chronic Fluoxetine Administration in Adolescence"
Institute: National Institute of Mental Health (NIMH)
Principal Investigator: Bruno Averbeck
Intramural Animal Study Proposal: IPC-01-09
Project Number: MH002902
Start/end: 2007–present
Funding: $9,034,371 total

At NIMH, the Non-Human Primate Core purchases many of the maternally deprived, at-risk for illness animals created in Suomi's laboratory for its own battery of experiments. Some of these studies expose the animals to additional acute startle and isolation[22] in hopes of eliciting a pathological response to stress as a function of their early-adverse rearing conditions. For example, infants and juveniles are restrained inside tiny mesh cages or in restraint chairs and placed into startle chambers where they are deliberately startled by the presence of a human, loud auditory stimuli, or powerful bursts of air. To acclimate them to the chair restraint, the older animals spend up to an hour a day, every day, strapped to a chair for weeks *prior* to testing. In other experiments, the infant monkeys are caged with their mothers—who are chemically sedated so as to be unresponsive—and placed in a car seat.[23] Videos of these experiments indicate that infants are terrified and confused while they try to revive their mothers.

In addition to various oral, subcutaneous, and intramuscular administrations of drugs, some animals are surgically implanted with devices that allow intracranial administration of pharmaceuticals, requiring multiple surgeries, weeks of recovery and pain management, and constant monitoring for infection. According to the ASP, the purpose of this pharmaceutical treatment is to "define specific neural pathways important to the expression of emotional, social, or cognitive deficits associated with differential rearing histories." However, the exact drugs administered intracranially are not specified but described as "substances of interest [that] are likely to include NM concentrations of the neuropeptides oxytocin, vasopressin, CRH, MEK inhibitor PD98592, or GABA agonists such as muscimo and bicuculine, as well as genes attached to viral vectors (AAV-P11)." Without including this critical information in the ASP, there is no way for reviewers to evaluate the merits of the proposed experiments.

Some animals are injected with Interferon-alpha, which creates depressive-like symptoms in the monkeys and causes heightened sensitivity to pain, ahedonia, and anorexia. This procedure is classified as causing unrelieved pain and/or distress to those animals to whom it is administered. An unspecified number of animals in this project will be killed following pharmaceutical administration.

In their approved ASP to conduct these experiments (IPC-01-09), the experimenters argue that "these experiments could provide important insights about the pathoetiology as well as potential, novel treatments for human syndromes with social detachment." In their 2010 annual NIH Intramural Database report, they write, "A major public health concern has emerged regarding the treatment of children with psychotherapeutic drugs. This study seeks to inform this important concern." However, these statements seem to contradict other claims from this same project in a subsequent publication in *The American Journal of Psychiatry* in which the authors themselves conclude the following:

> "…[M]any findings from behavioral and biochemical studies in monkeys and other animals are not replicated in humans. Accordingly, this study cannot directly address the safety and efficacy of SSRIs in children and adolescents with psychiatric disorders. … [T]his animal model of maternal separation has never been validated as a measure of drug efficacy in humans[.] … The only way to know definitively whether SSRIs persistently upregulate SERT in humans would be to study our species"(p. 7-8).[24]

In addition to the projects and procedures described above, many animals from Suomi's LCE have been used for additional testing with the NIAAA. One project (Project Number: 1ZIAAA000214), which received $4 million dollars between 2007 and 2010, studied juvenile monkeys' response to acute social separation,[25] spontaneous alcohol consumption,[26] and even acute ethanol exposure,[27] which requires the animals to be restrained while high concentrations of ethanol are administered

intravenously. These alcohol exposure studies often result in alcohol addiction, increased aggression, and increased susceptibility to depression in macaques.[28,29,30,31] Other animals are transported to Wake Forest University to be used in Project 5U01AA014106 where they undergo additional alcohol exposure testing before being killed and dissected.[32,33,34] The Wake Forest study received $3,931,858 in funding from 2003 and 2011.

Inapplicability to human mental illness

The experimenters that are discussed above seek to justify the use of animals by positing that maternally deprived macaques model the effect of early-life stress on the development of mood and anxiety disorders in humans. In addition to fundamental differences in gene expression,[35,36,37,38] brain anatomy and physiology,[39,40,41,42] and development[43,44] among humans and other primates, these adverse environments *do not* adequately represent the type of early social and physical stressors that precipitate mental illness in human children and adults. In reality, sexual abuse, physical abuse, prenatal stress, parental drug abuse, parental mental illness and/or criminal behavior, and economic stress are more common early life traumas affiliated with later mental illness and often co-occur in affected individuals.[45,46,47] However, details regarding infants' *in utero* environment are not described in these studies, nor are details regarding the mothers' genetic makeup, rearing history, or mental health status—all of which are far likely more important contributors to the development of mental illness than the postnatal manipulations imposed by these researchers. Additionally, while macaque social structure may be as complex as human social structure, it is decidedly different from that of most modern human societies. For example, it is typical for infant macaques to stay in *constant* physical contact with their mothers for their first month of life,[48]making even the briefest separation stressful for infants as well as chronic separation more detrimental than can be expected in humans in most cultures. Therefore, any applicability of this nonhuman primate model is likely to vary dramatically across different human cultures with different social structures and traditional rearing practices. Even the "typical" mother-reared infants who are used as a control group in most of these experiments spend much of their time in barren, metal cages, and are subject to constant experimental testing, requiring multiple separations from their mother, and involving stress and/or fear-inducing tests.[22,49] These living conditions and frequent maternal separations likely impact the natural infant-mother behavior that would occur in the wild, and as reviewed below, increase the stress levels and mental health of all animals included in the study. The mother-reared infants cannot provide an accurate example of "typical" or "healthy" development for any species, and the additional stress of laboratory conditions confound the experimental stressors introduced in maternally deprived animals. Therefore, these studies using a "well controlled" nonhuman primate model fail to properly model the complex relationship between genes, early life experience, and mental illness in the human population. The evidence of this fact is that, collectively, the project has not resulted in any new treatments for human mental illness. Almost four decades ago, Stephen Suomi himself acknowledged the limited applicability that his monkey experiments would have to human mental illness. In 1977, he wrote,

> "...whether actual data obtained from nonhuman primates have added measurably to our understanding of human development is another matter....such cases are relatively rare. Most monkey data that readily generalize to humans have not uncovered new facts about human behavior; rather, they have only verified principles that have already been formulated from previous human data" (pg 203).[50]

Existing clinical research and nonanimal methodologies readily available

The principal investigators on the aforementioned projects contend that controlled studies of gene-environment interactions in humans are ethically and practically untenable. However, this contention is

inaccurate. Numerous large-scale epidemiological studies in humans have documented the effects of early life stress,[51,52,53] genetic risk,[54,55,56] and gene-environment interactions,[57,58,59,60,61,62] on abnormal social, emotional, and behavioral development. These studies include investigating the contribution of both genes and the environment in the development of mood disorders,[57,58] addiction,[63] depression,[64] and altered brain structure and function[65,66,67] in humans.

Recent human studies have also begun to unlock the complex biological and molecular mechanisms that underlie these gene and environmental interactions.[65,68,69,70] For example, McGowan et al.[65] and Klengel et al.[70] studied the interaction between early childhood trauma and genetic variation on gene transcription in the brains of humans. Similarly, in a large-scale study of nearly 200 individuals, Buchman et al.[69] tested the interaction between early-life psychosocial adversity, genetic make-up, and plasma levels of brain-derived neurotrophic factor, critical for brain development and plasticity. DNA methylation, studied in the brain tissue of monkeys killed in the NIH studies, can be non-invasively measured in monocytes and T-cells and correlated with neurotransmitter synthesis using positron emission tomography *in vivo* in humans, a technique recently used to determine the relationship between childhood aggression, DNA methylation, and serotonergic function in humans.[68] Postmortem studies using brain tissue from humans at different stages of development[71] as well as those from individuals suffering from or carrying genes associated with autism,[72,73] depression,[74] and schizophrenia[75,76] have identified critical differences in gene expression across age, species, and clinical populations. These groundbreaking studies have already begun detailing genetic *and* epigenetic effects on human brain structure, function, and development in humans suffering from mental illness—details not attainable from animal models.

Additionally, the mood-altering effects of the type of drugs being tested by the NIMH Non-Human Primate Core, including fluoxetine,[77] oxytocin,[78] diazepam,[79] and dopamanergic and serotonergic drugs such as raclopride and buspirone,[80,81] are already well documented in humans suffering from mental illness. These studies have been conducted with healthy volunteers,[82,83,84] children,[75,85,86] and patients with mental illness.[87,88] The impact that these drugs have on brain structure and function have also been evaluated in human volunteers,[78,89,90] and their neural mechanisms in healthy and ill children and adults are already well delineated.[91,92,93,94]

Impact on animal welfare

The physical and psychological harms of confining primates and other animals in laboratories and subjecting them to routine and experimental procedures are well established.[95,96] Primates experience increased stress from common laboratory procedures such as cage cleaning,[97] physical examination,[98] blood draws,[99] and restraint.[100] The mere physical presence of human experimenters and technicians increases stress in primates.[101,102] Numerous studies have demonstrated that even minor changes in primates' captive environment, including temporary changes in cage size or location, increase stress levels.[103,104] It is not surprising that decreased immune system functioning[105] and increased self-injurious behavior are common in primates in laboratories.[106,107]

Specific to the experiments in question, the intention of these projects is to create, psychological illness in primates. The numerous long-term negative outcomes of these motherless rearing conditions on monkeys have been well established for decades: mother-deprived infants exhibit excessive fearfulness and/or aggression,[48] produce excess stress hormones,[108] and frequently rank at the bottom of the social dominance hierarchy.[48] They exhibit motor stereotypies indicative of frustration and stress,[109] abnormal sleep patterns,[110] increased susceptibility to alcohol abuse,[111] and increased startle and stress responses to threatening stimuli.[112] Maternal deprivation affects serotonin pathway function[113,114] and

cerebral blood flow[115] and alters levels of brain-derived neurotrophic factor and nerve growth factor critical for normal brain function[116] and has long-term effects on brain morphology.[117] Both spontaneous and selectively bred genetic variations in the macaques interact with adverse rearing conditions, often exacerbating the already profoundly negative effects of adverse rearing.[118,119,120]

Moreover, several of the procedures in this protocol, including the "Auditory Reflex," "Response to Novelty," and "Human Intruder" tests, require infants to frequently be restrained and subjected to stress and fear-inducing procedures for several hours a day, causing acute distress to the animals during the experimental trials. The repeated restraint and social isolation, repeated exposure to startling sounds and frightening situations, and repeated blood draws, spinal taps, drug injections, and brain imaging procedures cause more than temporary or minimal distress to the animals and take an enormous toll on the psychological well being of these animals.

Given the extensive, long-term psychological and physical harm caused by maternal deprivation, and the extensive distress the individual test procedures caused to animals included in this protocol, it would only be appropriate to classify these protocols as "USDA Column D" ("Pain or Distress Relieved By Appropriate Measures") and/or "USDA Column E" ("unrelieved pain or distress"). However, the Animal Study Proposal (ASP 11-043) describing these procedures was classified as "USDA Column C," indicating that the animals would suffer only "minimal or no pain or distress." The investigators own research, cited above, document that this classification is inappropriate for this series of experiments. The ASP for these protocols was approved as "Column C" on May 02, 2011, and then again on April 16, 2014, through April 16, 2017. As a result of this misclassification, members of the Animal Care and Use Committee were not able to make an appropriate cost benefit analysis before approving the proposal. Moreover, investigators were not required to search for alternative, nonanimal methods for their studies—methods that, as described above, are readily available.

Additional independent review

To extend the depth of our analysis of these experiments, we have consulted with independent subject matter experts in the fields of mental health, medicine, anthropology, and primatology (they were not compensated in any way by PETA). Their concerns, which they have provided to PETA in writing, are as follows:

- *Extensive experiments proving the damaging effects of maternal deprivation and isolation were carried out on rhesus monkeys by Harry Harlow and his students in the 1950s, 1960s and 1970s. And even after proof had been obtained, Harlow continued to devise ever more stressful situations... These experiments, getting more and more extreme, were unbelievably cruel. Nevertheless researchers continued working in this field after Harlow's death, and continue to do so today. ....It is my understanding that monkeys are being subjected to what I consider inhumane experiments at a laboratory in Maryland that is, to some extent, funded by public money. I was shown a video in which infant monkeys were taking part in experiments which I considered extremely cruel and unacceptable.....I am shocked and saddened that this is so.*

  Dr. Jane Goodall, DBE
  Founder, the Jane Goodall Institute
  UN Messenger of Peace

- *"Given the current status and progress of the research (as assessed via the published literature), I can no longer see a potential benefit from such experimentation as is ongoing currently. I cannot consider the depicted experiments, designed to create and study psychopathology in monkeys, to be a valuable undertaking that will likely contribute to the health and well being of humans..... From the methodologies described in the proposals and articles and the written and visual documentation provided by PETA of actual laboratory procedures and activities, it is my assessment that the monkeys used in these experiments experience substantial psychological (and likely physiological) harm and that there is no current evidence that there will be any results from the studies that move our understanding of human psychopathology forward."*

  Dr. Agustín Fuentes
  Professor and Chair, Department of Anthropology
  University of Notre Dame

- *In the past, I conducted experiments on the impact of social deprivation on monkey intelligence and abnormal social behavior. I eventually chose to leave that area of research because I came to believe that those models did not accurately represent the development and presentation of human mental illness. I came to the view that those models could not adequately inform innovative directions for successful clinical intervention to justify the costs in suffering and pain. I see nothing to alter that view with respect to the program of primate deprived early experience research currently being conducted at the NIH.*

  Dr. John P. Gluck
  Emeritus Professor of Psychology, University of New Mexico
  Research Professor, Kennedy Institute of Ethics, Georgetown University

- *For the past three decades Suomi's group has deprived hundreds of infant macaques of maternal contact to cause them to suffer from a range of severe and persistent cognitive, social, emotional, and physical deficits. There is no compelling evidence that these studies are now or have they ever been beneficial to humans. This line of outdated and irrelevant research has unfortunately been allowed to proceed without proper scientific and ethical scrutiny by the NIH and the research community.*

  Dr. Lori Marino
  Executive Director, The Kimmela Center for Animal Advocacy

- *"The cause of mental illness in humans is unknown, but it is clearly complex and multifactorial. Some genetic studies are promising. Abusing monkeys, however, won't get us any closer to that understanding."*

  Dr. Jaymie Shanker
  Psychiatrist

- *"Taken as a group and without exception, these experiments are cruel, plunging infant monkeys into hellish conditions that they can neither control nor escape from. Ethically and morally, they have no place in science today. The cost to these animals is far too high. As we have seen, it is not as if the experiments lead to an earth-shattering breakthrough that could, in*

some moral calculus (though not PETA's and not mine), give us reason to think the cost was remotely worth it. This lack of justification is particularly true given the myriad of human-based research methodologies available to study the environmental, genetic, and social causes of mental illness as well as the fact that these experiments on monkeys often seek to replicate knowledge already ascertained in humans."

Dr. Barbara J. King
Chancellor Professor of Anthropology
College of William and Mary

- *"The scientific objections to continuing this research are immediately obvious. If the goal is to model neuropathologic/neurophysiologic substrates of human psychiatric diseases, then these efforts are hopelessly crude and antiquated, having long been superseded by in vivo neuroimaging studies of human patients with the psychiatric diseases of interest. Simply conduct a search in PubMed on any psychiatric diagnosis, such as psychopathic personality disorder, depression, schizophrenia, and a host of others, and you will find dozens of current, sophisticated, state-of-the-art neuroimaging studies comparing brain structure and function in patients and controls, clearly delineating structural and functional abnormalities in human patients. These patients, along with their early life experiences, genetic make-up, and medical histories, can be followed longitudinally to evaluate illness etiology and treatment efficacy. Modern research methodology has also allowed investigators to measure the separate and interacting contribution of genes and early environmental stress in the development and neural substrates of mental illnesses in humans. Postmortem studies of human brain tissue from individuals with mental illnesses or individuals carrying risk-alleles associated with psychiatric diseases are far better methods for clarifying the molecular etiologies of these complex ailments.... If the goal of the infant monkey psychological trauma experiments is not to eventually improve our understanding of human psychiatric diseases—as the above cited imaging, genetic, and epidemiological studies are already doing—then in the zero sum game of research funding, the National Institutes of Health (presumably referring to human health) should have nothing to do with them."*

  Dr. Lawrence A. Hansen
  Professor and Researcher, Department of Pathology
  University of California, San Diego, School of Medicine

- *"It is not surprising that monkeys reared under such adverse conditions at the NIH are physically, mentally, and emotionally unwell. However, despite the outcome being known, it is surprising that experiments in which these animals are deliberately subjected to extreme stress are allowed to continue. Moreover, monkeys are not humans, so any experimental findings that are true of monkeys would not necessarily be true of humans. If the researchers who are performing these experiments wish to argue that the monkeys are similar enough to humans in terms of emotional development that studies done on them can be applied to human development, then they must acknowledge that they are performing studies that cause intense pain and terror to their subjects, much as any human would experience intense pain and terror were these experiments performed on humans..... The American Psychological Association should not permit these experiments, which I believe are in violation of several sections of the APA Guidelines for Ethical Conduct in the Care and Use of Nonhuman Animals in Research. Specifically, Guideline I (2) states that "[T]he scientific purpose of the research should be of*

sufficient potential significance to justify the use of nonhuman animals" and notes that "psychologists should act on the assumption that procedures that are likely to produce pain in humans may also do so in other animals." Yet, in a 2014 paper published in The American Journal of Psychiatry, the experimenters acknowledge that their anti-depressant experiments on monkeys cannot be applied to humans, that maternal deprivation studies on monkeys have never been confirmed as an effective way to test the efficacy of drug treatments for human mental illness, and that the only way to test treatments for human psychological disorders is in humans."

Dr. Michael Radkowsky
Clinical Psychologist

- *"If these experiments are meant to parallel or predict the psychopathy and mental illness of human infants in the care of negligent, absent, and/or abusive mothers, they fail profoundly. Contrived maternal deprivation, chronic exposure to stressful experimental paradigms, confinement, and social isolation in laboratory settings do not parallel the types of early stressors experienced by most human mental illness sufferers. These laboratory versions of early-life adversity are too routinized and methodical to be representative of any real-world experiences faced by humans. The circumstances surrounding physical, social, emotional, and cognitive development in human beings is multifaceted and more complicated than those that can be imposed on infant monkeys reared in a laboratory. Good, creative research either cleverly sets up situations that allow behavioral and biological responses of interest to occur naturally, or it takes the form of field studies to observe real-world dynamics in a natural setting. The NIH experiments depicted on video include constraining infants in small cages and startling them with loud noises, trapping infants and then threatening them with human experimenters, or caging them with a drugged, unresponsive mother. These procedures do not accurately or creatively replicate the stressful situations believed to precipitate mental illness in humans."*

  Dr. Nora J. Johnson
  Clinical Psychologist
  University of Pennsylvania Health System

- *"I do not consider the depicted experiments, designed to create and study psychopathology in monkeys, to be a valuable undertaking that will likely contribute to the health and well-being of humans. Rather, the causes and manifestations of mental illness in humans are most effectively researched without the use of animals."*

  Dr. Tara West
  Professor, Social Psychologist
  CUNY School of Professional Studies

Conclusion

In a recent paper discussing the inadequacy of regulations governing experimentation on animals, bioethicist Dr. David Wendler of the NIH's Clinical Center called for greater restrictions on the use of primates in experiments, noting that existing regulations "do not mandate that the risks to which nonhuman primates are exposed must be justified by the value of the study in question."[121]

For decades the NIH has continued to review, approve, fund, and conduct the aforementioned studies that deliberately and repeatedly inflict severe and chronic harm to monkeys, are often not at all designed to help humans, or have extremely limited potential to elucidate the complex etiology of human mental illness and have not improved our treatments of these illnesses or human health in general.

These experiments represent an enormous financial burden to taxpayers, particularly as there are a myriad of accessible, humane research methodologies that are more directly applicable to mental illness and its treatment. Continuing to fund this suite of projects appears to be both scientifically and ethically unjustifiable.

References

[1] Ferrari, P. F., Vanderwert, R. E., Paukner, A., Bower, S., Suomi, S. J., & Fox, N. A. (2012). Distinct EEG amplitude suppression to facial gestures as evidence for a mirror mechanism in newborn monkeys. **Journal of Cognitive Neuroscience, 24(5),** 1165-1172.

[2] Vanderwert, R. E., Ferrari, P. F., Paukner, A., Bower, S. B., Fox, N. A., & Suomi, S. J. (2012). Spectral characteristics of the newborn rhesus macaque EEG reflect functional cortical activity. **Physiology & Behavior, 107(5),** 787-791.

Ferrari, P. F., Vanderwert, R. E., Paukner, A., Bower, S., Suomi, S. J., & Fox, N. A. (2
012). Distinct EEG amplitude suppression to facial gestures as evidence for a mirror mechanism in newborn monke
ys. **Journal of Cognitive Neuroscience, 24(5),** 1165-1172.

[5] Vanderwert, R. E., Ferrari, P. F., Paukner, A., Bower, S. B., Fox, N. A., & Suomi, S. J. (2012). Spectral characteristics of the newborn rhesus macaque EEG reflect functional cortical activity
. **Physiology & Behavior, 107(5),** 787-791.

e, L., Alleva, E., & Suomi, S. J. (2009). Early life stress as a risk factor for mental health: role of neurotrophins from rodents to non-human primates. **Neuroscience & Biobehavioral Reviews, 33(4),** 573-585.

[7] Dettmer, A. M., Novak, M. F., Novak, M. A., Meyer, J. S., & Suomi, S. J. (2009). Hair cortisol predicts object permanence performance in infant rhesus macaques (Macaca mulatta). **Developmental Psychobiology, 51(8),** 706-713.

[8] Newman, T. K., Syagailo, Y. V., Barr, C. S., Wendland, J. R., Champoux, M., Graessle, M., ... & Lesch, K. P. (2005). Monoamine oxidase A gene promoter variation and rearing experience influences aggressive behavior in rhesus monkeys. **Biological Psychiatry, 57(2),** 167-172.

[9] Spinelli, S., Schwandt, M. L., Lindell, S. G., Newman, T. K., Heilig, M., Suomi, S. J., ... & Barr, C. S. (2007). Association between the recombinant human serotonin transporter linked promoter region polymorphism and behavior in rhesus macaques during a separation paradigm. **Development and Psychopathology, 19(04),** 977-987.

[10] Erickson, K., Gabry, K. E., Schulkin, J., Gold, P., Lindell, S., Higley, J. D., ... & Suomi, S. J. (2005). Social withdrawal behaviors in nonhuman primates and changes in neuroendocrine and monoamine concentrations during a separation paradigm. **Developmental Psychobiology, 46(4),** 331-339.

[11] Barr, C. S., Newman, T. K., Shannon, C., Parker, C., Dvoskin, R. L., Becker, M. L., ... & Higley, J. D. (2004). Rearing condition and rh5-HTTLPR interact to influence limbic-hypothalamic-pituitary-adrenal axis response to stress in infant macaques. **Biological Psychiatry, 55(7),** 733-738.

[12] Champoux, M., Bennett, A., Shannon, C., Higley, J. D., Lesch, K. P., & Suomi, S. J. (2002). Serotonin transporter gene polymorphism, differential early rearing, and behavior in rhesus monkey neonates. **Molecular Psychiatry, 7(10),** 1058-1063.

[13] Higley, J. D., Suomi, S. J., & Linnoila, M. (1991). CSF monoamine metabolite concentrations vary according to age, rearing, and sex, and are influenced by the stressor of social separation in rhesus monkeys. **Psychopharmacology, 103(4),** 551-556.

[14] Westergaard, G. C., Mehlman, P. T., Suomi, S. J., & Higley, J. D. (1999). CSF 5-HIAA and aggression in female macaque monkeys: species and interindividual differences. **Psychopharmacology, 146(4),** 440-446.

[15] Higley, J. D., Thompson, W. W., Champoux, M., Goldman, D., Hasert, M. F., Kraemer, G. W., ... & Linnoila, M. (1993). Paternal and maternal genetic and environmental contributions to cerebrospinal fluid monoamine metabolites in rhesus monkeys (Macaca mulatta). **Archives of General Psychiatry, 50(8),** 615-623.

[16] Higley, J. D., Suomi, S. J., & Linnoila, M. (1992). A longitudinal assessment of CSF monoamine metabolite and plasma cortisol concentrations in young rhesus monkeys. **Biological Psychiatry, 32(2),** 127-145.

[17] Paukner, A., Huntsberry, M. E., & Suomi, S. J. (2010). Visual discrimination of male and female faces by infant rhesus macaques. **Developmental Psychobiology, 52(1),** 54-61.
[18] Paukner, A., Ferrari, P. F., & Suomi, S. J. (2011). Delayed imitation of lipsmacking gestures by infant rhesus macaques (Macaca mulatta). **PloS One, 6(12),** e28848.
[19] Little, A. C., Paukner, A., Woodward, R. A., & Suomi, S. J. (2012). Facial asymmetry is negatively related to condition in female macaque monkeys. **Behavioral Ecology and Sociobiology, 66(9),** 1311-1318.
[20] Bower, S., Suomi, S. J., & Paukner, A. (2012). Evidence for kinship information contained in the rhesus macaque (Macaca mulatta) face. **Journal of Comparative Psychology, 126(3),** 318.
[21] Paukner, A., Bower, S., Simpson, E. A., & Suomi, S. J. (2013). Sensitivity to first- order relations of facial elements in infant rhesus macaques. **Infant and Child Development, 22(3),** 320-330.
[22] Zhang, B., Suarez- Jimenez, B., Hathaway, A., Waters, C., Vaughan, K., Noble, P. L., ... & Nelson, E. E. (2012). Developmental changes of rhesus monkeys in response to separation from the mother. **Developmental Psychobiology, 54(8),** 798-807.
[23] Suarez-Jimenez B., Hathaway, A., Waters, C., Vaughan, K., Suomi, S. J., Noble, P. L., ... & Nelson, E. E. (2013). Effect of mother's dominance rank on offspring temperament in infant rhesus monkeys (Macaca mulatta). **American Journal of Primatology, 75(1),** 65-73.
[24] Shrestha, S. S., Nelson, E. E., Liow, J. S., Gladding, R., Lyoo, C. H., Noble, P. L., ... & Innis, R. B. (2014). Fluoxetine administered to juvenile monkeys: effects on the serotonin transporter and behavior. **American Journal of Psychiatry, 171(3),** 323-331.
[25] Spinelli, S., Schwandt, M. L., Lindell, S. G., Heilig, M., Suomi, S. J., Higley, J. D., ... & Barr, C. S. (2012). The serotonin transporter gene linked polymorphic region is associated with the behavioral response to repeated stress exposure in infant rhesus macaques. **Development and Psychopathology, 24(01),** 157-165.
[26] Lindell, S. G., Schwandt, M. L., Sun, H., Sparenborg, J. D., Björk, K., Kasckow, J. W., ... & Barr, C. S. (2010). Functional NPY variation as a factor in stress resilience and alcohol consumption in rhesus macaques. **Archives of General Psychiatry, 67(4),** 423-431.
[27] Schwandt, M. L., Lindell, S. G., Higley, J. D., Suomi, S. J., Heilig, M., & Barr, C. S. (2011). OPRM1 gene variation influences hypothalamic–pituitary–adrenal axis function in response to a variety of stressors in rhesus macaques. **Psychoneuroendocrinology, 36(9),** 1303-1311.
[28] Barr, C. S., Becker, M. L., Suomi, S. J., & Higley, J. D. (2003). Relationships among CSF monoamine metabolite levels, alcohol sensitivity, and alcohol- related aggression in rhesus macaques. **Aggressive Behavior, 29(4),** 288-301.
[29] Barr, C. S., Newman, T. K., Lindell, S., Shannon, C., Champoux, M., Lesch, K. P., ... & Higley, J. D. (2004). Interaction between serotonin transporter gene variation and rearing condition in alcohol preference and consumption in female primates. **Archives of General Psychiatry, 61(11),** 1146-1152.
[30] Barr, C. S., Dvoskin, R. L., Gupte, M., Sommer, W., Sun, H., Schwandt, M. L., ... & Heilig, M. (2009). Functional CRH variation increases stress-induced alcohol consumption in primates. **Proceedings of the National Academy of Sciences, 106(34),** 14593-14598.
[31] Schwandt, M. L., Lindell, S. G., Chen, S., Higley, J. D., Suomi, S. J., Heilig, M., & Barr, C. S. (2010). Alcohol response and consumption in adolescent rhesus macaques: life history and genetic influences. **Alcohol, 44(1),** 67-80.
[32] Alexander, G. M., Graef, J. D., Hammarback, J. A., Nordskog, B. K., Burnett, E. J., Daunais, J. B., ... & Godwin, D. W. (2012). Disruptions in serotonergic regulation of cortical glutamate release in primate insular cortex in response to chronic ethanol and nursery rearing. **Neuroscience, 207,** 167-181.
[33] Huggins, K. N., Mathews, T. A., Locke, J. L., Szeliga, K. T., Friedman, D. P., Bennett, A. J., & Jones, S. R. (2012). Effects of early life stress on drinking and serotonin system activity in rhesus macaques: 5-hydroxyindoleacetic acid in cerebrospinal fluid predicts brain tissue levels. **Alcohol, 46(4),** 371-376.
[34] Provençal, N., Suderman, M. J., Guillemin, C., Massart, R., Ruggiero, A., Wang, D., ... & Szyf, M. (2012). The signature of maternal rearing in the methylome in rhesus macaque prefrontal cortex and T cells. **Journal of Neuroscience, 32(44),** 15626-15642.
[35] Enard, W., Khaitovich, P., Klose, J., Zöllner, S., Heissig, F., Giavalisco, P., ... & Pääbo, S. (2002). Intra- and interspecific variation in primate gene expression patterns. **Science, 296(5566),** 340-343.
[36] Cáceres, M., Lachuer, J., Zapala, M. A., Redmond, J. C., Kudo, L., Geschwind, D. H., ... & Barlow, C. (2003). Elevated gene expression levels distinguish human from non-human primate brains. **Proceedings of the National Academy of Sciences, 100(22),** 13030-13035.
[37] Shi, L., Li, M., Lin, Q., Qi, X., & Su, B. (2013). Functional divergence of the brain-size regulating gene MCPH1 during primate evolution and the origin of humans. **BMC Biology, 11(1),** 62.
[38] Muntané, G., Horvath, J. E., Hof, P. R., Ely, J. J., Hopkins, W. D., Raghanti, M. A., ... & Sherwood, C. C. (2014). Analysis of synaptic gene expression in the neocortex of primates reveals evolutionary changes in glutamatergic neurotransmission. **Cerebral Cortex, bht354.**

[39] Balsters, J. H., Cussans, E., Diedrichsen, J., Phillips, K. A., Preuss, T. M., Rilling, J. K., & Ramnani, N. (2010). Evolution of the cerebellar cortex: the selective expansion of prefrontal-projecting cerebellar lobules. **Neuroimage, 49(3),** 2045-2052.

[40] Fu, X., Giavalisco, P., Liu, X., Catchpole, G., Fu, N., Ning, Z. B., ... & Khaitovich, P. (2011). Rapid metabolic evolution in human prefrontal cortex. **Proceedings of the National Academy of Sciences, 108(15),** 6181-6186.

[41] Hecht, E. E., Gutman, D. A., Preuss, T. M., Sanchez, M. M., Parr, L. A., & Rilling, J. K. (2013). Process versus product in social learning: comparative diffusion tensor imaging of neural systems for action execution–observation matching in macaques, chimpanzees, and humans. **Cerebral Cortex, 23(5),** 1014-1024.

[42] Rilling, J. K. (2014). Comparative primate neuroimaging: insights into human brain evolution. Trends in **Cognitive Sciences, 18(1),** 46-55.

[43] Geschwind, D. H., & Rakic, P. (2013). Cortical evolution: judge the brain by its cover. **Neuron, 80(3),** 633-647.

[44] Sakai, T., Matsui, M., Mikami, A., Malkova, L., Hamada, Y., Tomonaga, M., ... & Matsuzawa, T. (2013). Developmental patterns of chimpanzee cerebral tissues provide important clues for understanding the remarkable enlargement of the human brain. **Proceedings of the Royal Society B: Biological Sciences, 280**(1753).

[45] Green, J. G., McLaughlin, K. A., Berglund, P. A., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., et al. (2010). Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: associations with first onset of DSM-IV disorders. **Archives of General Psychiatry, 67(2),** 113-123.

[46] McLaughlin, K. A., Green, J. G., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2010). Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication II: asssociations with persistence of DSM-IV disorders. **Arch Gen Psychiatry, 67(2),** 124-132.

[47] McLaughlin, K. A., Gadermann, A. M., Hwang, I., Sampson, N. A., Al-Hamzawi, A., Andrade, L. H., ... & Kessler, R. C. (2012). Parent psychopathology and offspring mental disorders: results from the WHO World Mental Health Surveys. **British Journal of Psychiatry, 200(4),** 290-299.

[48] Suomi, S. J. (1997). Early determinants of behavior: evidence from primate studies. **Br Med Bull, 53,**170–184.

[49] Spinelli, S., Schwandt, M. L., Lindell, S. G., Heilig, M., Suomi, S. J., Higley, J. D., ... & Barr, C. S. (2012). The serotonin transporter gene linked polymorphic region is associated with the behavioral response to repeated stress exposure in infant rhesus macaques. **Development and Psychopathology,24(01),** 157-165.

[50] Suomi, S. J. (1976). Mechanisms underlying social development: a re-examination of mother-infant interactions in monkeys. In: Minnesota Symposium on child psychology (Vol. 10, pp. 201-228).

[51] Neigh, G. N., Gillespie, C. F., & Nemeroff, C. B. (2009). The neurobiological toll of child abuse and neglect. **Trauma, Violence, & Abuse, 10(4),** 389-410.

[52] Greeson, J. K., Briggs, E. C., Kisiel, C. L., Layne, C. M., Ake III, G. S., Ko, S. J., ... & Fairbank, J. A. (2011). Complex trauma and mental health in children and adolescents placed in foster care: findings from the National Child Traumatic Stress Network. **Child Welfare, 90(6).**

[53] Tottenham, N. (2012). Risk and developmental heterogeneity in previously institutionalized children. **Journal of Adolescent Health, 51(2),** S29-S33.

[54] Grabe, H. J., Schwahn, C., Appel, K., Mahler, J., Schulz, A., Spitzer, C., ... & Völzke, H. (2010). Childhood maltreatment, the corticotropin- releasing hormone receptor gene and adult depression in the general population. **American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 153(8),** 1483-1493.

[55] Grabe, H. J., Schwahn, C., Mahler, J., Appel, K., Schulz, A., Spitzer, C., ... & Völzke, H. (2012). Genetic epistasis between the brain-derived neurotrophic factor Val66Met polymorphism and the 5-HTT promoter polymorphism moderates the susceptibility to depressive disorders after childhood abuse. **Progress in Neuro-Psychopharmacology and Biological Psychiatry, 36(2),** 264-270.

[56] Caldwell, W., McInnis, O. A., McQuaid, R. J., Liu, G., Stead, J. D., Anisman, H., & Hayley, S. (2013). The role of the Val66Met polymorphism of the brain derived neurotrophic factor gene in coping strategies relevant to depressive symptoms. **PloS One, 8(6),** e65547.

[57] Taylor, S. E., Way, B. M., Welch, W. T., Hilmert, C. J., Lehman, B. J., & Eisenberger, N. I. (2006). Early family environment, current adversity, the serotonin transporter promoter polymorphism, and depressive symptomatology. **Biological Psychiatry, 60(7),** 671-676.

[58] Stein, M. B., Schork, N. J., & Gelernter, J. (2008). Gene-by-environment (serotonin transporter and childhood maltreatment) interaction for anxiety sensitivity, an intermediate phenotype for anxiety disorders. **Neuropsychopharmacology, 33(2),** 312-319.

[59] Armbruster, D., Mueller, A., Strobel, A., Lesch, K. P., Brocke, B., & Kirschbaum, C. (2012). Children under stress–COMT genotype and stressful life events predict cortisol increase in an acute social stress paradigm. **International Journal of Neuropsychopharmacology, 15(09),** 1229-1239.

[60] Carver, C. S., Johnson, S. L., Joormann, J., Kim, Y., & Nam, J. Y. (2011). Serotonin transporter polymorphism interacts with childhood adversity to predict aspects of impulsivity. **Psychological Science, 22(5),** 589-595.

[61] Drury, S. S., Gleason, M. M., Theall, K. P., Smyke, A. T., Nelson, C. A., Fox, N. A., & Zeanah, C. H. (2012). Genetic sensitivity to the caregiving context: The influence of 5httlpr and BDNF val66met on indiscriminate social behavior. **Physiology & Behavior, 106(5),** 728-735.

[62] Uher, R., Caspi, A., Houts, R., Sugden, K., Williams, B., Poulton, R., & Moffitt, T. E. (2011). Serotonin transporter gene moderates childhood maltreatment's effects on persistent but not single-episode depression: replications and implications for resolving inconsistent results. **Journal of Affective Disorders, 135(1),** 56-65.

[63] Enoch, M. A. (2011). The role of early life stress as a predictor for alcohol and drug dependence. **Psychopharmacology, 214(1),** 17-31.

[64] Aguilera, M., Arias Sampériz, B., Wichers, M., Barrantes Vidal, N., Moya Higueras, J., Villa Martín, E., ... & Fañanás Saura, L. (2009). Early adversity and 5-HTT-BDNF genes: new evidences of gene-environment interactions on depressive symptoms in a general population. **Psychological Medicine ISSN, 39(9),** 1425-1432.

[65] McGowan, P. O., Sasaki, A., D'Alessio, A. C., Dymov, S., Labonté, B., Szyf, M., ... & Meaney, M. J. (2009). Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. **Nature Neuroscience, 12(3),** 342-348.

[66] Sheridan, M. A., Fox, N. A., Zeanah, C. H., McLaughlin, K. A., & Nelson, C. A. (2012). Variation in neural development as a result of exposure to institutionalization early in childhood. **Proceedings of the National Academy of Sciences, 109(32),** 12927-12932.

[67] Frodl, T., & O'Keane, V. (2013). How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans. **Neurobiology of Disease, 52,** 24-37.

[68] Wang D., Szyf M., Benkelfat C., Provencal N., Turecki G., et al. (2012). Peripheral SLC6A4 DNA methylation is associated with in vivo measures of human brain serotonin synthesis and childhood physical aggression. **PLoS One 7(6).**

[69] Buchmann, A. F., Hellweg, R., Rietschel, M., Treutlein, J., Witt, S. H., Zimmermann, U. S., ... & Deuschle, M. (2013). BDNF Val 66 Met and 5-HTTLPR genotype moderate the impact of early psychosocial adversity on plasma brain-derived neurotrophic factor and depressive symptoms: A prospective study. **European Neuropsychopharmacology, 23(8),** 902-909.

[70] Klengel, T., Mehta, D., Anacker, C., Rex-Haffner, M., Pruessner, J. C., Pariante, C. M., ... & Binder, E. B. (2013). Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. **Nature Neuroscience, 16(1),** 33-41.

[71] Miller, J. A., Ding, S. L., Sunkin, S. M., Smith, K. A., Ng, L., Szafer, A., ... & Pletikos, M. (2014). Transcriptional landscape of the prenatal human brain. **Nature, 508,** 199-206.

[72] James, S. J., Shpyleva, S., Melnyk, S., Pavliv, O., & Pogribny, I. P. (2013). Complex epigenetic regulation of Engrailed-2 (EN-2) homeobox gene in the autism cerebellum. **Translational psychiatry, 3(2),** e232.

[73] Stoner, R., Chow, M. L., Boyle, M. P., Sunkin, S. M., Mouton, P. R., Roy, S., ... & Courchesne, E. (2014). Patches of disorganization in the neocortex of children with autism. **New England Journal of Medicine, 370(13),** 1209-1219.

[74] Duric, V., Banasr, M., Stockmeier, C. A., Simen, A. A., Newton, S. S., Overholser, J. C., ... & Duman, R. S. (2013). Altered expression of synapse and glutamate related genes in post-mortem hippocampus of depressed subjects. **International Journal of Neuropsychopharmacology, 16(01),** 69-82.

[75] Kunii, Y., Hyde, T. M., Ye, T., Li, C., Kolachana, B., Dickinson, D., ... & Lipska, B. K. (2014). Revisiting DARPP-32 in postmortem human brain: changes in schizophrenia and bipolar disorder and genetic associations with t-DARPP-32 expression. **Molecular Psychiatry, 19(2),** 192-199.

[76] Wockner, L. F., Noble, E. P., Lawford, B. R., Young, R. M., Morris, C. P., Whitehall, V. L. J., & Voisey, J. (2014). Genome-wide DNA methylation analysis of human brain tissue from schizophrenia patients. **Translational Psychiatry, 4(1),** e339.

[77] Emslie, G., Kennard, B., Mayes, T., Nightingale-Teresi, J., Carmody, T., Hughes, C., ... & Rintelmann, J. (2008). Fluoxetine versus placebo in preventing relapse of major depression in children and adolescents. **American Journal of Psychiatry, 165(4),** 459-467.

[78] Mah, B. L., Van IJzendoorn, M. H., Smith, R., & Bakermans-Kranenburg, M. J. (2013). Oxytocin in postnatally depressed mothers: its influence on mood and expressed emotion. **Progress in Neuro-Psychopharmacology and Biological Psychiatry, 40,** 267-272.

[79] Delgado, V. B., Izquierdo, I., & Chaves, M. L. (2005). Differential effects of acute diazepam on emotional and neutral memory tasks in acutely hospitalized depressed patients. **Neuropsychiatr Dis Treat, 1**, 269-275.

[80] Anderer, P., Saletu, B., & Pascual-Marqui, R. D. (2000). Effect of the 5-HT1A partial agonist buspirone on regional brain electrical activity in man: a functional neuroimaging study using low-resolution electromagnetic tomography (LORETA). **Psychiatry Research: Neuroimaging, 100(2),** 81-96.

[81] Nordström, A. L., Farde, L., Wiesel, F. A., Forslund, K., Pauli, S., Halldin, C., & Uppfeldt, G. (1993). Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects: a double-blind PET study of schizophrenic patients. **Biological Psychiatry, 33(4),** 227-235.

[82] Reynolds, B., Richards, J. B., Dassinger, M., & de Wit, H. (2004). Therapeutic doses of diazepam do not alter impulsive behavior in humans. **Pharmacology Biochemistry and Behavior, 79(1),** 17-24.
[83] Di Simplicio, M., Massey-Chase, R., Cowen, P. J., & Harmer, C. J. (2009). Oxytocin enhances processing of positive versus negative emotional information in healthy male volunteers. **Journal of Psychopharmacology, 23(3),** 241-248.
[84] McCabe, C., & Mishor, Z. (2011). Antidepressant medications reduce subcortical–cortical resting-state functional connectivity in healthy volunteers. **Neuroimage, 57(4),** 1317-1323.
[85] Davari-Ashtiani, R., Shahrbabaki, M. E., Razjouyan, K., Amini, H., & Mazhabdar, H. (2010). Buspirone versus methylphenidate in the treatment of attention deficit hyperactivity disorder: a double-blind and randomized trial. **Child Psychiatry & Human Development, 41(6),** 641-648.
[86] Gordon, I., Vander Wyk, B. C., Bennett, R. H., Cordeaux, C., Lucas, M. V., Eilbott, J. A., ... & Pelphrey, K. A. (2013). Oxytocin enhances brain function in children with autism. **Proceedings of the National Academy of Sciences, 110(52),** 20953-20958.
[87] Rickels, K., Downing, R., Schweizer, E., & Hassman, H. (1993). Antidepressants for the treatment of generalized anxiety disorder: a placebo-controlled comparison of imipramine, trazodone, and diazepam. **Archives of General Psychiatry, 50(11),** 884-895.
[88] Guastella, A. J., Howard, A. L., Dadds, M. R., Mitchell, P., & Carson, D. S. (2009). A randomized controlled trial of intranasal oxytocin as an adjunct to exposure therapy for social anxiety disorder. **Psychoneuroendocrinology, 34(6),** 917-923.
[89] Del-Ben, C. M., Ferreira, C. A., Sanchez, T. A., Alves-Neto, W. C., Guapo, V. G., de Araujo, D. B., & Graeff, F. G. (2012). Effects of diazepam on BOLD activation during the processing of aversive faces. **Journal of Psychopharmacology, 26(4),** 443-451.
[90] Domes, G., Heinrichs, M., Gläscher, J., Büchel, C., Braus, D. F., & Herpertz, S. C. (2007). Oxytocin attenuates amygdala responses to emotional faces regardless of valence. **Biological Psychiatry, 62(10),** 1187-1190.
[91] Ceccarini, J., Vrieze, E., Koole, M., Muylle, T., Bormans, G., Claes, S., & Van Laere, K. (2012). Optimized in vivo detection of dopamine release using 18F-fallypride PET. **Journal of Nuclear Medicine, 53(10),** 1565-1572.
[92] Loane, C., & Politis, M. (2012). Buspirone: What is it all about? **Brain Research, 1461,** 111-118.
[93] Tamaji, A., Iwamoto, K., Kawamura, Y., Takahashi, M., Ebe, K., Kawano, N., ... & Ozaki, N. (2012). Differential effects of diazepam, tandospirone, and paroxetine on plasma brain- derived neurotrophic factor level under mental stress. **Human Psychopharmacology: Clinical and Experimental, 27(3),** 329-333.
[94] Kanat, M., Heinrichs, M., & Domes, G. (2013). Oxytocin and the social brain: Neural mechanisms and perspectives in human research. **Brain Research.** [Epub ahead of print]
[95] Balcombe, J. P., Barnard, N. D., & Sandusky, C. (2004). Laboratory routines cause animal stress. **Journal of the American Association for Laboratory Animal Science, 43(6),** 42-51.
[96] Ferdowsian, H., & Merskin, D. (2012). Parallels in sources of trauma, pain, distress, and suffering in humans and nonhuman animals. **Journal of Trauma & Dissociation, 13(4),** 448-468.
[97] Line, S.W., Morgan, K.N., Markowitz, H., Strong, S. (1989). Heart rate and activity of rhesus monkeys in response to routine events. **Laboratory Primate Newsletter,28(2),**1-4.
[98] Golub, M. S., & Anderson, J. H. (1986). Adaptation of pregnant rhesus monkeys to short-term chair restraint. **Laboratory Animal Science, 36(5),** 507-511.
[99] Gordon, T. P., Gust, D. A., Wilson, M. E., Ahmed-Ansari, A., Brodie, A. R., & McClure, H. M. (1992). Social separation and reunion affects immune system in juvenile rhesus monkeys. **Physiology & Behavior, 51(3),** 467-472.
[100] Fuller, G. B., Hobson, W. C., Reyes, F. I., Winter, J. S. D., & Faiman, C. (1984). Influence of restraint and ketamine anesthesia on adrenal steroids, progesterone, and gonadotropins in rhesus monkeys. **Experimental Biology and Medicine, 175(4),** 487-490.
[101] Barros, M., & Tomaz, C. (2002). Non-human primate models for investigating fear and anxiety. **Neuroscience & Biobehavioral Reviews, 26(2),** 187-201.
[102] Suzuki, J., Ohkura, S., & Terao, K. (2002). Baseline and stress levels of cortisol in conscious and unrestrained Japanese macaques (Macaca fuscata). **Journal of Medical Primatology, 31(6),** 340-344.
[103] Crockett, C. M., Shimoji, M., & Bowden, D. M. (2000). Behavior, appetite, and urinary cortisol responses by adult female pigtailed macaques to cage size, cage level, room change, and ketamine sedation. **American Journal of Primatology, 52(2),** 63-80.
[104] Reinhardt, V., & Reinhardt, A. (2000). The lower row monkey cage: An overlooked variable in biomedical research. **Journal of Applied Animal Welfare Science, 3(2),** 141-149.
[105] Schapiro, S. J., Nehete, P. N., Perlman, J. E., & Sastry, K. J. (2000). A comparison of cell-mediated immune responses in rhesus macaques housed singly, in pairs, or in groups. **Applied Animal Behaviour Science, 68(1),** 67-84.
[106] Novak, M. A. (2003). Self- injurious behavior in rhesus monkeys: new insights into its etiology, physiology, and treatment. **American Journal of Primatology, 59(1),** 3-19.

[107] Rommeck, I., Anderson, K., Heagerty, A., Cameron, A., & McCowan, B. (2009). Risk factors and remediation of self-injurious and self-abuse behavior in rhesus macaques. **Journal of Applied Animal Welfare Science, 12(1),** 61-72.
[108] Dettmer, A. M., Novak, M. A., Suomi, S. J., & Meyer, J. S. (2012). Physiological and behavioral adaptation to relocation stress in differentially reared rhesus monkeys: hair cortisol as a biomarker for anxiety-related responses. **Psychoneuroendocrinology, 37(2),** 191-199.
[109] Barr, C. S., Becker, M. L., Suomi, S. J., & Higley, J. D. (2003). Relationships among CSF monoamine metabolite levels, alcohol sensitivity, and alcohol- related aggression in rhesus macaques. **Aggressive Behavior, 29(4),** 288-301.
[110] Barrett, C. E., Noble, P., Hanson, E., Pine, D. S., Winslow, J. T., & Nelson, E. E. (2009). Early adverse rearing experiences alter sleep–wake patterns and plasma cortisol levels in juvenile rhesus monkeys. **Psychoneuroendocrinology, 34(7),** 1029-1040.
[111] Fahlke, C., Lorenz, J. G., Long, J., Champoux, M., Suomi, S. J., & Higley, J. D. (2000). Rearing experiences and stress- induced plasma cortisol as early risk factors for excessive alcohol consumption in nonhuman primates. **Alcoholism: Clinical and Experimental Research, 24(5),** 644-650.
[112] Nelson, E. E., Herman, K. N., Barrett, C. E., Noble, P. L., Wojteczko, K., Chisholm, K., ... & Pine, D. S. (2009). Adverse rearing experiences enhance responding to both aversive and rewarding stimuli in juvenile rhesus monkeys. **Biological Psychiatry, 66(7),** 702-704.
[113] Bennett, A. J., Lesch, K. P., Heils, A., Long, J. C., Lorenz, J. G., Shoaf, S. E., ... & Higley, J. D. (2002). Early experience and serotonin transporter gene variation interact to influence primate CNS function. **Molecular Psychiatry, 7(1),** 118-122.
[114] Spinelli, S., Chefer, S., Carson, R. E., Jagoda, E., Lang, L., Heilig, M., ... & Stein, E. A. (2010). Effects of early-life stress on serotonin 1A receptors in juvenile rhesus monkeys measured by positron emission tomography. **Biological Psychiatry, 67(12),** 1146-1153.
[115] Ichise, M., Vines, D. C., Gura, T., Anderson, G. M., Suomi, S. J., Higley, J. D., & Innis, R. B. (2006). Effects of early life stress on [11C] DASB positron emission tomography imaging of serotonin transporters in adolescent peer-and mother-reared rhesus monkeys. **Journal of Neuroscience, 26(17),** 4638-4643.
[116] Cirulli, F., Francia, N., Branchi, I., Antonucci, M. T., Aloe, L., Suomi, S. J., & Alleva, E. (2009). Changes in plasma levels of BDNF and NGF reveal a gender-selective vulnerability to early adversity in rhesus macaques. **Psychoneuroendocrinology, 34(2),** 172-180.
[117] Spinelli, S., Chefer, S., Suomi, S. J., Higley, J. D., Barr, C. S., & Stein, E. (2009). Early-life stress induces long-term morphologic changes in primate brain. **Archives of General Psychiatry, 66(6),** 658-665.
[118] Barr, C. S., Newman, T. K., Shannon, C., Parker, C., Dvoskin, R. L., Becker, M. L., ... & Higley, J. D. (2004). Rearing condition and rh5-HTTLPR interact to influence limbic-hypothalamic-pituitary-adrenal axis response to stress in infant macaques. **Biological Psychiatry, 55(7),** 733-738.
[119] Barr, C. S., Newman, T. K., Lindell, S., Shannon, C., Champoux, M., Lesch, K. P., ... & Higley, J. D. (2004). Interaction between serotonin transporter gene variation and rearing condition in alcohol preference and consumption in female primates. **Archives of General Psychiatry, 61(11),** 1146-1152.
[120] Schwandt, M. L., Lindell, S. G., Higley, J. D., Suomi, S. J., Heilig, M., & Barr, C. S. (2011). OPRM1 gene variation influences hypothalamic–pituitary–adrenal axis function in response to a variety of stressors in rhesus macaques. **Psychoneuroendocrinology, 36(9),** 1303-1311.
[121] Wendler, D. (2014). Should protections for research with humans who cannot consent apply to research with nonhuman primates?. **Theoretical Medicine and Bioethics, 35(2),** 157-173.

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Tuesday, December 23, 2014 11:19 AM
To: Clark, Terri (NIH/OD) [E]
Subject: RE: Final Response for OLAW A4149-9Y

Thank you for this update, Dr. Clark. As there is no change to the overall assessment in response to OLAW's initial inquiry, I will send Dr. Gottesman an acknowledgement and add this information to the case file.
Axel Wolff

From: Clark, Terri (NIH/OD) [E]
Sent: Tuesday, December 23, 2014 10:19 AM
To: OLAW Division of Compliance Oversight (NIH/OD)
Subject: Final Response for OLAW A4149-9Y

Dr. Wolff – on behalf of the Office of Animal Care and Use, please find attached Dr. Gottesman's cover memo and NICHD's letter (and attachments) for the second component of this OLAW case file. Kind regards – Terri

Dr. Terri R. Clark, DVM, DACLAM // Director, Office of Animal Care & Use // Chief Veterinary Officer, CAPT, USPHS
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From: Clark, Terri (NIH/OD) [E]
Sent: Thursday, October 09, 2014 8:51 AM
To: OLAW Division of Compliance Oversight (NIH/OD)
Subject: Response for OLAW A4149-9Y

Dr. Wolff - on behalf of the Office of Animal Care and Use, please find attached the IC letters and Dr. Gottesman's cover memo for this inquiry. Kind regards - Terri

Dr. Terri R. Clark, DVM, DACLAM // Director, Office of Animal Care & Use // Chief Veterinary Officer, CAPT, USPHS
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The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General, 2014
More than 16 million Americans suffer from a disease caused by smoking.

DEPARTMENT OF HEALTH & HUMAN SERVICES

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DATE: October 14, 2014

TO: Michael M. Gottesman, M.D.
Deputy Director for Intramural Research, NIH

FROM: Director, Division of Compliance Oversight, OLAW

SUBJECT: Animal Welfare Investigation - Animal Welfare Assurance A4149-01 [Case 9Y]

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your October 8, 2014 letter responding to my September 9, 2014 request for information concerning nonhuman primate studies conducted at the National Institute of Child Health and Development (NICHD) and the National Institute of Mental Health (NIMH), NIH. Concerns had been raised by the People for the Ethical Treatment of Animals regarding undue psychological and physiological distress experienced by baby monkeys on these studies. According to the information provided, OLAW understands the following based on the explanations provided by both institutes:

1) Under an approved NIMH protocol, behavioral tests were conducted with infant macaques to evaluate differences in behavior and temperament. Tests included having an unfamiliar human approach the monkey and make eye contact, startling the monkey with an unknown noise, and having the monkey explore its environment while the mother was asleep or anesthetized. The monkeys' reactions ranged from no response to transient anxiety. Upon completion of each test the infants were returned to their mothers. These tests were not designed to cause discomfort, distress, or pain but rather to evaluate behavioral adaptive response to controlled environmental situations. The duration of each test was the minimum time necessary to generate viable data, acclimation periods were used, infants were moved with their mothers, and a testing cage was used which contained a fleece pad. Trained technicians performed the tests and animals were monitored by the veterinary staff.

2) The tests were designed to observe behaviors which were adaptive. If animals failed to adapt, the test would have been stopped.

3) The three different tests were conducted in three to ten minute experimental exposure sessions, the minimum amount of time needed to produce viable data. Infants were returned to their mothers immediately following the tests.

4) An animal model was necessary to examine neuronal development of behavioral paradigms and to control variables such as genetics, environment, and experience. This purpose of this study was to examine infant temperament and development in relationship to mental health disorders. The research examined the mother-infant bond and how this impacts risk factors for development of future syndromes such as separation anxiety disorders.

5) The number of animals used was reduced by conducting the study as a collaboration with NICHD, the minimal number of animals was used to obtain statistically significant data, and any negative impact to the animals was for the least amount of time necessary to obtain valid results.

6) Nonhuman primates were selected as the animal model due to their cognitive behaviors, social development, and similarity in neurobiology to humans.

7) The primates were housed either in group housing with their mothers, nursery reared with others, or alone. Single animals were placed in a group play cage with conspecifics for two hours per day and otherwise had visual, olfactory, tactile, and auditory contact with other infants.

8) The Principal Investigator and project manager had extensive experience working with primates. Staff had taken required training prior to working with animals.

9) During test procedures the infants were monitored by a camera or audio.

1) Under an approved NICHD protocol, the same three behavioral tests were included as they were collaboratively conducted as described above. The infants were reared under different conditions with some being separated from their mothers at 72 hours and nursery raised. These infants nursed from a bottle on a surrogate sack and received repeated human contact in the nursery. Peer raised infants were in group cages while singly housed ones were placed in a group play cage with conspecifics for two hours per day and otherwise had visual, olfactory, tactile, and auditory contact with other infants. Infant cages contained manipulanda and snacks for foraging. The infants were subjected to non-distressful behavioral tests and to CSF taps under anesthesia.

2) The testing procedures were not designed to induce discomfort, distress, or pain. Anesthesia was used to sedate the mother when an infant was removed for testing and infants were anesthetized for CSF taps.

3) The procedures were not considered distressful.

4) An animal model was necessary for this study to investigate the influence of the maternal-infant bond on behavior, temperament, and social competence of the infant. The need to control variables such as genetics, experience, and environment required the use of a nonhuman model.

5) The number of animals was reduced by conducting the study as a collaboration with NIMH.

6) Nonhuman primates were selected as the animal model because of genetic overlap with humans, similar physiology, similar behavior, and similar social and emotional development. The rhesus genome has been sequenced and there is extensive information on behavioral responses to environmental challenges.

7) The primates were housed as described above.

8) The nursery staff was experienced in working with infant primates and had taken required training prior to working with animals. The primates were under the oversight of an experienced veterinarian and individuals performing CSF taps received appropriate training in the conduct of the procedure.

9) Infants which were separated from the mothers were removed as soon as possible to prevent development of a bond. Singly reared infants were given various manipulanda, had contact with other infants and humans, and could forage.

Based on its assessment of these explanations, OLAW has a better understanding of the facts surrounding these studies and finds them to have been performed in accordance with the provisions of the PHS Policy on Humane Care and Use of Laboratory Animals. OLAW appreciates the prompt and thorough responses provided by the chairs of the Animal Care and Use Committees and finds no cause for further action by this Office.

Axel Wolff

Axel Wolff, M.S., D.V.M.

cc: Dr. Terri Clark
Dr. Karl Pfeifer
Dr. Richard Saunders
Dr. Richard Wyatt

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
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October 8, 2014

TO: Axel Wolff, D.V.M.
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare

FROM: Deputy Director for Intramural Research, NIH

SUBJECT: Animal Welfare Investigations - Assurance A4149-01 (Case 9Y)

This correspondence is in response to the inquiry you sent to on September 9, 2014 requesting information regarding studies conducted by the National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH) using infant macaque monkeys. The NICHD and NIMH Animal Care and Use Committees have provided responses to your questions which are attached in two separate enclosures.

The responses address your questions and provide information regarding the welfare of these animals to assuage concerns.

In addition to the information provided in this response, the NICHD ACUC will be further evaluating key issues raised directly by PETA to NICHD as related to Dr. Suomi's ongoing research efforts. That evaluation will be provided in a separate response.

Please contact me or Dr. Terri R. Clark, Director, Office of Animal Care and Use, if additional information or clarifications are required.

Michael M. Gottesman

Michael M. Gottesman, M.D.

Attachments

cc: Dr. Stratakis
Dr. Pfeifer
Dr. Saunders
Dr. Clark
Dr. Wyatt

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institute of Health
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Date: October 6, 2014

To: Michael M. Gottesman, M.D.
Deputy Director for Intramural Research, NIH

From: Richard Saunders, Ph.D.
Chair, NIMH Animal Care & Use Committee

James M. Raber, D.V.M., Ph.D.
Animal Program Director, NIMH

Subject: Animal Welfare Investigation – Animal Welfare Assurance A4149-01 [Case 9Y]

The following comments are provided in response to the NIH Office of Laboratory Animal Welfare's questions outlined in their September 9, 2014 memorandum relating to Animal Welfare Investigation-Case 9Y. The behavioral tests in question were conducted by the late Dr. James T. Winslow, Director, Nonhuman Primate Core, National Institute of Mental Health (NIMH), in collaboration with Dr. Stephen Suomi, National Institute of Child Health and Human Development (NICHD). It should be noted that Dr. Bruno Averbeck (NIMH) was not involved in any of the studies highlighted in the CBSnews.com article, and was only involved in the administrative close-out of the NIMH Nonhuman Primate Core following the untimely death of Dr. Winslow.

The questions raised center around three (3) behavioral tests conducted by the NIMH Nonhuman Primate Core that were designed to evaluate differences in the behavior and temperament of infant macaques. These studies included: a) Human "Intruder" Paradigm (HIP), where an unfamiliar human approaches the cage and makes eye contact with the animal; b) Human "Intruder" Startle Test (HIS), measurement of the animal's ability to be startled by an unknown noise with or without the presence of a human "intruder"; and c) a Novel Objects Test, where the animal's independent behavior and willingness to explore their environment was observed when the animal was not restrained by their mother who, for this study, was sleeping/anesthetized. Observation of the animal's adaptive response to these brief and mild situations varied widely, ranging from no response to transient anxiety-like behaviors (i.e. vocalizations, erratic movements, etc.). At the end of each test, the animal was returned to its mother. Although behavioral tests on nursery reared subjects were planned, none were conducted. All three procedures were conducted under Dr. Winslow's approved animal study protocol.

1) *Provide an explanation of how discomfort, distress and pain was avoided or minimized, consistent with sound scientific practices and research design. As noted in the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training, "Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals."*

The three behavioral tests in question were not designed to induce discomfort, distress, or pain; but rather to evaluate an animal's behavioral adaptive response to specific, controlled, brief and mild environmental situations. The potential for distress and/or pain were avoided or minimized in the following ways:

a. Selection of the appropriate test paradigm. The three tests selected were designed through discussion with subject matter experts and/or supported by published literature. The test paradigms selected are all repeatable and controllable in duration, frequency, and intensity.
b. Test periods were limited to the minimum time required to provide statistically significant data.
c. Acclimation periods were used prior to and between environmental changes. These acclimation periods facilitated the collection of statistically relevant results, shortened testing periods, and helped avoid or minimize the potential for accumulative distress to the animal.
d. Startle testing conducted in juvenile or adult macaques requires the animal's movements to be restrained by a chair which is subsequently placed on top of an accelerometer. To avoid having to completely restrict the movements of the more active infant, a special testing cage was designed for both the three and six month old animals. The testing cage permitted postural adjustments while preventing false startle readings. Animals were acclimated to the holding device prior to testing.
e. Once placed in the startle testing cage, animals were provided with a fleece pad for comfort.
f. The Novel Objects Test was designed to be conducted in the presence of the sleeping/anesthetized mother to avoid or minimize discomfort and distress to the infant monkey as well as remove the mother as a variable in the experiment.
g. Prevention of nursing during the Novel Objects Test: a) facilitated greater behavioral expression in infants; b) avoided the possibility of drug (ketamine) transfer between mother and infant; and c) shortened the testing period, thus avoiding or minimizing any potential for discomfort or distress in the infant.
h. In order to avoid or minimize distress during transport, infants were moved to and from the testing area with their mother.
i. After testing all infants were immediately returned to their mothers.
j. Only experienced technical staff, trained in the humane handling of both infant and adult nonhuman primates as well as the species specific signs of pain or distress, were permitted to conduct animal testing.
k. All animals were monitored closely by trained, experienced animal care staff and veterinarians throughout these behavioral assessments.

2) *Provide information on any procedures or circumstances that may result in more than momentary discomfort, distress, pain or injury and describe the methods used to alleviate this.*

The studies in question were not designed to induce discomfort, distress, or pain, but rather to evaluate an animal's behavioral adaptive responses to specific, controlled, brief, and mild environmental situations. None of the procedures in question induce more than momentary discomfort, distress or pain. The animal behaviors observed during the testing were adaptive in nature. Observations indicating that an animal was failing to cope, adjust, or adapt to the test situation would have resulted in the test being immediately stopped.

3) *Provide information on the steps which were taken to ensure that the use of stressors was the minimum to obtain valid results. Provide information on the timelines, habituation, mitigation or supportive actions taken to reduce stress to the minimum. Specifically address the length of the stress/fear inducing procedures involving the small restraint cage and the length of time the baby was on the sedated mother.*

The behavioral challenges outlined below are based on the Ainsworth strange situation test and the LAB-TAB test, both of which are standard tests in human developmental research (Ainsworth & Bell, 1970; Ainsworth, Bell, & Stayton, 1971; Ainsworth, Waters, & Wall, 1978; Ainsworth & Wittig, 1969; Booker, et. al., 2013). These test situations, when combined with the human intruder paradigm, have been previously used to study anxiety-like behaviors in nonhuman primates (Kalin and Shelton, 2003; Kalin, 1993). The acoustic startle response has been previously used to assess anxiety-like responses in rodents, nonhuman primates, and humans (Bakker et. al., 2009; McTeague et. al., 2013; Lang et. al., 2008). The following represent the steps taken to ensure that the use of stressors was held to the minimum required to obtain statistically valid results:

a. Human "Intruder" Paradigm (HIP): The HIP test consisted of two test sessions for each animal at three (3) and six (6) months of age. The test sessions were separated by a minimum of 24 hours. Each test session was comprised of four phases: a) *initial acclimation period*, subject alone in the test cage (10 minutes); b) *profile phase* in which a human "intruder" entered the room and presented their facial profile to the subject without making eye contact (10 minutes); c) *second acclimation period*, subject alone in test cage (10 minutes); and d) *stare condition phase* in which the same human "intruder" returned and made direct eye contact with the subject (10 minutes). The ten minute trial period was chosen because it had been shown in previous studies that it was the minimum time required to provide statistically significant data. The intensity of the test was controlled by limiting the proximity of the "intruder" to the test subject (~1 meter), as well as the look and mannerisms of the "intruder" (i.e. movements, gestures, body language, vocalizations, etc.). Observations indicating that an animal was failing to cope, adjust, or adapt to the test situation would have resulted in the test being immediately stopped. After testing, all infants were immediately returned to their mothers and monitored by investigative and care staff.

b. Human "Intruder" Startle Test (HIS): The HIS test consisted of two test sessions for each animal at three (3) and six (6) months of age. The test sessions were separated by a minimum of 24 hours. Each test session was comprised of four (4) phases: a) *initial acclimation period*, subject alone in the test cage (6 minutes); b) *profile phase* in which a human "intruder" entered the room and presented their facial profile to the subject without

making eye contact (3 minutes); c) startle without "intruder" phase (3 minutes); and d) *stare condition phase* in which the same "intruder" returned and made direct eye contact with the subject (3 minutes). The length of each test period was chosen because it was the minimum time required to provide statistically significant data. The intensity of the test "intruder" was controlled by limiting the proximity of the "intruder" to the test subject (~2 meters), as well as the look and mannerisms of the "intruder" (i.e. movements, gestures, body language, vocalizations, etc.). During each of the three minute test periods, profile, startle without "intruder", and stare, three ~0.5 second broadband acoustic pulses of 80-95 dB (measured at the test subject) were presented to test the startle response of the animal at one minute intervals. The noise decibel level of the stimulus was held at the lower end of the approved stimulus range because infant monkeys can be more easily startled than juvenile or adult animals. The animal's startle response was measured by use of an accelerometer which was placed under the testing cage. To avoid having to completely restrict the movements of an infant, a special testing cage was designed for both the three and six month old animals. The testing cage permitted postural adjustments while preventing false startle readings. Animals were acclimated to the holding device prior to testing. While restrained in the startle test box/cage, animals were provided with a fleece pad for comfort. Observations indicating that an animal was failing to cope, adjust, or adapt to the test situation would have resulted in the test being immediately stopped. After testing, all infants were immediately returned to their mothers and monitored by investigative and care staff.

c. Novel Objects Test: The Novel Objects Test consisted of one test session for each animal at three (3) and six (6) months of age. The test was conducted in the presence of the sleeping/anesthetized mother to avoid or minimize discomfort and distress to the infant monkey as well as remove the interference by the mother as a variable in the experiment. While similar temperament assessment studies conducted in humans typically verbally instruct the mother not to interfere with their child's behavior (Booker et. al. 2013), this is not possible with nonhuman primates. During this test, the infant chooses either to remain with their "sleeping" mother or explore their enriched environment interacting with the wide variety of toys available or consuming the available novel food items. Infants remaining with their mother displayed either no response or transient/minimal adaptive behaviors (i.e. increased frequency of "coo" vocalizations, erratic movements, etc.). Infants who choose to explore their environment would often first shake, slap, poke, or otherwise try to arouse their mother before leaving to explore. During their exploration, infants would periodically return to their mother and again shake, slap, and poke her before again leaving to explore their environment. For the 15-40 minutes of the study, the mother's breasts were wrapped with Vet-wrap to prevent nursing. Prevention of nursing during the test: a) facilitated greater behavioral expression in infants; b) avoided drug (ketamine) transfer between mother and infant; and c) reduced the testing period further avoiding or minimizing any potential for distress. The day prior to and the day after the Novel Object Testing, the infant was separated from its mother and placed in a single cage in an unfamiliar test room for 10 minutes as a control for the enriched environment containing its "sleeping" mother. Here again the 10 minute observation time was chosen because it was the minimum time required to provide statistically significant data. Observations indicating that an animal was failing to cope, adjust, or adapt to the test situation would have resulted in the test being immediately stopped. After all tests, the infant was immediately returned to its mother and monitored by investigative and care staff.

4) *Provide justification as to why alternatives to animals could not be used and indicate the potential benefits and knowledge to be gained.*

The studies in question were designed to establish a nonhuman primate model of infant temperament. In humans, infant temperament has been shown to affect developmental trajectory and is an important factor in a variety of mental health disorders (Hirshfeld-Becker, 2008; Fox et. al, 2005). In humans, however, the relationship between temperament and mental health is moderated in complex ways by factors such as rearing, peer interaction, social competence, psychopharmacological interventions, and numerous other variables which are impossible to fully incorporate into human-based developmental studies. The numerous physiological, biochemical, genetic, social, and environmental variables related to behavior necessitate the use of an animal subjects to understand the relationships of these variables in an environment where experimenters can systematically control many variables simultaneously. Although the behavioral tests in question are similar to those used in human subjects; the need to conduct them in animal studies under more controlled conditions is essential to fully understand the complex relationships that shape mental health and disease. Animal models enable controlled rearing paradigms, randomized drug trials and more invasive physiological assessments, including neuroimaging and post-mortem studies that are not possible in human populations. The approach that was taken in this instance was to adapt behavioral paradigms which have proven clinical relevance in humans, for use in nonhuman primates. The neurophysiology of these behaviors is only partially understood and their relationship to mood and anxiety disorders in humans is beginning to be established. Therefore, development of these behavioral paradigms in nonhuman primates would provide a better understanding of neuronal development while retaining the ability to control extraneous variables and randomize assignment of manipulations. In summary, the requirement to control, minimize, or evaluate various nondependent variables (i.e. experiential, genetic, environmental, etc.) makes controlled human studies unfeasible. Therefore, the experimental approach in these studies was designed to develop minimally invasive paradigms for nonhuman primates that would be directly relevant to the human condition.

The relationship between a mother and infant is essential for the infants' survival. To this end, teleological behavioral adaptations help to encourage physical proximity to the mother throughout the infantile period. Although this relationship has adaptive features, it can also have adverse consequences. Rearing of an infant, nonhuman or human, in an environment with either prolonged or repeated maternal separations can be associated with dysregulation of physiological systems and an increased risk of pathological psychological development (Coplan et. al., 2001; Levine, 2005; Meaney, 2001; Rutter, Kreppner, & Sonuga-Barke, 2009). In humans when these responses appear particularly marked, or are particularly disruptive, they are considered to be symptoms of separation anxiety disorder, an early form of psychopathology that predicts an increased risk of psychological problems later in life (Beesdo, Knappe, & Pine, 2009). Recent studies in human adults have found that differences in the response to maternal separation may be partially under genetic control (Way, Taylor, & Eisenberger 2009). The nonhuman primate studies in question provide an important step in the development of an experimental model to study the influence of the mother-infant bond on the behavior, temperament, and social competence of the infant. The potential benefits of these studies include: a) furthered understanding of the role of mother-infant relationships to temperament, social dominance, and behavior; b) insights into the mechanisms related to the neurological, genetic, and biochemical changes related to pathological psychological

development; and c) a model for the development and testing of novel medications for the treatment of separation anxiety disorders or other syndromes.

In addition to the above, in humans certain temperamental profiles are one of the more important early risk factors for mental health problems. The literature in humans, however, also suggests that an individual's temperament profile is particularly malleable across development. The genetic, environmental and developmental factors that contribute to high risk temperamental profiles or the factors that might alter the risk profile across development are currently unknown. An important aspect of this approach was that the rearing conditions, although controlled, were as naturalistic as possible. In the studies conducted here, the infants lived with their mothers and were embedded in a larger social group during the early rearing period. In addition, our assessments were designed to be short and to minimize the disruption between mother and infant that occur in nature. In between our behavioral assessments, the infants and mothers were not disturbed. The purpose of developing this experimental model in nonhuman primates was to establish a model in which we could begin to uncover temperament profile relationships in a controlled setting. Ultimately, we would hope to answer questions such as how to parent and socialize an extremely inhibited child or whether and when to begin psychotropic medication.

5) *Indicate the steps taken to replace, reduce, or refine the use of animal.*

There are no suitable alternatives to the use of animals that would meet the experimental goals outlined for this study. The number of animals used was held to the minimum required to obtain statistical significance. In addition, by working in collaboration with the NICHD to share animals and develop methodologies which would support the mission of both institutes, the number of animals required was further reduced.

Through the selection of test methodologies, which would identify and quantify an infant's normative changes taking place during early development, these studies are a refinement over earlier approaches which did not allow inferences to be made relating to the direct role of the infant in the adaptive separation response. The experimental paradigm used for these studies was refined to avoid or minimize the possibility of infant distress and used the shortest time periods required to provide statistically significant data.

6) *Provide the rationale for the age and choice of species used. The rationale should indicate the advantages of the species chosen and why alternative species are not appropriate. If less highly evolved or simpler animal models are available, provide the justification for using more advanced species.*

Much can be learned about neural regulation of social attachment from rodents; but rodents do not display the higher social order and cognitive behaviors of nonhuman primates. Nonhuman primates, like their human relatives, gather information about their environment visually unlike rodents that rely primarily on olfactory information. Although nonhuman primates lack human language, they produce categorical vocalizations, form clear social preferences with reciprocal interactions, and they are capable of performing complex cognitive tasks similar to those used in clinical assessments of human patients. The nonhuman primate brain has a well-developed temporal lobe and an extensive prefrontal cortex, regions that are largely undeveloped in the rodent. Both temporal and prefrontal regions may be important for the social and communicative functions observed in both the nonhuman primate and human. The brain of the rhesus macaque has an

additional advantage in that it has been extensively studied, making it possible to monitor changes in putative areas associated with social development and behavior.

Rhesus macaques live in large social groups and there is much documentation regarding the role of maternal contact and group interactions for normal development. In addition, the animals used for these studies originated from a long standing colony where the genetics of each animal, as well as their social standing has been documented and studied over numerous generations.

Proximity maintenance is a dynamic process, mediated by interaction between the infant and mother. Initially the mother's role (i.e. carry, retrieve, restrain, etc.) and infants role (i.e. following, clinging, etc.) are both active. Over time both roles become more passive as the infants requirement for maintaining proximity with its mother is lessened. Although normative patterns of separation anxiety-like behaviors and proximity seeking have been characterized in rodent models, clear models of this developmental process were previously lacking in nonhuman primates. Although developmental changes in mother-infant interactions are well documented in both humans and nonhuman primates (Ainsworth, 1985; Barr, 1990; Berman, 1980; Hinde & Spencer-Booth, 1967; Suomi, 2005), these are largely based on observational studies, where it is difficult to infer the specific role the infant plays during their early development (Hinde & McGinnis, 1977). A number of observational studies have also demonstrated a dramatic reduction in mother-infant interactions in rhesus monkeys across the first six months of life (Berman, 1980; Hinde & Soencer-Booth, 1967; Suomi, 2005).

Because of the growing interest in psychopathology in relation to continuity and discontinuity across development (Degnan & Fox, 2007; Degnan, Henderson, Fox, & Rubin, 2008; Fox, Henderson, Marshall, Nichols, & Ghera, 2005), these studies were designed to evaluate when meaningful individual differences in temperament and psychopathology emerge and to what extent this is mediated by development. Because of the similarity in neurobiology, development, and social patterns between rhesus monkeys and humans, these studies sought to characterize the normative pattern of maternal proximity maintenance behaviors in a group of captive bred rhesus macaques across the first six (6) months of life.

7) *Provide the description of the living conditions of the young nonhuman primates which are appropriate for their species and contribute to their health and comfort.*

Please see the response provided by NICHD related to the living conditions of the nonhuman primates.

8) *Provide a brief synopsis of the qualifications and training of the individuals directly involved in the conduct of procedures and handling of the primates.*

The studies were conducted under the direct oversight of the late Dr. James T. Winslow. Dr. Winslow received both his M.S. and Ph.D. in Experimental Psychology and Neuroscience from Tufts University in 1987. At the time of his death, Dr. Winslow had over twenty-five (25) years of primate research experience and over one hundred and forty (140) published articles, abstracts and book chapters in the area of neuroscience, animal behavior, psychology, and psychopharmacology. Dr. Winslow was required to complete the NIH training course entitled "Using Animals in Intramural Research: Guidelines for Principal Investigators" prior to being granted an approved protocol to

work with animals at the NIMH. Dr. Winslow was also responsible for the training of all personnel listed under his approved animal study protocol.

The Laboratory Supervisor/Projects Manager for the NIMH Nonhuman Primate Core had a M.S. in Psychology, an MBA, and approximately fifteen (15) years of experience with nonhuman primates. Additional technical support consisted of individuals with degrees (B.S, M.S.) in Psychology or Animal Behavior.

Prior to working with animals, all personnel conducting research under an animal study protocol are required to complete the NIH training courses entitled "Using animals in Intramural Research: Guidelines for Animal Users" and "Working Safely with Nonhuman Primates". These courses include information on the legal requirements of all personnel working with animals in research, recognition of nonhuman primate behaviors, and procedures for avoiding and treating bites, scratches and exposures to nonhuman primate body fluids. Personnel were further trained by the principal investigator and veterinary staff on: a) the experimental and behavioral procedures to be conducted; b) the humane and safe handling of nonhuman primates; c) the identification of species specific signs of pain and/or distress; and d) methodologies to avoid or minimize distress.

9) *Provide any additional salient information regarding measures taken to ensure the humane treatment of the baby primates used in the conduct of these studies.*

At no time during a test procedure were infants left unsupervised. For example, during all acclimation and test periods animals were monitored by camera and/or audio to ensure their safety and well-being.

References

Ainsworth, M. D. S., & Bell, S. M. (1970). Attachment, exploration, and separation: Illustrated by the behavior of one-year-olds in a strange situation. *Child Development*, 41, 49-67.

Ainsworth, M. D., Bell, S. M., & Stayton, D. J. (1971). Individual differences in strange-situation behaviour of one-year-olds.

Ainsworth, M. D. S., Blehar, M. C., Waters, E., & Wall, S. (1978). *Patterns of Attachment: A Psychological Study of the Strange Situation*. Hillsdale, NJ: Erlbaum.

Ainsworth, M. D. S. & Wittig, B. A. (1969). Attachment and exploratory behavior of one-year-olds in a strange situation. In B. M. Foss (Ed.),*Determinants of infant behavior*(Vol. 4,pp. 111-136). London: Methuen.

Ainsworth, M. D. (1985). Patterns of infant-mother attachments: Antecedents and effects on development. Bulletin of the New York Academy of Medicine, 61(9), 771–791.

Bakker, M.J., Tijssen, M.A.J., Van der Meer, J.N., Koelman, J.H.T.M, Boer, F. (2009). Increased whole-body auditory startle reflex and autonomic reactivity in children with anxiety disorders. Psychiatry Neuroscience, 34(4): 314-322.

Barr, R. G. (1990). The normal crying curve: What do we really know? Developmental Medicine and Child Neurology, 32(4), 356–362.

Beesdo, K., Knappe, S., & Pine, D. S. (2009). Anxiety and anxiety disorders in children and adolescents: Developmental issues and implications for DSM-V. The Psychiatric Clinics of North America, 32(3), 483–524.

Berman, C. M. (1980). Mother-infant relationships among free-ranging rhesus monkeys on Cayo Santiago: A comparison with captive pairs. Animal Behaviour, 28(3), 860–873.

Booker, R.J., Buss, K.A., Lemery-Chalfant, K., Aksan, N., Davidson, R.J., Goldsmith, H.H. (2013). The development of stranger fear in infancy and toddlerhood: normative development, individual differences, antecedents, and outcomes. Developmental Science 16:6, 864–878.

Coplan, J. D., Smith, E. L., Altemus, M., Scharf, B. A., Owens, M. J., Nemeroff, C. B., . . . Rosenblum, L. A. (2001). Variable foraging demand rearing: Sustained elevations in cisternal cerebrospinal fluid corticotropinreleasing factor concentrations in adult primates. Biological Psychiatry, 50(3), 200–204.

Degnan K. A., & Fox, N. A. (2007). Behavioral inhibition and anxiety disorders: Multiple levels of a resilience process. Development and Psychopathology, 19(3), 729–746.

Degnan, K. A., Henderson, H. A., Fox, N. A., & Rubin, K. H. (2008). Predicting social wariness in middle childhood: The moderating roles of child care history, maternal personality and maternal behavior. Social Development, 17(3), 471–487.

Fox, N. A., Henderson, H. A., Marshall, P. J., Nichols, K. E., & Ghera, M. M. (2005). Behavioral inhibition: Linking biology and behavior within a developmental framework. Annual Review of Psychology, 56, 235–262.

Hinde, R. A., & McGinnis, L. (1977). Some factors influencing the effects of temporary mother-infant separation: Some experiments with rhesus monkeys. Psychological Medicine, 7(2), 197–212.

Hinde, R. A., & Spencer-Booth, Y. (1967). The behaviour of socially living rhesus monkeys in their first two and a half years. Animal Behaviour, 15(1), 169–196.

Hirshfeld-Becker, D.R., Micco, J., Henin, A., Bloomfield, A., Biederman, J., Rosenbaum, J., (2008). Behavioral inhibition. Depression and Anxiety, 25: 357-367.

Kalin, N.H. (1993). The neurobiology of fear. Scientific American, May: 94-100.

Kalin, N.H., Shelton, S.E. (2003). Nonhuman primate models to study anxiety, emotion regulation and psychopathology. Annals New York Academy of Science, 1008: 189-200.

Lang, P.J., Davis, M., Ohman, A. (2000). Fear and anxiety: animal models and human cognitive psychophysiology. Journal of Affective Disorders, 61: 137-159.

Levine, S. (2005). Developmental determinants of sensitivity and resistance to stress. Psychoneuroendocrinology, 30(10), 939–946.

McTeague, L.M., Lang, P.J., (2012). The anxiety spectrum and the reflex physiology of defense: from circumscribed fear to broad distress. Depression and Anxiety, 29: 264-281.

Meaney, M. J. (2001). Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. Annual Review of Neuroscience, 24, 1161–1192.

Rutter, M., Kreppner, J., & Sonuga-Barke, E. (2009). Emanuel Miller Lecture: Attachment insecurity, disinhibited attachment, and attachment disorders: Where do research findings leave the concepts? Journal of Child Psychology and Psychiatry, 50(5), 529–543.

Suomi, S. J. (2005). Mother–infant attachment, peer relationships, and the development of social networks in rhesus monkeys. Human Development, 48, 67–79.

Way, B. M., Taylor, S. E., & Eisenberger, N. I. (2009). Variation in the mu-opioid receptor gene (OPRM1) is associated with dispositional and neural sensitivity to social rejection. Proceedings of the National Academy of Sciences of the United States of America, 106(35), 15079–15084.

Cc: Dr. Richard Wyatt
Dr. Thomas Insel
Dr. Susan Amara
Dr. Constantine Stratakis
Dr. Terri Clark
Dr. Eric Nelson
Dr. Bruno Averbeck
Dr. Stephen Suomi
Dr. Karl Pfeifer
Dr. Joseph Schech

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institute of Health
National Institute of Mental Health
Intramural Research Program
10 Center Drive MSC 1381
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Date: October 3, 2014

Through: Constantine Stratakis, M.D., D.Sc.
Scientific Director, NICHD

To: Michael M. Gottesman, M.D.
Deputy Director for Intramural Research, NIH

From: Karl Pfeifer, Ph.D.
Chair, NICHDH Animal Care & Use Committee

Subject: Animal Welfare Investigation – Animal Welfare Assurance A4149-01 [Case 9Y]

The following comments are provided in response to the NIH Office of Laboratory Animal Welfare's questions outlined in their September 9, 2014 memorandum relating to Animal Welfare Investigation-Case 9Y. The behavioral tests in question were conducted by the late Dr. James T. Winslow, Director, Nonhuman Primate Core, National Institute of Mental Health (NIMH), in collaboration with Dr. Stephen Suomi, National Institute of Child Health and Human Development (NICHD). Other procedures referred to in the news report or shown on the video footage that are performed by NICHD personnel include maternal-infant separation and subsequent nursery rearing, neonatal assessment (handedness test), and CSF taps. This NICHD response will primarily address these procedures where our program has oversight of the Dr. Suomi's studies, the LCE nursery and the care of the infant monkeys.

All research procedures in this study were approved by the NIMH ACUC; the animals used belonged to the NICHD lab of Dr. Suomi, the Lab of Comparative Ethology (LCE). Dr. Suomi informed his ACUC of all work conducted, including the collaborative work. His approved ASP included a description of all procedures conducted including those conducted under collaboration. Many of the questions raised center around three (3) tests conducted by the NIMH Nonhuman Primate Core that were designed to evaluate differences in the behavior and temperament of infant macaques. These studies included: a) Human "Intruder" Paradigm (HIP), b) Human "Intruder" Startle Test (HIS), and c) a Novel Objects Test. These specific tests are addressed fully in the NIMH response.

1) *Provide an explanation of how discomfort, distress and pain was avoided or minimized, consistent with sound scientific practices and research design. As noted in the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training, "Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals."*

The procedures in question were not designed to induce discomfort, distress, or pain; but rather to develop the research paradigm or assess the individual animal. How the potential for discomfort, distress, and pain were avoided or minimized each of these procedures is detailed below.

a. Maternal-infant separation and subsequent nursery rearing:

i. Mother and infant are separated as soon after birth as possible, always 72 hours.

ii. Infants that are hand reared in the nursery receive human contact multiple times each day, including being held in a species appropriate manner. In addition the receive indirect human interaction during routine husbandry duties

iii. Surrogate design mimics normal nursing posture and clinging behavior of rhesus infants. Fleece surrogate allow the infant to cling onto the substrate as they would with a live mother. The infant clings on upright and nurses from the attached bottle in the same position as if they were nursing from a mother in the animal runs. Surrogates are made from commercially manufactured ferret sacks which are hung from the side creating a pocket. This gives infants the choice to climb inside or cling to the outside of the sack.

iv. Socialization occurs in both nursery groups. Peer reared infants are housed with other infants in the same cage. Surrogate reared infants have the ability to touch cohorts in adjacent cages at all times and are given time in a play cage with other cohort members for approximately two hours a day. All infants have constant visual, olfactory, auditory and tactile contact with other infants in the nursery.

v. All infant cages have an enriched environment where novel items and manipulanda are rotated regularly, providing opportunities for exploratory behavior and stimulation. The additional stimulation allows for normal cognitive development and decreases stress. Natural foraging opportunities are provided when the youngest infant in a rearing group reaches 2 months of age. Foraging items rotate daily between grains, cracked corn, millet, sunflower seeds and trail mix. Afternoon snacks are provided which include peanuts, sweet feed, apples, bananas, popcorn, primatreats, oranges, grapes. On "Fun Snack Friday" infants are introduced to novel fruits and other

healthy food items. The goal of the enrichment plan is to provide novel, interesting and rotating feed items to developing infants.

vi. Behavioral assessments are performed on all non-human primates including nursery infants. These assessments continue through juvenile and adult. Nursery reared infants exhibit different behaviors but do not appear distressed; they are capable of adapting to normal daily stressors later in life.

b. Neonatal assessments:

These are adapted from human infant assessments including handedness test, imitation tests and the Brazelton battery of tests, depending on the age of the infant. They are performed on awake human newborns to assess whether the infant has normal responses and no neural deficits. They are not considered to cause pain or distress in human infants. These assessments are performed at different ages, as detailed in the ASP, from within one day of birth to post weaning age. The infant is swaddled in an absorbent pad and held by a human caregiver during this procedure. "Swaddling" involves holding and wrapping the infant as is done with human infants using a blanket and is comforting to the infant. The infant is returned to the nursery or its mother as appropriate to its cohort group as soon as possible after the assessment. When infants reach 2 months of age they will often receive a special food treat after completing cognitive testing.

The test shown in the news report where the swaddled infant is being held by a lab staff member is the handedness test, this test is to determine if the animal appears to be left handed or right handed.

c. CSF taps:

CSF taps are performed in humans as an awake procedure. On this study the rhesus are sedated with Ketamine for the safety of the human researchers and the animals themselves. The animals are given a dose of ketoprofen as CSF taps in humans are reported to occasionally cause a headache in the patient. Animals are monitored during recovery and assessed after for any sign of complications.

2) *Provide information on any procedures or circumstances that may result in more than momentary discomfort, distress, pain or injury and describe the methods used to alleviate this.*

None of the procedures in question were designed to induce discomfort, distress, or pain; but rather to develop the research paradigm or assess the individual animal's development. None of the procedures in question induce more than momentary discomfort, distress or pain. As currently approved none of the research procedures on the NICHD ASP are considered to be more than

momentarily painful or distressful. In response to PETA's allegations, the NICHD ACUC is reopening this question and will provide an additional response after their October meeting.

Procedures specified in the news report:

The restraint cage was used in NIMH studies and is addressed in their response. In NICHD studies, sedation of the mother is required so that the researchers can safely remove the infants for the behavioral studies described in the ASP. This occurs at days 14 and 30 (Brazelton battery with CSF and blood draws), at 2 months (blood draw), and around 4 months (behavioral bioassessment). After sedation with ketamine, the infant remains with the mother for the minimum time required for human safety which is typically around 5-10 minutes until the mother is fully sedated.

3) *Provide information on the steps which were taken to ensure that the use of stressors was the minimum to obtain valid results. Provide information on the timelines, habituation, mitigation or supportive actions taken to reduce stress to the minimum. Specifically address the length of the stress/fear inducing procedures involving the small restraint cage and the length of time the baby was on the sedated mother.*

The procedures discussed in this report are not considered to be more than brief, transient stressors. The two procedures specified in the directive above are addressed in the NIMH response

4) *Provide justification as to why alternatives to animals could not be used and indicate the potential benefits and knowledge to be gained*

The studies in question were designed to investigate the influence of the mother-infant bond on the behavior, temperament, and social competence of the infant. The numerous physiological, biochemical, genetic, psychopathological, neurological, social, and environmental variables related to behavior necessitates the use of an animal model. In addition, the requirements to control, minimize, or evaluate various nondependent variables (i.e. experiential, genetic, environmental, etc.) makes controlled human studies unfeasible. These scientific justifications are provided by the Principal Investigator and certified by his supervisor who confirms that the study has undergone peer review as part of the quadrennial review of the LCE research program organized by the NICHD Board of Scientific Counselors.

5) *Indicate the steps taken to replace, reduce, or refine the use of animal.*

There are no suitable alternatives to the use of animals that would meet the experimental goals outlined for this study. The number of animals used was reduced to the minimum required to obtain statistical significance. In addition, by working in collaboration with the NIMH to share animals and develop methodologies which would support the mission of both institutes, the number of animals required was further reduced.

Current practices regarding nursery and mother reared infants – breeding and birthing season are synchronized via use of non-invasive birth control methods. Infants are born during a limited window of time to ensure that they are raised as a cohort group. This allows the statistically necessary number of infants to be available during a specific time window, without having excess animals born throughout the year.

Additionally infants who are abandoned or neglected by their mothers in the mother-reared setting are brought into the nursery and raised by the human care providers. On the rare occasions when this occurs it saves the life of that infant and allows for one less human induced separation. In the wild, infants are often abandoned or neglected, especially by primaparous mothers, the infants in fully natural settings do not survive.

6) *Provide the rationale for the age and choice of species used. The rationale should indicate the advantages of the species chosen and why alternative species are not appropriate. If less highly evolved or simpler animal models are available, provide the justification for using more advanced species.*

Although numerous mammalian and non-mammalian species display clear-cut individual differences in response to environmental challenges, nonhuman primates provide the most compelling models of human phenomena in terms of (a) magnitude of genetic overlap, (b) homology of relevant physiological systems, (c) similarity of behavioral responses to both social and nonsocial environmental stressors, and (d) highly parallel patterns and sequences of social and emotional developmental processes. Among the nonhuman primates, rhesus monkeys (Macaca mulatta) are arguably the most preferred species because there already exists an extensive empirical background regarding biobehavioral responses to environmental challenges across a wide range of laboratory and field settings. The complete genome for rhesus monkeys has been sequenced, facilitating studies of specific gene interactions. No comparable data base exists for any other nonhuman primate species. Moreover, the LCE possesses a unique colony of rhesus monkeys, including appropriate breeders, for whom genetic pedigrees (including specific genetic polymorphisms) and characteristic responses to environmental challenge have already been established. It would take years, if not decades, to establish a comparable pool of subjects in another nonhuman primate species.

7) *Provide the description of the living conditions of the young nonhuman primates which are appropriate for their species and contribute to their health and comfort.*

All NHPs assigned to either the NICHD ASP in question, whether mother reared in group-housed runs or nursery reared are housed within standards of the Guide to the Care and Use of Laboratory Animals as per temperature range, light cycle, humidity and space requirements.

All infants in the Lab of Comparative Ethology (LCE) nursery receive daily care and handling by nursery staff. Peer reared infants are co-housed together in groups of four infants. Singly reared infants are in the same room and have constant visual, olfactory, tactile and auditory contact with other infants. Singly reared infants also receive about two hours a day in a group play cage with other singly reared cohorts.

All infants in the LCE nursery receive a variety of enrichment toys and manipulanda which are frequently changed in order to provide a more stimulating environment. Ample cage space allows the infants to climb around freely.

The cage environment includes a plush fleece "surrogate" to which they can hold onto, which mimics the way they would hold onto their mother. Infants can also climb into the surrogate pocket should they choose to do so. This surrogate and placement of a self-feeding bottle allows normal species positioning during nursing and resting. Mother reared infants are raised in group runs typically of one male, several females and their offspring. They have constant interaction with their peers and the older monkeys. The groups in these runs have a well-developed enrichment program, a view of the outdoors, and the ability to come and go from indoor to outdoor runs.

All NHPs in the NICHD program have semiannual behavioral assessments at a minimum to detect distress and behavioral abnormalities. If these are noted, the facility veterinarian, the research staff and the enrichment technician work together to address specific issues and needs of that animal.

8) *Provide a brief synopsis of the qualifications and training of the individuals directly involved in the conduct of procedures and handling of the primates.*

The primate nursery manager has over seven years of experience working with non-human primates. All nursery staff receive training specific to infant care, including appropriate handling, daily feeding and weighing, behavioral assessment and emergency/critical of neonatal rhesus before they are allow to work unsupervised in the nursery.

Prior to working with animals, all personnel conducting research under an animal study protocol are required to complete the NIH training courses entitled "Using animals in Intramural Research: Guidelines for Animal Users" and "Working Safely with Nonhuman Primates". These courses include information on the legal requirements of all personnel working with animals in research,

recognition of nonhuman primate behaviors, and procedures for avoiding and treating bites, scratches and exposures to nonhuman primate body fluids. Personnel were further trained by the principal investigator and veterinary staff on: a) the experimental and behavioral procedures to be conducted; b) the humane and safe handling of nonhuman primates; c) the identification of species specific signs of pain and/or distress; and d) methodologies to avoid or minimize distress.

Before performing CSF taps, a staff member would undergo a lengthy process of observing the procedure and then performing the task under supervision before being certified by the lab supervisor as proficient. The Facility Veterinarian can also perform CSF taps if needed.

The Facility Veterinarian has oversight of the care, health and welfare of all the NHP at the NICHD Shared Facility, including the nursery. The Facility Veterinarian has over 23 of NHP veterinary experience and has worked with non-human primates for over thirty years.

9) *Provide any additional salient information regarding measures taken to ensure the humane treatment of the baby primates used in the conduct of these studies.*

Specific to the maternally separated infants raised in the Lab of Comparative Ethology (LCE) nursery:

Infants are separated as soon as possible after birth. This practice is done to prevent development of mother-infant bonding and thus decreases the amount of stress at separation, particularly of the mother. The maternal-infant bond is thought to develop due to oxytocin release secondary to the infant nursing on the mother and is strengthened with time.

The facility enrichment program and the research enrichment program pay particular attention to animals which meet the criteria as requiring "special considerations". As outlined in the Animal Welfare Act section 3.81 "Environmental enhancement to promote psychological well-being" infants and juveniles should be provided with special attention and an enhanced environment to promote their psychological well-being. Infants are provided with a complex variable rotating manipulanda experience, are provided with daily social contact with conspecifics, receive positive human interactions and species specific foraging opportunities.

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Thursday, October 09, 2014 9:15 AM
To: Clark, Terri (NIH/OD) [E]
Subject: RE: Response for OLAW A4149-9Y

Thanks Terri. I'll send a response soon.
Axel

From: Clark, Terri (NIH/OD) [E]
Sent: Thursday, October 09, 2014 8:51 AM
To: OLAW Division of Compliance Oversight (NIH/OD)
Subject: Response for OLAW A4149-9Y

Dr. Wolff - on behalf of the Office of Animal Care and Use, please find attached the IC letters and Dr. Gottesman's cover memo for this inquiry. Kind regards - Terri

Dr. Terri R. Clark, DVM, DACLAM // Director, Office of Animal Care & Use // Chief Veterinary Officer, CAPT, USPHS
301-496-5424/7236 // clarkte@od.nih.gov // http://oacu.od.nih.gov

DEPARTMENT OF HEALTH & HUMAN SERVICES

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DATE: September 9, 2014

TO: Michael M. Gottesman, M.D.
Deputy Director for Intramural Research, NIH

FROM: Director, Division of Compliance Oversight, OLAW

SUBJECT: Animal Welfare Investigation - Animal Welfare Assurance A4149-01 [Case 9Y]

The Office of Laboratory Animal Welfare (OLAW) has received from the NIH Office of Communications and Public Liaison a link to the CBS News report regarding allegations raised by the People for the Ethical Treatment of Animals (PETA) about studies of baby monkeys at the National Institute of Child Health and Development (NICHD) by Dr. Stephen Suomi and at the National Institute of Mental Health (NIMA) by Dr. Bruno Averbeck. The allegations state that the nonhuman primates were subjected to undue psychological and physiological distress during the conduct of these studies. Peta also alleges that the information obtained from this work has already been established in the conduct of human studies.

In order for OLAW to have a better understanding of the facts surrounding these studies, please direct the NICHD and NIMA Animal Care and Use Committees, avoiding any conflicts of interest, to examine these allegations and address the following questions:

1) Provide an explanation of how discomfort, distress, and pain was avoided or minimized, consistent with sound scientific practices and research design. As noted in the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training, "Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals."

2) Provide information on any procedures or circumstances that may result in more than momentary discomfort, distress, pain or injury and describe the methods used to alleviate this.

3) Provide information on the steps which were taken to ensure that the use of stressors was the minimum to obtain valid results. Provide information on timelines, habituation, mitigating or supportive actions taken to reduce stress to the minimum. Specifically address the length of the stress/fear inducing procedures involving the small restraint cage and the length of time the baby was on the sedated mother.

4) Provide justification as to why alternatives to animals could not be used and indicate the potential benefits and knowledge to be gained.

5) Indicate the steps taken to replace, reduce, or refine the use of animals.

6) Provide the rationale for the age and choice of species used. The rationale should indicate the advantages of the species chosen and why alternative species are not appropriate. If less highly evolved or simpler animal models are available, provide the justification for using more advanced species.

7) Provide a description of the living conditions of the young nonhuman primates which are appropriate for their species and contribute to their health and comfort.

8) Provide a brief synopsis of the qualifications and training of the individuals directly involved in the conduct of procedures and handling of the primates.

9) Provide any additional salient information regarding measures taken to ensure the humane treatment of the baby primates used in the conduct of these studies.

Please provide the requested information or an interim report by **October 9, 2014**.

Axel Wolff, M.S., D.V.M.

cc: Dr. Terri Clark
Dr. Richard Wyatt

A4149-9Y

Wolff, Axel (NIH/OD) [E]

Subject: FW: PETA campaign launched

From: Myles, Renate (NIH/OD) [E]
Sent: Monday, September 08, 2014 9:16 AM
To: Sye, Tait (OS/ASPA); Baldauf, Sarah (OS/ASPA)
Cc: Burklow, John (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Quinn, Kevin (NIH/NIMH) [E]; Bock, Robert (NIH/NICHD) [E]; Gallagher, Alissa (NIH/NIMH) [E]; McElroy, James (NIH/NIMH) [E]
Subject: PETA campaign launched
Importance: High

Hi Tait and Sarah:

CBS' story on the monkey research posted today (see below) and PETA has launched its campaign: http://investigations.peta.org/nih-baby-monkey-experiments/. NICHD has set up their systems to handle the public inquiries which are coming in full force and NICHD/NIMH are prepared to take press inquiries on it. We'll send press inquiries up as ADDS to previously cleared request.

Thanks,
Renate

CBS News

Questions raised about mental health studies on baby monkeys at NIH labs

By Jessica Firger

(Video on Website)

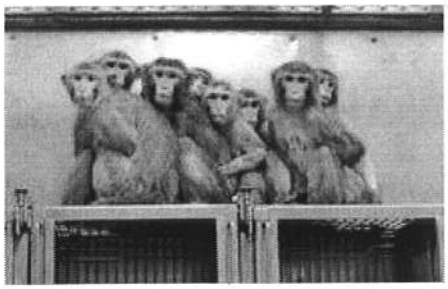
Newly released photos, video and lab reports document years of mental health studies conducted on baby rhesus monkeys at two federally-funded labs in the National Institutes of Health Intramural Research Program.

Through a Freedom of Information Act request, People for the Ethical Treatment of Animals (PETA) obtained more than 500 hours of video, hundreds of photographs, as well as animal study proposals and scientific reviews from the NIH, some of which were provided exclusively to CBS News for review.

The studies, which began in 2007, attempt to model some of the environmental risk factors associated with human mental illness, such as parental neglect and childhood abuse or trauma, in an effort to understand how they interact with genetic factors.

Methodologies used in the studies included separating baby monkeys from their mothers shortly after birth; sedating a mother in the baby's presence to see how it responds when she loses consciousness; intentionally startling monkeys with sudden, loud noises; and subjecting the monkeys to invasive procedures such as spinal taps and intracranial administration of medications.

As a result of its investigation, PETA is accusing the researchers of causing the baby monkeys undue harm, amounting to what it calls "child abuse."



7 Photos

Inside an NIH primate lab

These photos of rhesus monkeys, obtained by PETA, are part of research examining the impact of early childhood experiences on mental health

"The one thing that we have learned from these experiments from the NIH is that monkeys are like us in ways that matter," Justin Goodman, director of PETA's laboratory investigations department, told CBS News. "They need the love and comfort of their mothers when they're young, they need the companionship of the families and peers. When they're deprived of that they are devastated emotionally and physically."

In an email to CBS News, one of the lead researchers, Stephen J. Suomi at the National Institute of Child Health and Development (NICHD), disputed the accusation of abuse, insisting that the studies "are conducted with the highest ethical standards at specialized centers that employ professional staff and highly skilled caretakers to ensure humane care of these animals, and are in strict accordance with animal welfare regulations and accreditations." In addition to Suomi's lab, the experiments in question were also conducted at the National Institute of Mental Health under lead investigator Bruno Averbeck.

Goodman said PETA believes the experiments are not only cruel, they're also unnecessary because similar issues have already been studied in human populations or could be more effectively studied in other ways. Additionally, PETA says findings about mental health and mental illness in monkeys are not necessarily relevant to human brains, and none of the research being conducted has resulted in better or new treatments for human mental illnesses. Goodman said he believes these studies are "completely unjustifiable and scientifically they are absolutely fraudulent."

Some independent scientists who reviewed the studies at PETA's request echoed those concerns. "I can no longer see a potential benefit from such experimentation," Agustin Fuentes, Ph.D., Chair of Anthropology at the University of Notre Dame, told the group. "It is my assessment that the monkeys used in these experiments experience substantial psychological (and likely physiological) harm and that there is no current evidence that there will be any results from the studies that move our understanding of human psychopathology forward."

Suomi, however, maintains this research could prove to have great value for humans. "NIH supports studies involving monkeys to supplement the developmental studies of human beings," Suomi told CBS News. "The same behavioral, neurological and health changes seen in nursery-reared monkeys are seen in children who were orphaned from their mothers, or raised by depressed, abusive, or neglectful mothers. These findings assist researchers in identifying humans most likely to suffer negative effects in at-risk situations and develop behavioral and drug therapies to improve negative outcomes early in development."

Baby rhesus monkey at an NIH lab. Photos obtained by PETA were taken between 2009 and 2012.
NIH/PETA

Monkey research on childhood development has a long history, and one that is closely tied to criticism by animal rights activists. In the 1950s and 60s, the late Dr. Harry Harlow, then a professor of psychology at the University of Wisconsin, pioneered monkey research that explored theories of attachment in early childhood. The methodologies used in his lab, which included forced mating of mentally disturbed monkeys and isolating baby monkeys in dark chambers for as long as a year, were partially responsible for inciting the animal cruelty debate. Perhaps ironically, the impetus for much of Harlow's research was to better understand the nature of love.

PETA believes Suomi -- a former student of Harlow's -- and Averbeck have continued this legacy of animal exploitation using study models similar to those used in Harlow's lab. However, in their investigation, Goodman said PETA did not attempt to contact Suomi or Averbeck to discuss their research.

Dr. Constantine Stratakis, the scientific director of the NICHD, who oversees non-human primate research including that conducted by Suomi, told CBS News these studies are constantly monitored by the NIH's animal care committee and also consistently evaluated by the U.S. Department of Agriculture and the Association of Assessment and Accreditation of Laboratory Animal Care International, which is not affiliated with the NIH. Additionally, NIH scientists are required to justify why it would be necessary for their research to utilize an animal study model.

He said evaluations of the labs by these agencies have not indicated animal abuse and that the scientists take exceptional care of the animals. "They have names for these babies and birthdays for the babies," said Stratakis. "It's not that different from a human nursery."

PETA's investigation highlights a number of video clips obtained from the NIH, including footage of one test used to study the fright response in infants, in which a baby monkey is shown isolated in tiny mesh cage known as a "startle chamber," while researchers play loud and unexpected noises. The monkey is noticeably in distress and panicked.

But Stratakis said the cages are meant to protect the safety of the monkey since a panicked animal allowed to run free is likely to injure itself in these circumstances.

Stratakis added the methodologies depicted in videos are not currently used by the researchers. He said most of of the photos and videos in question are five years old; a spokesperson for the NIH said a majority of video footage obtained by PETA is from 2009.

"The protocols that are ongoing right now are different from the protocols that were in effect in studies conducted shown in the video," said Stratakis. "These studies have ended and just as the nature of most of our studies, when the goals are met the studies are concluded."

Stratakis added that the studies in question were initiated to observe how environmental and psychosocial factors experienced in early childhood have pervasive and long-term impact by influencing chemical reactions in the body and ultimately altering genes -- a fundamental and growing field of research known as epigenetics.

A number of well received and important papers have come out of Suomi's lab, said Stratakis. One benchmark study found that babies learn better when they see faces, and that an infant's efforts to mimic parents is a critical milestone in development. Another study, published in the journal Psychoneuroendocrinology in April, looked at how population density influences cortisol levels in the body. It found that when groups of monkeys were placed in smaller spaces, their physiological stress response increased, evidenced by higher cortisol levels found in their hair.

PETA asserts that researchers could gather similar data from humans using brain scans and other techniques. For their investigation, Goodman and his team consulted a number of outside experts, including world-renowned primatologist Jane Goodall and John Gluck, emeritus professor of psychology at the University of New Mexico and a research professor at the Kennedy Institute of Ethics at Georgetown University, who previously conducted similar research on social deprivation in primates.

"I eventually chose to leave that area of research because I came to believe that those models did not accurately represent the development and presentation of human mental illness," said Gluck in a statement prepared by PETA. "I came to the view that those models could not adequately inform innovative directions for successful clinical intervention to justify the costs in suffering and pain. I see nothing to alter that view with respect to the program of primate deprived early experience research currently being conducted at the NIH."

But Allyson Bennett, PhD , a professor in the department of psychology at the University of Wisconsin who previously worked alongside Suomi, said that human studies don't always produce consistent and reliable results. "What primate research gives you that's not possible in humans is the ability to control the environment," she told CBS News. She said studying development in infant primates allows for the consistency with factors such as food, shelter and sleep.

Bennett, who is also a member of Speaking of Research, a volunteer group of scientists and advocates who seek to raise awareness about the importance of animal research, said much of this research has also benefited animals living in both captive and natural habitats by identifying ways to help them thrive in places such as animal sanctuaries and zoos.

"In my experience scientists are deeply concerned about the animals they work with," said Bennet. "These are ethical and moral dilemmas all of us wrestle with."