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To: Michael M. Gottesman, M.D.
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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.

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