Fear, Anxiety, and Stress in the Laboratory: Why Nonhuman Primates Make Poor Research Subjects

Mary Beth Sweetland, Director of Research & Investigations Department
Philip Schein, Special Assistant to the President
PETA, 501 Front Street, Norfolk, Virginia 23510
marybeths@peta.org

We have compiled the following executive brief for the convenience of IACUC personnel to help negotiate and summarize the recent literature on this subject. It indexes and appraises the recent studies on the causes and effects of stress on primates in laboratories, including the reasons these factors can never be eliminated or controlled. The brief is organized as follows:

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1. Specific Laboratory Stressors of Primates

1.1 Housing and Social Stressors

Laboratory cages are physically confining and socially restrictive living spaces for primates, and these conditions impose unreasonable stresses upon them. Recent studies have confirmed the causes and effects of housing and social stressors on primates, including primates who are subjected to solitary lives in cages or those who are housed in cramped, crowded conditions. Other studies have shown the harmful consequences of separating primates from their cage mates and placing them together arbitrarily into new groups, altering power dynamics and systems of social support. In all these cases, imposing unnatural physical and social configurations on primates resulted in profound disruptions of species-specific behavior and physiological issues.[1,2,3,4,5,6,7,8,9,10,11]

- Cross, Pines, and Rogers (2004) and Soltis, Wegner, and Newman (2003), for example, demonstrated that both the presence of conspecifics or separation from conspecifics can be causes of acute stress. [12,13]

- Shapiro *et al.* (2000) and Reinhardt and Rossel (2001) documented how individual caging constitutes such a potent stressor as to produce immunosuppression.[14,15]

- Chase *et al.* (2000) and Bellanca and Crockett (2001) demonstrated that singly housed, socially restricted primates paced more, locomoted significantly less, were more aggressive, and manifested significantly more abnormal behaviors.[16,17]

- Boyce *et al.* (1998) noted that when confinement space is reduced, the crowded conditions result in a five-fold increase over six months in the incidence of violent injuries.[18]

- Cross, Pines, and Rogers (2004) documented how separating animals with social bonds stimulates a response consisting of behavioral agitation and adrenal activity, and Pines, Kaplan, and Rogers (2004) demonstrated how marmosets are negatively affected by any events adversely affecting a roommate. [19,20]

- Crockett *et al.* (2000) and Reinhardt (2000) demonstrated that even subtle changes in conditions of captivity such as different cage sizes and cage levels can be extremely stressful to primates.[21,22]

1.2 Environmental Stressors

Laboratory environments differ enormously from natural habitats, and recent studies have demonstrated that several of a laboratory's environmental conditions contribute to unacceptable levels of stress in primates, including ambient temperature, lighting conditions, loud noises, cage locations, and even the mere presence of humans in primate rooms. Although some laboratories have been able to make some small modifications in the environmental conditions of their laboratories, it is not possible for primates to live in

laboratories and participate in experiments without suffering from environmental stress.[23,24,25,26,27,28,29,30,31,32,33,34,35]

- Reinhardt and Reinhardt (2000a) demonstrated that poor lighting in laboratories frequently provides a cave-like housing environment for primates, particularly for those who are forced to live ground-dwelling lifestyles in bottom-tier cages. Reinhardt concludes that these conditions impair well-being and invalidate research data.[36]

- Cross, Pines, and Rogers (2004) documented how noise adversely affects primates in laboratories. Their mean levels of salivary cortisol during periods of disturbance were four times higher than normal.[37]

- Reinhardt and Reinhardt (2000b) recorded that primates exhibit apprehension and fear when an investigator or technician even enters the room.[38]

1.3 Husbandry Stressors

Primates in laboratories are subjected to a variety of routine animal husbandry procedures, all of which are experienced as stressful even when a laboratory follows best practices. The most sensitively conducted non-invasive and non-experimental procedures can create stressful conditions in captive primates. A study by Balcombe (2004) on the effects of routine husbandry on rats concluded that non-invasive manipulation occurring as part of routine husbandry, including lifting an animal, cleaning or moving an animal's cage, etc., resulted in "significant changes in physiologic parameters correlated with stress (e.g., serum or plasma concentrations of corticosterone, glucose, growth hormone or prolactin, heart rate, blood pressure, and behavior."[39] The effects on primates are that much more complex and profound. For example:

- Carstens and Moberg (2000) cautioned, "What might be viewed as innocuous manipulation of the animal may confound experimental results," and Wolfe (2000) confirmed that stress results from "both experimental and non-experimental sources."[40,41]

- Suzuki (2002) documented how plasma cortisol levels increased when a large adult male researcher entered the room, as macaques instinctively assumed the researcher to be a predator or rival.[42]

- Line *et al.* (1989) demonstrated that primates become significantly stressed when their room or cages are cleaned or they are tested for tuberculosis. Heart rates can remain elevated for hours after these events, and primates do not habituate to them.[43]

Capture is especially stressful for primates, and they frequently reveal their distress in obvious ways such as crouching, assuming defensive postures, diarrhea, fear grinning, attempting to flee, grimacing, suffering from rectal prolapse, screaming, struggling, or

making aggressive displays. Primates are frequently restrained and captured in laboratories, and they always experience restraint as stressful regardless of the method used. Common methods of restraint and studies that have demonstrated their stressful effects include anesthetics such as ketamine, board restraints, chair restraints, chute restraints, guillotine panels, manual restraint, squeeze cages, table restraints, tethering, and transfer boxes. In addition to capture and restraint, recent studies have demonstrated that primates are also significantly stressed by other routine husbandry procedures such as feeding, medical procedures, palpation, pregnancy examinations, and weighing.[44,45,46,47,48,49,50,51,52,53,54,55,56,57]

1.4 Protocol Stressors

All research protocols are stressful to primates, even those that are not specifically designed to produce stress. Most of these involve at least some of the following standard components which multiple studies have proved produce stress and skew data: behavioral testing, blood sampling, novel situations and environmental manipulation, stool sampling, reproduction techniques such as penile vibratory stimulation or electroejaculation, venipuncture, and saliva or urine sampling.[58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75]

- McAllister (2004) and Reinhardt and Reinhardt (2000) documented how using cortisol levels as a measure of stress are complicated by the use of invasive techniques that may increase hypothalamic-pituitary-adrenal HPA axis activity during sample collection.[76,77]

- Yeoman (1998) and Cui (1996) demonstrated the detrimental effects of stress on sperm yield and quality on samples collected through the highly stressful and painful method of electroejaculation.[78,79]

1.5 Pre-laboratory Stressors (When Applicable)

The effects of stress are persistent and may have begun before a primate enters a laboratory. These unknown variables, which may have already altered physiology and behavior as well as receptivity to new procedures, further complicate attempts at establishing reliable controls.

a) Prenatal and Early Rearing Sources of Stress

- Gorman and Coplan (2002) and Clarke et al. (2004) demonstrated that prenatal stress can produce profound alterations in biological factors such as regulation of hypothalamic-pituitary-adrenal (HPA) axis, biogenic amines, and immune function. Coe (2003) confirmed that the prenatal environment can alter behavior, dysregulate neuroendocrine systems, and affect the hippocampal structures in primates in a persistent manner.[80, 81, 82]

- Barr *et al.* (2003) and Lutz *et al.* (2003) documented that macaques with histories of early-life stress have also have exhibited impulsive aggression, incompetent social behavior, and increased behavioral and endocrine responsivity to stress. Tiefenbacher (2005) demonstrated that chances of primates developing self-injurious behavior is heightened by adverse early experiences and subsequent stress exposure.[83,84,85]

b) Capture and Transportation/Relocation Sources of Stress

- Laudenslager *et al.* (1999) described the magnitude of stress associated with original capture, noting that during the period of captivity, plasma cortiosol rose, plasma prolactin and growth hormone fell, and there was a significant rise in insulin.[86]

- Honess, Johnson, and Wolfensohn (2004) documented the stress caused by air transport and re-housing and reported that the behavioral changes which occurred never returned to levels at the original breeding facility within the first month, an experience that "may result in the compromising of the welfare of the study animals."[87]

2. Specific Effects of Laboratory Stressors in Primates

2.1 Biochemical, Physiological, and Epidemiological Effects

There is a wealth of information detailing the extent to which stress disrupts the major physical functions of primates and leads to the development of disease and other pathologies.

- Carstens and Moberg (2000), for example, report that the cumulative effects of several stressors on primates leads to diversion of resources that results in their suffering from immune incompetence and other pathologies such as loss of reproductive abilities.[88]

Laboratory stress in primates affects the biochemistry of their endocrine, immune, and reproductive systems. The endocrine system is the adrenal gland, including the cortex and the medulla, adrenal hormones, including adrenal androgens, cortisol, adrenal corticoids, corticosteroids, and glucocorticoids. It also includes the pituitary gland and its hormones, including trophic hormones, the pituitary-adrenocortical-hypothalamic system, thyroid gland hormones, catecholamines, luteinizing hormones, lymphoids, prolactin, and opiate hormones.[89,90,91,92,93,94,95,96,97,98,99,100]

Stress affects the immune system of primates in laboratories by altering general antibody responses, the character of lymphocytes—including B cells, CD4+ cells, CD8+ cells, and T cells—cytokine, interferon, hematocrit, hemoglobin, monocytes, natural killer cell (NK) activity, prostaglandins, and white blood cells.[101,102,103,104,105,106,107,108,109,110]

The reproductive system undergoes general changes as well. The organs affected are the pituitary-gonadal hormones, ovaries, placenta, the follicular phase and luteal phase of menstruation, testosterone, dihydrotestosterone, progesterone, pregnenolone, 17-hydroxypregnenolone, 17-hydroxyprogesterone, 20a-dihydroprogesterone, estrone, estradiol, DHA and DHAS, semen volume, and motility.[111,112,113,114,115,116,117,118,119,120]

The known physiological effects of stress in primates in laboratories include arteriosclerosis, osteoporosis, diabetes, changes in blood pressure, body temperature, circadian rhythms, ECG patterns, enzymatic shifts, heart rate, leukocytosis, metabolism, respiratory rates, sleep patterns, and weight gain or loss.[121,122,123,124,125,126,127,128,129,130,131,132,133,134,135]

- Gilmer and McKinney (2003) reported that the physiological effects of stress in primates included an altered hypothalamic-pituitary-adrenal response to stress, changes in diurnal temperature regulation, and alteration in immune function; Schapiro (2000) documented how diminished immune response is the most frequently observed consequence of prolonged or intense stress exposure.[136,137]

- Fuchs and Flugge (2004) documented how one month of stress reduced cell proliferation in the dentate gyrus and decreased the total hippocampal volume. . . . Stress also induced a constant hyperactivity of the hypothalamic-pituitary-adrenal axis and suppressed both motor and marking behaviors.[138]

These biochemical effects also make primates more susceptible to diseases, including bacterial infections, neutrophilia, parasitic infestations, and viral infections as well as doubling the possibility of endometrial cancer. Shivley (2004) and Boere *et al.* (2003) documented additional stress-induced pathologies such as higher incidences of diabetes, consumptive disorders, osteoporosis, arteriosclerosis, and gastric-duodenal ulcers. Bailey (2004) recorded how even prenatal stress altered bacterial colonization.[139,140,141,142,143,144]

- Shivley (1999) concluded from studies of monkeys that social stress caused by low social status may be the underlying mechanism affecting pathophysiology and disease.[145]

2.2 Behavioral and Social Effects

The myriad behavioral abnormalities that characterize primates in laboratories have been well known for decades and include bizarre postures such as floating limbs, self-biting, self-clasping, self-grasping, and saluting; stereotyped motor acts such as pacing, head-tossing, head-weaving, bouncing in place, somersaulting, and rocking; appetite disorders such as uncontrollable eating, insufficient eating, frequent drinking, feces-eating, and paint-eating; sexual disorders such as inappropriate orientation, homosexual behavior, sexual dysfunction, and autoerotic stimulation; disturbed activity patterns such as inactivity, hyperactivity, and temporally inappropriate behavior; and agonistic disorders such as hyper-aggressiveness, fear-grinning, screaming, acute diarrhea, struggling and

refusing to enter the squeeze cage; and self-abusive behavior such as self-biting, hair pulling, and self-scratching leading to physical harm.[146,147,148,149]

- Gilmer and McKinney (2003) demonstrated that early adverse experiences in primates can lead to behaviors including repetitive idiosyncratic behavior, increased self-directed behaviors, inappropriate expressions of aggressive behavior, nonmodulated patterns of consumption, and inappropriate sexual and maternal behavior.[150]

- Reinhardt and Rossel (2001) and The National Research Council (1998) documented how self-biting typically occurs in individually caged primates.[151,152]

2.3 Psychological and Cognitive Effects

Many of the social and behavioral effects of stress in captive primates have already been discussed in previous sections of this brief, and additional studies also illustrate its ill effects on primate psychology and cognitive functioning. These effects include degradations in their ability to engage in species-typical activities such as exercising, mating, raising children, maintaining mental well-being, engaging in normal forms of social companionship, performing routine tasks, and the ability to recognize predators.[153,154,155,156,157,158,159,160,161,162,163,164]

- Shivley (2005) documented how female cynomolgus monkeys suffered from signs of depression when they were isolated and exhibited lethargy, hormone disruptions, and higher heart rates—all of which are indicative of depression.[165]

- Gilmer and McKinney (2003) documented how early adverse experiences affected primates cognitively, resulting in such animals' requiring longer habituation time for any task. Arnsten and Goldman-Rakic (1998) and Moghaddam and Jackson (2004) demonstrated that noise stress impairs prefrontal cortical cognitive function in monkeys.[166,167,168]

3. General Characteristics of Stress for Primates in Laboratories

3.1 Primates Do Not Habituate to Laboratory Stressors

Experimenters frequently claim that primates in laboratories habituate to stress after a period of acclimatization, but this is untrue. Several recent studies have demonstrated that primates do not habituate to many stressors, even after years of exposure.[169,170,171,172,173,174,175,176,177]

Consider the following:

- Schnell *et al.* (1997) argued that it is impossible to completely inhibit the defensive reactions of primates to experimental procedures—even after long-term training. He demonstrated that primates in laboratories respond to restraint and venipuncture with marked, acute, and chronic increases in their heart rate and blood pressure even after years of experience as research subjects. Moreover, experienced primate research subjects have learned to anticipate restraint and venipuncture events by developing sustained patterns of cardiovascular stress.[178]

- Line *et al.* (1989) demonstrated that primates do not habituate to the stressors of room cleaning, cage cleaning, or tuberculosis testing. Line *et al.* documented how they became significantly stressed when their rooms or cages were cleaned or when they were tested for tuberculosis. Heart rates remained elevated for hours after these events, and primates did not habituate to them.[179]

- Gordon *et al.* (1992) demonstrated that experimentally naïve primates do not habituate to blood sampling procedures even after six weeks of exposure.[180]

- Honess, Johnson, and Wolfensohn (2004) reported that levels of stress a month after relocation from a breeding facility never returned to normal.[181]

- Lilly *et al.* (1999) demonstrated that primates did not acclimate to new housing situations even after 23 weeks in a new situation.[182]

- Golub and Anderson (1986) found that primates never adapted physiologically to the stresses of weekly blood sampling and manual palpation, even though they may have adapted behaviorally. Heart rate, blood pressure, respiration rate, and cortisol levels always rose during these procedures, even in primates who have experienced these procedures for 23 weeks.[183]

- Laudenslager *et al.* (1985) discussed how primates who are forced to endure separation experiences from their mothers or troop members frequently suffer from abnormal heart rates, body temperatures, circadian rhythms, EEG patterns, cellular immune function, and behavioral and neurological pathologies more than three years after the separation event. These changes persist for several years after the separation experience and may be permanent for some primates.[184]

3.2 Laboratories Cannot Eliminate Stressors

Sometimes experimenters and laboratory staff believe that they can improve or modify their laboratory environments and procedures to reduce or eliminate unwanted stress in the lives of the primates under their care. But this is almost always an impossible goal, even in the best of primate sanctuaries. Primates are simply too sensitive to stress, and laboratory environments are inherently too stressful for primates to live in them without suffering the unnatural and data-contaminating condition of ceaseless stress.

- Barros and Tomaz (2002) and Tatoyan and Cherkovich (1972) demonstrated that the mere presence of a human observer is capable of eliciting defensive attack and anxiety-related behavior. In many cases, the presence of human beings is even more stressful to primates than being restrained. [185,186]

- Schapiro *et al.* (2000) demonstrated that every type of laboratory housing for primates degrades the effectiveness of at least some components of their immune systems. [187]

3.3 Primates Hide Symptoms of Stress, and Many Symptoms of Stress Are Difficult to Diagnose and Detect

It is widely documented that primates not only hide symptoms of stress as defensive measures, but that symptoms of stress may be indiscernible or invisible to the investigator. Many primates in laboratories may look fine, but inwardly they are suffering from the damaging effects of stress in their biochemistry, physiology, psychology, and sociability. Usually only the most extreme forms of fear, pain, or suffering will cause primates to show the visible effects of their distress. [188,189,190]

- Coe *et al.* (1987) demonstrated that primates who are separated from their troops suffer from diminished immune system response, even though they do not appear debilitated or depressed. Coe concluded that it is not possible to visually identify the effects of diminished immune system response in primates that are suffering from separation experiences. [191]

Making diagnoses of stress more problematic is that the primate subject may also not be conscious of the physical effects of stress:

- For example, Carstens and Moberg (2000) discussed "stress-induced analgesia" and how psychological distress in primates can increase or decrease pain perception. [192]

Carstens and Moberg discussed as well how a tumor, for example, may elicit stress responses in an animal not conscious of the cancer. In a laboratory setting, such induced physiological pathologies are often an integral component, and many symptoms may not even be recognized as stress or be attributed to stress, as they may be the product of complex, interacting, and ambiguous physiological origins.

3.4 The Effects of Stress in Primates Are Complex and Interact

Stress is a complicated phenomenon, affecting multiple, interconnected systems, so that it is difficult to isolate as a single variable or effect. Primates react to stress in highly individualized and complex ways, especially at the biochemical level where the sympathetic nervous system, the hormonal systems, and the immune systems all interact

with each other in response to stressful conditions. The complexity of these responses means that experimenters are frequently unable to know if the data that they collect reflect the results of the experimental procedures or the stressed condition of the primate in the laboratory. The results, therefore, are ambiguous because experimenters cannot reliably identify the causes of the effects they measure. Included in this brief are indexed dozens of studies that demonstrate this fact. But a few studies deserve special mention because they have examined the complex reality of stress in primates directly:

- Norcross and Newman (1999) identified that stress "can differentially affect the hormonal response without differentially affecting the behavioral [response]."[193]

- Carstens and Moberg (2000) stated that the most reasonable strategy for measuring stress would be to monitor the responses of the four major defense systems (behavior, autonomic nervous system, neuroendocrine system, and immune system) since they are responsible for the biological changes that occur during stress; however, they argued that none of the monitoring has proved to be a reliable measure of stress or *distress* since no single system responds to all stressors.[194]

- Shively (2005) described depression in primates as a "whole-body disorder."[195]

- Schapiro *et al.* (2000) demonstrated that even though stress indexes in primates are usually measured singly for purposes of experimental clarity, the actual biochemical realities of stress in primates are extremely complicated. Every single measurable stress effect interacts with all of the others, making it impossible to limit the biochemical and physiological effects of stress to only a few biological systems.[196]

- Goncharov *et al.* (1979) demonstrated that stressors evoked not just a few, initial hormone responses, but generally elicited a broad range of multiple, concurrent responses involving much of the neurological and endocrine systems.[197]

- Coe *et al.* (1987) demonstrated that the endocrine and immune systems of primates in laboratories do not change in simple ways in response to stress and concluded that we must not underestimate the true complexity of the total effects that stress has on them.[198]

3.5 Stress Affects Individual Primates Uniquely

Stress is a highly variable phenomenon affecting individual primates in unique ways and making statistically reliable data problematic.

- Carstens and Moberg (2000), for example, stated that because there is currently no litmus test for distress, trying to recognize distress must be done on almost a case-by-case basis. They added the caveat that the same stressor can be manifested in a variety of responses in the same animal.[199]

Further complicating stress measurements are the intra-animal differences in how the four general defense systems respond in attempting to cope with the stressor. Early experience, genetics, age, and physiological state are examples of a multitude of moderators that influence the nature of a stress response. With traditional laboratory animals such as rodents, many of these variables can be more easily controlled and accounted for in the experimental design, but for some laboratory animals (e.g. nonhuman primates or random-source animals), it is extremely difficult to account for these modulators of the stress response because simple measures of hormones, autonomic nervous system activity, or immune response may be unreliable measures of stress outside the experimental paradigm.

- Gust *et al.* (1994) demonstrated that the biochemical reactions of individual primates to social stressors vary widely. Gust concluded that because social stressors are one of the most common and upsetting forms of stress among primates housed in laboratories, the large effects of social stress and the wide variability in responsiveness among individuals make it difficult to interpret experimental data derived from them.[200]

- Sapolsky (2001, 1993) demonstrated how stress affects primates uniquely and how primates respond to stress in highly individualized ways.[201, 202]

3.6 Stress Variables Cannot Reliably Be Controlled, Factored, or Generalized

The scientific integrity of studies involving laboratory-confined primates is inherently compromised because of the pervasive contamination of stress and the impossibility of accurately defining and controlling the spectrum of causes and effects of stress. (Bentson *et al.* 2003).[203]

- Moberg (1999) argued that not only can pain and stress cause distress, the biologic effects can also compromise experimental results. Carstens and Moberg (2000) further cautioned that there are neither "agreed-upon definitions" for terms such as pain and stress nor are there absolute, objective measures because animals cannot verbalize what they are experiencing.[204,205]

- Hawkins (2003) reported that indicators of pain, suffering, and distress in primates are largely subjective.[206]

- Reinhardt (2004) concluded that there is no control over the time during which an environmental disturbance is occurring, a factor that must be mentioned to explain possible incongruities of data.[207]

- Schnell *et al.* (1997) demonstrated that the acute effects of stress in primates have broad implications for the evaluation of pharmacological profiles of drugs used in biomedical research.[208]

3.7 Cross-Species Misconceptions

Despite overwhelming evidence, there are still researchers who do not recognize the significance of stress factors in research on primates.

According to Haller (DD 2001), "There is an important discrepancy between animal models of anxiety and human anxiety patients: While experimental animals are usually unstressed, patients usually have a long history of stress."[209]

However, an equivalent mistake is the assumption that stress research on primate models can be meaningfully extrapolated to humans. Just as pharmacological efficacy has great variation between nonhuman and human primates, the experimental data obtained from nonhuman primates have little generalizability beyond the simple, tautological recognition that induced stressors cause symptoms of stress.

4. Recommendations

Laboratories are stressful environments, and the primates who are held within them endure lives of ceaseless anxiety, pain, and fear. Some laboratories are more stressful than others, but no laboratory can reduce the stresses that primates experience significantly enough to raise animal-welfare conditions to an acceptable level, and no laboratory can reduce the stressors sufficiently to produce meaningful and reliable scientific data. Clearly disturbing experiments such as those conducted at Columbia University have little scientific import and egregious ethical consequences. In these studies, monkeys had metal pipes surgically implanted into their skulls for the sole purpose of inducing stress in order to study the connection between stress and women's menstrual cycles. We urge all IACUCs and affiliated institutions not to accept or approve further protocols involving primates in laboratories.[210]

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