Influence of mental states on somatic health in animals

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Much anecdotal evidence has accumulated over the millennia to support Aristotle's suggestion of a connection between mood and health. Clinicians in human medicine have long observed that "stress" contributes to the course of disease states and that social and environmental factors can influence susceptibility to illness and disease by altering the responsiveness of the immune system.[1] Since Solomon and Moos[2] first proposed then-speculative theoretic integration of emotion, immunity, and disease 35 years ago, a rapidly expanding body of clinical and experimental evidence—on humans and other animals—supports a strong interrelationship and bidirectional influence between emotional states and physiologic processes of somatic health. An extensive body of literature reveals the influence of emotional states on the course and outcome of physical illnesses in human beings; however, although the evidence for such a relationship in nonhuman animals is equally vast, these diversely reported data have not been comprehensively reviewed. Moreover, until recently, a biochemical rationale for the influence of mental states on somatic health was lacking. Recent advances in neuroscience have revealed a plausible biochemical mechanism for these interactions. The purpose of this report is to present evidence for the integration of mental states and physical health in nonhuman animals.

The Organism as an Information Network

All organisms, for optimal function and survival, must maintain and preserve the homeostasis and integrity of the body. In so doing, the organism must respond to a wide variety of threats and attacks from outside and within the body proper. An organism, as a whole, gathers and processes information, then responds to and interacts with the environment as an ensemble; the interaction is not by brain or body alone.[3] In preserving body homeostasis and integrity, all defense mechanisms—behavioral, immunologic, detoxification, wound healing—work cooperatively as a unit; to accomplish this, there must be a constant exchange of information throughout the body cells and systems to coordinate integrated and organized responses. The biological basis and evidence for such a body-wide system of communication was only theoretic speculation until results of recent research on neuropeptides and the anatomic distribution of their receptors revealed a mechanism by which various body systems that were believed to operate independently may communicate with and modulate one another in a single functional network of information exchange.[4,5]

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Neuropeptides, short chains of amino acids originally known for their role as neurotransmitters, function as hormone-like messenger molecules, transmitting information from the secreting cell to other cells by binding to and activating specific receptors on cell surfaces.[4] These peptides and their receptors have been conserved structurally in evolution and are widely distributed across phyla.[6] In the CNS of the recently evolved mammals, neuropeptides and their receptors are most densely concentrated in the limbic regions, classically known to contain the brain's emotional circuitry.[4,7] Among their other functions, neuropeptides play a large regulatory role in mental states; much evidence supports the role of opioids in controlling or mediating emotional and affective (feeling) states, such as pleasure,[6,8] pain,[9] and emotions of social bonding and attachments.[8,9] This is consistent with current evolutionary theory, which interprets mental states as serving the same goals as the physical body (ie, optimal survival and reproductive fitness).[10] As motivational guides for behavior, emotions appear to control psychobehavioral circuits, which generate adaptive behaviors during circumstances that challenge the homeostatic and existential integrity of animals.[8] The prominent role of opioid peptides in mental states has led to the postulation of neuropeptides as the biochemical mediators of emotions.[4]

Neuropeptides and their receptors originally were believed to be confined to and thus act solely within the nervous system. This view was changed radically in 1980 by Blalock and Smith,[11] who discovered that endorphins were produced not only by cells of the CNS but also by cells of the immune system. Their findings in human lymphocytes[11]—followed by that of Lolait et al[12] who found that mouse spleen monocytes secreted the mood-altering brain peptide endorphin, as well as ACTH—established that the immune system was communicating not only with the endocrine system but also with the nervous system and the brain, using a chemical mechanism that consisted of opiate neuropeptides and their receptors to code for information.[7,11] Results of subsequent studies revealed opiate receptors on lymphocytes, which indicated that opioid peptides, through activation of receptors on immune cells, were capable of modulating the immune system,[13] a finding borne out in results of studies that revealed stimulatory and inhibitory effects of opioid neuropeptides on mouse and guinea pig lymphocytes and macrophages in vivo.[14] With the additional finding that the CNS contains receptors for immunopeptides such as interleukins, cytokines, and lymphokines[7] and that interleukins may modulate the actions of opioid peptides in animals,[15] it became clear that the immune and nervous systems were communicating bidirectionally[7,16]; the immune system was capa-

ble of sending information to the brain via immunopeptides and receiving information from the brain via neuropeptides.[7] Results of subsequent studies[7] revealed that opiate and other neuropeptide receptors were not confined to nervous tissue, but are found throughout the body (eg, throughout the gastrointestinal tract).[4] Results of research on disease states revealed certain cancer cells to contain neuropeptide receptors and the behavior of these cells to be influenced by peptide binding, thus enabling certain cancer cells to be modulated by the brain and neuropeptide network.[6] Opioid peptides, such as β-endorphin and bombesin, enhance, respectively, the rate of tumor cell metastasis[14] and growth[17]; opioid agonists and antagonists are capable of retarding tumor growth.[14] Growth and tissue localization of tumor and macrophage cells are thereby influenced by neuropeptides released in the brain, as well as the body, as the result of cognitive, emotional, or other stimuli.[6] Results of these studies helped confirm that neuropeptides and their receptors form a network of information exchange, which extends throughout the brain and body, including the immune system,[4] that the nervous system is directly implicated as part of the process by which the body maintains health,[7] and that there is a functional link among the body's cellular defense and repair mechanisms, endocrine glands, brain, behavior, mood, and emotions.[4]

At the same time, results of studies continued to elucidate the long-recognized integration of the endocrine and nervous system revealing, for example, that stress-induced immunomodulation in animals is mediated through glucocorticoid hormones and endogenous opioids, among other biochemical processes.[18] The influence of the hypothalamic-pituitary-adrenal axis on immunologic function was determined to be one of the most important mechanisms of intersystemic communication.

Emerging from this large body of research was the view of the organism as an "information network,"[7] constantly exchanging information to respond to the demands of the environment in a coordinated and systematic way. Experimentally, there was a chemical mechanism through which the nervous, immune, and endocrine systems could communicate. Results of neuropeptide research confirmed that the view of an autonomous immune system was no longer valid. Evidence indicated that all body systems interact continuously to maintain homeostasis, linking all body systems together into a single, undissociated organism, with the entire complex served by a biochemical mechanism that also regulates mental states.

Effects of Cognitive Mental States

Clinical evidence for the link between the brain and immune system was revealed in a series of groundbreaking experiments in the 1970s by Ader and Cohen,[19] who expanded on earlier research by Russian investigators. In the 1920s, Russian scientists found that classical conditioning—the method of learning used by Pavlov to train his dogs to associate the sound of a bell with the presentation of food—could be used to train the immune system. If a neutral stimulus, such as a particular sound or taste, is presented repeatedly (ie, paired) with the presentation of an antigen, eventually the presentation of the neutral stimulus alone without the antigen will induce the same stimulated immune response. Russian investigators found that pairing a trumpet blast with an injection of bacteria in guinea pigs and rabbits would eventually lead to an immune stimulation upon just hearing the sound of the horn. Immune responses could be suppressed or enhanced.[5,7] Ader and Cohen[19] demonstrated that the immune system can be conditioned to suppress humoral and cell-mediated immune responses. Working with rats, they paired the neutral stimulus of a sweet taste (saccharin) with the immunosuppressive drug cyclophosphamide. When the drug was discontinued and saccharin alone was given, the immune system had the same immunosuppressive effect as the drug had elicited.[19,20] Results of these studies caused a major conceptual shift in the fields of neurobiology and immunology, as the body systems always believed to operate independently were now seen as a functionally integrated circuit.[11,16]

Subsequent studies yielded findings with promising clinical applications. Using the same technique of classical conditioning that resulted in immunosuppression, experiments performed in mice with autoimmune disorders revealed that the onset of disease could be significantly delayed when compared with a control group of mice.[20]

The link of cognitive mental states to bodily effects in systems other than the immune system revealed similar responses to classical conditioning. In dogs, conditioning was applied to toxic reactions and illnesses in general. A dog given a daily injection for 8 to 10 days of a drug (morphine) that caused vomiting, defecation, and sleep was then given an injection of water that resulted in the same adverse effects. Eventually the response did not require an injection; the mere arrival of the experimenter in the room evoked the physical response.[21] The investigators concluded that conditioned reflexes may play a very important role in immune responses, as well as a multitude of other diseases, including asthma, heart disease, and neuroses. In such disorders, onset or exacerbation may occur as the result of conditioned stimuli that have nothing in common with the real cause of the illness.[21]

Recently, a new relationship between cognitive mental states and somatic states recently has been revealed by strong evidence that, through operant learning, autonomic processes can be brought under voluntary control in animals.[22] Using biofeedback based on positive and negative reinforcement, cats, rabbits, and rats have learned to raise and lower their arterial blood pressure.[23] Rats learned to increase and decrease renal blood flow, glomerular filtration rate, and rate of urine production.[24] Monkeys could be trained to slow their heart rate and attenuate the tachycardia of exercise, and they can perform this behavior reliably.[22] Monkeys are able to learn to use biofeedback to self-regulate increases and decreases in hand temperature.[25]

Effects of Emotional Mental States

Results of many studies have indicated that emo-

tional states strongly influence somatic processes in the animal body. Broadly, emotional states in animals are associated with a wide array of health effects ranging from immune modulation to tumor enhancement to cardiovascular and renal disorders.[26]

Anxiety and fear—Effects of anxiety and fear, 2 closely related emotional states, have been studied extensively in nonhuman animals. Anxiety and other emotional and psychosocial stresses in experimental animals result in low immunocompetence to cancer, infective agents, and other disease processes that the body resists with cell-mediated immunity.[27] Viral and neoplastic diseases are enhanced in animals subjected to emotional stress; the mechanism of enhancement is at least partially through compromised immunologic competence of the host. Emotions and anxiety in animals can have lethal consequences.[27] Emotional stimuli profoundly affect cellular and humoral defenses in animals.[1] Emotional stress in the form of fear of punishment will alter activity of the immune system of the rat.[28] Mice maximally protected from chronic anxiety and other environmental stressors had significantly less incidence of mammary tumors.[29] Juvenile pigs handled in an unpleasant manner (lightly slapped, snout noose used, brief electric shock) had high corticosteroid concentrations and slowed growth rate, compared with pigs handled in a pleasant manner.[30] Cynomolgus monkeys fed a moderately atherogenic diet were challenged by threatened capture and physical handling. The increase in heart rate during the challenge period was directly proportional to the degree of atherosclerosis on necropsy, indicating that emotional stimulation is related to the development of atherosclerosis and that the degree of pathologic change is proportional to the degree of emotional stimulation, as measured by cardiovascular responsiveness.[31] The onset of clinical signs of idiopathic lower urinary tract disease in cats is associated with aversive environmental stimuli.[32]

Anxiety in dogs in the veterinary clinic is associated with high blood pressure, which can be erroneously diagnosed as hypertension.[33] This condition is analogous to a syndrome in human patients termed "white coat hypertension," in which blood pressure increases as a result of the anxiety experienced in the environment of the doctor's office.[33] In mice, a sustained increase in systolic arterial pressure resulted from psychosocial stimulation (eg, confrontation and conflict with other mice, confinement to small spaces, subjecting animals to threats from predators).[34]

In mice[35] and rats[1] exposed repeatedly to an experienced fighter, the subordinate had a low primary antibody response. A dominant rat that loses its social position becomes an outcast and the object of aggressive chases and challenges by virtually all other colony members; if not removed from the colony, these rats soon die from gastrointestinal bleeding and infections.[1]

Fear has been induced in wild rabbits by repeatedly exposing trapped rabbits to dogs. The emotional response induces an acute thyrotoxicosis of such severity that death ensues.[36] Termed by the investigators "fright-thyrotoxicosis," this represents a noncorticoid mediated pathophysiologic response to severe psychologic trauma. In a study on the effects of fear, guinea pigs and rabbits were given digitalis and exposed to a fear-inducing stimulus. The groups exposed to the stimulus had clinical signs of digitalis toxicosis; no such adverse effects were apparent in the control group, which received the same dose of digitalis but was not exposed to the fear-inducing stimulus.[37,38]

Social emotions—Emotions associated with social affiliation and bonding, regulated largely, if not solely, by endogenous opioids,[9] caused a wide variety of pathologic effects if social bonds are disrupted, severed, or impaired. Disruption of the mother-infant bond adversely affects health at all ages. Completely weaned squirrel monkeys that were separated from their mothers had immune suppression at 7 and 14 days after separation.[39] Those monkeys that were placed in cages with others had less immunosuppression than those caged alone.[39] Squirrel monkeys separated from their mothers at 6 months old experienced suppressed immune function (ie, low antibody response). Infant monkeys placed in a familiar home environment or with familiar peers had a lesser degree of separation-induced immune suppression. Environmental familiarity and social companionship inhibited the emotionally induced immunosuppressive effects of separation.[40]

In a 2-year study of male cynomolgus monkeys, members of 1 group were allowed to remain with the same social partners for the entire period; whereas, those in the second group were assigned new partners each month. Animals in the "unstable" group had reduced immune function, compared with those in the "stable" group.[41] Disruption of social relationships caused a significant decrease in survival among Rhesus monkeys inoculated with simian immunodeficiency virus, as compared to simian immunodeficiency virus-positive control monkeys not separated from familiar social companions.[42] Social affiliation can mitigate the adverse immunologic consequences of social stressors in nonhuman primates.[43,44] Separation anxiety in dogs, resulting from separation of dogs from the human companions to which they have formed social bonds, can cause intestinal disorders such as diarrhea and bloody stools.[45]

Other emotional states—To maintain proper function and organization, brains of the higher animals appear to require optimal stimulation; too much or too little is a cause of distress.[46] Boredom, the emotion resulting from insufficient mental stimulation, causes emotional distress and influential effects on health in animals.[47] In farm animal species, understimulation from a socially deprived environment resulted in higher mortality and physiologic changes, such as a high incidence of atherosclerosis.[48] Conversely, enriching the environment results in improved reproduction and endurance against disease.[47] Increasing the complexity and stimulation of the environment has a favorable effect on health and results in low susceptibility to disease in nonhuman primates.[49]

Anger was induced in laboratory dogs by having another dog challenge their access to food.[50] Cardiac

evaluation of these animals revealed myocardial ischemia characterized by low coronary arterial blood flow, high coronary vascular resistance, and electrocardiographic changes indicative of impaired myocardial perfusion.[50]

Psychologic State of Helplessness

A specific type of mental state that is cognitive and emotional has been induced experimentally in a variety of animal species; that is, the experience of helplessness.[51-54] In addition to the emotional component, helplessness has a cognitive component in the appraisal of one's situation. The critical element of helplessness is control; helplessness is the perception of no control over one's environment. Results of extensive research, using the classic experimental method of escapable and inescapable electric shock—wherein animals either would or would not have the control to escape from or turn off the shock—has revealed the differential effects of control, and the findings have led consistently to the conclusion that the ability to control or predict environmental stressors is of fundamental value to the organism[1] and critical for the modulation of cellular and humoral immunity. Lack of perceived control over a stressor is related to the development of diverse stress-induced pathologic changes, immunosuppression, and tumor enhancement[1]; conversely, control and predictability permit animals to cope with stressors and are protective against adverse somatic effects associated with a variety of forms of stress.[53,54]

Results of experiments that have used escapable and inescapable shock in animals have revealed significant differences in effects on health. Inescapable shock suppresses natural killer cell activity in rats[a] and suppresses T-cell lymphocyte responsiveness to mitogens,[51] indicating that psychologic states that involve a loss of control are critical in modulating immune function. In rats, inescapable shock results in low tumor rejection and low survival.[52] Stress of inescapable shock caused earlier tumor appearance, exaggeration of tumor size, and low survival times; escapable shocks had no such effects.[55] The effects of predictability of the stressor stimulus were examined.[53] Rats subjected to tail shocks developed gastric ulcers only if they could not predict when the shocks would occur, whereas those that could predict but received the same amount of shocks did not develop ulcers.[53] Results of these studies indicate that immunomodulation and tumor rejection are not a function of shock per se, but are a function of the ability to control or predict shock.[52] These results indicate that the psychologic experience of helplessness exerts a strong influence on somatic health and disease states. Shock avoidance has been the classic experimental method for inducing and studying helplessness; however, this psychologic state can result from a variety of stressors. For example, isolation, which makes social control impossible, may be considered a favorable psychobiological condition for tumor growth.[1] From the results of these studies, it is reasonable to conclude that the experience of helplessness is an important modulator of the immune-suppressive and tumor-enhancing effects of stress, and opioid peptides are involved in mediating these immunologic and oncologic effects.[18]

Variable Effects of Mental States on Somatic Health

Taken together, the complex data on the physiologic effects of psychosocial factors suggest that such factors have a marked impact on the humoral and cellular defense mechanisms and, in general, the health of animals. However, the data are not consistent; evidence supports the notion that psychologic stressors differentially affect health mechanisms.[1] In general, psychologic and emotional stress results in low resistance to infective agents and enhances tumor induction and development in animals.[18] However, several reports found that stress has a protective effect against infection, hence, stress has immunomodulatory effects that can be stimulatory or suppressive. In addition, stress in some reports has been found to retard tumor growth.[18] Much of this inconsistency is now attributed to the helplessness/control factor. Other variables appear to play a role; for example, the nature and chronicity of the stress (a biphasic effect of stress has been elucidated whereby some forms of acute stress are immunosuppressive and some forms of chronic stress mildly immunoenhancing),[3] the type of infective agent, tumor lines, housing and social conditions, and animal species.

In summary, the literature on the influence of mental states on somatic health in nonhuman animals supports a number of conclusions. It appears that all body systems of the organism communicate with and influence one another; mental states exert a profound effect on the course and outcome of health and disease states; the influence of mental states is complex and multifactorial and results in beneficial and detrimental modulation of physical health; "stress" can not be considered all good or bad; the adverse effects of emotional stress are a scientific reality despite some contradictions in the experimental data[29]; the sense of control is a critical determinant of physical well-being; and all known pathologic processes in animals are, to some extent, subject to the influence of psychosocial interventions of one kind or another.[56]

[a]Shavit Y, Ryan SM, Lewis JW, et al. Inescapable but not escapable stress alters immune function. *Physiologist* 1983;26:A–64.

References

1. Bohus B, Koolhaas JM. Psychoimmunology of social factors in rodents and other subprimate vertebrates. In: Ader R, Felton DL, Cohen N, eds. *Psychoneuroimmunology*. 2nd ed. New York: Academic Press, 1991;807–830.

2. Solomon GF, Moos RH. Emotions, immunity, and disease. *Arch Gen Psych* 1964;11:657–674.

3. Cunningham AJ. Mind, body, and immune response. In: Ader R, ed. *Psychoneuroimmunology*. New York: Academic Press, 1981;609–617.

4. Pert CB, Ruff MR, Weber RJ, et al. Neuropeptides and their receptors: a psychosomatic network. *J Immunol* 1985;135:820–826.

5. Solomon GS, Kay N, Morley JE. Endorphins: a link between personality, stress, emotions, immunity, and disease? In: Plotnikoff NP, Faith RE, Murgo AJ, et al, eds. *Enkephalins and endorphins: stress and the immune system*. New York: Plenum Press, 1986;129–137.

6. Ruff MR, Pert CB. Neuropeptides are chemoattractants for human monocytes and tumor cells: a basis for mind-body communi-

cation. In: Plotnikoff NP, Faith RE, Murgo AJ, et al, eds. *Enkephalins and endorphins: stress and the immune system*. New York: Plenum Press, 1986;387–396.

7. Pert CB. *Molecules of emotion*. New York: Scribner, 1997;90–196.

8. Panksepp J. Brain opioids—a neurochemical substrate for narcotic and social dependence. In: Cooper SJ, ed. *Theory in psychopharmacology*. Vol 1. London: Academic Press, 1981;149–175.

9. Panksepp J, Herman BH, Vilberg T, et al. Endogenous opioids and social behavior. *Neurosci Biobehav Rev*1980:4:473–487.

10. Tooby J, Cosmides L. The past explains the present: emotional adaptations and the structure of ancestral environments. *Ethol Sociobiol* 1990;11:375–424.

11. Blalock JE, Smith EM. Human leukocyte interferon (HuIFN-alpha): potent endorphin-like opioid activity. *Biochem Biophys Res Commun* 1981;101:472–478.

12. Lolait SJ, Lim ATW, Toh BH, et al. Immunoreactive B-endorphin in a subpopulation of mouse spleen macrophages. *J Clin Invest* 1984;73:277–281.

13. Gilman SC, Schwartz JM, Milner RJ, et al. B-endorphin enhances lymphocyte proliferative responses. *Proc Natl Acad Sci U S A* 1982;79:4226–4230.

14. Shavit Y, Terman GW, Martin FC, et al. Stress, opioid peptides, the immune system, and cancer. *J Immunol* 1985;135:834–837.

15. Ahmed MS, Llanos QJ, Dinarello CA, et al. Interleukin 1 reduces opioid binding in guinea pig brain. *Peptides* 1985;6: 1149–1154.

16. Blalock JE, Harbour-McMenamin D, Smith EM. Peptide hormones shared by the neuroendocrine and immunologic systems. *J Immunol* 1985;135:858–861.

17. Cuttitta F, Carney D, Mulshine J, et al. Bombesin-like peptides can function as autocrine growth factors in human small cell lung cancer. *Nature* 1985;316:823–825.

18. Shavit Y. Stress-induced immune modulation in animals: opiates and endogenous opioid peptides. In: Ader R, Felton DL, Cohen N, eds. *Psychoneuroimmunology*. 2nd ed. New York: Academic Press, 1991;789–806.

19. Ader R, Cohen N. Behaviorally conditioned immunosuppression. *Psychosom Med* 1975;37:333–340.

20. Ader R, Cohen N. Behaviorally conditioned immunosuppression and murine systemic lupus erythematosus. *Science* 1982; 215:1534–1536.

21. Metal'nikov S, Chorine V. The role of conditioned reflexes in immunity. *Ann Pasteur Inst* 1926;40:893–900.

22. Engel BT, Talan MI. Hemodynamic and respiratory concomitants of learned heart rate control during exercise. *Psychophysiology* 1991;28:225–230.

23. Vasilevskii NN, Sidorov YA, Kiselev IM. Biofeedback control of systemic arterial pressure. *Neurosci Behav Physiol* 1992;22: 219–223.

24. Miller NE, DiCara LV. Instrumental learning of urine formation by rats; changes in renal blood flow. *Amer J Physiol* 1968; 215:677–683.

25. Gruber BL, Taub E. Thermal and EMG biofeedback learning in nonhuman primates. *Applied Psychophysiol Biofeed* 1998; 23:1–12.

26. Henry JP. The induction of acute and chronic cardiovascular disease in animals by psychosocial stimulation. *Int J Psych Med* 1975;6:147–158.

27. Riley V. Psychoneuroendocrine influences on immunocompetence and neoplasia. *Science* 1981;212:1100–1109.

28. Croiset G, Heijnen CJ, Veldhuis HD, et al. Modulation of the immune response by emotional stress. *Life Sci* 1987;40:775–782.

29. Riley V, Fitzmaurice MA, Spackman DH. Psychoneuroimmunologic factors in neoplasia: studies in animals. In: Ader R, ed. *Psychoneuroimmunology*. New York: Academic Press Inc, 1981;31–102.

30. Hemsworth PH, Barnett JL, Hansen C. The influence of handling by humans on the behavior, growth, and corticosteroids in the juvenile female pig. *Horm Behav* 1981;15:396–403.

31. Manuck SB, Kaplan JR, Clarkson TB. Behaviorally induced heart rate reactivity and atherosclerosis in Cynomolgus monkeys. *Psychosom Med* 1983;45:95–108.

32. Buffington CA, Chew DJ, DiBartola SP. Interstitial cystitis in cats. *Vet Clin North Am Small Anim Pract* 1996;26:317–326.

33. Kallet AJ, Cowgill LD, Kass PH. Comparison of blood pressure measurements obtained in dogs by use of indirect oscillometry in a veterinary clinic versus at home. *J Am Vet Med Assoc* 1997; 210:651–654.

34. Henry HP, Meehan JP, Stephens PM. The use of psychosocial stimuli to induce prolonged systolic hypertension in mice. *Psychosom Med* 1967;29:408–432.

35. Beden SN, Brain PF. Studies on the effect of social stress on measures of disease resistance in laboratory mice. *Agg Behav* 1982; 8:126–129.

36. Kracht J. Fright-thyrotoxicosis in the wild rabbit, a model of thyrotrophic alarm-reaction. *Acta Endocrin* 1954;15:355–367.

37. Natelson BH, Gover E, Cagin NA, et al. Learned fear: a cause of arrhythmia onset in the presence of digitalis. *Pharmacol Biochem Behav* 1989;33:431–434.

38. Natelson BH, Cagin NA. The role of shock predictability during aversive conditioning in producing psychosomatic digitalis toxicity. *Psychosom Med* 1981;43:191–197.

39. Coe CL, Lubach G, Ershler WB. Immunological consequences of maternal separation in infant primates. In: Lewis M, Worobey J, eds. *Infant stress and coping*. San Francisco: Jossey-Bass, 1989;65–92.

40. Coe CL, Rosenberg LT, Levine S. Effect of maternal separation on humoral immunity in infant primates, in *Proceedings*. 1st Int Workshop Neuroimmunomodulation 1984;208.

41. Cohen S, Kaplan JR, Cunnick JE, et al. Chronic social stress, affiliation, and cellular immune response in nonhuman primates. *Psycholog Sci* 1992;3:301–304.

42. Capitanio JP, Lerche NW. Social separation, housing relocation, and survival in simian AIDS: a retrospective analysis. *Psychosom Med* 1998;60:235–244.

43. Laudenslager ML, Boccia ML. Some observations on psychsocial stressors, immunity, and individual differences in nonhuman primates. *Am J Primatol* 1996;39:205–221.

44. Coe CL. Psychosocial factors and immunity in nonhuman primates: a review. *Psychosom Med* 1993;55:298–308.

45. Voith VL, Borchelt PL. Separation anxiety in dogs. *Compend Contin Educ Pract Vet* 1985;7:42–52.

46. Wemelsfelder F. Boredom and laboratory animal welfare. In: Rollin BE, Kesel ML, eds. *The experimental animal in biomedical research*. Boca Raton, Fla: CRC Press, 1990;243–272.

47. Wemelsfelder F. Animal boredom: is a scientific study of the subjective experiences of animals possible? In: Fox MW, Mickley LD, eds. *Advances in animal welfare science 1984/85*. Washington, DC: The Humane Society of the United States, 1984;115–154.

48. Duncan IJH. Animal behaviour and welfare. In: Clark JA, ed. *Environmental aspects of housing for animal production*. London: Butterworths, 1981;171.

49. Chamove AS, Anderson JR, Morgan-Jones SC, et al. Deep woodchip litter: hygiene, feeding and behavioural enhancement in eight primate species. *Int J Stud Anim Prob* 1982;3:308–314.

50. Verrier RL, Hagestad EL, Lown B. Delayed myocardial ischemia induced by anger. *Circulation* 1987;75:249–254.

51. Laudenslager ML, Ryan SM, Drugan RC, et al. Coping and immunosuppression: inescapable but not escapable shock suppresses lymphocyte proliferation. *Science* 1983;221:568–570.

52. Visintainer MA, Volpicelli JR, Seligman MEP. Tumor rejection in rats after inescapable or escapable shock. *Science* 1982; 216:437–439.

53. Weiss JM. Psychological factors in stress and disease. *Sci Am* 1972;226:104–113.

54. Seligman ME. *Helplessness: on depression, development, and death*. San Francisco: WH Freeman and Co, 1975;21–44, 166–188.

55. Sklar LS, Anisman H. Stress and coping factors influence tumor growth. *Science* 1979;205:513–515.

56. Ader R. Psychosomatic and psychoimmunologic research. *Psychosom Med* 1980;42:307–321.