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To characterize predictors of individual variation in immune responses and to assess some of the soluble physiological mediators of the relationship between psychological factors and immunity. Initially, the studies focused on the effects of social relationships and housing conditions on immune responses in the rhesus monkey. Later, the research addressed some of the long-term effects of early rearing conditions on the physiological set points for certain immune responses. Similar types of relationships between psychological factors and immune responses were investigated in several human studies. Finally, the major thrust of the work focused on the physiological and psychological effects of a major cytokine, interleukin-1. Our studies examined the endocrine and immune effects of exogenously administered IL-1, and also characterized its actions on cognitive and emotional processes. We also found that the cells in the CNS produce higher levels of IL-1 during periods of stress			
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FINAL TECHNICAL REPORT**N00014-90-J1543**

Principal Investigator: Dr. Christopher Coe
Contractor: University of Wisconsin-Madison
Contract Title: Immunological Consequences of Social Stratification and Change
Award: 03/01/90 - 08/31/92, \$173,158

Research Objectives:

To characterize predictors of individual variation in immune responses and to assess some of the soluble physiological mediators of the relationship between psychological factors and immunity.

Results:

Social variables. During the initial phase of the ONR award, a series of studies was conducted to assess the influence of social housing on immune responses (lymphocyte proliferation, natural killer cell activity) in the young adult male rhesus monkey (Coe, 1991; 1993). These assessments demonstrated that under stable housing conditions, social relationships had a minimal effect on these immune measures, but when relationships were in the process of change, there were marked alterations that lasted for several weeks. These physiological alterations were evident after both the formation and separation of pairs of male subjects. Attempts to correlate the immune changes with increases in plasma cortisol indicated that they were generally associated with activation of the endocrine system, but could not be specifically attributed to mediation by adrenocortical hormones (Friedman, Coe & Ershler, 1991).

Social control. During the course of one study on older monkeys, it became evident that monkey's lack of control over the experimental manipulations might be contributing to the aversiveness of the social stimulation (Coe, Ershler, Champoux, & Olson, 1992). With a specially designed cage, it was possible to provide monkeys with a degree of environmental control over the level of social stimulation they received. In this case, the immune changes previously observed following the introduction of new social partners did not occur.

Predictors of individual variation. An important theme of our research has been the investigation of primary variables that account for variation in immune responses across individuals. In the monkey this research has focused on early life events that might influence the trajectory of development and the physiological set points at which certain immune responses are established (Coe, Lubach, et al., 1992, 1993; Lubach, Coe and Ershler, in press; Lubach, Kittrell, & Coe, 1992). For example, in 3 published papers

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we have shown that early rearing conditions can influence the level of lymphocyte proliferation that one observes in the young rhesus monkey. Further, some of the differences can be explained by variation in numbers of CD8+ lymphocytes circulating in peripheral blood. In addition, we have begun to demonstrate that disturbances during pregnancy can also affect the development of the fetus, influencing the maturation of the thymus, and influencing neurological and immune responses that will be observed later in life (Schneider and Coe, 1992; Schneider, Coe and Lubach, 1993).

Recently, these basic science studies of developmental immunology in the monkey infant have acquired a more clinically applied significance. We have begun to test the efficacy of mucosal AIDS vaccines in the young primate. These studies involve the use of an attenuated strain of *Salmonella typhimurium* containing a plasmid expressing SIV gag sequences. This preliminary research has evolved into a larger collaborative program and a grant on the subject is currently under review (see below).

The results from study of the nonhuman primate model have also led us to directly investigate similar questions in humans. It has been hypothesized that fetal disturbance may affect the immune system indirectly via its effects on the central nervous system, and specifically by an influence on brain asymmetry. To test this hypothesis, we conducted a study in college-age subjects, which demonstrated an association between EEG activity in the frontal cortex and their baseline levels of natural killer cell activity (Kang, Davidson, Coe et al., 1991). Specifically, it was found that women with more left frontal brain activity showed higher levels of lymphocyte cytotoxicity than did women with relatively more right frontal brain activity. These results concurred with other work showing that high right frontal cortex activation is associated with a predisposition for depressive affect and a negative cognitive attributional style.

Our primate studies on the effects of acute disturbance on immunity led us to test whether we could elicit similar effects in humans. We demonstrated that acute cognitive and emotional arousal induced by a writing task could significantly alter natural killer cell activity (Strauman, Lemieux, and Coe, in press).

In ongoing and future studies we will be pursuing the question of the long-term consequence of early trauma in a number of research areas. We have obtained preliminary evidence that early sexual abuse can lead to a chronic activation of sympathetic tone and have an NIMH grant pending to extend this evaluation into immune assessments of women suffering from posttraumatic stress disorder induced by childhood abuse (see below). We are also interested in evaluating the potential impact of early CNS damage in the young host on the later development of immune response. To investigate this question, we currently have a grant pending with the Cerebral Palsy Foundation.

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Soluble mediators of neuroimmune relationships

Initially, our research focused on the relationship between stress-induced immune responses and the endocrine system, but recently the primary focus of the ONR-supported research has been on the possible influence of cytokine mediated immune and behavioral changes. Specifically, our studies assessed the physiological and psychological effects of the ubiquitous cytokine, interleukin-1 (Friedman, Boinski, and Coe, submitted; Friedman, Coe, and Ershler, submitted). In a series of studies, we have assessed the effects of exogenously administered recombinant IL-1alpha in the rhesus monkey. This work has:

- (1) established the efficacious dose for eliciting physiological and behavioral changes in the monkey
- (2) demonstrated a biphasic relationship, with low doses in the physiological range (1ng per monkey) increasing lymphocyte proliferation and lytic activity, whereas at higher doses in the pharmacological range (10-50µg) IL-1 inhibits the same immune responses.
- (3) shown that the immune inhibition is probably mediated by the secondary effects of IL-1 on the pituitary-adrenal axis,
- (4) documented a number of behavioral actions, indicative of "sickness type behavior" at the higher doses of IL-1. These behavioral effects include somnolence and anorexia.

Moreover, we have found that acute disturbance of the monkey significantly increases the levels of IL-1 found in cerebrospinal fluid from nondetectable levels into the pg/ml range. We are currently investigating the possible relationship between these changes and shifts in cell trafficking into the CNS after similar experimental manipulations.

Publications during this funding period:

- Coe, C.L. (1991) Is social housing of primates always the optimal choice? In: Through the Looking Glass: Issues of Psychological Well-Being in Captive Nonhuman Primates. M.A. Novak and A.J. Petto (eds.), American Psychological Association Press, Washington, D.C., pp. 78-92.
- Friedman, E., C.L. Coe and W.B. Ershler (1991) Time dependent effects of peer separation on lymphocyte proliferation in juvenile squirrel monkeys. Dev. Psychobiol. **24**:159-173.
- Kang, D-K, Davidson, R.J., Coe, C.L., Wheeler, R., Tomarken, A.J., Ershler, W.B. (1991) Frontal brain asymmetry and immune function. Beh Neurosci. **105**:860-869.
- Coe, C.L., Ershler, W.B., Champoux, M, and Olson, J. (1992) Psychosocial factors and immune senescence in the aged primate. Annals NY Academy of Science. Supp.: Neuroimmunomodulation

650:276-282.

- Lubach, G.R., Kittrell, M.W., and Coe, C.L. (1992) Maternal influences on body temperature in the infant primate. Physiology and Behavior **51**(5) 987-992.
- Coe, C.L., Lubach, G.R., Schneider, M.L., Dierschke, D.J., and Ershler, W.B. (1992) Early rearing conditions alter immune responses in the developing infant primate. Pediatrics **90**(3): 505-509.
- Schneider, M.L., Coe, C.L., and Lubach, G.R. (1992) Endocrine activation mimics the adverse effects of prenatal stress on the neuromotor development of the primate infant. Devel. Psychobiol **25**(6): 427-439.
- Coe, C.L. (1993) Psychosocial factors and immunity in nonhuman primates: A review. Psychosomatic Med. **55**: 298-308.
- Coe, C.L., G. Lubach and W.B. Ershler (1993) Le role immunologique de la mere. In: Le langage des bebes. M-C. Busnel (ed.), J. Grancher, Paris.
- Schneider, M.L. and Coe, C.L. (1993) Repeated stress during pregnancy impairs neuromotor development of the primate infant. J. Devel. Behav. Pediatr. **14**(2):81-87.
- Strauman, T.J., Lemieux, A.M., and Coe, C.L. (1993) Self-discrepancies and natural killer cell activity: The influence of negative psychological situations on stress physiology. J. Pers. Soc. Psychol.
- Coe, C.L., Kemnitz, J.W., and Schneider, M. L. (in press) Vulnerability of placental antibody transfer and fetal complement synthesis to disturbance of the pregnant monkey. J. Med. Primatol.
- Lubach, G.R., Coe, C.L., and Ershler, W.B. (in press) Effects of early rearing on immune responses in infant rhesus monkeys. Brain, Behavior and Immunity.
- Friedman, E., Coe, C.L., and Ershler, W.B. (under review) Bidirectional effects of interleukin-1 on immune responses in rhesus monkeys. Brain, Beh., Immunity.
- Friedman, E., Boinski, S., and Coe, C.L. (under review) Interleukin-1 induces sleep-like behavior and alters call structure in juvenile rhesus macaques. Am.J. Primatol.

Training Activities.

One graduate student, Gabriele Lubach, was supported by the initial ONR award, and went on to complete her dissertation in 8/90. She is currently a Research Associate at the University of Wisconsin and supported by an NIMH award to C.L. Coe. A second graduate student, Ms. Andrine Lemieux was directly supported by the ONR contract extension. She has gone on to achieve an NRSA fellowship, starting on 6/1/93 and will be conducting her dissertation research during the coming year. Two other graduate students benefited indirectly from the fact that the ONR support enlarged our psychoneuro-immunology program. Elliot Friedman used a portion of the

interleukin-1 studies as the basis of his dissertation research. He will be starting a postdoctoral fellowship with Dr. Michael Irwin, Department of Psychiatry, UCSD, on 7/1/93. Duck-Hee Kang participated in one of the human studies and went on to obtain an NRSA fellowship and to complete her dissertation research on psychoneurimmunological questions in adolescent asthmatics.

Women - 3 (1 Asian-American)
Men - 1
Non-citizens - 0

Awards/Fellowships: A number of grants and fellowships have been awarded, which are derivative of the ONR contract.

Coe, C.L.

NIMH (MH41659) Prenatal stress and immune responsiveness. 7/1/89 - 6/30/93, \$140,119 annual direct.

co-investigator

NIMH (MH43454) Emotional reactivity and anterior brain asymmetry. (P.I.: R. Davidson), 8/1/91 - 7/30/93, \$35,000 immune-related component.

Ersbler, W.B.

NIH, Calorie restriction and aging in nonhuman primates 6/1/89 - 5/30/94 (\$160,816 annual direct).

Kang, D.H.

NRSA Predoctoral Fellowship 9/1/90 - 8/31/93, \$11,800 annual.

Lemieux, A.

NRSA Predoctoral Fellowship 6/1/93 - 5/31/96, \$11,800 annual.

Pending applications under review:

Coe, C.L.

NIMH (41659-09) competing renewal of Prenatal Stress and Immune Responsiveness, 12/1/93 - 11/30/98

NIMH (MH51787) co-investigator on Abuse-Related PTSD: Validity and Health Implications (P.I.: T. Strauman), 12/1/93 - 11/30/95.

NIH Pediatric Model of Vaccine Efficacy (project in collaborative program entitled Oral Vaccines to Elicit Mucosal Immunity for SHIV (P.I.: D. Pauza), 12/1/93 - 11/30/97.

Cerebral Palsy Foundation co-investigator on Neuroimmune Consequences of Cerebral Palsy (P.I.: M. Schneider), 9/1/93 - 8/31/95.