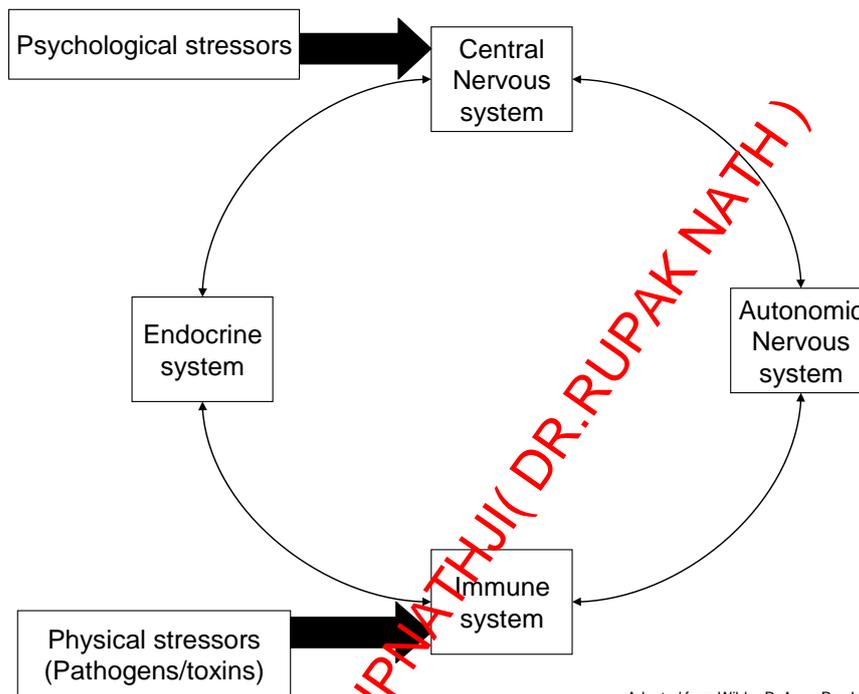


“The nervous system and immune system speak a common biochemical language and communicate via a complete bidirectional circuit involving shared ligands such as neurotransmitters, hormones and cytokines” (Blalock, 2005).



Adapted from Wilder R. Annu Rev Immunol 1995; 13:307-38

“Psychoneuroimmunology” and “neuroendocrinimmunology” mean much the same. They both deal with the interaction of 4 fields (psychology and the neurological, endocrine and immune systems).

A brief chapter on this topic is justified as 1) these 4 fields have evolved separately and their interactions have not been widely described, and 2) the impact of immune system on these other system is not yet well covered in psychiatric textbooks.

“**Stress**” is the central issue and is defined as a general body response to initially threatening external or internal demands. Longer definitions mention disturbance of homeostasis, and much of this chapter deals with mechanism which work to restore steady state homeostasis.

**“Cytokines”** are a category of “signaling molecules” which enable cellular communication. The distinction between cytokines and hormones is becoming less clear/important. Cytokines are produced by immune cells, particularly, monocytes and macrophages, (but also by brain neurons and glial elements; Breder et al, 1988). Recent research indicates that cytokines induce nitrous oxide production, and that this gaseous molecule has a powerful influence on the secretion of hypothalamic peptide and classical neurotransmitters (Rettori et al, 2009).

**“Circumventricular organs”** (CVOs) are structures bordering the 3<sup>rd</sup> and 4<sup>th</sup> ventricles, which are outside the blood brain barrier. They allow penetration of the barrier by hormones, neurotransmitters and cytokines.

**“Sickness behavior”** refers to the symptoms associated with inflammation (low mood, reduced appetite, increased fatigue and social withdrawal). This follows penetration of the blood brain barrier and access to the hypothalamus of cytokines released from activated immune cells (and toxic products from bacterium cell walls).

Interestingly, many of these symptoms are shared with depressive disorder. Studies report 16-45% of patients treated with interferon (IFN)-alpha develop depressive symptoms during the course of therapy (Hauser et al, 2002). This is not to suggest that all depressive disorder is an immune response (although the case has been made that a sub-set of depression may be of immunological origin; Howren et al, 2009), but it alerts us to the difficulties which may be encountered when making psychiatric assessments of physically unwell patients.

### **The neuroendocrine system**

Hans Selye (1937) was the pioneer of “biological stress”. He demonstrated that a noxious stimulus (called a stressor) induces the release of adrenal cortical steroids. Thus, from the earliest stress response investigations, neural system and endocrine system interactions were noted, leading to the concept of the “neuroendocrine system”.

When stress impacts on the brain, there are two outflow pathways to the periphery. One is mentioned in the above paragraph (commencing at the paraventricular nucleus of the hypothalamus) and involves the release of CRH, ACTH and eventually, cortisol from the adrenal cortex.

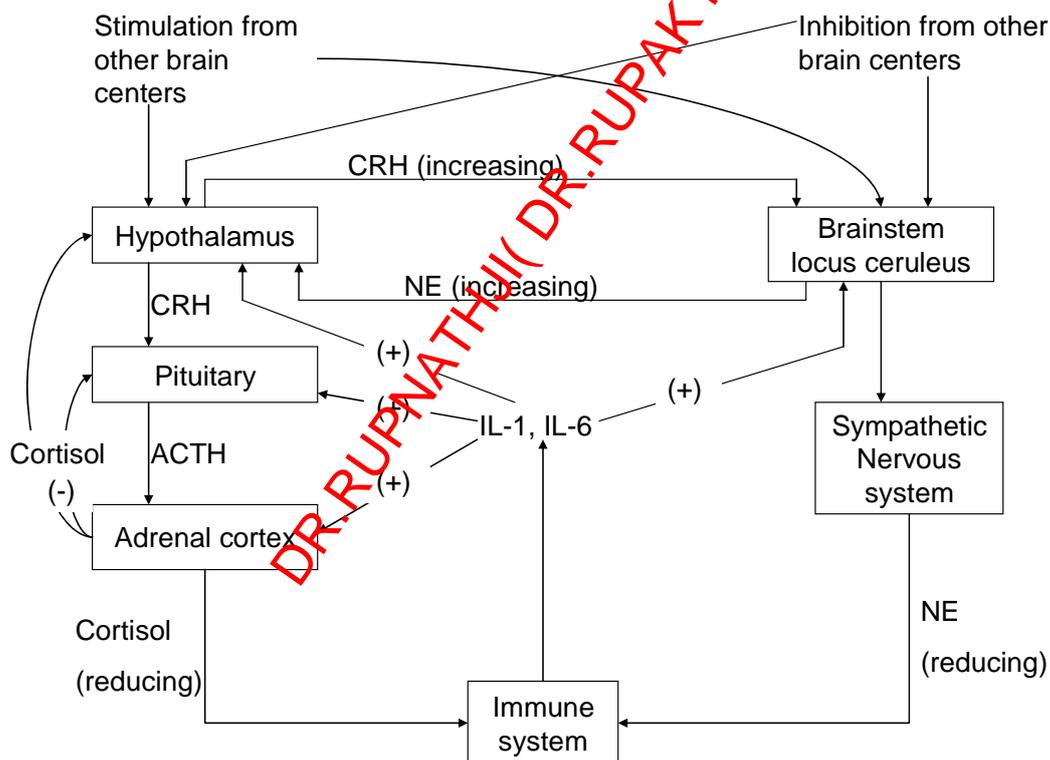
The other involves the sympathetic nervous system (commencing with CRH stimulation of the locus ceruleus in the brain stem), and is conceptualized as having three parts. First, neural communication leading to release of adrenaline from the adrenal medulla. Second, neural communication with cells and tissues with an immune function (liver, spleen, bone marrow, thymus, lymph nodes, skin and gastrointestinal system). And third, neural communication which directly prepares the body for action (dilating blood vessels to the muscles, constricting blood vessels to the skin, etc).

## The immune system

Whereas the neuroendocrine system responds to potentially dangerous non-physical stimuli (sight of a hungry lion/creditor, or being publicly identified as a pedophile), the immune system responds to physical assault (in the form of pathogenic micro-organisms and tumor cells).

The immune system is highly complicated, with components including an intact skin through to specialized cells (Killer T cells) and specific molecules called antigens.

Of particular interest in the current chapter (which attempts to integrate the immune and neuroendocrine systems) are chemicals (neurotransmitters, hormones and cytokines) which are released by the cells of one system and impact on the cells of the other. (The notion that there is more than one system, is of course, arbitrary, and reflects the history of scientific discovery.)



Adapted from Wilder R. Annu Rev Immunol 1995; 13:307-38

## Modulation

A comprehensive account of the bi-directional modulation of these systems is beyond the expertise of the current author. Instead, some examples are offered, which support that

these systems are highly integrated. Future research can be expected to provide additional details and open new therapeutic avenues.

### **The immune modulating the neuroendocrine system: examples**

1. Cytokines, interleukin-1 (IL-1), IL-2, IL-6, tumor necrosis factor-alpha (TNF-alpha) and interferon-gamma (IFN-gamma) pass through the circumventricular organs and impact on the hypothalamus, leading to fever and sickness behavior.
2. Cytokines impacting on the HPA lead to cortisol release from the adrenal cortex (Chowers et al, 1996; Dunn et al, 1999).
3. Immune cells synthesize IFN which passes the blood brain barrier, impacts on brain and may cause “depression” (Hauser et al, 2002).
4. Lymphocytes synthesize hormones including ACTH, prolactin and growth hormone (Wilder, 1995).
5. Cytokines (associated with peritoneal infection) are transported via the vagus nerve to, and stimulate, the hypothalamus (Watkins and Maier, 1999).
6. Acetylcholine and adrenaline neurotransmitters, and hormones [recently, melatonin] are endogenously produced in the immune system (Blalock, 2005).

For (simplified) details, see the following table:

Source	Hormone/neurotransmitters
Lymphocytes	Acetylcholine, melatonin
T Lymphocytes	ACTH, endorphins
B Lymphocytes	ACTH, endorphins
Macrophages	ACTH, endorphins
Splenocytes	Adrenalin, CRH,
Megakaryocytes	Neuropeptide Y

### **The neuroendocrine modulating the immune system: examples**

1. Sympathetic/noradrenergic nerve fibers innervate important organs and systems related to the immune system, including the liver, spleen, thymus, bone marrow, lymph nodes, skin, and digestive tract and respiratory apparatus (Montoro et al, 2009).
2. Adrenergic receptors are located on lymphocytes (Hadden et al, 1970).
3. Catecholamines and corticoids suppress the production of IL-12 by immune cells (Elenkov and Chrousos, 1999).
4. Increased cortisol suppresses immune function (McEwen et al, 1997).
5. Cortical steroids directly affect immune cells, increasing the production of IL-4, 10 and 13 (DeKruyff et al, 1998).
6. Neuropeptide, neurotransmitter and neuroendocrine hormone receptors are located on immune cells (Blalock, 2005).
7. Neurotransmitters (acetylcholine, noradrenaline, serotonin, histamine, glutamic acid, GABA), neuropeptides (ACTH, Prolactin, Vasopressin, Bradykinin, Somatostatin, VIP, SP, Neuropeptide Y, enkephalin, endorphin), neurological

- growth factors (NGF) and hormones (adrenalin and corticoids) modulate immune function (Montoro et al, 2009).
8. Neurons synthesize IL-1 and other cytokines (Breder, 1988).

## **Clinical aspects**

### The Holy Grail

The Holy Grail of psychoneuroimmunology is built around the question of whether psychological factors (presumably modifiable) can, through moderation of the immune system, influence the onset and outcome of physical diseases.

Diseases of particular interest include infections (such as hepatitis and AIDS), autoimmune diseases (such as rheumatoid arthritis and multiple sclerosis) and cancer.

Possible psychological interventions include the talking and relaxation/hypnosis therapies and in the broader context, social engineering to reduce loneliness, isolation and poverty.

Earlier findings were encouraging:

1. Healthy students under examination stress manifest a decrease in indicators of cellular immune response (Glaser et al, 1986).
2. Stressful life events can play a part in the onset and exacerbation of auto-immune diseases (Homo-Delarche et al, 1990).
3. Cognitive-behavioral interventions have been associated with improved physical symptoms of some auto-immune disorders (Radojevic, 1992).
4. Some studies involving education and psychological treatment have demonstrated increased cancer survival (Spiegel et al, 1989; Fawzy et al, 1993).

More recent work continues to promise benefits from psychological therapy for physical disease (Armaiz-Pena, 2009), but progress has been slow. An important review (Miller and Cohen, 2001) somewhat unexpectedly, found that the immune system shows little response to psychological intervention, and another (Montoro et al, 2009) did not find chronic stress to be an intrinsic cause of allergy.

While psychological therapy improves the outcomes in certain physical disorders, it is not yet established that this is attributable to alterations in the immune system (that is, the benefits of reduced distress, relaxation and increased confidence may simply enable individuals to deal better with their disorder).

Psychoneuroimmunology/neuroendocrineimmunology has been proposed as the explanation of the poor health status associated with poverty and low social status (Littell, 2008; Kemeny 2009). While some such elements may be involved, much further work is needed before definitive conclusions can be made on this topic.

### Non-Holy Grail stuff

1. Should a sub-section of depression prove to be due to immune dysregulation (Eisenberger et al, 2010; Janssen et al, 2010), a new avenue for treatment (for this sub-section, at least) will be opened (Piser, 2010). There is already a suggestion that the augmentation of antidepressants with anti-inflammatory agents (aspirin, celecoxib) can be beneficial (Blume et al, 2011).
2. Unsurprisingly, PTSD has disturbed psychoneuroimmunological features (Pace & Heim, 2011). We can expect such findings to lead to therapeutic advances.
3. Some evidence suggests cognitive decline and dementia may also be associated with “over-expressed cytokines” (McAfoose and Baume, 2009).
4. Epigenetics is a most exciting new field which has given us a biological mechanism by which “psychosocial world” can modify our neurological-endocrinological-immunological inner world (Mathews & Janusek, 2011).

### **Conclusion**

Close integration and bi-directional communication between the neuroendocrine and immune systems has been comprehensively demonstrated. Work reviewed in this chapter provides possible mechanisms by which such disease prevention and improved outcomes might be achieved.

Evidence indicates that psychological therapy may improve the outcome of physical disorders. However, it is not yet proven that these improvements are the result of alterations in immune function (although at least in some cases, this is probable).

Depression, PTSD, dementia and other disorders may have unexpected roots, and new therapies may be quite close. And, epigenetics, at last, provides a mechanism to bridge the psychological-physical divide.

### **References**

- Armaiz-Pena G, Lutgendorf S, Cole S, Sood A. Neuroendocrine modulation of cancer progression. *Brain Behav Immun* 2009; 23:10-15.
- Blalock J. The immune system as the sixth sense. *Journal of Internal Medicine* 2005; 257:126-138.
- Blume J, Douglas S, Evans D. Immune suppression and immune activation in depression. *Brain, Behavior, and Immunity* 2011; 25:221-229.
- Breder C, Dinarello, C, Saper C. Interleukin-1 immunoreactive innervation of the human hypothalamus. *Science* 1988; 240, 4850, 321-324.

- Chowers I, Hammel H, Eisenman J, et al. A comparison of the effects of environmental and preoptic heating and pyrogen on plasma cortisol levels. *American Journal of Physiology* 1996; 210:606-610.
- Cohen S, Herbert T. Health psychology: psychological factors and physical disease from the perspective of human psychoneuroimmunology. *Annual Reviews Psychology* 1996; 47:113-142.
- DeKruyff R, Fang Y, Umetsu D. Corticosteroids enhance the capacity of macrophages to induce Th2 cytokine synthesis in CD4+ lymphocytes by inhibiting IL-12 production. *Journal of Immunology* 1998; 160:2231-2237.
- Dunn A, Wang J, Ando T. Effects of cytokines on cerebral neurotransmission. Comparison with the effects of stress. *Adv Exp Med Biol* 1999; 461:117-127.
- Eisenberger N, Berkman E, Inagaki T, Rameson L, Mashal N, Irwin M. Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. *Biological Psychiatry* 2010; 68:748-754.
- Elenkov I, Chrousos G. Stress hormones, Th1/Th2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease. *Trends in Endocrinology and Metabolism* 1999; 10:359-368.
- Fawzy F, Fawzy N, Hyun C, et al. Malignant melanoma: effects of an early structured psychiatric intervention, coping, and affective state on recurrence and survival six years later. *Archives of General Psychiatry* 1993; 50:681-689.
- Glaser R, Rice J, Speicher C, Stout J, Kiecolt-Glaser J. Stress depresses interferon production by leukocytes concomitant with a decrease in natural killer cell activity. *Behavioral Neuroscience* 1986; 100:675-678.
- Hadden J, Hadden E, Middleton E. Lymphocyte blast transformation. Demonstration of adrenergic receptors in human peripheral lymphocytes. *Cell Immunol* 1979; 1:583-595.
- Hauser P, Khosla J, Aurora H, et al. A prospective study of the incidence and open-label treatment of interferon-induced major depressive disorder in patients with hepatitis C. *Molecular Psychiatry* 2002; 7:942-947.
- Homo-Delarche F, Fitzpatrick F, Christeff N, Nunez E, Bach J, Dardenne M. Sex steroids, glucocorticoids, stress and autoimmunity. *Journal of Steroid Biochemistry and Molecular Biology* 1991; 40:619-637.
- Howren M, Lamkin D, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosomatic Medicine* 2009; 71:171-186.
- Janssen D, Caniato R, Verster J, Baume B. A psychoneuroimmunological review on cytokines involved in antidepressant treatment response. *Hum. Psychopharmacol. Clin Exp* 2010; 25:201-215.
- Kemeny M. Psychological responses to social threat. *Brain Behav Immun* 2009; 23:1-9. Social status impacts on the endocrine and immune systems.
- Littell J. The mind-body connection: not just a theory anymore. *Social Work Health Care* 2008; 46:17-37.
- Mathews H, Janusek L. Epigenetics and Psychoneuroimmunology: mechanisms and models. *Brain, Behavior, and Immunity* 2011; 25:25-39.
- McAfoose J, Baume B. Evidence for a cytokine model of cognitive function. *Neuroscience and Biobehavioral Reviews* 2009; 33:355-366.
- McEwen B, Biron C, Brunson K et al. The role of adrenocorticoids as modulators of immune function in health and disease. *Brain Res Brain Res Rev* 1997; 23(1-2):79-133.

- Miller G, Cohen S. Psychological interventions and the immune system: a meta-analytic review and critique. *Health Psychology* 2001; 20:47-63.
- Montoro J, Mullol J, Jauregui I et al. Stress and allergy. *J Invest Allergol Clin Immunol* 2009; 19, Supple 1: 40-47.
- Pace T, Heim C. A short review on the Psychoneuroimmunology of posttraumatic stress disorder: from risk factors to medical comorbidities. *Brain, Behavior, and Immunity* 2011; 25:6-13.
- Piser T. Linking the cytokine and neurocircuitry hypothesis of depression: translational framework for discovery and development of novel anti-depressants. *Brain, Behavior, and Immunity* 2010; 24:515-524.
- Radojevic V, Nicassio P, Weisman M. Behavioral intervention with and without family support for rheumatoid arthritis. *Behavior Therapy* 1992; 23:13-30.
- Rettori V, Fernandez-Solari J, Mohn C et al. Nitric oxide at the crossroads of immunoneuroendocrine interactions. *Neuroimmunomodulation: Annals New York Academy Science* 2009; 1153:35-47.
- Selye H. The significance of the adrenals for adaptation. *Science* 1937; 85:247-248.
- Wilder R. Neuroendocrine-immune system interactions and auto-immunity. *Annual Review Immunology* 1995; 13:307-338.
- Spiegel D, Bloom J, Kraemer H, Gotthel E. Effect of psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet* 1989; ii:901.
- Steinmann L. Elaborate interactions between the immune and nervous systems. *Nature Immunology*. 2004; 5:575-581.
- Watkins L, Maier S. Implications of immune to brain communication for sickness and pain. *Proceedings of the National Academy of Science USA* 1999; 96:7710-7713.
- Wilder R. Neuroendocrine-immune system interactions and auto-immunity. *Annual Review Immunology* 1995; 13:307-338.

DR. RUPNATHUKUR RUPAK NATH