

# The Mind and Body are Connected with Each Other Through Psychoneuroendocrine and Reticuloendothelial System

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## ABSTRACT

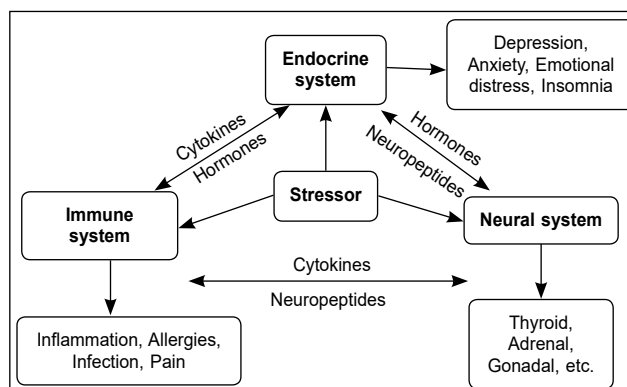
Psychoneuroendocrinology (PNEI) is the study of the interaction between psychological, neural, endocrine and immunological responses, which was first described in 1936. There is a unity of mind and body (reflected in term mind and body medicine); and psychological factors must be taken into account when considering all disease states. Although most physical disorders are influenced by stress, conflict or generalized anxiety, some disorders are more affected than others. The concept of PNEI system propose that stressful event triggers cognitive and affective responses which, in turn induce sympathetic nervous system and endocrine changes and these ultimately impair immune function. The present review provides an overview of the fundamental literature on PNEI and its interaction with chronic low-grade cellular inflammation processes, hormetic processes, longevity with reference to resilience as a key factor in natural/pathologic evolution of aging. And consequently with the homoeopathic standpoint where dynamic, functional and structural plane been correlated.

**Keywords:** Psychoneuroimmunology, stress, psychiatry, allergy, longevity, specificity and non-specificity hypothesis

Psychoneuroendocrinology (PNEI) is involved in studying the interactions between psychological, neural, endocrine and immunological processes. PNEI system represents a self-regulation network implicated in the homeostasis of the organisms, in the maintenance of chemical-physical-neuropsychological balance in response to various stimuli. The concept of the PNEI system came into being in the second half of the 20th century and gained potential in the seventies and eighties when the existence of a network of immunoneuroendocrine interactions was confirmed by means of several experiments. In the nineties, Ader further disseminated the key concepts of PNEI, after the discovery that the lymphocytes (immunological cells) produce TSH (hypophyseal hormone) and other molecules with neuroendocrine activity. The confirmation of the interdependent relationship between immunological and neuroendocrine mechanisms has given way to a

re-evaluation of diagnostic and therapeutic pathways in longevity medicine. The PNEI system, from the morpho-functional aspect, includes the (patho-) physiological mechanisms proper of human psyche, neurological system (limbic system and namely hypothalamus in primis), endocrine system (e.g., hypophysis and receptor glands) and immunitary system. All of these form part of an integrated self-regulation network aimed at psychosomatic homeostasis in response to endogenous and exogenous stimuli (Fig. 1).

Medicine is adapting the concept of illness and its modus operandi based on it. Emotions, mental



**Figure 1.** PNEI: Interconnections and signalling among psyche, neural, endocrine and immune systems.

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attitude, lifestyle, social support and nutrition are being increasingly appreciated as having a pivotal role in the processes of diagnosis and treatment of any disease. The way the PNEI system functions, underscores how psychosocial elements are abstract expressions of a subjective experience. Additionally, their value is also expressed through concrete pathophysiological clinical manifestations that depend on the individual-environment relationship.

Evidence indicates that chronic low-grade cellular inflammation (CLGCI), neurodegenerative and cardiovascular disorders, obesity, diabetes, cancer and senescence are all associated with PNEI system activity. Health refers to the ability to adapt to one's environment. It does not represent a fixed entity. It varies for every individual, depending on their circumstances. According to this comprehensive and modern view of health, PNEI system seems to have a significant role in the processes of aging. The imbalance between emotional and physical stimuli has a link with an ongoing series of phenomena that include and affect biological, psychological and social aspects within human life.

### PNEI AND INFLAMMATION

PNEI provides the biological basis of a bidirectional relationship between the endocrine, immune and neuropsychological networks in physiological and pathological conditions. Psycho-emotional and affective state of an individual appear to affect the course of a pathological organic event. The key process through which the PNEI system intervenes in most diseases is inflammation in terms of interactions with the CLGCI. Chronic stress, or distress, is representative of the persistent disequilibrium of the PNEI system pillars. It acts on the hypothalamus-hypophysis axis and the whole endocrine system, thus altering the cortisol level. Stress promotes inflammation of the tissues due to an increase of cortisolemia and the increase of inflammatory cytokines (i.e., interleukin [IL]-1, tumor necrosis factor [TNF], IL-6). They go on to activate the immunitary system in a proinflammatory sense. Extensive innervation of lymphoid organs by neurovegetative fibers, releasing norepinephrine, acetylcholine and neuropeptides has been noted. The plexuses of sympathetic nerve fibers surrounding the arterial vessels which penetrate the lymphoid organs are also known to play a significant role. The interaction occurs through immune cells, particularly those of innate immunity that are associated with inflammation processes. Mast cells release histamine

and other active substances, thus causing vasodilation and inflammation. These cells are present under the skin and the mucous membranes of the body, and also in fundamental organs, including the brain. Mast cells can be activated in an inflammatory sense by the key neuropeptides, including calcitonin-gene-related-peptide, substance P, neuropeptide Y, nerve growth factor, vasoactive intestine peptide, as well as by adrenaline, noradrenaline and other substances released by nerve fibers. The vegetative nervous system has the potential to modulate the inflammatory processes by interaction with the mast cells and other relevant immune system components.

Recently, inflammation has been recognized as one of the vital causal processes in atherosclerosis and altered lipid profile. CLGCI and hyperdyslipidemia have been tied to several causal factors. The correlation between psychic depression, chronic stress and alterations in the blood fat profile (dyslipidemia) has long been known. The science of PNEI system describes how all the compartments affect and are affected by the inflammatory processes. For instance, the immune system is affected by the alterations related to depression and dyslipidemia.

Dantzer and colleagues have shown that by the release of cytokines in the brain, an inflammatory condition is established that leads to alteration in neuronal activity causing depression and a procession of symptoms termed "sickness behavior". Chronic stress and inflammation also heighten the risk of cancer and metastasis, more so in the lymphoglandular system. Increased production of neuropeptides and stress hormones can cause an alteration in the signaling of cell proliferation (i.e., mammalian target of rapamycin [mTOR]/autophagy pathways), as well as an increase in cortisol, with consequent dysregulation of immune response, insulin and leptin. A meta-analysis involving 165 controlled studies in oncology revealed that psychosocial distress is linked with an increased incidence of cancer, worse prognosis and an increase in mortality.

Evidence thus clearly indicates that psychological emotions and stress can translate into an inflammatory process that bidirectionally involves the entire PNEI system and the target organs.

### PNEI AND LONGEVITY

Chronic inflammation is involved in many pathogenetic processes. In early 2000s, Franceschi called "inflammaging" the combination of CLGCI, as the basis of any chronic degenerative process and senescence.

Several causes may be associated with the initiation and worsening of inflammatory processes. These may be of organic and psychological/social nature.

### The Interaction Between PNEI and Psychophysical Aging

A study revealed that a positive childhood from the psychosocial point of view may ensure a better cardiovascular function. Another study on the psychosocial factors which interfere on healthy aging demonstrated that depression is the most relevant, while the perceived health status, ego integrity, self-achievement, self-esteem and participation in leisure activities were beneficial factors. Yet another study suggested that senescence is a process that can be enhanced by self-estimation and self-perception of own aging with an increase of 7.5 years in the lifespan, compared to the subjects who negatively interpret their aging process. This result was achieved irrespective of economic-social status, gender, loneliness and disability.

The individual level of feeling of well-being has been shown to predict greater longevity, irrespective of family, genetic and shared environment factors. One of the most relevant prospective investigation on long-term aging and its link with biological and psychosocial factors collected information on: a) The physical and mental state; b) several possible risk factors (i.e., smoking habit, alcohol consumption); c) psychosocial features such as the enjoyment of a career, the experience of retirement and the quality of family life. The study aimed to identify biological/psychosocial predictive factors of healthy aging. The Harvard grant study highlighted some key findings: a) Alcoholism had the most destructive power, strongly correlating with neurosis and depression; b) smoking was the next factor that led to early morbidity and death; c) financial success depended on warmth in human relationships and, beyond a certain level, not on subjects' intelligence; d) the human warmth of the relationship of mother-child positively impacted the rest of life; e) higher warmth of the relationship in childhood with fathers had a correlation with lower rates of anxiety for adults and greater "satisfaction of life" at 75 years of age. The study concluded that the warmth of human relationships has the greatest positive impact on life-span and satisfaction.

Telomere length is a significant longevity index and is negatively influenced by chronic stress and depression. A study assessed women with psychological tests of stress measurement and biological tests, including telomere length measurement, telomerase activity and

cellular oxidative stress. Chronic stress in the mothers of sick children was found to be associated with lower telomerase activity, lower telomere length and greater cellular oxidative stress. In the same study, subjects practicing meditation (mindfulness) had greater telomerase activation and longer telomeres.

In another study, epigenetic changes related to chronic stress were highlighted among pregnant women suffering from chronic stress. The study revealed that the telomeres of the offspring are also affected, which will be statistically shorter both for infants and adults. Another study conducted on infants showed a strong difference in telomere length linked to their psychological and behavioral state. Children with greater emotional reactivity, measured by psychological tests, had increased cortisol and heart rate, and exhibited a reduction in telomere length in cells. Oxidative stress has a key role in several aging processes.

There is ample evidence on the inter-relationship between PNEI pathways, CLGCI and aging science that points to the correlation between the negative psycho-emotional factors and social chronic stress and worse longevity and a lower quality of the aging processes.

### PNEI: A HORMESIS-BASED SYSTEM

Hormesis is a Greek term that means "stimulate". It was used first in 1943 by Southam and Ehrlich to indicate a specific dose/response relationship. Hormesis is a highly conserved phenomenon in the functioning evolution of animal/vegetal organisms, and is marked by a dose-dependent biphasic response. The hormetic stimulus - be it a biochemical substance, a physical stress or a psychological event - at low doses, can stimulate metabolic pathways, while at high doses, it leads to a negative effect on the metabolic processes. PNEI system responds to hormetic principles as a whole. Resilience and adaptation have a key role to play in longevity. Both these features are greatly affected by the state of health of PNEI system. Any psychological, physical or biological stressor positively or negatively alters the PNEI components and vice versa. At low doses and for a short duration, acute stressors may play a role in longevity medicine, leading to a beneficial adaptation response, thus enhancing the tolerance level to further exposure to stressors at higher doses. Stimuli that may induce a hormetic response include fasting, limited cold/heat exposure, moderate exercise, resistance respiratory training, polyphenols ingestion, oxygen deprivation or hyper-exposure, radiations, spiritual/intellectual/social stimulation.

The three main proinflammatory cytokines (IL-1, IL-6, TNF- $\alpha$ ) are produced at low doses from microglial cells and astrocytes in the brain, especially in the hypothalamus, hippocampus, thalamus and basal ganglia, as part of the physiological processes of brain activation. Even in the presence of T cells, microglial cells take on a protective profile, which stimulates neurogenesis, especially in the hippocampus. In case of inflammatory activation with high doses of cytokines, the microglial cells adopt a distinguishable profile, giving way to blocking of neurogenesis.

An experimental study demonstrated that an immune deficiency is related to a blockage of hippocampal neurogenesis. A stimulating environment or a non-stressful physical activity, instead, lead to a moderate release of a few inflammatory mediators that stimulate neurogenesis by increasing the concentration of brain-derived neurotrophic factor (BDNF), the vital neurotrophic substance targeting neuronal growth and synapses development.

Excessive inflammation causes brain damage also as a consequence of the blockage of new neurons formation. The limbic system comprises of hypothalamus, amygdala and other neuronal structures. It rules basic urges and desires together with temperature and sleep regulation, and is strictly involved in PNEI functionality. The primary hormetic stressors which interact with limbic system are represented by caloric restriction, fasting, cold/heat exposure and other forms of required adaptation. These stimuli affect the hypothalamus and amygdala regulation. The limbic system may respond less to conventional medicine, drugs, intentional behaviors, especially at long-term. Hormetic pathways may impact the limbic system more stably. For instance, with fasting through increase of dopamine receptors, or with high/low temperature exposure through BDNF increase.

### MANAGEMENT APPROACHES TO IMPROVE PNEI SYSTEM

Several procedures can have a positive impact on the PNEI system.

- ⦿ Slow breathing – It leads to carotid baroreceptors regulation; blood pressure and heart rate reduction; reduction of excess cortisol.
- ⦿ Contra-resistance respiratory training – It yields carotid baroreceptors regulation; reduction in blood pressure and heart rate; improves resilience.
- ⦿ Meditation – It regulates carotid baroreceptors; reduces blood pressure and heart rate; reduces excess cortisol; correlation with greater telomere length and long life expectancy; resilience improvement.
- ⦿ Prayer – It is associated with carotid baroreceptors regulation; blood pressure and heart rate reduction; excess cortisol reduction; improvement of resilience.
- ⦿ Autogenic training – It leads to carotid baroreceptors regulation; blood pressure and heart rate reduction; excess cortisol reduction; resilience improvement.
- ⦿ Vagus nerve stimulation (neural therapy, acupuncture, massages) – It regulates peripheral inflammation; TNF- $\alpha$  reduction.
- ⦿ Nutrition and nutraceuticals (polyphenols, omega-3 fatty acids) – They reduce oxidative stress; activate anti-inflammatory pathways; activate hormetic processes; protect against cognitive decay and mood alterations.
- ⦿ Melatonin supplementation – It is associated with regulation of sleep-wake cycle; cerebral and immune-endocrine metabolism support and controls chronic stress (cortisol).

### PSYCHONEUROIMMUNOLOGICAL EFFECTS

Communication between the brain and immune system:

- ⦿ Stimulation of brain sites alters immunity
- ⦿ Damage to brain hemispheres alters immunity (hemispheric lateralization effects)
- ⦿ Immune cells produce cytokines that act on the central nervous system (CNS)
- ⦿ Immune cells respond to signals from the CNS.

Communication between neuroendocrine and immune system:

- ⦿ Glucocorticoids and catecholamines impact immune cells
- ⦿ Endorphins from pituitary and adrenal medulla act on the immune system
- ⦿ Activity of the immune system is correlated with neurochemical/neuroendocrine activity of brain cells.

Connections between glucocorticoids and immune system:

- ⦿ Anti-inflammatory hormones enhance the organism's response to a stressor
- ⦿ Prevention of the overreaction of the body's own defense system
- ⦿ Regulators of the immune system
- ⦿ Impact cell growth, proliferation and differentiation



- Lead to immunosuppression
- Suppress cell adhesion, antigen presentation, chemotaxis and cytotoxicity
- Increase apoptosis.

Corticotropin-releasing hormone (CRH):

Release of CRH from the hypothalamus is affected by stress.

- CRH regulates the hypothalamic-pituitary-adrenal (HPA) axis/stress axis
- CRH regulates the secretion of adrenocorticotrophic hormone (ACTH)
- CRH is widely distributed in the brain and periphery
- CRH regulates the actions of the autonomic nervous system (ANS) as well as the immune system. Stressors that increase the release of CRH tend to suppress the function of the immune system. On the other hand, stressors that depress CRH release potentiate immunity.
- Centrally-mediated as peripheral administration of CRH antagonist does not affect immunosuppression.

### CONCEPT OF EVOLUTION OF DISEASE FROM HOMOEOPATHIC STANDPOINT

Variegated forms and expressions of phenomenon of life are due to susceptibility. Susceptibility refers to an inherent quality of all the living beings to react to a stimuli in the environment. The sophisticated control system of psychoneuroendocrine system and reticuloendothelial system help to maintain an effective harmony over a wide range of environmental circumstances to balance the functioning of the vital force or spiritual dynamic at all levels and in all areas is thus assured. Disease evolves from dynamic plane to functional plane and then to structural plane. Man is a complete psychobiological unit of life and disease evolves centrifugally from center to periphery or from within outwards. At the level of spirit, when the will is altered, misdirected, weakened and distorted, there occurs a loss of hold of value system. Erosion of value system and ethical norms leads to thinking and thinking perceptions and discriminations get blunted as a result. This gives rise to indecision which leads to unbalanced, uncontrolled, ungoverned, exotic, spasmodic, irrational, contrary, contradictory, inappropriate and ambivalent attitude and behavior, functions and activities.

When intellect level is affected, first of all, learning responses are erased. The conflict arising from blocked

desires, impulses, urges drive expressions through various channels such as: a) Altered imaginations, b) altered psychological functions, c) drop in performance and efficiency, d) disturbed intellectual performance, e) emotional disturbance, f) altered psychophysiological functions, g) structural alterations and h) altered behavior.

From peripheral expressions, one has to project backwards to perceive the mental state to treat the patient. At physical level, disease evolves in centripetal manner, i.e., from periphery to center, from less vital organ to more vital organ.

Dr Hahnemann, about 200 years back, observed that disease is not simply an affection of a part but its existence is due to combination of various factors like emotional sphere, genetic predisposition and various morbidic agents.

### CONCLUSION

Since the seventies, data have pointed to a role for PNEI in the aging process and in degenerative diseases. Lately, a significant role has been attributed to PNEI system in psychiatric diseases. Chronic stress and psychological/social discomfort may lead to pathophysiological clinical manifestations and interfere with the immune system and favor CLGCI and inflammaging, where the latter process is known to play a key role in different pathologies, from autoimmune diseases, diabetes, atherosclerosis to neurodegeneration and cancer.

Literature evidence points to several measures improving PNEI function, such as stress management, nutrition, nutraceuticals (e.g., polyphenols, melatonin), that may have a role in targeting CLGCI and aging processes. Hormetic stressors may represent a potential mechanism to stimulate PNEI system, eventually leading to an improvement in terms of resilience and healthy aging.

### SUGGESTED READING

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