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Congress Report:
International Congress of Neuroimmunomodulation, ISNIM-99

by Ario Conti and Georges J.M. Maestroni
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Science and art need not be in conflict because both require use of imagination, cognitive insight, discipline and creative application. Conceptual shifts in neuroimmunoscience have offered new validity to intuitive belief regarding the connection between mind – body unit, external and/or internal stimuli such as viruses and bacteria, primordial environmental stimuli such as light:dark cycle, moon cycle, humidity, etc.... In the last two decades many new factors such as climate changes, air pollution, and their social and environmental effects are becoming increasingly sophisticated.

On the other hand research on NIM and its interdisciplinary research spanning immunology, neurobiology, neuroendocrinology, and behavioral sciences is growing exponentially; indeed, it may be the fastest growing field in biomedical sciences. The International Society for Neuroimmunomodulation, founded only a few years ago (1985 Dubrovnik), now has active members in 40 countries. This revolution in the basic sciences will undoubtedly lead to a corresponding revolution in clinical practice and, most importantly, in the area of preventive medicine.

Modern scientific evidence of interactions among the nervous, endocrine and immune systems dates from the late nineteenth century, although this concept was certainly known to the ancients in Asia, Europe, Africa, and the Americas. In the past two decades, the mechanisms of these interactions, known today as neuroimmunomodulation (NIM), have been investigated from subcellular to the behavioral levels, using the modern tools of receptors and membrane physiology, biochemistry, pharmacology, immunology, chronobiology, and genetics. Proceedings of different ISNIM congresses have been published with a great success and a large number of papers have been accepted: the previous volumes on neuroimmunomodulation research such as the *Proceedings of the First International Workshop on NIM (1984) Bethesda, USA* [Spector et al., 1985], *Neuroimmune interactions: proceedings of the Second International Workshop on Neuroimmunomodulation, May 1987, Dubrovnik, Yugoslavia* [Jankovic et al., 1987], *Ontogenetic and phylogenetic mechanisms of neuroimmunomodulation (1990) Florence, Italy* [Fabris et al., 1992] and *Neuroimmunomodulation: molecular aspects, integrative systems and clinical advances (1996) Bethesda, USA* [McCann et al., 1998] constitute a four-volume state-of-the-art collection representing most of the areas of research in the exponentially growing field of neuroimmunomodulation.

Tables of contents of this basic book of NIM suggest some of the depth and breadth of the subject matter: molecular biology, genetics, neurosciences, immunology, cell biology, physiology, endocrinology, chronobiology, pharmacology, anatomy, biochemistry and the behavioral sciences, as well as many contributions from oncologists, gerontologists and other clinical aspects.

1987: Dubrovnik, Yugoslavia: A new discipline named *"Neuroimmunomodulation"* by N.H. Spector or with major emphasis on behavior aspects as *"Psychoneuroimmunomodulation"* as it was defined by R. Ader was born. This discipline is devoted to study the interactions at different morphologic and functional levels among the immune system, the nervous system and the endocrine system. In fact this science is an old science or, as defined by B.D. Yankovic (1987) *"…neuroimmunomodulation is a modern reflection in neurosciences and immunosciences of the ideas and experience of philosophers and ingenious observers of ancient Egypt, Greece, China, India and other old civilizations that the mind is involved in the defense against diseases…"*

1999: Lugano, Switzerland: 12 years ago NIM was regarded by many conventional scientists as a kind of witchcraft. Today it may be the fastest growing area of research in the biomedical sciences in the world. More than 124 invited speakers and over 140 posters on 15 different topics have been focused on the state of the art of Neuroimmunomodulation.

Sessions devoted to pro- and anti-inflammatory cytokines evidenced the importance of the connection and the balance between the immune, neuroendocrine and nervous systems. In particular the role of cytokines has been stressed (for ex. IL-1α and β) and their receptors distributed on brain and immune tissues upon infection events which induce a release of many hormones such as CRH, VP, GHRH and somatostatin. On the other hand a decrease of pro-inhibiting hormones, DOPA, LH, TRH, has been reported. Moreover, alteration of infectious agents or experimentally induced infections, such as LPS, seem to be mediated by nitric oxide synthetase (NOS) which induces the production of NO and, therefore, the modulation of "infection hormones." In fact during certain pathological conditions iNOS-derived NO is produced in the brain. Studies are in progress to understand its role in experimental allergic encephalomyelitis, multiple sclerosis and AIDS patients where iNOS has been observed in microglial cells and/or infiltrating macrophages.

Interleukins stimulated by inflammatory agents may have a negative effect on the brain. In particular IL-1 induces brain damage, ischemia, trauma and excitotoxic injury. Upregulation of IL-1 receptor by IL-4, IL-10 and TNF-α and the consequent inhibition of IL-1 may prevent such damages of the brain tissue.

According to the dialogue between the periphery and the center, peripheral inflammation may induce the brain to produce IL-1β, IL-6 and TNF-α. Such cytokines injected with small non pyrogenic doses induce hyperanalgesia which seems to be caused by PGE2 which in turn acts on EP3 of the hypothalamus, while injection of the same cytokines with high pyrogenic doses induce analgesia via PGE2 on EP1 hypothalamic receptor. Consequently to an infection action and pyrogenic effects, some scientists are working on the role of antipyrogenic molecules. Among them α–MSH, arginine, vasopressin, glucocorticoids, TNF-α, IL-10 and the most recent P450 which is a cytochrome of the arachidonic metabolism and appears to be the contrebalance of PGE.

Inflammation has been since many years connected with stress phenomena. Experimental evidence supports that stress hormones such as glucocorticoids, catecholamines (epinephrine, norepinephrine) and histamine are modulating TNF-α, IL-12 and Il-10. In particular these end products of stress inhibit TNF-α and IL-12 on T_{H1}, while they stimulate IL-10 which from one side inhibits T_{H1} and on the other hand stimulates T_{H2} and tumoral activity. The balance T_{H1} vs T_{H2} and vice versa through stress hormones may increase the susceptibility of the organism to certain viral or bacterial intracellular infections or tumors that are protected against by T_{H1} dependent immunity. The same for Lupus erythematosus and atopic reactions that are dominated by T_{H2} response.

Among hormonal effects and roles of α-MSH have been largely investigated in NIM. α-MSH is a peptide involved in fever, inflammation and microbial invasion. In inflammatory cells, both at the peripheral levels and at the central nervous system, the production of proinflammatory cytokines is modulated. α-MSH neuroimmunomodulation has been evidenced in cutaneous inflammation as well as in delayed type hypersensitivity. More generally, skin produces α-MSH and melanocortin receptor-1 (MC-R1) is expressed on the tissue. Moreover, the production of inflammatory cytokines such as IL-2, IFN-γ and IL-1 by monocytes, macrophages and dendritic cells is modulated by α-MSH. A down regulation of dendritic cells (CD86) and pre B cells (CD40) by α-MSH with a stimulation of IL-10 has been also reported. The action of α-MSH as modulators of cutaneous inflammation can be summarized as 1) general action on peripheral host cells, 2) through action on host cells within the brain to moderate local inflammation and 3) via descending neural antiinflammatory pathways that control inflammation in peripheral tissues. Prolactin and GH, which in parallel with α-MSH are largely studied by neuroimmunologists, are involved in many neuroimmunomodulatory and hematopoietic mechanisms: in particular prolactin has been involved as a survival factor for T lymphocytes in early and late T-lymphocyte activation events such as immune response, in autoimmune diseases and tumor/viral cell defense.

On the other hand lymphocytes, and perhaps particularly B lymphocytes, participate actively in the complex interaction between GH and the immune system. Both prolactin (PRL) and growth hormone (GH) present a pleiotropic action, which is necessary for vertebrate growth, mammary differentiation and immune system function. Many studies using different models *in vitro* (granulocytes, neutrophiles, thymocytes, NB2 T-cell line, human-B lymphoblastoid cell line IM-9, etc...) as well as molecular biology models (RT-PCR, western-blot analysis, receptor detection and binding affinity, detection of PRL and GH-gene, etc...) are in progress to understand the specific function of these hormones and to address possible autocrine and/or paracrine effects under normal and pathological conditions opening new perspectives in clinical settings.

Neuroimmunomodulation occurs also at the periphery where important interactions between immune, endocrine, and nervous products and functions appear to be evident. Natural killer cells, γδ T lymphocytes and CD-5$^+$ lymphocytes, are key mediators of the natural immunity. NK cytotoxicity is regulated by cytokines and hormones such as IL-2, INFs, prolactin and GH, while the regulation of γδ T lymphocytes and CD-5$^+$ lymphocytes is less investigated. It seems that, for example, CD-5$^+$ lymphocytes produce germline coded natural antibodies that are polyspecific and able to recognize a great variety of microorganisms, cancer cells and selfcomponents.

NIM is an important component also in the control of the salivary secretion by nitric oxide. In fact in many experiments, exposure to endotoxins such as LPS leads to a co-induction of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) that are important in the pathophysiology of infection. Nerve growth factor (NGF) and neurotrophins (NTs) represent other important mediators of NIM. In fact NGF has trophic and topic effects on nerves and direct and indirect effects on immunocompetent cells such as for example modulation of lymphocyte functions, activation of mast cells and release of histamine, stimulation of hematopoietic cells and differentiation of eosinophils and basophils/mast cells. Moreover NGF is increased in chronic inflammatory diseases such as rheumatoid arthritis, gastrointestinal parasitic infections, hyperalgesia, allergic reactions and chronic rhinitis. Concerning NTs there is evidence for mutual interactions between NTs and cytokines. In glial cells different transcription factors such as NF-kB, c-AMP-responsive element binding protein (CREB) and activator protein 1 (AP-1) are involved in NT induction. An important role of IL-6 in connection with NTs has been reported: in fact, it seems that IL-6 with its receptor induces a specific pattern of NTs in astrocytes in certain brain regions indicating that the IL-6 system mediates a local supply of NTs that participates in diverse functions of CNS such as protection of neurons from insults, neural survival and neuroimmune response.

The bidirectional communication between the nervous and immune system involves also classical neurotransmitters such as catecholamines which are produced not only by nervous cells but even by immunocompetent cells (lymphocytes) and a down regulation between the two systems is evident. IL-1 and IL-6, which represent two products of the immune system, stimulate some products of the HPA axis such as glucocorticoids which in turn may modulate the immune response directly on inflammatory sites. On the other hand it has been demonstrated that human lymphocytes produce itself products of the HPA axis such as for example urocortin. Leukemia inhibitory factor (LIF) which belongs to the neuropoietic cytokine family also plays a central role in coordinating the neural and immune responses to injury and inflammation of neurones. In fact, injury of peripheral nerves induces the induction of LIF mRNA in Schwann cells. The cytokine is necessary for the induction of many neuropeptides in the injured neurones and LIF has chemotactic properties for peritoneal macrophages. In CNS LIF is necessary for the normal astrocyte, microglial and inflammatory reactions that follow injury, while in periphery LIF negatively regulates neurogenic inflammation and can be analgesic. Further studies deserve to be done for example in Alzheimer's disease and other CNS pathologies.

Melatonin (N-acetyl-5-methoxytryptamine), NIM and hematopoiesis represent one of the most investigated fields of research. In particular in regard to melatonin, attention has been focused on its immunoregulatory and antioxidant functions. Melatonin has been largely investigated as an immunomodulator and recently melatonin has been detected in mouse, rat and human bone marrow: measure of N-acetyltransferase and hydroxymethyltransferase activity and/or gene expression demonstrated that bone marrow could represent an endogenous source of the indoleamine. Concerning the melatonin regulation some data presented at ISNIM99 lead to the hypothesis that the central nervous action of melatonin is primarily mediated by membrane receptor, whereas direct effects of melatonin in the periphery could mainly be mediated by RZR/ROR nuclear receptor. Regarding melatonin function, it has been confirmed that melatonin enhances IL-2 and IL-6 production by human lym-

phocytic and monocytic cells. Concerning the localization of melatonin receptor data seems to be controversial because from one side melatonin seems to work on nuclear receptor (periphery) and membrane receptor (CNS), while in some human cell lines (Jurkat, U937) both nuclear (RZR/RORα) and membrane (Mel1a) receptors have been detected.

Many researchers are focusing their attention on the neuroimmunomodulation of bone marrow and hematopoietic cells involving other molecules than melatonin. In particular effects of preprotachynin-I peptides (PPT-1) are expressed in bone marrow stromal cells and fragments of PPT-1 (SP 1-4; SP 4-11) are involved in the production of cytokines providing a fine regulation on hematopoiesis. Other adrenergic and neuropeptides – containing nerve fibers project into the bone marrow and terminate in association with stromal cells and within the parenchyma producing significant stimulation or inhibition of hematopoiesis. Cannabinoids, such as anandamide, stimulate hematopoietic cells growth through a Cb2 receptor and in some conditions work in synergy with IL-3. These synergy cannabinoids, C2b receptor, and IL-3 may play a function in homing and/or migration of hematopoietic precursor cells and could be involved in leukemogenic processes. Each one of these phenomena can be connected and/or mediated by light effects. In fact light can modulate the immune response via the classical nervous pathway (eye - nucleus suprachiasmaticus - hypothalamus – pituitary and pineal gland) or directly acting on the skin with a direct effect on circulating lymphocytes. In the first case light inhibits melatonin, norepinephrin, acetylcholine, stimulates cortisol, serotonin, GABA and DOPA, and alterates vasointestinal peptide (VIP), gastrin-releasing peptide (GRP) and neuropetide Y modulating mood and circadian rhythm which in turn acts on the immune system. In the latter, direct effects of circulating lymphocytes allow a release of interleukins and growth factors which via autocrine and/or paracrine pathways influence the immune response.

The complex network including central nervous system, endocrine system and immune system to be complete and dynamic involve many coping patterns and adptation which considers physiological, emotional, cognitive, behavioral and interpersonal/situational dimensions. Many models have been presented and studies involving schizophrenia, depression, prenatal influences, illness, normal and disturbed sleep in connection with the immune system have been reported and are in progress in many laboratories. For example, impaired activation of the peripheral immune system in schizophrenic patients has been described already long before the era of neuroleptic therapy. However with new modern tools offered by immunocitochemistry such as measure of sICAM, activating cytokines IL-1 and IL-2, adhesion molecules LFA-1 and VLA-4, seem to be related to the development of schizophrenic disease and possible therapeutic applications are not far behind.

Psychological disturbance and/or hormonal treatment with ACTH and dexamethasone in prenatal individuals have been studied in monkey's model and it seems that infant's immune responses, i.e. lymphocyte proliferation, cytolytic activity and cytokine release and anemia, continue to show evidence of prenatal events. In cancer patients treated with IL-2 and IFN-γ a depression is frequent and this does not seem to be correlated with the toxicity of the treatment nor to be mediated by an alteration in the expression of cytokines at the pituitary and brain levels but to other parameters. In any case intersection between cytokines, immune system derangement and depression is clear, but the exact nature of this intersection is still elusive.

Sleep is involved in the homeostatic regulation of the body and the immune system. Sleep deprivation, an important illness which seems be accentuated by the lifestyle of our era, is believed to adversely affect host resistance to infectious diseases. Some studies correlate the sleep deprivation with alteration of natural and cellular immunity. At ISNIM-99 many reports were focused on the correlation between EEG sleep measure and natural killer cell activity in patients with major depression, the decline of immune functions (NK activity, LAK cell activity, stimulation of IL-2 production) in primary insomniac patients similar to patients affected by major depression, the reduction of natural and cellular immunity following a modest loss of sleep due to either late- or early night partial sleep deprivation, the nocturnal sleep-related increase of circulating levels of IL-6, and the decrease of IL-6 and increase of IL-10 in alcoholic patients who show disordered sleep and a prominent loss of slow wave sleep. All mechanisms underlying the relationship between sleep and modulation of the immune system remain unknown, but it seems that they could have implications for understanding the physiological function of sleep in the maintenance of health.

Oncology and neuroimmunomodulation represent a highly investigated field as basic research. In fact many scientists are studying connections between the immune, the nervous and the immune system in relation to the development of cancer. For example one of the major investigated fields is related to the regulation of apoptosis cell death by Bcl-2 family, while other studies focused their attention on the role of stress and chemotherapy in con-

nection with the pineal gland and melatonin. It is really a pity that at ISNIM-99 clinical studies related to neuroimmunomodulation were poorly represented. Paolo Lissoni, a real pioneer in this field, showed that IL-2, IL-12, melatonin and other pineal hormones such as 5–methoxytryptamine and 5-methoxytryptophol may modulate the immune system and be effective in the treatment of human neoplasms. But in oncology a long-standing problem is the connection and link between mind and body: the central question is whether psychological processes can influence the immune system. Some immunologists argue that there is insufficient evidence for a connection between the nervous and the immune systems: others accept that there is such a connection but deny that psychological processes could be involved. The discussion about this important point should be postponed to the next century or millennium!

Cytokines, which represent mainly products of the immune system, are largely investigated by neuroimmunologists in connection with the neuroendocrine and nervous functions. Super-antigens such as Staphylococcal Enterotoxin stimulate a strong response by the immune system expressed as a clonal expansion and expression of IL-1β, IL-2, TNF-α, IFN-γ and IL-4. This immune response is followed by a state of energy and the non-responsiveness induced by the superantigen consisted of changes in concentration of the sympathetic neurotransmitter noradrenaline and of serotonin in the spleen and thymus, a modification in the ratio noradrenaline/adrenaline in adrenals and modification of concentrations of catecholaminergic and serotoninenrgic metabolites in brain tissues. Moreover, changes in concentration of noradrenaline, adrenaline, corticosteroids and glucose are observed also in the blood.

Systemic inflammation induced by endotoxin or cytokines induce transient behavioral (I), autonomic (II) and neuroendocrine responses (III). These primary responses disappear after 1 day. It is important that they induce a long lasting sensitization to a second encounter up to three weeks. Non immune stressors such as novel environment, footshock and amphetamine may act similar to long lasting sensitization and the consequent activation of the immune system may induce a reprogramming of the mechanisms of both the immune and stress responses which can be within and outside of the brain. Alteration of neuron hypothalamic Corticotropin Releasing Factor (CRH) and changes in vasopressin in connection with the above mentioned changing factors may be related to risk factors of depression.

In parallel with this hypothesis that the immune activation can enhance the vulnerability to stressors and represents a risk factor for depression, in the case of dementia of the Alzheimer Type (DAT) changes related to immuno-neuroendocrine organization have been also reported. In fact in DAT patients, hormones belonging to the HPA axis, GH, PRL and MLT are increased. Moreover also immune system parameters such as NKCC, TNF-α are completely modified. If in normal physiological aging immunoneuroendocrine parameters are preserved, DAT hormones and NK disfunctions could contribute to altering neuroendocrine functions. Finally, these alterations contribute to inducing immunoneuroendocrine mechanism of neurodegeneration (I) and dementia (II). Cytokines like IL-1β, LPC 18:0, catecholamines and serotonin are able to stimulate the physiological production of IL-6 by the anterior pituitary gland and, in vitro, by C6 glioma cells. About the mechanism it seems that IL-1β and LPC 18:0 may lead to a release of IL-6 via a kinase cascade which includes cAMP proteinase.

Multiple mechanisms related to different cytokines such as IL-1, IL-6 and TNF-α affect the hypothalamus-pituitary-adrenal axis (HPA) and the couple TNF / IL-1 exert the stimulatory action in different types of cytokine/glucocorticoid target cells such as glioma, pituitary, fibroblastic and epitheliod cells. In particular, IL-1 and IL-6 induce hypothalamic increase of TRP and serotonin and an increase of adrenal ACTH and corticosterone. On the other hand TNF-α seem to be involved on hypothalamic noradrenaline metabolism. Noradrenaline may be involved in response to IL-1 but not in the activation of IL-6 and TNF-α. However, the network is clearly more complex: other molecules are able to stimulate the HPA axis, i.e. adrenal cortex to release IL-6 and TNF and the IL-mRNA cellular content. Among these molecules ACTH, angiotensin II, endotoxin, serotonin, dopamine and adenosine are undoubtedly the most representative.

Which could be the possible role of IL-6 and TNF-α released by the adrenal cortex? Some conclusions at ISNIM-99 speak in favor of a possible role in adrenal function: dynamic cytokine effects on adrenal steroids (I) and modulation of cytokines in chronic but not acute regulation (II) seem to be implicated in adrenal functions.

In this dialogue between brain and immune system, leptin has been suggested to serve as a peripheral messenger to converge signals from the periphery to the brain. In fact, this important molecule appears to be involved in the homeostasis in pathophysiological events occurring during infections. In the case of an infection the HPA axis and cytokines can be deranged and frequently a weight

loss (I) and anorexia (II) are observed. In this case glucocorticoid, endotoxin and cytokines stimulate leptines which in turn may inhibit the HPA axis.

Hypothalamus represents one of the terminals of the HPA axis and is a center for release of pro- and hormones which act directly on the pituitary and the latter participate in the paracrine and autocrine networks by releasing hormones and cytokines. For example the hypothalamus releases GHRH which stimulates the pituitary gland for GH. This hormonal way is suppressed by paracrine and endocrine Insulin Growth Factor-1 (IGF-1) whose pituitary receptor subserves negative feed-back control of the GHRH-GH axis. GH and ACTH are also induced by cytokines which compromise the gp130 signal transducing subunit family, including IL-6 and LIF which receptors are expressed on the pituitary cells. Hypothalamus and hypophysis, whose compartments concern neural (catecholamines receptors) and glial (glucocorticoid receptors) structures, release LHRH which acts on gonads via the HPA axis. But LHRH interacts also with organs and cells of the immune system. Gonads, via the release of estrogens modulate the release and hormonal and immune functions of LHRH. In particular, it appears that estrogens are important regulators of the differentiation of certain brain nuclei (I), play a role in the maintenance of normal brain life throughout the life (II), shape the activation of the HPA axis upon stressful stimuli (III), are involved in the regulation of the sex dysmorphism (IV) and finally they increase the vulnerability of the female sex to autoimmune diseases such as multiple sclerosis where the proportion with males is 2:1 (V).

Anterior pituitary cells release a protein mediator with the same sequence of macrophage inhibiting factor (MIF). MIF is present within corticotrophic cells, macrophages and T cells which upon stress events (proinflammatory stimulis and/or glucocorticoids) are released and act as antiiflammatory, antiimmunosuppressive effects of steroid on macrophages and T lymphocytes. The new protein mediator released by anterior pituitary gland seems to be a new counter-regulator of glucocorticoids action within the immune system.

A Neuroimmunomodulation Congress without a symposium devoted to the neuroendocrine control of thymus is not complete. In fact, thymus is known to be considered by immunologists the central organ of the immune system. However for neuroimmunologists, thymus belongs to the complex network of brain, endocrine system and immune system. As a pivotal organ murine and avian thymus and bursa of Fabricius in avian are involved in modulating the complex glucocorticoid cascade from cholesterol to the end products corticosterone in cortisol. This is because the thymus possesses all enzymes and cofactors required for glucocorticoid hormones but to be functional in glucocorticoid metabolism the intact thymic architecture and connection with other systems are necessary. It has been also reported that thymus glucocorticoid production follows a different pathway than the adrenal and the circadian rhythmicity. The role played by glucocorticoid in the T cell development, in the kinetic of a such an important development, researchers are inquiring about gene marked precursor cells and thyming homing of these cells. The main conclusion is the confirmation that thymus is considered to be a very important organ at the crossroads of neuroimmune interactions in which multiple cell interactions can control developmental cell fate and the morphogenesis. Moreover thymus, as a central organ of the immune system, is potentially involved in the pathogenesis of several autoimmune diseases through impaired regulation of thymocyte differentiation.

The neuroimmunomodulation network is under the control of many hormones such as GH, prolactin, vasopressin as well as cytokines and related molecules. However, important molecules which have a behavioral connection should be of a great importance: they are opioid and opiates. In fact olfactory stimuli, which are considered naturalistic stressors for mice, and some model of stress odor exposed such as keyhole limpet hemocyanin (KLH) induce an increased immune response with an increased production of IgM and IgG antibodies and analgesia. A second restimulation of mice with KLH induces a stimulation of T_{H2} cells which release IL-4. It is now clear that KLH modulates the T cell response such as a decrease of T helper 1 (T_{H1}) and increase of T helper 2 (T_{H2}) and the consequent cytokine production. All these KLH effects are blocked by naltrexone and/or naloxone which inhibits the IL4 production, the analgesia and the modulation of T_{H1}/T_{H2} cytokine production. In the latter KLH induces IL-4 production while naltrexone block this metabolic way and induces IL-2 and INFγ. In parallel with opioid, morphine has been studied by a periaqueductal injection in the brain gray matter where μ and not δ or κ ligands are effective in suppressing the immune function. In fact, an inhibition of the natural killer activity in spleen, an inhibition of the T cell proliferation in spleen respectively thymus and an inhibition of the peritoneal macrophage function have been reported upon morphine periaqueductal injection in the brain gray matter. Other studies reported that morphine injected in rat induces a decrease of blood lymphocytes independently from the involve-

ment of HPA axis, while the same morphine induces an increase of circulating IL-6 which can be abrogated in adrenalectomized rats. These morphine effects are mediated via activation of opioid central receptors as demonstrated by the block induced by naltrexone. Closely with opioids, cannabinoids shape antinociception, hypothermia, sedation and hypotension. Cannabinoids and μ opioid receptors overlapped in the brain and both are present in the immune system. Stimulation of such molecule receptors may result in changes in different immune parameters which may be mediated through distinct peripheral mechanisms.

Neuroimmunomodulation includes also the large field of the mosaic represented **by autoimmune diseases**. Many models are used by scientists, among them models of collagen induced arthritis, adjuvant induced arthritis, experimental autoimmune encephalomyelitis and uveitis are currently used as models for drug of abuse and because they show abnormalities in corticosterone production. Genetic work using genome wide QTL linkage technique allowed to definition of different genomic loci QTL which are involved in the regulation of severity/susceptibility to the above mentioned autoimmune diseases. Scientists agree about the complexity of a study of the genetic control of autoimmune disease. In fact autoimmune diseases have to be associated also to neuropsychiatric feature, anxiety, depressed mood, personality structure which are related to disregulation of a stress response and the hormonal balance. It is indeed the case of Sjögren Syndrome (SS), a common autoimmune rheumatic disorder characterized by the above mentioned factors and a hypoactivity of the HPA axis. Low ACTH and low cortisol at the pituitary and andrenal level, alteration in the thyroid function (Thyrotropin releasing hormone TRH). Also in the inflammatory arthritis in rats, systemic lupus erythematosus in mice and thyroiditis in chicken the HPA axis seems to be a pivotal reference. In particular, when the axis is blunted it appears to be a disregulated sympathoneural response, a defect in the steroid (deficiency or relative deficiency of androgens/estrogen) and neuropeptide releases and an abnormal production of cytokines by the immune system (IL-1, TNF-α, IL-6). The consequence is an increment of the autoimmune disease susceptibility, i.e. rheumatoid arthritis. Although the relevance of stress in many pathologies of autoimmune diseases, allergies, tumors, etc... is widely accepted by the scientific community, the underlying biological mechanisms of stress-related exacerbation of symptoms related to these pathologies are not completely understood.

Among different studies related to stress should be considered the neuroendocrine responses and allergies in which effects of enviromental factors favoring the allergen-specific T_{H2} response in allergic subjects, the olfactory Pavlovian conditioning of allergic rhinitis, the protective effect of androstenetriol and andostenedriol against lethal radiation. Glucocorticoids and oxidative stress play a role also in bacterial, parasite and non-AIDS infections. In fact glucocorticoid responses have been found to suppress inflammatory reactions by inhibiting the traffic of immune cells. Moreover, it was demonstrated that restraint stress and psychosocial stress differentially affected the pathophysiology and survival in the mouse influenza model. On the other hand oxidative stress is implicated as a pathogenic factor in a number of viral infections such as exacerbation of pathogenesis of coxsackievirus B3. In the specific case the immune function and cytokine pattern post infection were altered by the oxidative stress. Stress and glucocorticoids abrogate also the immunity to tuberculosis and in the mouse model glucocorticoids can cause such a T_{H1} to T_{H2} switch. It seems that the equilibrium point of the cortisol/cortisone shuttle in infected lungs is shifted toward cortisol while the T_{H1} response is declining. Then after the shift to T_{H2} has taken place, the equilibrium shifts towards cortisone. Physical, social and psychological stressors disrupt physiologic homeostasis which results in the activation of the HPA axis and is characterized by a rise in serum glucocorticoids which in turn reduces macrophages and T-lymphocytes activation. Androstenediol counter-regulates the influence of stress on antiviral immune responses via cell recruitment to the draining lymph node, lung NK cell activity, and $CD4^+$ T cell activation and IFN-γ production. Furthermore androstenediol blocked the influence of glucocorticoids on inflammatory cytokine secretion, i.e. IL-1β and TNF-α. More generally hormones such as androstenediol may function to increase the immune responses that are important for controlling viral infection possibly by counter-regulating glucocorticoid function as suggested at the transcriptional level.

Other studies on this specific neuroimmunomodulation field have been done employing various inhalational anesthetics, i.e. halothane and nitrous oxide (N_2O). It has been reported that these drugs are proposed to increase fluidity of cell membrane in the CNS. The consequence is that this process disrupts the blood-brain-barrier and promotes the viral neuroinvasion and increases the mortality. This practice may put certain popula-

tions, anesthetized patients and operating room personnel, at a greater risk during viral infections. Viral infections have been discussed in a particular session devoted to HIV infection. The natural history of HIV infection has been strongly influenced by the use of combined anti-retroviral therapies. Such therapies have been found to be effective, however, some unexpected effects such as conditions involving fat metabolism and disruption and immune system derangements (increase IL-12, decrease IL-10 and TNF-α, increase CD14+/DR+) seemed to be of great importance. On the other hand some researchers focused their presentation on pathogenic mechanisms of HIV/gp120 in the neuroendocrine disregulation of AIDS, on changes in Cortisol/DHEA ratio in HIV-positive men related to immunological and metabolic/nutritional perturbations, and cytokines – immunoendocrinologic axis - glucocorticoids in HIV infections.

The proceedings of the IV International Congress of Neuroimmunomodulation, i.e. ISNIM-99, will be published in the last year of the millennium by the New York Academy of Sciences and the book will records the presentations relating to advances in the understanding of the neuroimmunomodulation according to modern methologies and technologies, the science of the third millennium.

Address of the author:
Dr. Ario Conti, Ph.D.,
Center for Experimental Pathology,
Istituto Cantonale di Patologia,
6601 Locarno 1, Switzerland
E-mail: ario@bluewin.ch
TEL: +41 91 278 8884; FAX: +41 91 796 20 43

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