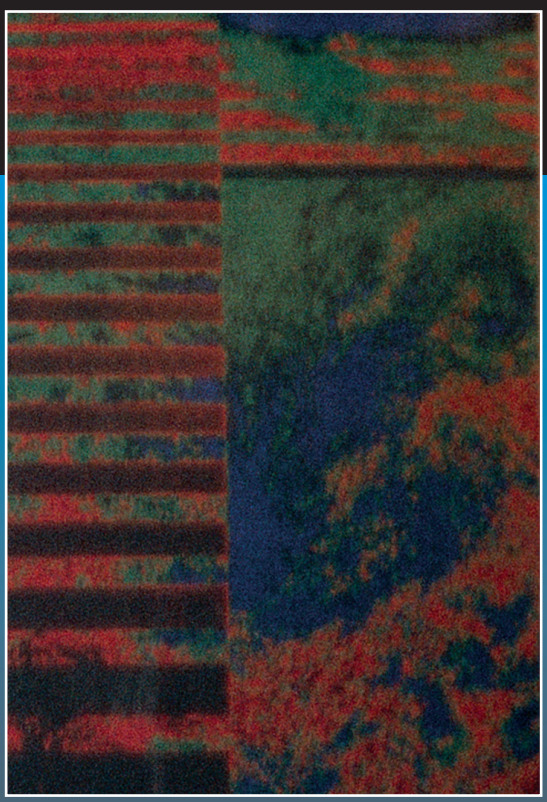
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Social and Cultural Psychoimmunology



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Social and Cultural Psychoimmunology

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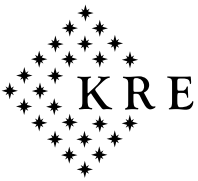
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Imre Lázár

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PREFACE WITH HOLISTIC CONTOURS

> *Man is not an indifferent hanger for carrying a disease. Man is the larger part of the disease. Temperament affects even skull fractures. It affects the coloration of acute diseases and especially certain chronic and maybe non-exogenous disease types, which cannot be properly understood or judged unless we follow the internal and typically more significant threads of their etiology into the unique tangle of individual characteristics.*
>
> László Németh: Új szempontok
> a status praesens felvételében
> (New Aspects for the Assessment
> of the Status Praesens), 1968 [1925]

If we understand the above sentences as the philosophy of treatment or a medical approach, GPs and surgeons, psychiatrists, or specialists might follow their covert intentions. Social psychoimmunology arouses interest in the person and fate of the patient in the frame of social-psychophysiological background knowledge and, at the same time, allows for the targeted supplementation of the tools of extended interview applying narrative medicine and the treatment of the patient with the help of suitable patient instructions, psychoeducation, cognitive behavioral therapy, and relaxation.

At the same time, when the biopsychosocial revolution of medicine was rising, research into neuroimmunomodulation began in immune laboratories in the seventies, in addition to research into the physiology of stress, which had already become part of the biomedical approach by then.

The findings of psychoneuroimmunology (PNI) contributed to strengthening the social neurosciences and developing *ecological interpretations* of physiological phenomena. The neuroendocrine-immune system results from *natural selection* itself; it is a mesh of innate adaptive responses to the *natural and socio-cultural environment*. The immune system's development is equally sensitive to pathogens

and nutritional, neuroendocrine, and psychosocial factors. The antigen-dependent mechanism of the so-called clonal selection itself follows Darwinian logic within the body. The individual's success in obtaining optimal nutrition enhances conditions for optimal immunocompetence while during malnutrition the mass of the thymus decreases, the cellular immune response is weakened, and the number of circulated T-cells is reduced. Psychosocial and civilizational conditions exert long-lasting influence on immune-competence. Early-life psychological traumas and even being surrounded by an environment with an excessive lack of antigens as an infant, can both lead to permanent immunological changes.

Maybe it was precisely this challenge of the human ecological interpretation of fate that diverted general practitioners' attention from the psychoanalytical hermeneutics toward psychotherapies treating maladaptive modes of operation of families struggling to get by in the *Berne*-ian games or reinforcing psychosomatic symptoms, which provided the foundation of the so-called *narrative medicine.*

To attribute a pathogenic role to disorders of personality-dependent adaptive responses to the environment's challenges was not a concept invented by the psychosomatic medicine of the 20th century. The idea, which one can find in the healing Canons of ancient China, is much elder: the "seven emotions" that are brooding, fright, anger, sorrow, fear, grief, and maybe even excessive joy can become the source of illness. The threat of loss, or grief that may be symbolized in the consciousness of the individual forcibly adapting to the sociopsychological and physical-technological game rules of the environment lead to profound biochemical changes depending on the classification of the experience; and understanding the transformation of the symbolic meaning of the specific situation into a neurohormonal pattern, as well as its scientific representation, are the demystifying tasks of research laboratories.

Perhaps it is not an exaggeration to say that this psycho-physiological vulnerability incorporated into our existence is the mysterious driver of human cultural history, the inspiration of founders of religion, and a fundamental physiological and life philosophical question hiding deep within yoga, Buddhism, and even the religious advocacy of love and understanding typical of our Christian culture.

The Horatian concept of the *aurea mediocritas*, the golden mean, the Stoics' dispassionate philosophy dedicated to maintaining balance, and the hedonistic Epicureanism can be seen as homeostasis of approaches to the protection of health. This principle of balance is present in the regulatory processes of behavior, emotional balancing, and neuroendocrine communication, as we will see in the ill patients' behavioral dynamics and sleep physiology.

The complex network schemes built by S-O-R (stimulus–organism–response) might represent the logic of adaptive behavior, reflecting chains of information flow with several transcripts at different interfaces in the line or preferably along the web's edges. Situational semantics provided a new approach for the modeling of the relationship in which social, physical, technological, and environmental information is possible to be reflected in some diseases through remarkable transformations, presenting the disease and the situation as parts of a whole in their unique pattern.

The Engelian turn of the bio-psycho-social paradigm explicitly expressed the importance of this information flow through the network of networks that is built up of dynamically connected social, psychological, somatic, and molecular-genetic layers.

In 1977, the Yale Conference on Behavioral Medicine had a strong impact on the history of psychosomatic medicine. The participants, like Joseph Matarazzo, Redford Williams, David Shapiro, and Gary Schwartz, defined a new framework for the former psychosomatic medicine, as the study and treatment of diseases, disorders, or abnormal states in which psychological processes and reactions are believed to play a prominent role. There were several opinions regarding the identification of psychosomatics with behavioral medicine. Some considered them identical; others expressed the opinion that behavioral medicine was only a fraction of psychosomatic medicine, while others viewed behavioral medicine as implying psychosomatic medicine and additional areas of medical and psychological concern. The wider definition of behavioral medicine extended the former borders of psychosomatics, proposing *behavioral medicine* as the field concerned with the development of behavioral-science knowledge and techniques relevant to the understanding of physical health and illness and the application of this knowledge and these techniques to prevention, diagnosis, treatment, and rehabilitation. The disciplines contributing to the study of behavioral phenomena include psychology, sociology, anthropology, education, epidemiology, biostatistics, and psychiatry.

These disciplines must be coupled with the biological and medical sciences relevant to understanding the disease processes under study. The networking position of behavioral medicine is apparent from an epistemological perspective, too.

The following matrix clarifies the deep connection with network medicine. In this matrix a disease is indexed at the sociological, epidemiological, anthropological, psychological, biomedical, and physiological levels of networks, and this is a multidimensional analysis with reference to different times (risks, pathophysiology, prognosis, treatment, and rehabilitation) and agencies.

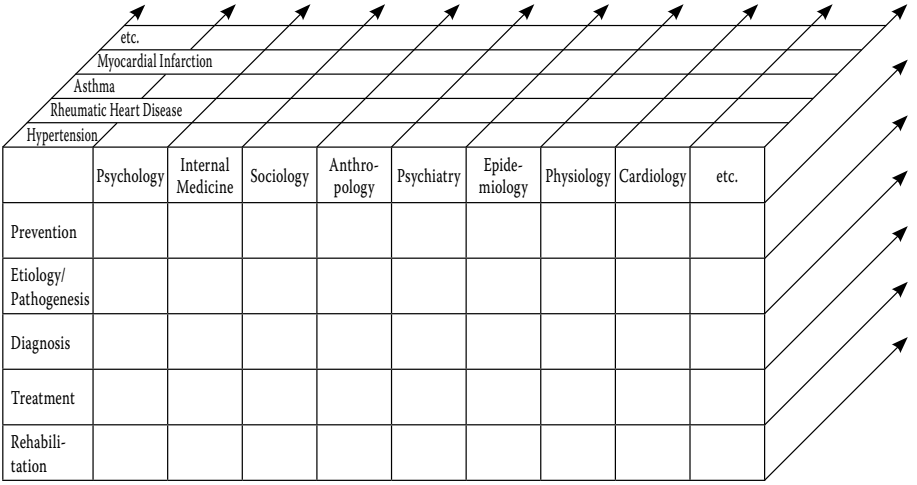


Figure 1. The matrix of biopsychosocial medicine (Proceedings of Yale Conference 1977)

Sociosomatic framework for behavioral network medicine

Sociosomatics offers a comprehensive interpretive framework for multilevel integrative analysis of human adaptation, disease processes, and healing. Evidence-based knowledge of social neurosciences, neuroplasticity research, and social epigenomics provides a basis for understanding the interconnected sociocultural, psychological, and pathophysiological networking processes. To model these multiple looped network relationships together, we need an organic, "hybrid" ontology between the individual and their environment that interprets the individual along with their social, technological, and knowledge environment, which also provides an opportunity to rethink stress models. The Man-Environment-Organism (M-E-O) model allows us to place the world of psychosomatic phenomena in a sociocultural context. Thus, the psychosomatic relationships of social, cultural, religious, political, workplace, and family social relationships can be examined through a unified network model, which we illustrate with socio-psychoimmunological examples. This multilayered, networked approach offers new avenues in the areas of lifestyle medicine, occupational health, and renewable evidence-based psychosomatic internal medicine, which is at the heart of networked medicine.

The social and knowledge space surrounding the suffering person changes in time and is culturally bound; in its close fabric of interaction, it shapes the image and healing practice of physical and mental suffering. Medical anthropology, with focus on the cultural aspects of health and disease, deals with a sociosomatic phenomenon, biocultural adaptation. The term sociosomatics

was first used by Golenhofen (1966) in connection with the psychosomatic aspects of cardiovascular phenomena, and Pauli (1997) drew attention to the integration of psychosomatics and sociosomatics with a public health emphasis. However, the concept became best known through the anthropological vocabulary of Kleinman and Becker (1998), who integrated the domain of interpretation of psychosomatics into the social context and focused on the interactions between somatic, psychic, and social processes. This sociosomatic (or socio-affective) sensitivity differs from the body-soul dualism of the traditional psychosomatic approach, emphasizing the autonomy of internal "psychological" states because this approach extends the range of interpretation to the physical-cultural impact of social and cultural, political, and religious conditions. Sociosomatics, according to Kleinman, requires a renewable technical language that can express how moral categories become emotions, political and economic experiences, mortality, and morbidity.

Sociosomatic bridges connecting the world of social phenomena with biological ones incorporate the cultural features of socially mediated perceptual, cognitive, and affective processes and are transcribed into endocrinological, immunological, and neurophysiological processes. Therefore, psychophysiology may become a medical anthropological explanatory model (Lázár, 1994).

Culture-specific explanations of symptoms and complaints result from the interaction of cognitive-affective, psychophysiological, and sociocultural processes (Kirmayer and Gómez-Carrillo, 2019). Cognitive patterns and cultural models affecting the patient's state are evolving through continuous interactions with others, physicians, and facilitators, and the technological environment (IT, medical high tech) is playing an increasingly important role in this process.

The Hungarian health psychology discourse kept pace with all this; just let's take, for example, the Hungarostudy research series of behavioral epidemiology led by Mária Kopp, and the oeuvre of decades-long health psychological research and teaching of Péter Molnár and Béla Buda. In the *Addendum* of this book, one can read the abstract volumes of two satellite symposia of the 5th International Congress of Psychophysiology (Budapest, 1990). The one on *Cultural Psychophysiology* was held in Szirák, while the other one, also the first European Conference on *Psychoneuroimmunology*, was held in Martonvásár.

Sociosomatics examines the social course and influence of disease, the social construction of disease experience, and the causal social factors that underlie the physiological response in the sociocultural context that frames the experience of physical and mental illness. The orientation of sociosomatics includes somatic metaphors of social disharmony and symptom patterns outlined as a culturally colored syndrome or local idioms of suffering. The sociocultural extension of psychosomatics also means that we need to consider the impact of social factors on an individual's psychophysiological processes. Certain social stressors may also increase the risk of certain illnesses.

The rise of psychoneuroimmunology is a typical example of the sociosomatic interpretation of human disease. Its core explanatory model is based on insights of neuroimmune modulation, the bidirectional communication between neuroendocrine and immune systems enabled by shared receptors and cross talk of messengers, and their integrated neuroendocrine-immune information pathways consisting of neurotransmitters, interleukins, neuropeptides, and hormone, including even myokines and adipokines.

These evolutionary patterned communication networks create a *network of networks* throughout the whole body, including the brain and all the organs. In the social-psychological, cognitive-evaluative, emotional and neurovisceral associations, connections, and circles, regulative positive and negative feedback loops create unity of cognitive, emotive, visceral, molecular, receptoral, and transcriptomal-genetic levels. The prehistory of psychoimmunology is mostly shared with psychosomatics, and its hermeneutic and heuristic features are close to what network medicine offers (Lázár, 2020).

This network medicine offers a new paradigm to rethink psychoneuroimmunology in an extended human ecological context. Network medicine understands social-psychoimmunological phenomena through the networked structures and processes among neural networks, neuroimmune, endocrine-immune, immune-immune interaction patterns at organ, cellular, molecular and genomic levels, including supraindividual social networks. Social processes embedded in the cultural web of meaning influence deeply human behavior, psychophysiologial patterns and health.

Behavioral immune phenomenology focuses on social interaction, xenophobic aversion, changes in human interactions reshaping social ties in periods of pandemies, like in the case of present days COVID plague. Diseases are also influenced by social conditions, socioeconomic determinants.

The human ecological model of M-E-O (Man-Environment-Organism) concept (Lázár, 2001) includes these interwoven nests and niches of natural, social, technological and infospherical environments surrounding the human actor and its communities.

The M-E-O model is a human ecological explanatory model based on the tetrahedron environmental ecodynamic framework, where natural, social, technological and infospheric niches are permanently (re)constructed by the human actor along permanent in(ter)fluences, and these niches may relate to each other in a different economic/ecological manner. The M-E-O model implies coevolutionary processes based on the concept of niche construction, Kenneth Boulding's theory of ecodynamics (1978) and the tetrahedron ecodynamic framework (Lázár, 2001), in which interacting natural, social, technological and ideospheric niches influence each other in an ecodynamic (competitive, predating, symbiotic, neutral or saprophytic) manner through human agency.

This model offers a proper network frame for exploring the social and cultural analysis of psychoimmunological pathodynamics of several diseases, including Alexander's "Holy Seven" psychosomatic diseases – hypertonia, peptic ulcer, bronchial asthma, rheumatoid arthritis, Crohn's disease and ulcerative colitis, Graves' disease, and neurodermatitis – with newly discovered psychoimmunological features.

Natural, social, technological and informational features of illness are interwoven in Berkman's ecological model, too. He points to the mediating role of social networks between the macrosocial environment and the network of psychosocial processes (Berkman et al., 2000). COVID experiences prove Berkman's thesis, because social upheavals, demonstrations, or anomic deviant community behavior make people more vulnerable and susceptible to infectious disease outbreaks, while social distancing diminishes reachability.

Combining the M-E-O model and Berkman's concept, we might draw a four-dimensional network frame for socio-cultural psychoimmunology.

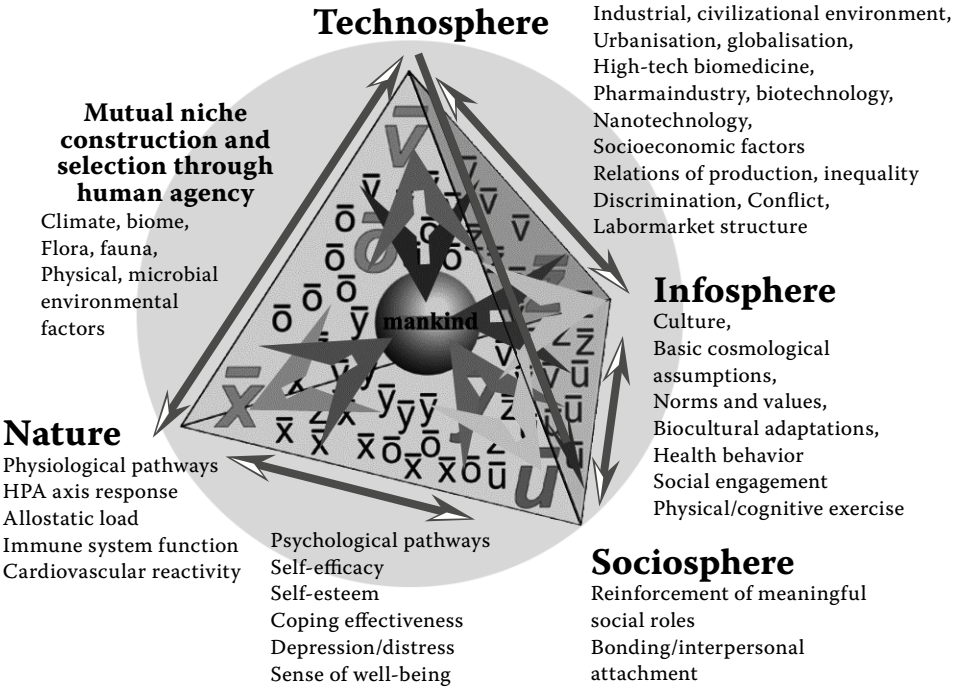


Figure 2. Integrated cultural-sociosomatic networks

Social hierarchy, imbalance of social status, dominance, submission, social support are features and indexes of social network dynamics, which are deeply embedded in social cultural norms, perceptions and expectations and mediated to the abyss of the body through psychophysiological processes

shaped by psycho-developmental determinants. This way, social networks can influence psychophysiological networks, creating a social-somatic continuity. The mental representations of social hierarchy, shame, loss or social support, control and joy are transferred by neuroendocrine-immune informational pathways (Lázár, 1991). In case of infectious diseases, it is obvious that human relationships and social dynamics – as network features – shape routes of infections. But the same can be told about "infective health behavior patterns" in subcultures (drug consumption, smoking habit) or issues of lifestyle medicine like problems of sedentary lifestyle, civilizational diseases, junk food consumption and consumerist addictions. These are strongly shaped by technospherical and infospherical determinants and environmental pressures. The deep psycho-developmental factors of personal stress-biological mechanisms are also embedded in culture of motherhood shaped by climatic, social-, and technocultural determinants, as we will examine in the following chapters.

The cultural, economic and psychological background of risk factors for several chronic diseases have been enriched by psychoimmunological considerations, as IL6 became as important morbidity index as smoking and obesity in the inflammation theory of atherosclerosis. This way, psychological experience of social networks, coping and resilience cannot be detached from sociocultural factors in the wider environment.

The association between bereavement and cancer morbidity and mortality; the marital stress, the psychoimmunological consequences of impending unemployment and long-term loss of job, loss of status prove the importance of social network dynamics. According to Berkman, large-scale population studies have identified social isolation as a significant predictor of higher morbidity and mortality from ischaemic heart disease, cancer, or chronic respiratory diseases (Berkman 1995). Social support, marital status and larger social network size are associated with greater cancer survival rates (Pinquart and Duberstein, 2010). Furthermore, there are abundant data verifying the connections between network size and risk factors like smoking, obesity and physical activity. These health risk factors are represented internally in mediator networks, with intertwined adipokine and myokine-PNI network interactions.

The external, worksite, peer and familiar social network analysis and tracing the network routes and pathways of psychoneuroimmunological network should be connected for a unified social and cultural PNI approach. Slavich and Irwin (2014) put this pathway analysis in an evolutionary frame in their *social signal transduction* theory of depression.

PSYCHOIMMUNOLOGY, ANTHROPOLOGY AND HUMAN ECOLOGY IN AN EVOLUTIONARY FRAME OF NETWORKS

The neuroimmune "foresight"

The neuroendocrine effects triggered in the brain by threatening environmental stimuli can create a preparatory pathogen-host defense effect on the innate immune system, as a result of which the redistribution of the cells included in the native immune response and their migration toward the exposed area were detected. All of this ensures an increased rate of healing after an injury. This response can be mobilized by predators' presence or the emergence of a significant conflict situation. In the opinion of Slavich and Cole (2013), the mobilization of the native immunity is not only an evolutionary remnant but something that can be triggered by symbolic threats, social conflict, rejection, isolation, and exclusion as well. Let us consider the genetic basis of the neuroendocrine and immune systems of mammals when investigating their immune system. We can identify a typical pro-inflammatory/anti-inflammatory response pattern by examining the leukocytes' transcriptome circulated in the body, that is, the set of RNA typical of the cell.

Under normal circumstances, the sympathetic nervous system's activity increases the so-called conserved transcriptional response to adversity (CTRA) with the help of the adrenergic receptors, and the HPA axis activity reduces the CTRA-dependent inflammatory response as a result of the released cortisol.

However, in chronic social isolation, the threat of grief, and post-traumatic stress reduced the activity of the anti-inflammatory glucocorticoid receptor (GR). Therefore, the conserved transcriptional response to adversity is triggered by threatening, stressful, or permanently uncertain adversity, as indicated in Antoni's report (2012). The threat of grief, traumatic stress, social isolation, low socioeconomic status, or a cancer diagnosis result in a pro-inflammatory transcriptional shift of cytokines. In experimental animal models, social instability, low social rank, and repeated defeat also resulted in a CTRA. Such challenges increase the activity of the genes responsible for the inflammatory immune response to extracellular pathogens and bacterial infections and inhibit the genes responsible for the antiviral immune response to intracellular pathogens. The facts that it increases the rate of CTRA, wound healing, and response to infection in an actual physical threat, indicate the selective

evolutionary advantage. However, it is apparent from the observations that the CTRA is also activated by several symbolic, social, anticipated, or imagined emergencies experienced in everyday life. In the event of prolonged perceived or real danger, social or physical threat, a glucocorticoid resistance might develop, which may lead to more severe inflammation or depression. On the other hand, the stress management techniques of behavioral therapy can reduce the CTRA in cancer patients, and the lower CTRA rate is coupled with a lower rate of remission and a higher rate of survival in such patients.

Therefore, the immune system's mobilization and the increase of white blood cells in predicted danger are a unique phenomenon associated with the "immune subconscious". Anticipation is a shared ability of neuroimmune systems and involves the mobilization of the neuroimmune system in question in response to perceived or real adversity, this could include the CTRA phenomenon as well; however, anticipation also includes potentially increasing the oversensitivity reaction of the skin by way of stress hormones. Anticipation is related to the emotional states of fear and anxiety; the cortical and subcortical conscious and subconscious processes can trigger a neuroimmune response. This is complemented by the agency of the amygdala and the relevant attention, learning, and arousal phenomena, as well as the increased activity of the endocrine and vegetative nervous system. The "presumption" of anticipated events, the imaginative activity, is performed on the brain's same networks as the neural activities based on sensory information. Therefore, the experience-based anticipation of significant events can influence neuroendocrine regulation.

In the event of associations of suitable duration being created during immune conditioning, the conditioned stimulus itself can trigger the same effect as the unconditioned stimulus, which can be disturbed by the denervation of the spleen. Therefore, immune conditioning includes the ability of neuroimmune learning as well.

The strength of the learned associations depends on several factors, such as hypnotic susceptibility and absorption, connected not only to increased conditionability but also to the increased reactivity of the vegetative nervous system and the immune system. It should be mentioned in connection with the so-called state-dependent learning process that behaviors are more easily recalled in a situation corresponding to the state in question. State-dependent learning is typical of the immune system's behavior in the case of a prolonged oversensitive reaction, and based on Cohen's work (2000), the immune system interprets the antigens within the framework of cognition.

The specific immune response depends on the integrity of the structural information acquired on the spot, acquired in the past, or acquired congenitally. Immune cognition converts the antigen pattern into a chemical signal within the framework of an evolutionarily fixed and state-dependent neuroendocrine-immune syntax. The immune system responds not only to a recognized

antigen but also to an antigen evaluated in its context. *Psychoimmunological cognition is the sum of evolutionarily developed adaptive patterns of synergistically connected cognitive systems.* The object of psychoimmune cognition is an environmental factor characterized by internal logic, grammar, and syntax, similar to any signal system.

The stressors, significant from a psychoimmunological view, are rich in meaning within the context of the individual's life history; therefore, Cohen (2000) believes that stress can be considered a unique language with an appropriate syntax and personal semantics. Neuroimmune stress is such a "linguistic" phenomenon that should be examined within its multilayer syntax framework, in the widest cultural psychoimmunological context.

Psychoimmunology embedded in sociocultural networks

The disease is a coded message from fate. However, the patient is the protagonist of their fate, and fate is shaped by the dramatics played out on a sociopsychological stage. Disease happens in the body's evolutionary structure, but this story is locked into the microecology of the inner world and the natural and sociocultural macroecology of existence. It is this eco-logic that creates the context for signals of socio-psychoimmunology. When pursuing the discovery of information on disease events, the neuroendocrine and immunology signals turn into reporting signals, psychoimmunology becomes a multidimensional semiotic problem, the evolutionary background of signals turns into etymology, and stress and its consequences become a narrative.

This is how fate becomes a psychosomatic dramaturgy, and the ecological framework for it is provided by the recognition that health and illness are phenomena that measure the success of biocultural adaptation. Anyone interpreting these processes slowly realizes that they are faced with micro-level happenings of evolution on this ecological stage.

Human beings who can be interpreted independently from their surroundings are a thing of the past, knowing the environmental crisis of the new millennium. Systems theory, ecological anthropology, the understanding of humankind and its environment in an organic unit (Lázár 2001, 2011) or Bruno Latour's interpretation of humankind and its inanimate environment in one unit, as a human/non-human hybrid, all help to understand psychosomatics as a part of human ecology.

Looking at the various levels of sociosomatic relations, it is possible to unfold a web of meanings that work on more than one level, where the bodily and mental, social and cultural aspects of abstract concepts such as loss, threat, control, helplessness, hope, shame, serenity and ego strength may be investi-

gated in a specific cultural context, in a given historical, geographic and cultural setting.

The challenging concept of *socio-psychoimmunology* also implies that behavioral science uses an explanatory model for phenomena described by the mutuality of neural and immune processes, the morphologic aspect which often sets *boundaries* to professional thinking as well is replaced by the "*information anatomy*" of phenomena, which opens up the boundaries. This perspective provides a common horizon for the web of public health, socio-psychological, cognitive-behavioral, psychobiological, neuroendocrine, and immunology phenomena, woven with multi-level feedback processes. This step may mean a change of approach, shifting from the Vesalian galaxy to the cybernetic paradigm of Wiener and Neumann, or the *information paradigm* of Engel's bio-psycho-social approach. Using the word 'network' involuntarily puts the phenomenon in question up as an offer for network studies. Even the model created about it is showcased in network-like graph designs where hubs are interconnected. Socio-psychoimmunology offers rich sources for the new discipline of network medicine, outlined as a new paradigm by Barabási, Gulbahce, and Loscalzo (2011).

Jorgensen (1993) is right to consider psychoimmunology to be the answer given by the 'body-soul' model's *dualism* spanning from Plato through Descartes to the present. This answer is formulated in the non-linear open system model of social, cultural, and ecological systems; the mind, the soul, and the body. Krippner (1994) talks about the postmodern reformulation of the body/soul issue, indicating an 'intercultural' rapprochement between biomedicine, humanistic psychology and behavioral medicine. In an article comparing paradigms of medical history, Levin and Solomon (1990) discuss a new discursivity concerning and re-interpretative discussion of the human body in the framework of behavioral science, which bridges science's objective body image with the empirical body complemented by a human meaning.

Kaplan (1991) discourses on the socio-psychology of the immune system when calling attention to the interaction between the four explanatory factors of dysphoric response, immune-suppressive behavior, life events and experience that constitute a burden, and vulnerability, emphasizing the significance of investigating the immune-suppressive processes between psychosocial factors and the illness process.

Cacioppo (1994), a paradigm-creating representative of socio-psychophysiology, uses the term 'social neuroscience' when comparing the immune indicators of subgroups that may be characterized by a particular response in heart frequency by investigating the role of social-emotional factors. His investigation confirmed definite correlations.

The protection of the *ego* and the *immunobiological self* is connected in adaptation processes. This is why it is possible to state that the *neuroimmune*

system, which has evolved in the course of selection mechanisms operated by evolutionary processes, has 'developed' for solving complex adaptation problems, in which the adaptive social algorithms and the solutions for adaptive problems in immunobiology show overlap and integration at the regulatory level. This is of particular importance at the level of socio-psychoimmunological phenomena. Therefore, when considering behavior to be the central concept in terms of adaptation to the environment, it is possible to talk about it as an immunological behavior. This is especially important knowing that the immune system is influenced by neurological and neuroendocrine factors that organize human behavior. The body's *neuroimmune adaptation* is a central issue of behavioral medicine, whether looking at the efforts to interpret contagious and tumor, autoimmune and allergic diseases from the perspective of personality and behavior, or thinking about the adaptive role of signals coming in from the immune periphery in organizing illness behavior.

Behavior should be interpreted in its cultural, social and communicative context, as detecting the gestures and facial expressions of the other person may already be organized into an internal, visceral response, by virtue of the psychophysiological mechanism of empathy. Naturally, all this is subject to the learning processes taking place in the early stages of the mother–child relationship, which adds value by imprinting. That is why it is no surprise that damage to early bonding is also in the focus of epidemiologic investigations by behavioral medicine.

The aspect of socio-psychoimmunological interpretation is conspicuous also in animal experiments based on ethology and sociobiology, when looking at the disturbance in bonding between the mother and the offspring and the joint immunology variables of animal behavior, and also when the goal is to investigate immune indicators that accompany the position in the pecking order or changing amidst behavior shown in the given animal population in response to an intruder.

Looking at important variables of human psychoimmunological investigations, such as social support, control, ego strength, inhibited power motivation, dominance or submissivity, high-score life events, or divorce, grief, retirement or loss of job experienced as a stressor; or learned helplessness, a state of depression or loneliness – there is no need to explain why an emphatic extension of the scope of interpretation – with the name *socio-psychoimmunology* – is justified.

Therefore, socio-psychoimmunology is a discipline partly associated with social neuroscience, which strives to understand the biological aspects of social processes and social behavior. Applying the network metaphor, the hubs connecting the different levels of movement fit a two-way (downward/upward) causal network of connections on these social, psychological, neuroendocrine, and immunology networks that is perpendicular to those networks and which

ensures information transfers and paths, regulated and chaotic flows of signals between systems, from the cultural-spiritual level to the genetic, molecular networks. This is how beliefs, morals, emotions, behaviors, psychophysiological reactions, and epigenetic events become components of a common network of happenings.

Humans are social beings, rather than a species of lone individuals, in terms of human ethology heritage, too. The social structures, mother–child relations, relationships and group relationships, families, small and large groups that have risen from the fabric of human existence, and even culture and civilization themselves all developed together with the fixation or suppression of neurological and endocrine mechanisms and patterns. Social existence has influenced the survival or destruction of these patterns. The concept of social psychophysiology as a discipline emerged in the late '80s, concurrently with the completion of the first draft of this paper, indicating an interdisciplinary turn at the age.

According to Cacioppo (2015): "the field of social neurosciences represents a new paradigm that embraces animal as well as human studies, patient as well as nonpatient studies, computational as well as empirical analyses and neural as well as behavioral research." If so, why do we talk about social and cultural psychoimmunology? He offers an answer, too: "Humans are a highly symbolic, meaning-making species and our social environment contributed to the development and expansion of our cognitive capacities."

Social neuroscience implies evolutionary and ecological perspectives, even if the biological focus makes it difficult to integrate complex cultural and social considerations. The niche construction based neo-evolutionary framework might help to bridge these different frames of understanding based on the coevolutionary reciprocity of socio-cultural changes and evolution. The four-dimensional concept of evolution based on interrelationships of genetic, epigenetic, behavioral and symbolic inheritance systems (Jablonka and Lamb, 2005) supports the tetrahedron M-E-O model with its natural (genetic), behavioral and social (epigenetic), cultural (symbolic inheritance) and technological (influencing all inheritance systems) dimensions. This multidimensional inheritance and selection dynamics are based on several conceptual paradigms, like the problem of information flow, transfer and reception, storage and processing (Aspray, 1985), the cognitive framework, the insights to internal neural network representations of social environment, the understanding of learning and conditioning phenomena; and they also helped connect the social and the cultural, bridging the gap. All of these help to adapt the network paradigm to the efforts of social and cultural neuroscience, which might be redefined with the words of Harmon-Jones and Winkielman (2008) as

> an integrative field that examines how nervous, endocrine and immune systems are involved in socio-cultural processes. Social neuroscience is nondualist in its view of humans, yet it is also non-reductionist and emphasizes the importance of understanding how the brain and body influence social processes as well as show how social processes influence the brain and body. In other words, social neuroscience is a comprehensive attempt to understand mechanisms that underlie social behavior by combining biological and social approaches.

Embodied social experience

Social structures have a considerable impact on the embodiment of reality, our emotional patterns responsible for psychosomatic events, the functioning of the brain and the body. These social factors influence the interweaving of neuroendocrine, immune, and metabolic processes.

This internal unity is also reflected in the context of socioneurology by the image formulated by László Németh in the past century:

> These three organs make up one unit; the vegetative nervous system is the front of personality turning inwards, and the mind is its front turned outwards. They are stimulated and harmonized by internal secretion. These three organs, interwoven manifold between them, govern the body.

This internal world is permeated by the adaptive (and maladaptive) programs of socio-psychophysiology that have been fixed in the course of evolution, dynamizing it or possibly whisking it into traps in the course of life. This is foreign to clinical thinking, as mainstream science has considered social and biological explanations to be incompatible for a long time over the course of the 20th century. However, social-psychophysiology considers the connections and complementarity between social and biological levels of an organization to be confirmed, where the multi-level joint analysis of the molecular, cellular, organ and body levels, personal, social and societal systems allows for a socio-psychoimmunology interpretation. This multi-level analysis requires tools from social studies, behavior research, sociopsychology, cognitive psychology and neuropsychology, which help to understand processes together with investigations into the immune system.

The neurobiological investigations and image analysis of cerebral processes, functional MRI, positron emission tomography (PET) have provided new means of research. Simpler techniques, such as measuring skin resistance or the electromyography of mimic muscles, which can paint a partial image of psychoimmunology events together with the immune processes investigated, can also assist in exploring the immunologic consequences of socio-psychological processes.

Given that the correlations underlying socio-psychoimmunological events are often rooted in ethology, experiments with animals are also very useful.

Socio-psychoimmunology has become a key issue in behavioral sciences with public health significance due to its socially embedded nature and socio-psychological features. In fact, we need to attempt to define new categories in the behavioral science interpretation of immunological processes.

The success of biocultural adaptation is measured by the *effectiveness of neuroimmune adaptation* in a broad range of diseases (tumor, contagious, allergic, and autoimmune conditions). Socio-psychoimmunology scrutinizes this human ecology phenomenon spanning system levels of the bio-psycho-social systems, which is why the *theory of socio-psychoimmunology may be deemed to be a model that explains human ecology as well as medical anthropology.* It is an ecological model because socio-psychoimmunology analyzes the correlations of the social environment around the person and the internal information environment. The networked ecological connections between the cognitive-behavioral phenomena characteristic of the person that are subject to the person's condition, the integrated psycho-neuroimmune communication and regulatory processes of the inner world, and the physical, chemical, energy, microbiology aspects of the natural environment and the body's own cells and tissues are investigated together.

As psychobiological processes are organized in a social, emotional-cognitive space, the behavioral medicine interpretation of adaptation processes occurring at different levels, i.e. at cell level, between organs on a neuroimmune basis, and also of cognitive-psychological and socio-psychological adaptation processes at the level of socio-psychoimmunological basis offers supplementary therapeutic opportunities for the immune-pathological disease.

Socio-psychoimmunology is also sensitive to the messages of ethological and socio-biological patterns outlined by experiments conducted with animals, as these processes can be unveiled at the depths of human behavior as well. Having regard to the human ecological view of nature given by stress processes and bio-social adaptation, and the complexity of the underlying zoosemiotic heritage and socio-semiotic processes sensitive to meaning, this kind of sensitivity is a necessity in everyday medical practice as well.

The events of socio-psychoimmunology, life events, mental patterns, the logic of responses stemming from personality, the experience, and the bodily consequences of all these appear in the chain of responses under scrutiny as a text to be decoded, offering the basis for the approach of narrative medicine.

To start off, let us match life situations with a social context, personality patterns, and response modes and emotions with their PNI consequences in the spirit of correlations known from socio-psychoimmunology. Cultural framework is an important extension of this sociosomatic approach.

Blurring the barriers

Information builds formations. Long-lasting information pathways are generating stable structural relations in an emerging complex system. This progress in complexity has also been a primary focus of anthropology since Herbert Spencer, but understanding the ways of formation, stabilization, and incorporation of the adaptive information pathways is still somewhat enigmatic. How competing actors turn to cooperate in symbiotic ways and how their replication becomes synchronized is a real enigma of the evolution both at chemical, cellular, and social level is. Lynn Margulis (1991) analyzed how multicellular organisms might have emerged from a long-lasting association of different cells. Even our somatic cells are co-replicating a mix of a eucaryote and a procaryote organism (mitochondrion) with different DNA and RNA. Our plasma saved the salty composition of the seas of the evolutionary past that the ancient cells had to adapt to.

Biocultural adaptation as an ecological core problem of medical anthropology creates such a structuring role in frames of information flow. The natural and physiological dimensions (*ecological framework, stress paradigm, pain, nocebo and placebo issues, psychophysiology of healing communication and symbolic healing etc.*), just as the social dimension (*medical system, social stratifications and inequalities, roles, institutions, policies, economic and political power, social suffering, etc.*), and the infospherical layer *(cosmologies, beliefs, discourses, cognitive-behavioral elements, narratives, expectations, etc.*) might be translated into the paradigm of information flow creating patterns and structures.

This structure-forming dynamism of information flow is the core problem of Latour's Actor Network Theory (1996), too, which implies the observation of the constantly shifting networks of relationships between human and laboratory equipment, objects and other factors. ANT has an information-based network framework, where nothing observable exists outside those relationships. All the factors involved in a social situation are on the same level, and thus there are no external social forces beyond what and how the network participants interact at present. For an anthropologist, this enforces the four-dimensional (technospherical, infospherical, natural and social) vision and understanding of the cultural phenomena. This way, ideas, processes, artifacts and any other relevant factors are seen as organic in creating social situations as humans. ANT holds that social forces do not exist (alone) in themselves, and therefore cannot be used to explain social phenomena without the capacity of non-human, environmental actors, and participants in these networks. These blurred borders help to reorganize and map the relations of things, signs, and humans, creating a particular material-semiotic approach. Latour defines the connections between his resources in a similar way as the M-E-O theory does in the tetrahedron framework: natural and technospherical, social, and infospherical contexts.

> Three resources have been developed over the ages to deal with agency. The first one is to attribute to them naturality, and to link them with nature. The second one is to grant them sociality, and to tie them to the social fabric. The third one is to consider them as a semiotic construction, and to relate agency with building of meaning. The originality of science studies comes from the impossibility of clearly differentiating between these three resources. Microbes, neutrinos of DNA are at the same time natural, social and discourse. They are real, human, and semiotic entities in the same breath. (Latour, 1996)

Latour considers the modernist separation of the human and the natural or non-human side rooting in the scientific revolutions of the seventeenth century and regards it as a culture-bound, particular organization of the world that separates Nature and Culture into two distinct ontologies. In Latour's paradigmatic criticism, modernity categorizes the world according to a binary that sorts humans from non-humans, subjects from objects in a purifying manner. In this framework, the social is the result of the associations or links that bind together scientific, political, cultural, economic, and other practices. This way, technology, nature (as the observed object of the scientist), discourses, metaphysics, taxonomies as mixed social products, and personal contributions together create the hybrid, generating new knowledge of the given reality.

This fluid, ever-changing dynamism of generating transient chimeras of technological artifacts, discourse patterns, mental maps, interpersonal cooperations, and natural constructions-reconstructions, re(invented) memetic patterns leads to new technologies, and new cyborg hybrids as well. This net of reality is woven from the threads of significance, as Geertz emphasizes, and generates a web of meaning. In human–non-human hybridization, we can explore a network "anatomy" and an information/sign flow-based "physiology", figured through metaphors of nodes and loops. Knowledge and the social-cultural environment are generated by a continuous chimeric reconfiguration of human–non-human hybrids of technology, knowledge bases, monetary and military interests, legitimizing discourses, and evidence-based data control.

This dynamism might be revealed in different ways, as we can read in Deleuze and Guattari. The "physiological" patterns of these chimeroid co-relationships between human and non-human arrangements might be presented as transient, unstable assemblages, where assemblage consists of "things" or pieces of "things" gathered into a single context. Deleuze and Guattari (1987) conceive assemblages as products of dynamic features, and relational routes, lines and measurable speeds via "ceaselessly established connections between semiotic chains, organizations of power, and circumstances relative to the arts, sciences, and social struggles", where the constitutive elements are continuously replaced through innovations and sometimes via paradigm shifts.

The way, how information becomes formation, is how unstable assemblages develop into more or less fixed, co-replicating structures. Patterns of biocultural adaptation, "crystallized" and ritualized beliefs, customs and habits, and social-scientifically stabilized protocols of healing are phenomena "in-between", social, infospherical, technological gestalts: "socorgs", "technorgs", "inforgs", "natorgs": in four-dimensional extension of cyborg anthropology.

The M-E-O model (1994) and the ANT (Actor Network Theory) in the 1980s created by Callon, Latour and Law (in Muniesa, 2015) and Latour's "hybrid" concept (1996) show converging elements, with a common conclusion, that modernist nature/culture dualism is no longer an appropriate framework to describe our reality.

However, the M-E-O model was inspired not by Latour and Callon, or the postmodernist Guattari, but by system-based medical anthropology, Benjamin Paul, Edward Wellin, and the ecological economists: Ekins and Boulding.

The Latourian approach suits to the medical anthropological understanding of human biocultural agency regarding to health, illness and healing in sociocultural context. The growth and structure of knowledge could be analyzed and interpreted through the interactions of actors and networks. Actants denote human and non-human actors in a network set of relations based on their functional relevance. One might map the relations that are simultaneously material (between things) and infospherical (as concepts in semiotic terms). ANT assumes that many relationships are both material and semiotic. The clusters of actors involved in creating meaning are both material and semiotic.

On the other side, the application of ecology in medical and health matters rests upon the close interrelatedness described above. If we start from the simplest "textbook" definition, ecology examines the interactions between populations and their biological-physical environment. According to Lieban, disease reflects failure of adaptation, while healing and health is an index of successful biocultural adaptation. More specifically, the understanding of individual diseases and their healing can be incorporated into an ecological model, by their nature. Wellin's model assumes that changes in (infospherical, social, technological, and natural) environmental factors cause changes in many characteristics of populations and individuals. All of these relevant environmental impacts are displayed; thus, in principle, it is noticeable and can be registered. Medical ecology has a very well-crafted model and methodological tool, thanks to the excellent summary work of medical anthropologists in this field, such as McElroy and Townsend (2019). However, according to critics of the medical ecology paradigm, the model overly underestimates the role of political ecology. Political ecology, as opposed to cultural and biological ecology, examines the role of historical interactions between human groups. True or not, criticism of classical medical ecology might be extended

in the four-dimensional way, explored above. The complexity of this is illustrated by Lázár's (2001) Man-Environment-Organism (M-E-O) model (see *Figure 3*).

The objective of the model is to represent the eco-values along with the four most important environmental systems: (1) the natural environment, (2) the sociosphere, (3) the technosphere, and (4) the infosphere. The network of the four systems is visualized with a tetrahedron representation. The four environmental systems are posited to the peaks of the tetrahedron and the individual and social communities at the center form the final "people-centered spherical model". With regard to the dual nature of the M-E-O model, one might realize that our internal environment is built along similar environmental systems as the external environment, i.e., that "the internal world is infused with energy, material and information flows in the same way as external ecosystems". This recognition also provides an excellent link between understanding several behavioral and medical psychology problems.

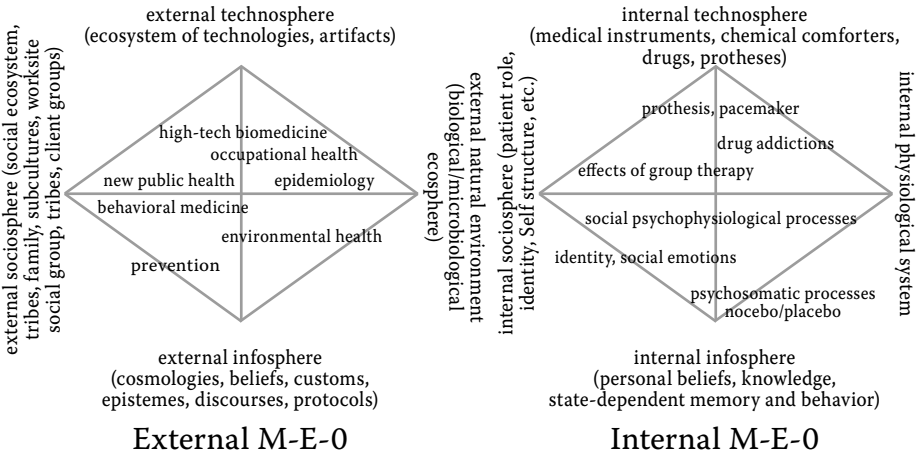


Figure 3. The double ecoscape of M-E-O (Lázár, 2001)

As we have seen, the theoretical systems of the above four bio-cultural approaches to medical anthropology differ in several ways, nevertheless, they share the use of the concept of bio-cultural evolution, the concept of adaptation–maladaptation, and the role of social organisms. Perhaps the most ecological representation of the notion: "everything is related" is the spherical topology of the relationships, and it only seems to be a symbolizing game if we rectify this sphere, transforming it into a human ecological tetrahedron-like relationship system, as described above (Lázár, 2001). This can dissolve and transform the so-called "nature–nurture" conflict and divide it into a natural and sociocultural environment, as a tetrahedron of ecologically connected natural, social, technological and knowledge environments.

The "rectification" of "spherical" ecological and ecodynamic conditions in this way is not a self-serving game. It creates a four-vector environmental space that provides a means of orientation and framework for the cultural anthropological interpretation of all human phenomena, since all phenomena, be they a matter of use, complicated discourse or healing practice, have a natural, social, technological and knowledge aspect at the same time. Thus, this four-vector, four-dimensional relationship model and event space seeks to visualize the dynamics of coexistence by offering a schematic "co-ontology".

Cultural anthropologies: human ecology in a network framework

From the very early steps of cultural anthropology, culture was interpreted as a complex and holistic entity, a comprehensive totality implying an enumeration of aspects of the cultural content of several kinds. Tylor (1958 [1871]) called it a *complex whole,* which includes "knowledge, belief, art, law, morals, custom, and any other capabilities and habits acquired by man as a member of society." He articulated an implicit system concept with this definition, and this implicit system concept includes pathways, dynamic interrelationships, and the mutual influence of different human ecological layers surrounding the human being.

Tylor's unilinear evolutionism followed a "one-way progress" perspective. The cultural relativist turn of Boas (1930) kept culture also in its *social behavioral-cognitive* and *communicative* frame. But one could reveal a new element in his particularist approach: *products* generated by the habits themselves were thought to be influencing the culture's objects. Contemporaries of Tylor and Boas were not blind to artifacts, objects, technology even economy and exchange, at all. One can mention the archaeologist Pitt Rivers with his large collections of artifacts, or Richard Thurnwald and Marcell Mauss, and others too. However, it took decades for technology and the sphere of objects, artifacts, machinery, and know-hows to gain equal rights in cultural anthropological interest and imagination.

From the beginning, social anthropology was based on the assumption that social "superorganism" has its power and dominance over the individuum, as stressed by Radcliffe-Brown and Kroeber. The socio-centered culture concept was expressed by Ward (1903) by these words: "A culture is a social structure, a social organism if anyone prefers, and ideas are its germs."

The radical turn of the first epoch of anthropology was enforced by biopsychological functionalism of Bronislaw Malinowski (1944), who made a further step towards that multidimensional view of culture, including motives, drives, needs, satisfactions and a dynamic interference with the surrounding environment for the sake of survival. He extended the cultural intellectual, moral, and

belief-oriented biases towards social structure, crafts, and goods. Malinowski drew plus two dimensions beyond the classic meaning of culture, the technospherical, and the sociospherical.

Even the holism of Ruth Benedict gained a social, behaviorally reductive frame in her pattern concept. It was the neo-evolutionist turn of Leslie White and Julian Steward that shed more light on technological adaptation to environmental challenges and natural environmental pressures humans had to face. Their new foci, natural determinism and technological possibilism, generated a modified view of culture as an adaptive environmental game player. In the 40s, culture could not be understood anymore without technology. Kluckhohn and Kelly stressed the importance of the cognitive-behavioral features of culture with environmental accents. Early, in the Twentieth Century, social and-cultural anthropology arrived in the "bay" of biocultural adaptation paradigm, not very far from Malinowski's biopsychological functionalism and the structural-functionalism of Radcliffe-Brown.

The technology or technosphere as a determining factor was mentioned by the particularists without explicit evolutionary framing, nevertheless, even these early insights represented such proto-ecological statements, where technological surroundings are "that part of the environment which man has himself created and to which he must adjust himself" (Willey 1927). Folsom (1928) dissociated human and his/her technology, emphasizing: "Culture is not any part of man or his inborn equipment. It is the sum total of all that man has produced: tools, symbols, most organizations, common activities, attitudes, and beliefs". In Marxist anthropology, the totality of all social phenomena in their interrelation is not the result of culture, but the mode of production, with its two important sub-concepts, the forces of production and the social relations of production.

Leslie White, the neo-evolutionist anthropologist, clearly articulated the multidimensional character of the culture, differentiating the technological, social organizational, and ideological spheres from each other. White emphasized the determining role of technology, which depends on its effectiveness and volume of "harnessing" and the transformation of energy. Similarly to Julian Steward and Leslie White, Marvin Harris also defined culture as superstructure based on technology and economic adaptation following Marx's categories, but his approach lent crucial importance to demographic dynamics in sociocultural evolution.

Shifting from Technosphere to the natural environment, we slightly move from possibilism to determinism. Cultural ecology is the study of human adaptations to social and physical environments. Human adaptation refers to both biological and cultural processes that enable a population to survive and reproduce within a given or changing environment. Environmental determinism, also known as *climatic determinism* or *geographical determinism*, was

based on the view that the physical environment sets limits on the human environment. Julian Steward was one who interpreted the patterns of human behavior/culture associated with using the environment and assessing behavior that influences the belief system and other parts of the cultural complex. The diverse environmental challenges let Steward draw a picture of "multilinear" cultural evolution based on the various ways of adapting to different environments. Steward considered technology and economics as decisive factors determining the development of a given culture, and political systems, ideologies, and religions were understood as secondary products in an evolutionary frame, Steward also stressed the importance of ecosystems and physical environments influencing cultures. Turning to the dynamic unity of the adaptive game of culture and its environment, ecological anthropology became "study of cultural adaptations to environments" or "the study of relationships between a population of humans and their biophysical environment." Roy Rappaport (1999) explored the relationship between culture and the natural environment as expressed by rituals in the processual relationship between the two.

If we bring the sociosphere in front, we will find a different perspective again. *Social Anthropology* itself studies social structures and organization, customs, economic and political organization, law, patterns of production, exchange, and consumption, family structure, and kinship, child-rearing and socialization. The above-mentioned *Structural functionalism* is a way of understanding society as a system where social structures shape society as a whole. It explores social structures and social functions embodied in customs, roles, institutions, and rules and traditions. *Symbolic interactionism* offers social context to perceived reality developed by interaction with others. Even physical reality does exist by an individual's social definitions, and that social definitions do develop in part or relation to something "real." Culture and behavior are defined by a reflective, socially understood meaning, people respond to reality via the social understanding of reality.

The infosphere remained continuously the most intimate and pervasive content and environment of human being immersed in the culture all along with the history of social and cultural anthropology. From Tylor to Geertz, from Ruth Benedict to Mary Douglas, symbols, ideas, significations, rules, and customs needed detailed representations, thick descriptions and emic sensitivity and humble attention. The infospherical human is "an animal suspended in webs of significance he has spun." *Symbolic and interpretive anthropology* is the study of cultural symbols and how those symbols can be interpreted to understand a particular society better. *Interpretive anthropology* is concerned with the operations of "culture" rather than how symbols operate in the social process. *Symbolic anthropology* is concerned with the operations of "society"

and how symbols operate within it, and studies symbols and the means, such as myth and ritual, by which humans assign meanings to these symbols to address fundamental questions about human social life. *Structural anthropology* is based on Claude Lévi-Strauss' idea that people think about the world in (neurophysiologically based, universal) terms of binary opposites: high and low, inside and outside, person and animal, life and death. This way, every culture was supposed to be understood in terms of these opposites. Structuralist anthropology focuses on meaning, as established by contrasts between various aspects of culture, and sees actions as being separate from the actors (Claude Lévi-Strauss, Edmund Leach, and Rodney Needham).

It seems so that these different (natural, social, technological, or infospherical) reference systems generate different anthropologies. One thing is common: they use strict borders between agent and environment, and between each other as well. One must choose a point of perspective, a point of view.

When anthropology is an object of radical ecologization, these environments are organized in one ecosystem and fused into an integrated "ecopicture". Comparing the definitions of culture reflect different foci, and common behavioral terms, like learning and performing, habits, adaptation, communication in frame of complex holistic, sometimes ritual patterns. From the definitions, there are four environmental frameworks emerging, the infospherical, the sociospherical, the technospherical and the ecological natural foci.

Table 1. Category content analysis of cultural definitions

Principal definitions	Categories	Comments
Infospherical focus		
E. B. Tylor: *"Culture … is that complex whole which includes knowledge, belief, art, law, morals, custom, and any other capabilities and habits acquired by man as a member of society."* (1958 (1871), 1)	Anthropological school with unilinear evolutionarism	Complex whole of *knowledge, belief, art, law, morals, custom, acquired habit*
F. Boas: "*Culture embraces all the manifestations of social habits of a community, the reactions of the individual as affected by the habits of the group in which he lives, and the products of human activities as determined by these habits."* (1930, 79)	Cultural relativism and historical and geographical particularism	Manifestation of *social habits*
C. Wissler: "*a culture is a definite association complex of ideas. Culture is the world sum-total of past and present cultural ideas. Culture consists of the entire stream of inactive and active cultural ideas from the first in the cosmos to the last."* (1916, 197)	Culture area approach	Complex of *ideas*

R. Benedict: *"complex whole which includes all the habits acquired by man as a member of society."* (1931, 806)	Configurationalist approach describing a culture as a personality	Complex whole of *acquired habits*
C. Osgood: *"Culture consists of all ideas concerning human beings which have been communicated to one's mind and of which one is conscious"* (1940, 25)		Complex of *communicable ideas*
C. Kluckhohn & W.H. Kelly: culture is *"a summation of all the ideas for standardized types of behavior. By culture as a descriptive concept, I mean all those mental constructs or ideas which have been learned or created after birth by an individual. . . The term idea includes such categories as attitudes, meanings, sentiments, feelings, values, goals, purposes, interests, knowledge, beliefs, relationships, associations."* (1945, 97.)	Values Orientation Theory	Summation of ideas (*attitudes, meanings, sentiments, feelings, values, goals, purposes, interests, knowledge, beliefs)* governing behavior
C. Geertz: Culture is a complex assemblage of texts that constitutes a web of meaning. (1984)	Symbolic anthropology, Interpretive anthropology	Interpretive view of culture
Technospherical focus		
B. Malinowski: *"the integral whole consisting of implements and consumers' goods, of constitutional charters for the various social groupings, of human ideas and crafts, beliefs and customs"* (1944, 31)	Economic anthropology, biopsycholo gical functionalism	Emphasis on the *material: goods, crafts, consuming*
C. Kluckhohn & W.H. Kelly defined *culture as a complex whole which includes artifacts, beliefs, art, all the other habits acquired by man as a member of society, and all products of human activity as determined by these habits*. (1945)		Emphasis on the *material: artifacts, products*
C.A. Ellwood: *"culture includes the whole of man's material civilization, tools, weapons, clothing, shelter, machines, and even systems of industry; and, on the other hand all of nonmaterial, or spiritual civilization, such as language, literature, art, religion, ritual, morality, law, and government* (1927)	Sociology of cultural evolution	Emphasis on the *material: tools, weapons, clothing, shelter, machines*
J. Folsom: *"culture is the sum total of all that is artificial. It is the complete outfit of tools, and habits of living, which are invented by man and then passed on from one generation to another." It is the sum total of all that man has produced: tools, symbols, most organizations, common activities, attitudes, and beliefs.* (1928, 15)	Social economics	Cultural *as artificial* and *productional,* complete outfit of tools

Natural focus		
J. Steward: In a multilinear evolutionary frame, the variation of cultures is expressed in the complexity of social organizations as being limited to within a range of possibilities by the environment	Cultural ecology	Environmental *determinism and possibilism*
M. Harris: Culture is based on the simple premise that human social life is a response to the practical problems of earthly existence.	Cultural materialism	Social life is *adaptation to earthly constraints*
R. Rappaport: The adaptive value of different cultural forms depends on maintaining the pre-existing relationship of a population with their environment. (1999)	Ecological anthropology	Culture as *adaptation to the environment*
Sociospherical focus		
H. Spencer: explored the holistic nature of society as a social organism.	Unilinear evolutionarism	Sociosphere as organism
A. Kroeber: uses the term superorganism for the society		Sociosphere as superorganism
B. Malinowski: *"the integral whole consisting of implements and consumers' goods, of constitutional charters for the various social groupings, of human ideas and crafts, beliefs and customs"* (1944, 31)	Biopsychological functionalism Holistic ideational, social, material	Integrity of sociospherical, infospherical, technospherical
A.R. Radcliffe-Brown: Social anthropology formulates and validates conditions of existence of social systems and observable regularities of social change.	Structural functionalism social dynamism	Sociospherical Technospherical Infospherical

The four environmental dimensions, or the four surrounding game players of ecological challenges and adaptive means, emerged together: nature, sociosphere, technosphere and the infosphere and were thought to be alone the culture itself for a long while.

Each of the four dimensions has its own anthropological discourse: nature feeds physical anthropology and environmental/ecological anthropology, technosphere offers frames for cyborg anthropology, economic and other applied anthropologies including technological issues. The infospherical orientation helped the revival of interpretive and symbolical anthropology as pure culturalist paradigms, leading to strong debates with cultural materialist or other naturalist anthropological discourses.

Anthropology, presented as a biocultural science, is a scandal to the culturalists, and foolishness to the structuralists. It hurts particularist relativism with its biological norms and standards and overwrites social constructivism with its naturalism. Medical anthropology creates a balance between naturalism

and culturalism, and the study of biocultural adaptation transforms anthropology into almost a natural science. However, medical anthropology is the most effective way to approximate and approach the "quintessential" fifth environment surrounding the other four, the Transcendent or Supernatural. It opens up the gates of the fifth sphere, leading fieldworks among faith healers, sorcerers, shamans, and clairvoyants, exploring the supernatural along with the study of healing agencies.

It opens up territorial and methodological issues creating grids and borders, too. There are also grids inside of medical anthropology based on its diverse disciplinary gravitation from the beginning.

Medical anthropology had a long gestation period, when its central themes, illness causation, cultural epistemes of health and illness, illness and sanction, voodoo death, shamanism, witchcraft and sorcery, rituals and alike, where investigated and depicted in ethnographies by cultural anthropologists.

But in this covered period, the early contributions of Rivers, Clements, Ackerknecht, Hallowell, or those contributing to particular fields like the anthropology of body or the nocebo. Such examples are the exploration of Azande sorcery and ritual healing by Evans-Pritchard or the narratives about voodoo death of Claude Lévi-Strauss in his *Tristes Tropiques*. The researchers among Eurasian shamans also gathered rich material, and the history of medicine and ethnomedicine also played an essential role in creating the paradigm of medical anthropology. These researchers developed the broad and firm basis of the later mature medical anthropology with a shared hidden *focus on adaptation*.

Rivers' magical, religious, and experience-based naturalist /scientific/ medical paradigms reflect different ecological adaptational strategies in his paradigmatic work "*Medicine, Magic and Religion* (Rivers, 1924). Rivers understood the native healing customs as adaptations, where the dependent variable was the observed or reported behavior, and the independent causal variable was the above-mentioned adaptive framework, the group's "attitude toward the world" determined by the underlying cosmological assumptions. Healing is a way of adaptation, that is why Clements, who explored the geographical diffusion of cultural traits like causal explanations of illness, was exploring biocultural adaptation, too. The other forefather of medical anthropology, Ackerknecht, also followed ecological logic when immersing medical belief and behavior in the cultural whole with functional interrelatedness, just like Benjamin Paul. The latter set up a system-based approach for understanding the cultural logic of medical practice. Wellin's concept of the medical system *(Figure 4)* demonstrated ecological and a system like interrelatedness of infospherical, technological, social, and natural compartments of the medical system in biocultural adaptation.

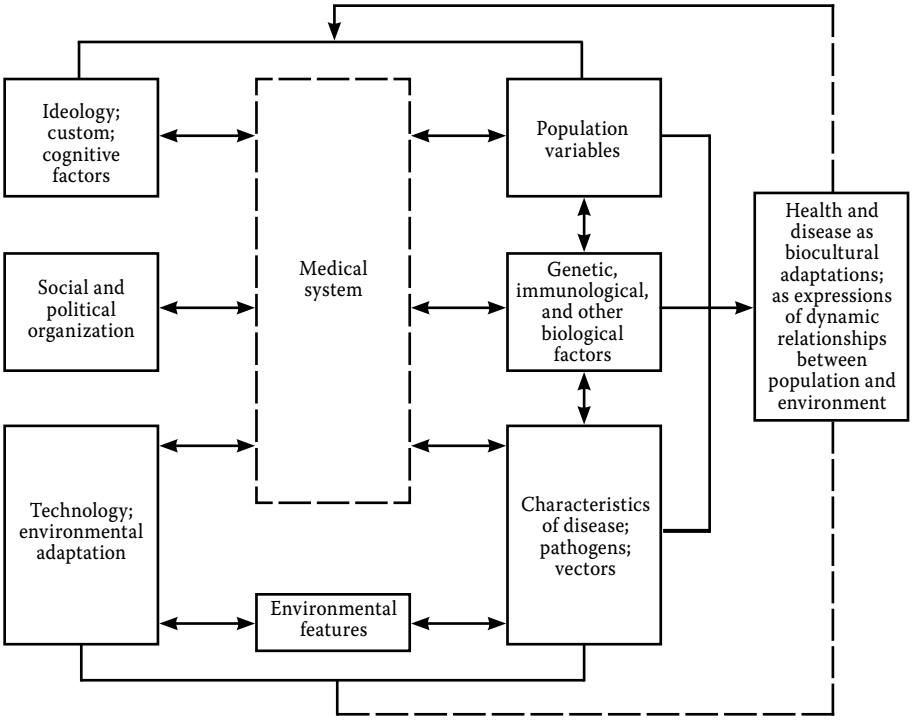


Figure 4. Ecological model with cultural and biological parameters (Wellin 1977)

This way, medical anthropology transcends the natural, social, and technological gravitation of its orientation and fuses it in a frame of a system-like unity, as Wellin's ecological model of the medical system presents.

The eco-logic of medical anthropology is based on the extension and evolution of the meaning of culture uncovered above, the development of system-oriented thinking, the emerging idea of adaptation and environmental dynamics, ecological interrelationships which became the central idea of the fifties, at the birth of medical anthropology represented by Paul Benjamin, Edward Wellin, George M. Foster and Alexander Alland.

Foster proved the importance of qualitative analysis in understanding the culture of health and illness, where anthropology, being more interested in cultural phenomena, is a complementary and not competitive science to medical sociology, which has a deeper interest in social structural aspects of healing.

Medical anthropology is not a pure culturalist counterpart of the quantitative medical sociology, as a qualitative social science, as it has two other surplus dimensions. It incorporates bioecological, physiological and psychological knowledge, and the medical humanities.

Medical anthropology has a unique, inherent epistemological tension. As social and cultural anthropology is suspicious of normality because of its particularism and cultural relativism, the biocultural paradigm transcends this culture-boundedness with its objectivism and natural standards. On the other hand, its inherent particularism pluralizes the key cultural categories of health, illness, and healing derived from different basic cosmological assumptions. Finally, medical anthropology might fuse and integrate the biological sciences, the social sciences, and the humanities.

Medical anthropology is part of cultural anthropology, also known as a branch of applied anthropologies. However, it might cover all branches and philosophies of cultural anthropology, plus it is also a bridge between cultural and social anthropology and physical anthropology.

After its "disciplinary birth" in the fifties, its routes were diverted into ecological, ethnomedical-ethnographical, clinically applied, and critical medical anthropological frameworks, or with other words: technological, natural, infospherical, and social-political directions. Following the four-dimensional logic, we can list the infospherical, technospherical, sociospherical, and eco-natural dimensions of medical anthropological thematization, categories and representations, as shown below in the next *Figure*.

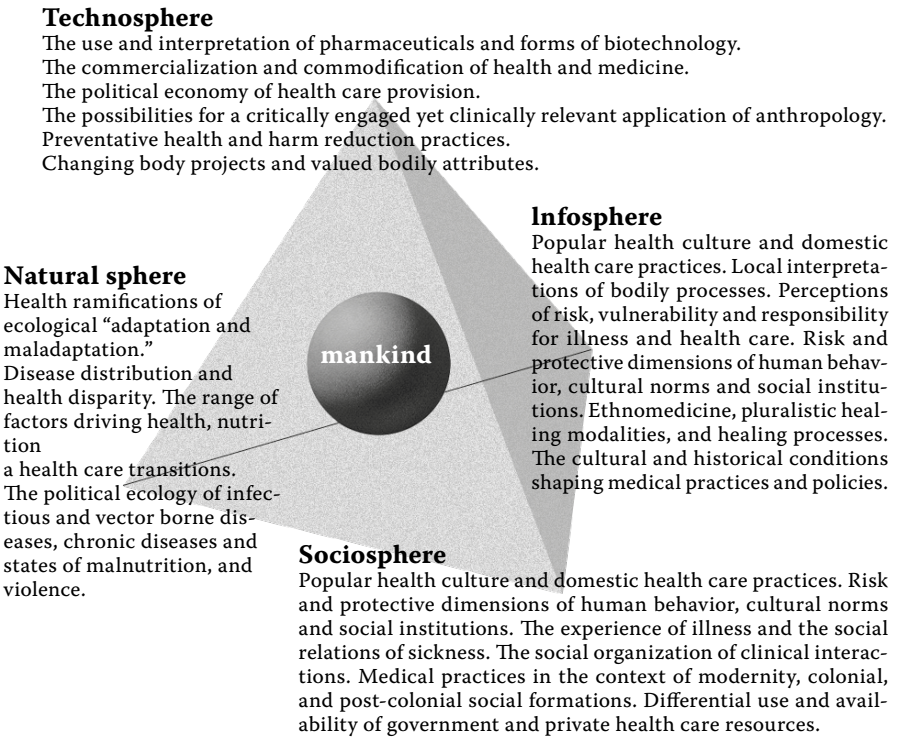


Figure 5. Tetrahedron model of medical anthropological issues

Human ecology of an extended attachment theory in the M-E-O model

The empathic attitude towards nature, social, or ideological patterns depends on personality traits. The panrelational ecodynamic M-E-O model includes the interwoven niches of natural, social, technological and infospherical environments of the human actor and its communities. The implication of attachment theory in the M-E-O model might help to elucidate the psychological background of insensitivity and detaching drives, which make people insensitive towards the values, interests or sustainability of natural, social or intellectual surroundings. Creating links between the hostile, competitive dynamics of the late modern economic habitus and the developmental psychology of A type behavior connected to anxious, avoidant secondary attachment organization offers a common human ecological framework, which helps us to apply Angyal's concept of homonomy/autonomy in understanding place of human attitude in environmental sustainability.

The human-object hybrid concepts (hybrids and/or rhizomes) of Latour and Deleuze offer a special perspective for human ecological application of attachment theory in frame of reference of environmental sustainability of all kinds: social, infospherical, technospherical and natural. Hybridization, the transient or enduring tight relationship of interactive human-non-human complexes might be framed in terms of actor-environment bonds, in frame of psychological attunement, commitment, intensive mutual agency in context of extended understanding of adult attachment. The empathic attitude towards nature, social, or ideological patterns creates a deeply embodied and lived connection with the Significant Other, be they Homeland, cultivated or wild natural environment, intellectual tradition or even a technospherical "organism", equipment, software, technosystem, medical instruments and alike.

On the other hand, the inability of bonding, the alienation and traumatic detachment generate critical difficulties in social, organizational or professional life and the environmental affairs. Detachment and disconnection of the natural, social, technological and infospherical environments from each other for a longer period leads to unsustainability, as well.

Human agency in this extended human ecological context is strongly shaped by personality, attitudes and habitus governed by the so-called "Internal Working Model" (IWM) as a result of early social learning generating human ecological dispositions towards the natural, social and cultural environment. In the period of human imprinting, a baby is seeking a Significant Other, later to become a decisive part of the cognitive-emotional attachment system, which "attachment drive" might find its target beyond interpersonal dimensions in the objects of natural, social or abstract infospherical environments. Bowlby

called this the internal working model representing early social experience, the emotional arousal that influences the development of interpersonal relationships, perceptions and expectations. The IWM may also be shaped or distorted by natural conditions, technological milieu and rituals and belief system shaping maternal behavior and child rearing, as economic, sociopolitical and ecological factors are seen as constantly forcing shifts in interpersonal dynamics at the level of culture and family which in turn are bound to cause variations in internal working models.

The IWM is formed in the so-called attachment organization. This attachment organization, which may be viewed as a symbiotic transactional psychophysiological and behavioral homeostatic ring of mother and child in the first year establishing a source of security (or stressful insecurity in case of "bad-enough" mothering).

The attachment organization is an early determinant of two basic human ecological features: the personal, social "habitus" framed in the concept of IWM (internal working model) and the internal psychophysiological pattern of stress response.

Maternal behavior may provide security (which is sensitive, accepting, cooperative and always accessible). A mother who refuses such security to the child is described as being inconsistent, lacking response or showing refusal. The abusive, insensitive or negligent mothering might cause anxious, avoidant secondary attachment organization, where baby diminishes empathy towards mother, detaching himself or herself from the mother. Babies compensate for the insecurity of this relationship in two ways, according to Ainsworth and Mary Main. One way is the A-type secondary attachment, the anxious-avoidant secondary attachment organization, when the baby becomes relatively independent. If the baby suffers from uncertainty, nevertheless, evoking the attention of the mother, who compensates him/her for the transient insensitivity, an anxious/ambivalent pattern of attachment might emerge. This is the so-called C type secondary attachment. In this case, the baby develops an anxious attachment, high physiological arousal, inhibited aggression and low self-esteem. Children handicapped by insecure attachments are characterized by low self-esteem, low-motivation and performance, problems in social adjustment, and a weak sense of danger, which are all integrated parts of cultural behavior.

The different attachment organizations may be seen as metaphoric patterns of ecologic behavior of independence/dominance (a dominant feature of A type personality), harmonic optimization and on the other pole, submissive anxiety and worry (a dominant feature of C type personality). In frame of human ecological reference, the IWM formed in the given attachment organization works as human ecological cognitive schema, as a long term, enduring

psychological structure, mode of processing and organizing information, including affects that provide templates that guide and direct an individual's interactions in the interpersonal and impersonal world.

Hazan and Shaver constructed an analogous typology for Adult Attachment styles as well, with the following categories: secure, dismissive-avoidant (as in A type) anxious-preoccupied (as in C type), and one additional: fearful-avoidant. These roughly correspond to infant classifications: secure, insecure-ambivalent, insecure-avoidant and disorganized/disoriented. That is why we found it very striking to see an extremely high rate of the avoidant tendency (above 58%) of dismissive-avoidant (37.9%) and fearful avoidants (20.4%) together, while we found low, only 31.4% secure attachment of the informants based on the questions of the Adult Attachment Survey of Bartholomew in the Hungarostudy 2013 Survey (Csóka, Lázár, 2013). In the M-E-O model, the detached, the harmonic and the preoccupied, anxious-ambivalent agency generate diverse variable logic towards the natural and sociocultural environment via a human niche constructive agency. The different, embodied attachment styles and drives generate different dynamics of hybridization, and human ecological organizations.

The harmonic strategy to optimize the relationships with the Natural, Social and Cultural environment: a balanced "tetrahedron" needs a balance of mastery and submission regarding the surrounding reality. The interaction between these attached systems generates a resource of personal energy. The polarity between the surrounding environment and the person generates a bipolar dynamism, with one force pulling the Self towards the environment and another pulling the Self towards the Ego, or in the words of Angyal: homonomy and autonomy. Autonomy is about detachment, an egocentric drive expressing the tendency of dominance or mastering the environment, by asserting oneself as a separate being. Homonomy is the opposite, 'selfless' pole of the biosphere, the embedded and attached status of the Self.

In Angyal's binary framework of autonomy versus homonomy, one can reveal a common element: both autonomy and homonomy operates through human extensions and hybridization. The Autonomic claim for control over Nature or the Social environment presses the person to apply Technological and Infospherical means strengthening its dominance over the Nature or Social as the Other. These efforts of dominance lessen empathy, altruism, harmonization and self-limitation, and creates disposition towards A type behavioral patterns, which might be a developmental consequence of A type secondary (anxious, avoidant) attachment organization. The Autonomy as basic environmental drive is a central feature of the ethics of Homo Economicus, too.

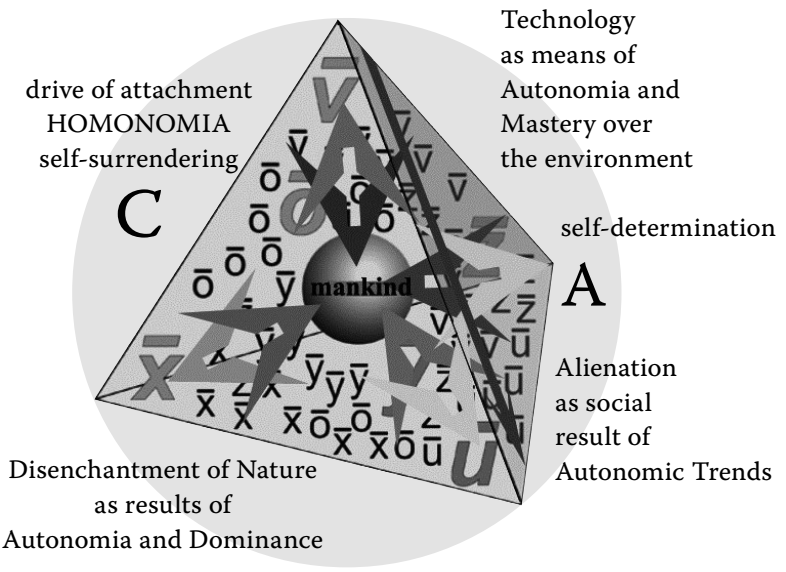


Figure 6. Angyal's homonomy and autonomy in the frame of the M-E-O model

The connection between Angyal's Autonomy and the stereotype of high-status-conscious, high-achieving employee (usually the leader), who pushes himself in the cage of deadlines and rigid time structures, hating both delays and ambivalence gains outstanding importance in the contemporary competitive business atmosphere. It is very meaningful that at the very first time of publication of ATBP, the editorial comments of Lancet (1981) called the readers' attention to the fact that the concept of Type A risk behavior could result in a "demotion" in status, in job function, in the regard of colleagues and possibly in personal income. Finally, Type A behavioral pattern has been questioned, and only its toxic component, the hostility remained in focus. The behavioral pillar of today's competitive neoliberal global (post)industrial machinery could not be stigmatized. The dominants must work – as it is expected – with the highest efficiency, and they will have the highest quality of health care. It is much harder with the C type victims, (an also fading personality concept) because they take a bigger part of social suffering, they are more sensitive, and self-repressive, and their illnesses like cancer and chronic allergic or autoimmune diseases (of course in the presence of individual biological vulnerability) are not solved.

They represent a painful version of homonomy, a self-submissive attitude towards the social environment. They are welcome too, as an affiliate, enthusiastic labor power, anxious, but inhibited in showing aggression. These considerations may play a role in that A and the C type risk personality discourse was muted under the ethical command: "not to blame the victim".

The vanished framework of A and C type behavior is also part of sustainability discourse, including the human dimension of the endangered environment.

Homonomy means attunement to the natural environment with its organic laws, dynamism and aesthetics, while autonomy against nature, gained by mechanistic ways and technology, implies simplified, engineered and technologized attunement. The same happens to the bureaucratized and secularized social environment, and we know this sort of hybridization under the term of "homo faber" and "homo economicus".

Society is not built on dyadic transactions but is organized as a jungle of interdependencies woven from mutualism and competition, and the same may be told about the relationship between the actor(s) and his/her/their environments. These technological, ideological, social or natural kinds of environments are all partners and predators at the same time, and offer means of extensions, occasional or enduring hybridization as well. They create emergent realities through creative interaction with each other and us. Their joint interactions are beyond any single entity's control, and the relevant part of the environment has an intimate relevance to the actor in its niche as a part of this holistic but nevertheless partial unit. This relationship is a mutual, circular and integral element of co-creation, which needs a permanent attunement on behalf of the adaptive agent. This environmental game is a continuous co-evolutionary process, where populations of ideas, technological artifacts, or institutionalized social discourses and collective representations may compete or cooperate with each other through the human agency, through transient or enduring human-non-human hybrids including not only artifacts but the social and discourse extensions. This way they may elevate or lower the chance of replication of the other (artifact, idea or even human) populations or cause destruction of competing niches. This happens with the natural environment in the case of techno-industrial pollution, or outdated technologies within the market race, or political models, power systems under the oppression of technological paradigm shifts (like in case of industrial and postindustrial revolutions).

The instable, open "rhizomic" view of circular influences by Deleuze and Guattari (1987) or the Latourian pathways of transient chimerization or hybridization framed in the Actor Network Theory create an open horizon for consequences. But the system logic of the emerging patterns – with its affinity to an auto-poetic and homeostatic balance stabilized by negative feedback loops between the interactive spheres – makes the M-E-O system sustainable. This homonomic view of human embeddedness is also reflected by the M-E-O tetrahedron model, but in these models the human-technological-social and infosperical hybridizations are viewed as enduring patterns resisting change.

These organized patterns of human–natural environment, artifact, discourse and social forms complexes with their circular logic of influence are embodied in subsistence patterns, forms of biocultural adaptations, cultures, social roles, professions and patterns of technologies, architecture, governing, family life, music or war, in all kinds of human agencies.

Homonomy is an existential and human ecological metaphor for harmonic bonds and attunement to the sustainable environment, while autonomy refers to a detached, and dominating attitude and drive over the environment of all kinds. The health psychological gains and pressure for personal perception of control and mastery must be kept in mind, when the personal psychological development, lays on the unconscious basis of early social experience. The view of these transient human–nonhuman organizations creates a fluid, dynamic, ever-changing frame for human agency engaged in its transactive environment.

The human being is embedded in its environments and shares them. Nature, social systems, technological dimensions, the noosphere and transcendental environment all generate a plural, but a common framework of hermeneutics.

Even a focal, psychological understanding of human beings cannot be restrained into a purely analytical, experimental frame of reference. András Angyal offered his synergistic scope, referring to the person and its environment, "as aspects of a single reality which can be separated only by abstraction". Angyal sees the human being as a detached actor in his world and he is expressed by the term autonomy with the content of self-determination, an egoistic pole of the biosphere representing the tendency of mastering the environment, with a self-perception of separateness. Angyal also makes us remember that there is another relatively 'selfless' and attached status of environmentality, which he calls *homonomy*, with the tendency to fit oneself to the environment by willingly subordinating oneself to something that one perceives as bigger than the individual self.

The flow of permanent transitions favors habitus of detachment, weaker bonds and readiness for change, while nostalgic inertia, strong attachment to the passing patterns, set of objects, social structures and ideas are seen as difficult blockage in the process or progress. This way personality types evolved on the basis of distorted attachment organizations, like A type competitive, workaholic and hostile behavioral pattern with its higher achievement may be selected against the harmonic B type behavioral pattern with its moderate, "idyllic" conduct at the (battle)fields of worksite achievements.

If we dichotomize the autonomy versus homonomy, detachment versus attachment, dominance and accumulation versus harmonization, optimization, it might lead us to opposing economic metaphors of non-sustainable accumulative dominant and sustainable cooperative optimizing strategies.

WEAVING THE CULTURAL-SOMATIC NETWORKS – RECONSIDERING ATTACHMENT THEORY IN A CULTURAL-SOMATIC CONTEXT

The rites of birth are social constructions, but how do they construct social reality from the beginning? They may be considered as part of the generator or modulator of mothering behavior exerting a long-lasting effect on the so-called "internal working model" governing the infant's social behavior. The rituals around the birth, just like healing rituals, are also holistic patterns reflecting the belief system, the framework of social attitudes and the technology of the whole culture, as well.

According to attachment theory, the mother–child bond as a homeostatic system is at the core of the socialization process as a sensitive object of those rituals, which as holistic collective representations concentrate and mediate environmental influences. As the birth process is immersed into the given environmental, social, technological and cultural context, one can suppose that these contextual influences are acting through the mother–child relationship and the developmental process of the child in a mutual framework of the reproduction of the child and its culture.

We may hypothesize the so-called "traumatic learning", an accentuated form of learning sometimes leading to physiologic consequences in cases of regressive states of sickness. Realizing the importance of this experience, we may suppose that this learning process consists of perceptions of Gestalts of ritual behavior on the side of the parents. On the other hand, the child can learn neglect, or selective attention towards different kinds of symptoms and causes of diseases, which implies a hidden taxonomy of lay nosology. The experience of healing rituals is part of the collaborative learning of the given culture. This kind of learning is an experience-based, holistic and non-analytic, non-literal way of assimilating cultural values, connections, patterns and behaviors through healing rituals and actions, behavioral displays and sentiments. The healing rituals around childhood illnesses may be part of social regulation, too. The symbolic connotations of bodily symptoms like diarrhea and supernatural, spiritual causation models linked with social, intrafamilial disruptions are vehicles of patterned social meaning as we see in the case of Kulina (Pollock, 1996). In this case, the healing ritual with the sick child works

by modulating the behavior of the parents. This sample proves the importance of the ecological approach in anthropological understanding.

The purpose of this chapter is to explore the role of culture in shaping rituals of pregnancy, birth and baby nurturing and healing and the role of these rituals in shaping culture through the child's personality and belief system.

Birth rituals

It is not always easy to distinguish between understanding in terms of technology and ritual because seemingly irrational practices can be functional, and rational technologies may be expressions of rationalist myths excluding fundamental dimensions of reality of a world, which is neither rational, nor irrational – rather, it is non-rational (Geertz, 1984). These arguments turned to be explicit by presenting biomedical birth practices as culture-bound technocratic birth rituals (Davis-Floyd, 1990) or by questioning the role of surgical episiotomy during birth. As Davis-Floyd introduced the concept of technocratic birth, she revealed the role of the obstetrical rituals that configure, shape and medicalize the otherwise natural process. These rituals put the birth into medical context. The criticism of the surgical interventions pays attention to statistical facts showing that the earlier mentioned rate of Caesarean section was 4% in 1970, and reached 24.4% by 1987, during which there were no subsequent improvements in infant and maternal mortality rates. The passive role of the mother during the birth, the technocratic and institutional control over the procedure creates a cultural framework for the newborn too, who will grow up in a technocratic and institutionally controlled society that subverts some of his natural needs.

The natural essence of the birth or breastfeeding process can be ritualized as a counter-medicalization or counter-consumerist behavior. That can be observed in "the home birth" movement. One can find several samples in Europe like the AlterNatal movement in Hungary. It may also be part of a traditional maternal practice, like in the Netherlands, where one-third of mothers deliver their children traditionally: in home circumstances with the help of midwives. The myths of "natural" and the myth of "technocratism" or "biomedical security" are strongly influencing the ritual behavior of mothers. We have mentioned already that mothers choosing home birth are older, more educated, more feminist, better read about childbirth, more likely to be multiparous than labor-ward mothers (Cunningham, 1993). The feminist ideologies of paternalist biomedical control over female nature reflect the role of mythologies in creating different narratives and consequently different behaviors and rituals, as well.

Rituals and taboos post-partum

There is a period of impurity after birth. Perhaps it is the result of experiencing the dangers and complications, which threaten the newborn and the parents, which can be enhanced by more frequent strains and interactions. In the Balinese culture, the first ceremony for the newborn is held on the 42nd day after birth in the case of a first-born child, marking the end of the period of seclusion and impurity of the parents. There is a transient period, when the baby is given only a (disgusting) nickname like Caterpillar, or Mouse, perhaps for the sake of avoiding the interest of evil spirits. The second ceremony called *neloeboelanin* takes place on the 105th day, when the baby is given its real final name, and the greatest ceremony; when the hair is cut for the first time, is on the 210th day, the *otonin* is when the baby's feet are ritually put on the floor.

In order to avoid the malevolent spirits, it was customary to put the baby's clothes on back to the front or, having seen a beautiful baby, to remark "what an ugly kid" in the Hungarian peasant traditions. These gestures had the same protective purpose as the creation of a sterile environment for the birth or putting of medication in the neonate's eye. Cleanliness may mean freedom from spiritual dangers and freedom from infective germs, too. The rooming-in custom, based on scientific theories (or myths) for the protection of the mother–child relationship from the very first moments is analogous to the so-called "Boldogasszony ágya" custom or ritual behavior presenting undisturbed closeness of mother and child for six weeks after delivery. During this period, the relatives in the extended peasant family cook for the mother and visit her, extending the impact of imprinting by the mother to the circle of the whole family including second cousins and beyond. It was general that in the first weeks the *bába* (traditional birth attendant) visited the mother and the massage and the bath helped to regain the mother's vitality. They also offered sacred protection to the baby by putting a rosary into the swaddle, or hymn book under the bolster. Nobody was allowed to visit the baby before the baptism (Bernád, 2004).

The postpartum taboos are rules regulating the sexual behavior of the mother, which assists in the proper timing of the next birth for the sake of optimal feeding of the baby. The long intervals between births protected by these beliefs and, partly, ritual behavior may offer better chances for proper nutrition of the child, closer psychological intimacy and give a sense of security (in psychophysiological and microsocial senses) and immunological protection from infective diseases. These together may determine the fate of the child.

Maternal decisions with regard to breastfeeding and early weaning may be the result of: practical considerations, constraints of maternal illness, loss of breast milk, or the result of mothers going to work due to economic pressures. These considerations can be modulated by myths shaped by the consumerist

influence of advertisements (of breast milk substitutions), which can cause serious problems in the Third World environment because of the lack of transmissible immunoglobulin, and nutrients in breast milk. Weaning is considered to be a stage of transition, which puts the baby at risk of illness mainly resulting in diarrhea. Most of the mothers mention needing God's support to get through the weaning period in Egypt according to Harrison's study (1993). In this study, the timing of weaning reflects ritual contents because it is forbidden in the "sinful" month 'Muharam' and similarly the period of Ramadan has always been an object of consideration. There are other risk factors, like *mushahra*, the presence of a menstruating or newly married woman or a man just after cutting his beard. The Egyptian mothers in Cairo prefer to time the weaning towards the end of the Islamic month to protect the child (Harrison et al., 1993). These considerations together create a ritual context for a biological act of weaning, which impacts the child profoundly.

The rules, scientific regulations, taboos and ritual prescriptions governing behavior have the same function: creating order and security in uncertainty, and creating closed Gestalt, and wholeness around the important life events. This does not mean adaptivity, health or optimal adjustment at all. On the contrary, it may create serious handicaps, maladjustment and long-lasting difficulties or may draw long lasting marks on the expression of a civilization.

Personality and culture – psychoanalytic approaches

The name of Géza Róheim is to be mentioned first. As a trained orthodox psychoanalyst, he considered culture in general to be a defense system directed against the fear of losing an object and separation anxiety. He attributed cultural differences to differences in the patterns of infantile nurturing (Róheim, 1968). Kardiner modified the orthodox Freudian dogma regarding the integration of culture and personality. In his model, the *primary social institutions* or social-economic frameworks create the child–rearing practices while the particular child training practices determine the so-called *basic personality structure* and the *secondary institutions* like art, religion and rituals, which are partly the products of this basic personality structure (Kardiner, 1945). During the development of the child the unconscious conflicts and anxieties are institutionalized in the secondary institutions, which are derivative projective systems expressing personality needs and providing a means of satisfying them. This dynamic model offers an ecological framework as well, because changes in subsistence may alter child-rearing practices with possible adaptive modifications of basic personality structure. The conditions of secure mothering and the proper gender socialization to guarantee the optimal maternal behavior in the mother–child system may be viewed as

general tendencies in the compared traditional cultures, based on a cross-cultural survey comparing 110 traditional, primitive cultures (Barry, Bacon, Child, 1957). In 82% of the cultures, they could prove the higher skills of caregiving, nurturing, and in 61% of the cultures, the girls were more responsible, while dominance, Self-centered dignity and achievement-centered attitude were higher in the case of the boys in 87% of these cultures under research.

The contextual, environmental variables also may play a role as the study showed 20%-30% local differences in these patterns. The exceptions are very informative, too. In her first field study, Mead found different, reciprocal situation among the Papua New Guinea tribe, the *Tchambuli* (now they are called *Chambri*), where in a sort of matriarchal system the power was in the hands of women as they were the primary food suppliers. Within many marriages, Tchambuli men were reported to fear their wives, because of their belief that in an intimate situation within a marriage, a husband's hair or bodily fluids could potentially be given to a sorcerer, to be used against them by their wives; this made men wary. This male anxiety regarding the secret magical power of females appears in the Kalevala (*Väinämöinen* and the Nordic woman of Pohjola), in the conflict of Jason and Medea, cultures with chthonic and telluric cosmologies or in the European cases of witchcraft accusations and genocides. That proves: beyond biological, ethological determinants, gender roles are strongly shaped by economic, cultural and environmental factors, too. The relationship with the mother seems to be crucial in a culture with particular regard to its emotional climate.

Whiting and Child used psychoanalytic theory as the source of their hypothesis, but they unified these concepts with the general behavior theory. They compared more than 70 tribes with a co-relational method to examine their hypotheses in a cross-cultural framework.

Rituals of childhood sickness and cultural personality

It is interesting that Whiting and Child used the ethnic explanatory models for illness and techniques of therapy as indices of personality characteristics of the typical members of a given society. The customary reactions to illness are universal and comparable. These include beliefs about the causes of sickness, prevention and healing rituals. These are part of the projective system – as Kardiner, for one, finds the secondary social institutions likeable to magic, religion, and rituals. Whiting considered the healing rituals to be a projective test of the given society as a whole. According to this logic, healing rituals are not just influencing the culture, but they are the most forceful expressions and indices of it. These traits correlate to two kinds: child training practices and beliefs concerning the causes of illness. Child training practices

shape the child's personality, which later – as an adult personality – will influence the illness causation model. According to their hypothesis, similar childhood experiences may produce similar unconscious fixations and conflicts as neurotic tendencies expressed by the belief system of the given culture.

The analysis and comparison of traditional healing practices were driven by five variables of the causal model: agency (sorcery, spirit, etc.), patient responsibility (blaming of the patient, primary or secondary), act (failure of a ritual act, breaking taboos, incest, etc.), materials (cold versus hot food, poisons, menstrual blood, etc.), and means (ingested, interjected, contact, removed, lost). All these factors must be included in the analysis, and the given pattern must be classified. Whiting and Child quantified the illness-related cultural pattern, counting the categorized diseases and weighting them according to the frequency and seriousness. They paid attention to the intensity of belief, as well.

Following the same logic, with the therapy they created agency variables (the role of the person in the therapy), materials (employed in curing and healing), means (restoring the patient's soul, removing the agent responsible for the illness, etc.) degree of isolation (of the patient during the illness) and the effect of the therapy.

Based on Freudian considerations, they predicted that if the child training practices of a society were such so as to make oral behavior, especially rewarding to its members, then in the face of anxiety with regards to illness they might resort to some sort of oral behavior as a healing exercise. However, in the case of negative fixation and dominance of the oral character of a particular society, anxiety induced by an illness might provoke generalized responses of worrying about oral matters as a possible cause of illness. The indulgence in, or restrictions of particular types of behavior can create satisfaction or socialization anxiety as basic experience, which acts towards shaping the personality, and consequently forms adult neurosis and projected belief systems. According to their theoretical frameworks, the oral explanations include eating or drinking bad food, poison, verbal spell and incantations. The anal explanations imply defecation, urine, odor, use of these in rituals, carelessness, leftover foods, nail parings, hair cuttings, sex excretions as well as failure of the rituals. Sexual explanations are used when sexuality is thought to be responsible for illness or sexual excretions, and menstrual blood is blamed. Dependence explanations are taken into consideration when loss of soul is responsible for an illness, or spirit possession is the cause (Supernatural dependence on parental figures).

Whiting uses customary reactions to illness as indices of personality characteristics immersed in the given culture, because reactions to illness – according to his opinion – are influenced by personality. In his classification system, we find the next subdivisions of "socialization" items among the other content categories: techniques of inculcation, weaning and food training, sex-training,

independence training, aggression training, transmission of skills, beliefs and cultural norms. According to Whiting's theory, the explanatory models and healing beliefs related to disease are part of the cultural reproduction of the whole cultural system, as well. They found positive correlations between given types of anxiety-generating child training practice and the same types of explanatory models of illness in 39 societies in a highly significant manner. The oral socialization faults were found to be correlated with oral explanations of illness.

Whiting and Child were criticized partly because they did not consider the mutual relationships of the societies compared. For example, in the case of love magic as a cultural trait related to reducing sexual anxiety, the correlations between geographical, regional position were higher than correlations between child rearing practices and love magic (Driver, 1966). Shweder's "counter"-postulates even question the whole approach of culture and personality theory, emphasizing that early childcare practices do not per se have predictable consequences for adult character and that individual differences in conduct do not widely generalize across various contexts, as proposed evidences for broad cultural integration are not convincing (Shweder, 1991).

The debates on the work of Whiting and Child were extended by Constanzo's multitrait/multimethod reanalysis of their data. He analyzed all of the possible correlations between the five socialization systems and the five parallel illness explanatory systems, and showed that beside the high correlation of oral socialization anxiety and oral illness explanatory models, it can be correlated even better with anal and sexual illness explanations (Constanzo, 1974). So, the specificity of intercorrelations can be seriously questioned. Shweder's final judgment was that culture and personality theory cannot achieve parsimony and validity simultaneously.

Culture and personality revisited: attachment organizations and personality

If we avoid the Freudian frame of reference, we can keep the determining role of mother–child bond without its "libidinal and Oedipal myth". To avoid the stigma of unproven generalizations, we use Bowlby's attachment model offering an ethological by-pass road to this concept with a scientifically supported framework.

In the first six weeks of an infant's life, the period of human imprinting, a baby is seeking a Significant Other, later to become a decisive part of the cognitive-emotional attachment system. Bowlby (1969) called this the internal working model, which might determine adult social relationships, the emotional arousal that influences the development of interpersonal relationships, perceptions and expectations (Freedman and Gorman, 1993). The Internal Working Model

(IWM) is permanently ingrained in the mental or emotional representation of early social interactions. These interpersonal, intersubjective domains are believed to form an internal guiding structure for future behavior in more or less comparable situations. IWM's are normally acquired from parents, who are enduring, and beyond conscious control, influencing emotional reactions in a broad spectrum of relationships. IWM governs both the subjective and external aspects of behavior, enabling us to reconstruct the dynamics by which behavior patterns tend to repeat through the generations (Freedman and Gorman, 1993). In this way, IWM may influence the given culture indirectly, too. The IWM may be distorted by the rituals of birth and healing. The attachment system between mother and child is particularly vulnerable in the first hours and days immediately after the birth. Technocratic birth and early separation from the mother may distort attachment that is basic to social behavior (Bowlby, 1973).

Attachment organizations and the grammar of sociability

Maternal behavior may provide security (which is sensitive, accepting, cooperative and always accessible). A mother who refuses such security to the child is described as being inconsistent, lacking response or showing refusal. Babies compensate for the insecurity of this relationship in two ways, according to Ainsworth and Mary Main (Ainsworth, 1978; Main, 1990). One way is the A-type secondary attachment, the anxious-avoidant secondary attachment organization, when the baby becomes relatively independent. The other way is the so-called C-type secondary attachment. In this case, the baby develops an anxious attachment, high physiological arousal, inhibited aggression and low self-esteem. Based on these considerations, three core hypotheses emerged, according to which the caregiver sensitivity leads to secure attachment (*sensitivity hypothesis*), the secure attachment leads to later social competence (*competence hypothesis*), and the children who are securely attached use the primary caregiver as a secure base for exploring the external world (*secure base hypothesis*).

Children handicapped by insecure attachments are characterized by low self-esteem, low motivation and performance, problems in social adjustment, and a weak sense of danger, which are all integrated part of cultural behavior (Bretherton, 1985). As the first research regarding the attachment was implemented in cross-cultural setting in Baltimore and Uganda (Ainsworth, 1967), the so-called strange situation procedure was applied in other African communities like the Gusii or Guiessi in Kenya (Kermoian & Leiderman, 1986). The attachment classification, found for the Gueissi dyads, was similar to the findings from Western studies, with 61% demonstrating secure attachment to their mothers and 54% to other non-maternal caregivers. Alloparenting was

also observed, where mothers carried out physical caring activities while non-maternal caregivers were more involved in socializing and cognitive development activities *(Attachment Across Cultures – Research Report)*.

One can find alloparenting among Hausas in Nigeria (Marvin, Van Devender, Iwanaga, LeVine & LeVine, 1977), too. Marvin showed that polymatric (multiple mother figures) care of infants influences attachment behaviors and demonstrated a *preference for one relationship over all the others.* The preferred maternal figure was the one who held them most frequently and had more opportunities to interact with the child. Hausa mothers, being sensitive to their infants' signals, restricted their infants from physically moving around to explore their surroundings. The primary importance of the mother is supported by the Israeli observations, as well, where Sagi et al. (1985) found a higher rate of secure attachment among those children in the Kibbutz who returned to their parents to sleep for the night compared to those sleeping in a collective sleeping arrangement at night – they showed a higher proportion of insecure attachment. Other Israeli studies also show an over-representation of ambivalent attachment when compared to international data.

It is interesting to involve culture with Confucianist norms, which value family life and interrelatedness. There were several studies with converging results over the dominance of a secure child as normative, and a high value of secure attachment and mothering based on the Chinese philosophy. Hu & Meng led classic Strange Situation research in Beijing, and found 68% secure and 32% insecure attachments. They found that mothers of secure infants were more involved in childcare than mothers of avoidant infants.

According to Van IJzendoorn and Sagi, a universal interrelationship between maternal sensitivity and the security of attachment systems may be taken as cross-cultural invariable (Van IJzendoorn, Sagi, 1999). One can also see secure attachment as a universal basis for later social competence (Cassidy and Shaver, 1999). Beyond their ethological-biological background, the attachment systems proved to be culturally dependent and variable in their cultural context. Comparing American and Japanese data, Rothbaum (2000) proved that dominant attachment strategies may shape dominant norms and the communication networks of given cultures, and on the other side, they are also partly products of these networks.

According to Shweder's point of view, the early childcare practices do not per se have predictable consequences for adult character. This statement is challenged by the research on attachment organizations and by the related personality development models (Blatt et al., 1993).

There are opposite data, too. An anthropological report from Brazilian shantytowns with miserable circumstances showed that between mother and child a close, supportive relationship may develop despite earlier child neglect or distanced mother–child bond (Scheper-Hughes, 1985). At the same time,

this may even be a *result* of child neglect, reflecting a traumatic bond (Weil, 1992).

The widest corpus of proof came from a distinct field of *parent–child research*, from the PARTheory Meta-analytic procedures were used to pool information from 43 studies worldwide to test one of the major postulates of parental acceptance–rejection theory (PARTheory). According to the meta-analysis of these cross-cultural studies (Khaleque and Rohner, 2002), existing evidence strongly suggests that a true – perhaps causal – relation exists between the childhood experience of parental acceptance rejection and subsequent psychological adjustment in both children and adults. Rohner (1975) summarizes the results of a significant holocultural study of 101 well described pre-industrial societies distributed widely throughout the main geographic regions and culture areas of the world (Rohner, 1975). Another early study of the Pacific region, including a controlled comparison of three sociocultural groups in the Pacific (i.e., Maori community of New Zealand, traditional highland community of Bali, and the Alorese of Indonesia), where – as described by anthropologists – children tended to be rejected by their parents (Rohner, 1960). An 18-month ethnographic and psychological community study was led also in West Bengal, India (Rohner & Chaki-Sircar, 1988). Rohner led his studies in the Western societies as well, where at least 50 intracultural psychological studies were made, by more than two dozen researchers in the United States and internationally. Collectively, these studies have tested several thousands of children and adults within at least 28 nations and language groups internationally (Rohner, 2002; Rohner&Rohner, 1980). These studies also include every significant ethnic minority in the U.S. (i.e., Asian Americans, African Americans, Hispanic Americans, and Native Americans) as well as middle-class and working-class European Americans.

Cross-cultural studies of attachment organizations: an ecological approach

To avoid the traps of the linear causal determinations, it is better to apply a multi-dimensional, ecocontextual framework of determining factors and their mutual interrelations. The ecocontextual approach is part of the main discourse in the field. The conflicts of psychobiologist generalizations, overemphasizing species-specific human ethologist invariants and culture-specific bias toward the peculiarities and exotic issues can be overcome with a multidimensional, ecological approach (LeVine, 1996). We need a complex approach because the historical and cross-cultural differences of the rituals compared, are rooted in human ecological differences consisting of natural, technological and cultural contexts.

Beatrice B. Whiting and Carolyne P. Edwards created a contextual model of social behavior in their cross-cultural research, too. They revealed that the differences in the profiles of behavior between geographic regions separated by space, history and ecology are pronounced, while in the same geographic regions, like among the Kokwet, Kisa, Kariobangi, Ngeca and Nysongo tribes of Kenya, the interactions are similar. If we put the rituals of birth and the healing practices in the focus on these interrelating natural, socio-, techno-, and ideospherical environmental systems, then it is obvious that these exercises have their natural, technological, social settings and characters. The ecocontextual approach is not alien from the main anthropological discourses in the field. The conflicts of psychobiologist generalizations, overemphasizing species- specific human ethology invariants and culture-specifically focusing on the peculiarities and exotism can be overcome with a multidimensional, ecological approach (LeVine, 1996).

Even the biopsychologic functionalist content of ethological wisdom and evolutionary determinism may be overwritten by the diverse facts. The criteria for secure attachments are not always supported by the closeness of mother and child carried in piggybacking. This is mirrored by the Liberian field experiences among Kpelle mothers, who "carry their babies on their backs and nurse them frequently but do so without really paying much direct attention to them; they continue working or... socializing". We know well that there are cultures who practice "Spartan" child rearing customs. Perhaps Mead's Mundugumor society may offer this example. Therefore, the report about the Guusi mothers by LeVine with the observed weakened eye contact within the attachment ring might not be an instance of optimal child rearing. In this case, the mothers rarely looked at or spoke to their infants and toddlers, even when they were holding and breastfeeding them. There are other challenging reports also, like in the case of the Mazahuas, when a "mother holds a nursing baby in her arms, she frequently has a distracted air and pays almost no attention to the baby" (Paradise, 1996). These insights included a covert moral content behind the female decisions about the Androgyn within and around them.

Attachment parenting versus detachment parenting

The ethologic, psychological and cultural insights to the physiological language of mother–child relationships exerted influence on the "grassroot" biopolitics of mothering as well. Early gender debates articulated a counter maternal atmosphere in feminist circles. In her work, *The Second Sex,* Beauvoir found biology as an *unacceptable deterministic fate* rendering women subservient to the requirement of the species to procreate. Although breastfeeding is a symbol of biological defense, the feminist opinion itself is a counter-natural

modernism in Beauvoir's philosophy. Breastfeeding may be a real symbol of bio-psycho-social protection, as beyond feeding and providing psychological security, long-term or extended breastfeeding appears to protect children from infections and the development of allergies. The ego- and gender-centric modernist and counter-naturalist Beauvoir saw breastfeeding as a sort of enslavement. The attachment parenting movement was also given a *non-value-free* name, the *militant lactivism* (Faircloth, 2013) representing an ideological and moral turn of the self-scape of mothers through their practice of *intensive parenting*. This style of care endorses close parent–child proximity and typically involves long-term, on-cue breastfeeding, baby 'wearing' and co-sleeping as part of a 'family bed' philosophy. The other term, closer to the focus of our book is the *attachment parenting*, based on the hypothesis by Katharine Dettwyler, the US biological anthropologist saying that: "humans are designed to breastfeed their children for anything between 2.5 and 7 years old."

The scientifically supported facts, listing the benefits for the children, do not permit much hesitation or resistance. Attachment parenting promotes independence, as securely-attached children are more likely to explore on their own (Mercer, 2006), but at the same time it enhances emotional availability as well (Easterbrooks et al, 2000). The behavioral studies proved that children receiving greater levels of maternal support showed "higher levels of positive mood, more constructive coping, and better emotional regulation in the classroom" (Kerns et al., 2007). They are regulating their own negative emotions much better (Davidov and Grusec, 2006). The same study found that maternal warmth was associated with better regulation of positive emotions. The gains in sociability were also supported by the studies because such children engaged in warm, mutually responsive relationships with their mothers and developed stronger consciences and compliance, empathy and prosocial behavior (Kochanska and Murray, 2000). Securely-attached children showed fewer internalizing and externalizing behavioral problems, too (Moss et al., 1998). In attachment parenting, co-sleeping is also an object of debate. The results of the study supported this ideology too, children (aged 3–8) who slept in their parents' rooms showed lower daily levels of the cortisol stress hormone (Waynforth, 2007).

This agrees with the Hungarian ethnomedicinal experiences of long-term breastfeeding as a belief and practice, which has been kept alive in Hungarian *Palóc* communities. We gathered narratives about four-year-old children who were still being breastfed, for the sake of contraception. The etic reasoning is supported by the fact that breastfeeding may sustain elevated levels of prolactin resulting in continuous contraceptive effects. Personal psychophysiological rewards may turn attachment – a resource of *intimate social, psychological and moral wellness,* both for the child and the mother – into a transcendental, ethic issue. As *Manifestos* of "militant lactivism" expose: "Attachment parenting" may find itself in a missionary agency of evangelization of the good news

regarding the embodied sanctity of the maternal bond. They wrote on their web page:

> Through education, support, advocacy and research, our principal goal is to heighten global awareness of the profound significance of secure attachment – not only to invest in our children's bright futures, but to reduce and ultimately prevent emotional and physical mistreatment of children, addiction, crime, behavioral disorders, mental illness, and other outcomes of early unhealthy attachment. (https://www.linkedin.com/company/attachment-parenting-international)

This commitment may induce moral anxiety in those, having strong skepticism regarding these insights. Faircloth (2012) urges to avoid the tribalization of committed and activist parents, and to cool the debate down by recognizing that this is about more than just individual choice becoming a highly moralized affair for mothers' practices. Badinter (2010) turns our attention towards validating attachment, attentiveness and parental fulfillment in the frame of 'intensive parenting'. However, Badinter (as Faircloth) also finds 'intensive parenting' problematic, in its meaning where mothering is a way of construction of female identity and a vehicle for personal fulfillment for women, where the earlier committed feminism can easily be converted to a committed 'maternalist' language. The same dilemma emerges regarding classical feminism if we shift our focus of mother–child conflicts arising before birth and indeed in the womb, as the prenatal psychology does.

Prenatal psychology "re-defines the nature of the human prenate as an aware, communicative, and vulnerable being", emphasizing: "positive prenatal and perinatal experiences have a lasting influence on health, human relationships, and society" (APPPAH, 1983).

The consequences are serious, because the risks of developmental, psychological and social handicaps in the case of children, rejected prenatally, are higher according to Verny (2013).

This debate extends the conflict of Mothernist versus Modernist gender view, where the dual-union of mother and child is in focus both before and after the birth. We can understand this cognitive conflict and polarization by using Angyal's term, *homonomy* versus *autonomy*, or by drawing the poles of attachment versus detachment.

While the moral commitment is obvious to give the most secure start to a life (if it survived the risk of the abortion) nevertheless there are examples of detachment parenting too, as Lancy (2012) offers in his overview. Anomie or intergenerationally transferred distorted attachment patterns may feed these anomalies, which may evolve into culturally characteristic features of the given family culture. The early sociological comparative works of the culture of the family written by Westermack (1891) or Sumner (1906) have already

shown the dark side of the family, as well. The reports about the practice of infanticide among Innuits and other people, child rearing without fathers in North India confronted readers with the plural realities of mothering. Many examples prove a wider social net of attachment, like in the case of alloparenting, where the members of the extended family network participate in child rearing from the young sisters up to older women, lightening the mother's burden and thereby increase her fertility and her productivity.

Other ways, like wet-nursing, adoption and fostering may warn us to accept the detached ways of parenting, which can culminate in the *sale of infants*. Social anomies are reflected by the destruction or break of social ties, and institutions. Dysfunctional families may mirror this social degradation. Conflict may be a dominant part of communicative codes and the atmosphere of the family, where mothers disguise their children's sex, refer to them with bad or fake names in an effort to deflect the envious thoughts of other women in the neighborhood. Because of hatred, vindictiveness and envy some people decide to attack the rival or someone they dislike by sorcery. A child may be a target of malevolence and voodoo transgressions. The declaration of unwanted children expressed by the mother or the grandmother puts a serious burden on the optimal attachment experience, resulting in children with risky emotional destinies. Lancy cites Murphy, who found among the Mundurucus of Amazonas Basin that they killed the illegitimate children at birth, along with twins and children with birth defects.

"If the child does survive it is referred to as "tun" which means excrement. They are not abused, but they cannot marry due to their indefinite status" (Murphy, 1985). In Africa, among the Songye albino, the dwarf, and hydrocephalic children are expected to die. "They are handled as 'bad', thought to be supernaturals who have been in contact with sorcerers in the anti-world; they are not believed to be human beings, and they are expected to die" (Devleiger, 1995).

A different burden emerges when the mother has a mental illness like bipolar depression, which may disturb attachment as well as generate high rates of insecurity and disorganized/ disoriented attachment. Painful reasons for detachment or attachment also rest in the mother's drug addiction where both the physical and psychological absence of the parent (due to hospitalizations, psychopathic land extreme or subsocial lifestyles and disabilities) contributes to inconsistent, erratic parenting leading to insecure attachment patterns.

Based on these diverse experiences, we can accept that – although attachment is an evolved ethologic phenomenon that is universal – distortive environmental impacts may transform the attachment. The complex approach, implying the historical and cross-cultural differences in child rearing can reflect human ecological particularities emerging from the natural,

technological and cultural contexts. LeVine's framework is close to the so-called M-E-O model.

This human ecological explanatory model based on the tetrahedron environmental ecodynamic framework (Lázár, 2001), where natural, social, technological and ideospheric niches are constructed by the human actor, and these niches may relate to a different economic/ecological manner with each other: namely competitive, predating, mutualist-symbiotic, neutral or parasitic, or even saprophytic-scavenger ways (Lázár, 2013).

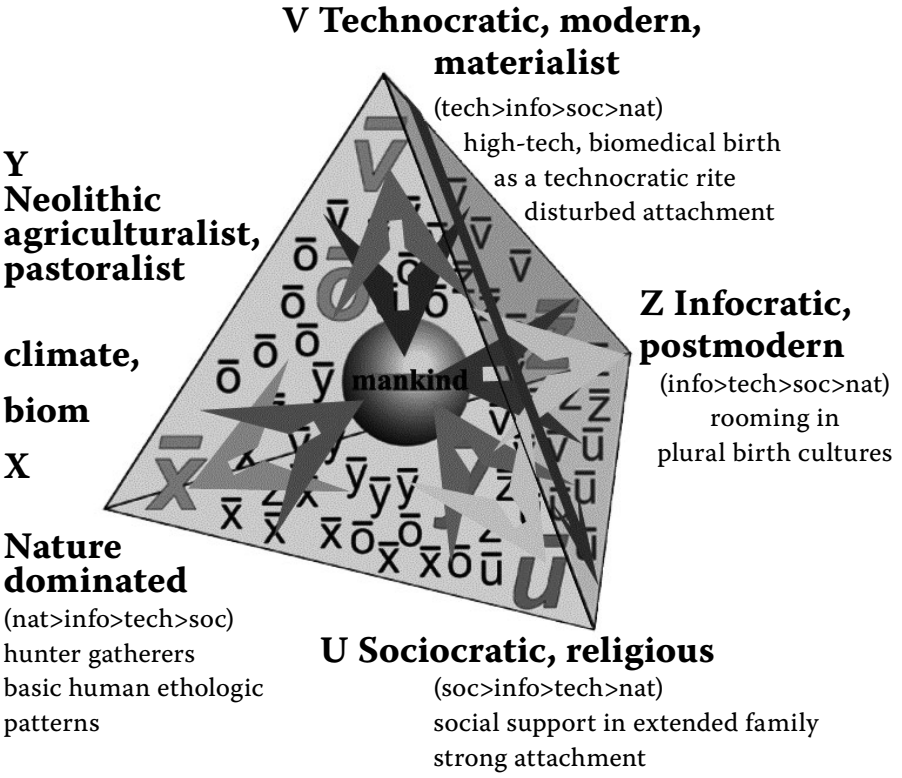


Figure 7. Historical paradigms of social patterns and child rearing complexes in M-E-O context (Lázár, 2015)

X: Nature dominated: archaic magical complex: Various kinship systems, archaic group relationships, Traditional Birth and Child Rearing Complex, socially embedded material life (Gift systems, reciprocity);

U: Sociocratic, religious: Extended family, traditional communities, socially embedded material life (Gemeinschaft), Traditional Birth and Child Rearing Complex, secure attachment ideal;

V: Technocratic, modern, materialist: Nuclear family, institutionalized, rationalized social life (Gesellschaft) Technocratic Birth and detached

disembedded market economy, Child Rearing Complexes tendencies towards distorted attachment.

Human agency is – based on the above anthropological considerations – partly a result of early social learning, determined by the so-called early working model, which generates a human ecological disposition towards the natural, social and cultural environment. The internal working model (Bowlby, 1969) represents the early social experience and may also be shaped or distorted by natural conditions, technological milieu and rituals and belief systems shaping maternal behavior and child rearing. The M-E-O model implies coevolutionary processes based on the concept of niche construction (Lewontin, 1983, Odling-Smee, 1994), Kenneth Boulding's theory of ecodynamics (1978) and the tetrahedron ecodynamic framework (Lázár, 2000), in which interacting natural, social, technological and ideospheric niches influence each other in an ecodynamic (competitive, predating, symbiotic, neutral or saprophytic) manner through human agency (Lázár, 2013). Rohner's Parental Acceptance–Rejection Theory (PARTheory) (1986) is also a cultural, contextual model using cross-cultural research dealing with the major causes and consequences of parental acceptance and rejection in the given culture. The *Sociocultural system subtheory* deals with sociocultural factors such as household type or form of subsistence economy, explaining why some parents are warm, loving whereas others are neglecting/rejecting. Rohner's attention is extended to the total fabric of society, beliefs and behavior of the given sociocultural context is (or is not) influenced by the frequency of acceptance or rejection of their children. Through distorted mental representations of themselves, they tend to have low self-esteem, seeing themselves as being unlovable, and hence they develop a negative world view. The consequence may be an emotionally charged adult, with a distorted mental representation of the world and hostile, treacherous, untrustworthy, or otherwise negative human relationships. Such people are shaped by these environments, which are constantly interacting with each other. The attachment organizations are in the focus of these determining influences, which, through the so-called internal working model, may suffer long-lasting distortions or alterations.

Ecological and climatic considerations undoubtedly influence mother and child bonding in any given culture. In the Northern countries, for instance, infants were often kept in cradles; in the South on the other hand, piggybacking was typical in traditional societies. Freedman and Gorman described the logic of the culture generating function of attachment organizations through a particular system concept.

> The many interacting factors are seen as operating within a macro- system, with so-called deterministic elements (e.g. genes) affecting "higher" levels (e.g. predominant temperament in a culture), but with reverse causation also occur, when contextual levels (e.g., shifts in socio- economic status) affect lower levels (e.g., differences in child rearing). (https://www.sciencedirect.com/science/article/pii/106173619390037R)

The subsistence systems (hunter-gatherer, agricultural or industrial- technological) have a deep influence on the cultural pattern of child delivery and attachment too. Freedman's cross-cultural study of the child/mother attachment system showed variations in the various different cultures. They concluded that the mode of intergenerational transmission of internal working models is the same for neurotic patterns and certain culture-wide patterns, essentially blurring the boundaries between the two. Their conclusions lend a particularist framework to the normative, ethological concept because entire cultures appear to exhibit insecure attachments. It is especially noteworthy in the case of the results of Hungarostudy 2013, where, according to the results based on the Adult Attachment questionnaire by Bartholomew, the sum of dismissive and fearful-avoidant independent style exceeded 50% of the informants (Csóka and Lázár, 2013). According to their research, a broad variety of attachment modalities have been proven viable, and the propensity to attach far outweighs the importance of the quality of attachment in their concept. For instance, in the example in Iceland cueing for independence was typical with lack of confidence between mother and child and the practice of keeping distances. Arab mothers typically punish children and disapprove of their behavior, these are factors that help form a low esteem in the child, making him or her prone to accept a hierarchical society. With Chinese mothers, Freedman found that they strive for perfection and control coupled with a limitation of the needs of the child. "I won't pick him up, that shall teach him that crying does not take him anywhere" (Freedman and Gorman, 1993). This corresponds to the model of Barry, Child and Bacon, who say that children in farming societies are taught obedience, while in the societies of shepherds and rural societies the aims of child rearing are to achieve pronounced independence and competence (Barry et al., 1959). Further family context differences appear when comparing East–West cultural differences as separateness versus connectedness, individualism versus collectivism, and perhaps detached versus attached motives (Takeshi, Lau, 1992).

These diverse models show how a culture shapes birth rituals, child rearing practices and healing rituals, and, consequently, how these rituals help to reproduce the belief systems, values and practices shaping the given culture. These models induce us to be aware of the risks of overgeneralization and

theoretical projections; risks which can be overcome by an ecologist, multidimensional approach and faith in the facts.

Sociosomatic transfer mechanisms of distorted early mother–child attachment

The sociocultural-somatic logic of psychoimmunological consequences of distorted mother–child attachment includes the prenatal period. Infants of mothers with prenatal depression exhibit an increased cortisol response to stress and are at risk for future behavioral disorders, as prenatal depressed mood leads to altered methylation status of the newborn's GR gene (NR3C1) in umbilical cord blood mononuclear cells. This way maternal mood might shape the infant's future stress responsiveness through epigenetic mechanisms (Derke 2015). Persistent activation of HPA system as consequence of delayed disturbance of mother–childmother–child relationship can lead to altered immune function. On the other side, the secure presence of attachment figures leads to an attenuated activity of the sympathetic nervous system (Diamond, 2001), and hormones, released by stress-induced HPA activity, are also influenced by proximity to and separation from social partners. This way, the mother–child attachment system may be seen as an emotion regulation device (Vrtička and Vuilleumier, 2012), where insecure-avoidant, harmonic or insecure-ambivalent attachment organizations exert different regulatory effects on individuals' affective and physiological responses to distress (Gross, 2007).

We might see the above secunder attachment organizations as kinds of adaptation. In the case when the caregiver is not available or punishing, the secondary attachment strategy represents an *escape* reaction and is associated with a deactivation of the attachment system to prevent frustration and additional distress caused by attachment figure unavailability.

In the case of anxious secunder attachment organization, the secondary attachment strategy consists of a *resistance* response in terms of attachment system hyperactivation aiming at intensifying proximity-seeking attempts to demand or force the attachment figure's attention, love, and support according to Vrtička (2017).

Insecure attachment of the child leads to a heightened physiological reactivity to stress. According to Gander and Buchheim (2015), during the Strange Situation, ambivalent infants have higher cortisol level, and they tend to show more right prefrontal activity, whereas avoidant infants have increased heart rate from separation long into reunion, an increased cortisol level and they tend to exhibit more left prefrontal activity which is associated with the inhibition of emotional attachment behavior like crying. Securely attached

individuals show lower physiological arousal in heart rate and skin conductance in challenging stressful situations, while insecurely avoidant/dismissing individuals suppress their emotions, masking of negative affect. Individuals with a secure attachment representation show a lower increase in skin conductance levels from baseline to questions asking them to recall experiences of separation, rejection and threat compared to the other groups. Insecurely ambivalent/preoccupied individuals use hyperactivating strategies showing more negative affect and less autonomy.

Chronic social disconnection or disturbed mother–child attachment organization can inhibit the glucocorticoid receptor's ability to transduce HPA axis cortisol signals into anti-inflammatory cellular responses associated with both increased basal levels of inflammatory gene expression in circulating immune cells and increased cellular responses to microbial stimuli. The SNS also shows altered regulatory dynamics in the absence of stable social connections, but these often develop in a sensitizing, rather than desensitizing, direction (as observed for glucocorticoid signaling). For example, in macaques, several months of low-grade social instability can upregulate arborization of the SNS nerve fibers that innervate lymph nodes (involved in coordinating immune responses). Moreover, observational studies of humans experiencing chronic social disconnection show elevated proinflammatory cytokine levels and increased proinflammatory cytokine gene expression, according to Eisenberger and Cole (2012).

PNI AS A PRODUCT AND TOOL OF EVOLUTION

He whom fate wishes to keep shall burn in hope until death.
He whom fate wishes to lose – it condemns him to helplessness.
Domokos Szilágyi

The adaptive human being lives in a state of constant dialogue. The environmental adversity they interpret and their physical, mental, symbolic, and concrete responses can all be placed within a coherent linguistic framework and interpreted as text.

The biblical idea worded by a Hungarian protestant preacher, János Sylvester (1541) as follows: "Kezdetben vala az beszíd" ("In the beginning, there was speech") can be evidenced by the continuous information flow of the neuroimmune system. The neuroimmune network is in constant communication with its environment. In the context of the existence of the adapting Human, information becomes an in-formed structure, verbs become the body, and neuroimmune communication becomes a physical, embodied event. The activation of evolutionarily imprinted patterns, the traces of learned experiences, and information patterns emerging from the depth together often distort reality and might overwrite the given situation's interpretation. We evaluate the impact of the outside world based on schemes ingrained in our minds. Our empathy often exposes us to involuntary impulses and painful compassion. Our mirror neurons connect us to the emotional occurrences of the social environment. The rational response to adversity is provided by the ability to remember, analyze, and learn. However, this learning can be the basis for inadequate patterns to become imprinted. Even, without any actual challenge, rumination on memorial contents may distort our bodily peace.

In the context of stress

So far, we have been investigating signals and the informational pathways, translation mechanisms, cognitive layers, and "ecosystems" they create; however, stress is about the *story* that incorporates these signals into a narrative and gives them meaning. Therefore, stress-medicine cannot be separated from the practice of narrative medicine, which involves bringing this multi-layered

story to the surface and placing it in the focus of cognition. Stress reflects the cultural and social situation, upbringing, worldviews, fears, and resilience of the individual and their stress-biological and health-psychological abilities and aptitude. However, this all plays out not as a monodrama but as a melodrama, comedy, or even a tragedy with many actors. This multi-factorial microdramaturgy is especially apparent in the case of the complex inner physiological occurrences of stress.

With the body exposed to the siege of stimuli by the environment, humans receiving the touches of reality are "destined to be stressed" even if their intellect and technological advancement significantly increased their adaptability and expanded the boundaries of their living spaces. However, with the development of the technological environment and in possession of the intellectual potential arising from cultural evolution, the number of stressors experienced by these humans, which wear down their reserves of adaptability, did not decrease, on the contrary...

The new industrial/postindustrial and techno-informational social environment still activates the same old archaic biological responses. Cannon described emergency reaction – this response mode observed in the edge cases of environmental adversity, as an essential range of adaptive behaviors. Therefore, he identified the vegetative nervous system and the adrenal medulla as the main actors on the neurobiological, dramaturgical stage of the fight-or-flight alternatives. The set of symptoms (mydriasis, piloerection, energy mobilization, palpitations, increase in heart rate) triggered by catecholaminergic stimuli prepare the subject of the event for physical exertion. Obviously, the range of appropriate behaviors is limited in our social world full of symbolic struggles.

Hans Selye (Selye János 1907–1982) expanded Cannon's model of vegetative nervous system adaptation to include the endocrine and immune system organs. Stress as a general adaptation syndrome (GAS) is "a non-specific response to an environmental stimulus affecting the body". However, this aspecificity is not generally true, as Pacak and Palkovits (2001) show concerning central neuroendocrine processes' stress-specific nature. The emphasis is on the intensity of the response given to the stimulus pattern. *Eustress* is a response generated within the effective range of healthy stress, while the term *distress* refers to the physiological changes following adversity that exceeds the acceptable load.

When outlining the stress model, the neuroendocrine-immune connections become apparent early on. Selye described an aspecific response as the triad of *adrenal enlargement* (hyperfunction), peptic ulcers, and *thymo-lymphatic involution*, triggered by increased cortisol levels.

By doing so, he implicitly discovered a unique neuroendocrine-immune process (unnamed then), as part of which the adaptive response profoundly

influences the immune system through the neuroendocrine channels. His and the followers' oeuvre filled a neuroendocrine thesaurus, required to interpret the language of these interactions.

When interpreting stress, we should keep in mind specific essential motifs: although almost all adaptation challenges and life events cause stress, only chronic stress, which exceeds our capacity to cope and is thus uncontrollable, excessive, and unnecessary, should be avoided. The reaction to the stressor is only one part of the full behavioral response. Spielberger placed particular emphasis on the shearing effect of objective environmental adversity when defining stress, according to which the danger factor is present regardless of the individual's assessment. At the same time, Sarason emphasized the internal assessment of the external stimulus pattern. The meaning of stress has undergone significant changes during the lifetime of the term.

The ergotrophic/trophotropic concept by Eppinger and Hess (1909, 1915) can be considered one of the forebearers of the term, and Cannon (1932) called the adaptation model based on the dialectics of the sympathetic/parasympathetic vegetative nervous system the wisdom of the body. In the emergency response theory, the active fight-or-flight situation is contrasted with the calmer "tend or mend" state, when the individual collects their strength. Selye lifted the significance of the hormonal system, the HPA axis, and the stress hormones to the level of the vegetative nervous system model and discovered the significance of the adrenal cortex in addition to the adrenal medulla in 1936. He recognized that the body reacts to every environmental stimulus with the same *aspecific*, three-phase alarm/resistance/exhaustion response. Stress became specific when Mason, Volkman, and Lazarus began shedding light on the specific nature of psychological stress and the meaningful nature of the stress effect and its response from the sixties onward. Stress was never clearly a synonym for evil. Selye also differentiated between good and bad stress, the concepts of eustress and distress. However, Munck et al. (1984) put renewed emphasis on the interpretation of the phenomenon when they identified the function of stress as the protection of the body's tissues against the body's reactions. Similarly, McEwen (1998) also associated a positive meaning with stress, the concept of the "homeostasis" of struggle, the so-called *allostasis*.

Langner defined physical stress and psychosocial stress as distinct terms. According to strain theory, the perceptive, cognitive component is dominant; therefore, physical stimuli are classified as threatening or neutral based on their cognitive, emotional assessment. Past experiences, fantasies, and naturally, the individual's psycho-physiological character in question define the situation and the significance of the stimulus together as a pattern of organismic variables. On the other hand, the technical analogy of a *strain* also brings up the issue of elasticity. Following the exhaustion of the reserves typical of

the individual, the physiological response mode changes, homeostasis becomes fragile and chronic response modes develop possible unproductive behavioral dysfunction, and the loss of emotional balance can be expected.

Therefore, the body's integrity requires unified and harmonic psychological and neuroimmune homeostasis, whether the stressor is physical, symbolic, or a pathogen. The ties of common regulation maintain this unity. For example, the bone marrow's sympathetic innervation mobilizes the hemopoietic reserves or resources of the bone marrow during an infection, as stated by von Bernhardi et al. (2010). However, in the opinion of Pavlov and Tracey (2012), the vagus nerve slows down the inflammatory response to endotoxins. Therefore, the nervous system actively contributes to immune homeostasis. The immune system plays a similar role in the organization of behavior during illness due to the neuropsychological mechanisms triggered by immune mediators, such as fever, aversion to stimuli and reclusion, sleep, and loss of appetite. In the opinion of Dantzer (2004), illness behavior itself is an allostatic defensive reaction, an adaptive pattern, the organization of which includes the heightened levels of the proinflammatory IL-1, IL-6, and TNF-alpha triggering the adaptive illness behavior and physiological pattern, which are unpleasant but promote recovery. The phenomena include slow-wave sleep, anorexia, weight loss, psychomotor retardation, lethargy, inhibited exploratory and social behaviors, reduced libido, decreased sexual drive, anhedonia, and a lack of motivation.

The evolutionary role of neuroimmune stress

Huether (1996) pointed out not only the function of stress to protect the body even against itself but the evolutionarily selective "usefulness" of stress processes as well. However, all of this requires an explanation in the case of chronic immunopathological disorders since it raises questions about why evolution did not select against this range of disorders. Chronic illness means a disadvantage and intense selective pressure for those living in a natural environment when obtaining food or avoiding predators. On the other hand, chronic inflammation could trigger reproductive inhibition along the HPA axis. During severe inflammatory stress, in addition to increased IL-6 levels, a reduction of testosterone can be observed, the level of which is not restored for at least a week.

In the case of rheumatoid arthritis or juvenile idiopathic arthritis, the long-term increase in IL-6 levels is complemented by a reduction in testosterone production. One explanation is that there was no opportunity for selection, since the reproductive period of *homo habilis* was not longer than 25 years, while chronic immune disorders that lead to disability generally only emerge after 35.

We have to take adaptive advantages into account as well. We find several cases of ambiguity when trying to interpret stress; just think of the immunosuppressive function of cortisol, which is either negative and self-disarming or, on the contrary, protects the body's tissues from exaggerated inflammation. Depression and immune depression could also follow some hidden adaptive logic, which we have to evaluate in the context of evolutionary processes. We are experiencing selective evolutionary pressure from pathogens, predators, and competitive or hostile fellow humans at the same time. Amidst these responses to microbiological, behavioral, and social pressures, which often interfere with each other, the neuroendocrine and immune reactions and adaptive behavioral patterns that successfully protect us against injuries and infection will survive. The adaptive illness behavior is complemented by reclusion (anorexia, anhedonia, inhibited behavior, "depression"), the reorganization of the energy balance, and the slowing down of inflammatory processes (immunosuppression).

The double-edged challenges of the microbial environment

Our microbiological environment creates selective pressure on human evolution as well. However, the positive adaptive value of this microbial milieu is also great. The natural environment, which is rich in pathogens with low pathogenicity and serves as the evolutionary environment of humans, provides the mediators that *hold back the immune response* of our bodies with an important physiological role, such as the anti-inflammatory cytokine, IL-10, TGF-beta, Treg and Breg cells which both play an inhibitive role and are equipped with regulators, and the M2 macrophages, which contribute to immune regulation.

It was none other than Strachan (1989) who pointed out the problem in the *hygiene hypothesis:* if the body fails to encounter a sufficient amount of low-pathogenicity but a high-diversity microbial environment in the first years of life due to civilizational reasons, the underdeveloped Treg cell functions will not be able to help the adult humans who strive for hygienic sterility. Allergic and autoimmune disorders will always threaten them due to their weakened inflammatory inhibitor immune mechanisms.

The microbial "stowaways" can be our teachers, can become "co-workers" producing useful metabolites, vitamins, and trace elements, but they can also be the source of stress caused by chronic inflammation, which could be coupled with chronic psychosocial stress as well, leading to a dangerous feedback loop.

This is where the concept of the "leaky gut" belongs, too, the idea that the gut might be permeable for microbes, which places particular importance of innate immunity. Psychosocial stress triggers the mobilization of the

lymphocytes in the primary limbic organs with catecholaminergic innervation. At the same time, the mobilized myeloid cells (e.g., monocytes) activate the inflammatory information pathways and the *inflammasome*, which contains protein 3 (NLRP3) that in turn contains NF-κB, NOD-, LRR- and pyrin domains, by detecting the DAMPs (damage-associated molecular patterns) and PAMPs (pathogen-associated molecular patterns) from the "leaky gut", which leads to IL-1 beta and IL-18 production through caspase-1 activation. The activation of NF-κB triggers TNF-alpha and IL-6 production as well.

In the opinion of Miller and Raison (2016), all of this indicates a deep molecular connection between stress, mental, and inflammatory adaptation processes in a neuroimmune context.

Behavior in an immuno(logical) context

An expanded immunological model can also be created based on the evolutionarily imprinted adaptive behavioral patterns connected to the microbial environment. If we investigate the defense against pathogens as a unique ecoimmunological game, we have to include phenomena interpreted on the behavioral and social levels in the scope of terms to interpret in addition to immunological networks. The latter is simpler; the practice of vaccination, legally regulated hygienic requirements, organized and institutionalized epidemiology, the pharmaceutical research, development, manufacturing, sale of antibiotics and antiviral medications, and the healthcare treatment of infectious patients indicate the success of this network.

The evolutionarily imprinted cognitive and behavioral patterns require expanding immunity at cellular and molecular level, known as the so-called BIS *(behavioral immune system)*, a crucial element of social and cultural psychoimmunology.

If we interpret the BIS within the context of psychoimmunology, ecoimmunology gains even more emphasis. The BIS is a defensive, preventative behavioral pattern that helps the organism avoid pathogens and disease in an instinctive manner while following the society's social norms and cultural patterns in question. At a depth of this behavior, the latent threat of a pathogen-rich, unknown environment and situations can be found. The proponents of the theory claim that the preference for our group and local habitat, the sensory checking of food before consumption, the natural behaviors when coming into contact with microbial flora during commensalism, and the unknown's avoidance are all ethologically well-founded parts of the BIS. Disgust is an essential phenomenon for the BIS's adaptive processes, which is a pattern shared between the cognitive, neurovegetative, and immunological network components.

The avoidance of disease is a category of human ethology, but it is present in animals as well. Schaller and Park (2011) interpreted this immunological pattern expressed on the behavioral level as the identification of the presence of environmental pathogens and a collection of emotional and cognitive responses to the disease and the related threat, as well as of psychological mechanisms and behavioral patterns aimed at avoiding pathogens. Therefore, the authors supplement the classic immune system's reactive biological response (CIS) to pathogens with a primarily evolutionarily imprinted, instinctual, preventative mechanism in the BIS. In truth, these are overlapping systems, since the illness behavior selected for inflammatory cytokines, which serve to conserve the organism's energy, avoid further adversity, and promote recovery, can also be thought of as a behavioral immunology (BIS) pattern. However, in addition to disgust, which regulates the avoidant behavior, we have to notice the patterns that mobilize preparative behavioral elements and reach the immune system and the subject that identifies a threat.

On the other hand, the infection itself may also elicit disgust and lack of appetite, which means that the activation of the CIS (classic biological immune response) triggers the preventative BIS as well, in which their shared structures within the central nervous system, such as serotonin, also play a role. This network-based approach includes the genetic network in the scope of the investigation as well. Preventative behaviors toward pathogens are also associated with an increased avoidance of danger, reduced extraversion, and lowered interest in the environment, for which the IFNG_874 A allele appears to be responsible.

Our evolutionary-psychological interpretation framework allows more room to investigate pathogens' effects on social structure and personal psychological processes, such as intergroup emotions, especially those eliciting avoidance, inhibition, or disgust. These characteristics are reflected in the preference for members of the group (infection avoidance), selective choice of partners, kitchen techniques, and taste preferences in food culture. Selective contact with animals in the environment (avoided animals that are considered infections versus pets, the differentiation of foods and non-foods, forbidden, holy, and everyday foods), and behavioral patterns (clothing, contact ban, etc.) are also part of the set of avoidance behaviors in high-risk situations. We can include the preference for an environment based on adaptation to pathogens (philopatry) and the avoidance of strangers in the defense reactions, according to Thornhill and Fincher (2014). However, the shared interpretation of behavioral immunology and PNI takes into account the behavioral, psychological, neuroimmune, and genetic-molecular networks together with the appropriate level of the social system, and calls attention to their shared evolution, thus following an ecological framework for interpretation and the principles of the network paradigm at the same time.

Since pathogens were one of the most critical selective and balancing factors in the evolution and population control of humankind, in addition to the undoubtedly symbiotic functions (gut microbiome, etc.), the defense was formed soon as human organizations (social networks, discourses, institutions), hospitals created for the prevention and elimination of such pathogens.

The success was honored, as the Christians selflessly treated leprosy- or plague-infested patients and brought them honor high enough to convert others. A similar great success was brought to allopathic biomedicine, when the first experiences of germ theory with vaccination, later the invention of Salvarsan and Penicillin, the development of microbiology, immunology, and epidemiology reached widespread results in changing the epidemic face of diseases. This means that human development responds to the threat and challenges of pathogens on various network levels (cells, molecular, neuroimmune, psychological, behavioral, social-institutional, cultural). This game maintains continuous selective pressure. Biological evolutionary jumps integrate biochemical response modes, genetic-molecular and immune-biological response modes. These are complemented by newer and newer evolutionary "updates" (cell-level networked immune response, native-adaptive immunity); sometimes, a superstition or behavioral pattern is excluded from the scope of variants, but epidemics can make smaller groups of people disappear entirely forever. The coevolutionary drama of the host organization and the pathogen leaves a trace on the host organization's population and the genetic and phenotypical patterns of the pathogen. That coevolutionary drama creates a continuous, mutually adaptative interplay. This is why we find cast-specific infectious diseases, genetically determined immunological patterns within specific groups of people, or specific geographical areas. A prominent example of coevolution is the heterozygote of sickle cell anemia, which provides partial protection against malaria in the areas where malaria is endemic. The heterozygote infects the water-bound agricultural population, while the hunter-gatherer people living in a nearby forest are free from its influence. The present COVID-19 pandemic proves the social and cultural psychoimmunological relevance, how the pandemic reshapes personal and social behavior under the lockdown in a changing cultural context. The transformation of business dynamics, and the technological features of everyday job experience (home office, internet-based communication in healing and teaching activities (Zoom, Teams), organized transferring of foods and goods to home, and strict worksite (and home) hygienic regimes together show the cultural shift in BIS. The harsh economic losses in GDP, and the deep crisis of several economic sectors (tourism, transportation, services) allowed for radical concepts for the economic "Great Reset" and social engineering agency. These prove the network dynamism of social and cultural psychoimmunological phenomena, too.

The adaptivity and maladaptivity of the stress response and illness behavior

If we compare the list of phenomena related to illness behavior and depression and their physiological and behavioral characteristics, we can find surprising parallels between them.

Table 2. Similarities between depression and illness behavior

Illness behavior	**Major depression**
Anhedonia	Anhedonia
Anorexia	Anorexia
Reduced libido	Reduced libido
Cognitive dysfunction	Cognitive dysfunction
Psychomotor retardation	Psychomotor retardation
Lethargy	Lethargy
Weight loss	Weight loss
Sleep disturbances	Sleep disturbances
Hyperalgesia	Lower subjective pain tolerance
Social isolation	Social isolation
Sad, depressed mood	Sad, depressed mood
Sense of worthlessness/guilt	Sense of worthlessness/guilt
Suicidal ideation	Suicidal ideation

Therefore, the optimization of the processes of retreat, hiding, and healing in the background almost requires social reclusion, the inhibition of sexual, explorative, and territorial behavioral forms. We suspect blocked and optimized processes in the physiological deep as well during the stress response accompanying the inflammation of extensive injuries and protecting the organism's own tissues.

Against the civilized lifestyle and environment, which limit the natural microbiological challenges and the new, often purely psychosocial stressors, the adaptive patterns, which represented an advantage back in the day, no longer provide protection. The evolutionary heritage is derailed, phenomena emerge latently and in a prolonged manner, and what protected us in one situation becomes an underhand pathogenic mechanism in another. What used to be biological protection and retreat now becomes a psychological symptom, a biological pathogen, and a damaging psychosocial factor.

This evolutionary riddle is expressed in the bidirectional relationship of depression and immune depression (as well as the dysfunctional inflammatory phenomena), in attachment disorders, or in posttraumatic psychobiological changes, such as in the immunosuppressive effect of the stress feedback confirmed to be misaligned through positive DST, as well as in the inflammatory theory of depression.

All of this implies that evolutionarily adapted mechanisms are imprinted with their high costs. However, these costs become part of the evolutionary "quality assurance" as well. "Whoever has will be given more, and they will have an abundance. Whoever does not have, even what they have will be taken from them." This system provides additional advantages to the most successful.

Control and loss of control

Looking back at our reasoning, which placed the mind within a (co)evolutionary-theoretical framework, the joint interpretation of fate, soul, and body also elevates the immune system itself, which is connected to social-psychological dispositions and experiences, to the level of evolutionary factors and subjects of evolutionary changes. Among stress theorists, this was also attempted by Huether (1996); among the components of his general model, we find behavior-level analysis as well as behavioral and organ/organ-system mechanisms interpreted in a neurohormonal context. His model fits the paradigm of network-based principles and the bio-psycho-social interpretation well.

Table 3. Psychophysiological response to stressors

Experienced	**Anticipated**	**Imagined**
	Endangering event	
psychosocial conflict	loss of psychosocial support	loss of psychosocial competence
disruption of psycho-emotional homeostasis		
emotional response (denial, anger, guilt, grief)		
behavioral response		
Stress controllable non-controllable		
active coping		passive coping
reorientation, compensation		anxiety, depression

Table 4. The evolutionary role of stress mechanisms

Evolutionary role of stress mechanism		
Environmental (climate, nutrition, etc.)	Within the species (population density)	Interspecies (the relationship between predator and prey)
Physiological consequences	**Stress**	**Behavioral consequences**
immune suppression, circulatory disturbances, renal dysfunction inhibited gonadotropin and sexual hormones release		disturbed foraging and hygienic behavior decreased sexual behavior status loss in the social hierarchy
stress-stimulated pathology		stress-induced reproductive disturbance
Elimination of non-adequate genotypes		

We have to face the fact that animals and humans developed in a dangerous environment full of predators in chronic stress. Adamo (2012) raises the question: how can the negative effect of chronic stress on immunity have an adaptive value? It is precisely the disadvantageous circumstances that provide an answer, since, in her opinion, the long-term insufficiency of food resources and disadvantageous circumstances promote the proper metabolic and physiological changes of stress hormones, which could contribute to survival even despite the increased infectious capacity and reduced resistance. This is an especially important question since the infection itself is a stress-activating factor. It triggers the production of stress hormones; therefore, we can talk about *neuroimmune stress* as well. The most important value of this stress response is that it slows down the inflammatory tissue processes and autoimmune processes. Therefore, behavioral-immunological interactions can have different outcomes depending on the ecological context.

Perhaps it is the latent gain of the inner context that provides an answer to the question posed by Heuther: how could have our behavioral-neuroimmune system develop to incorporate such disadvantages and reduce defensive abilities, survival, and reproductive ability during prolonged stress.

Barnard and Behnke (2001) believe that this gain was expressed in the immune response's energy trade-off dynamic, and cost and risk/benefit ratio. The "optimization" of the conditions of the energy-intensive immune response, such as the reduced energy requirement of sleep and reclusion, as well as the adaptive advantages of reduced metabolism, could be the explanation. For this, we have to examine the gain-loss and risk-reward balances. The adaptive risk of illness behavior is that the active fighting, self-preservation, and reproductive behavioral patterns are blocked, loss of appetite and even anorexia may develop, and the individual becomes reclusive and prone to sleep. It has to hide,

its limited resources have to be optimized for survival and recovery through the adjustment of the internal allostasis and metabolism patterns. This means that immunity should be interpreted in adaptively optimized trade-off situations and contexts. As we will see, in James Henry's model, the immune system's neurohormonal medium is different during a struggle, in a losing situation, or during a prolonged threat. In fact, life history is a series of such optimizing switches and changes, where the aim of this energy investment could be growth, survival, or reproduction. The authors mention life strategy-dependent immunological trade-off logics. In this trade-off logic we might find the importance of human personality, life events, developmental factors, and changes. Naturally, the behavior of the individuals changes as a result of the severe immune-depressive consequences to reduce potentially immune-depressive activities.

In the case of animals placed into a new group, which is a situation full of threats and aggressive interactions, the level of testosterone is reduced, which eliminates the difference between the typically high testosterone-levels detected in dominant individuals and the low levels detected in submissive individuals. However, if we place immune readiness in the center of our evolutionary construct, we have to admit that an obviously energy-intensive basic readiness is necessary for all organisms, even in the absence of an infectious agent. The illness behavior exhibited in the case of an infection reallocates resources to combating the infection, the lack of appetite and the reclusive state leads to a redistribution of resources according to an evolutionary pattern, while immunity can be placed under pressure during the prolonged physical or mental struggle for survival. Therefore, concerning the dynamics of self-preservation and reproduction, during the evaluation of the paradoxes of welfare, hardship, and failure, evolutionary correlations can serve as the foundation of a social-psychoimmunological approach.

Table 5. The emotional, behavioral, and neuroendocrine levels of stress responses

	Level of perception	
	Level of processing frontotemporal cortex limbic system	
	Level of emotions	
rage	fear	depression
	Level of behavior	
struggle/effort	escape	accepting to lose control
	Neuroendocrine reaction	
noradrenaline + testosterone +	adrenaline +	cortisol + testosterone -

In the case of the social-psychoimmunological approach, situations, social experiences, historical fate-related experiences, and their psychological meanings are translated into nervous system patterns and the network patterns of discrete hormones, neuropeptides, and interleukins, as well as neurobiological fate patterns with ruthless directness, which then lead to the death of the individual and a reproductive disadvantage for the group. This is supported by the typology created by James Henry, which compares the fate- and neurobiological patterns of winning, struggling, and self-defeating, losing individuals, which is confirmed in the scope of interpretation of social psychoimmunology as well.

In the case of individuals who lost control, the HPA axis's increased activity leads to the negative neuroimmune consequences of stress. Long-term regulatory dysfunctions could render the individual susceptible to illnesses with various immune pathologies if the individual already had a higher level of susceptibility. The negative hormonal consequences could also prevent reproduction. In the winner's case, the patterns of fight-readiness and active struggle and an increased secretion of sex hormones all help the successful further expansion. The human analogy of the weaker food-seeking, lowered territorial, sexual, and hygienic behavior elements observed in the case of experimental animals exposed to chronic stress or the control-less state of submission does not require further proof in connection with the loss of control in cases of grief, depression, and other states involving the loss of objects.

Early trauma and its role in different selection trajectories

What factors expose individuals to the above mechanisms at an increased rate? Are there any personality-level or individual stress-biological disadvantages that make it more likely that an individual would end up on the losing side? Therefore, the social-psychoimmunological interpretation of the physiology of our bodies is an exercise in evolutionary and ecological context. These hermeneutics show the immune system as a double agent of evolution, which protects us from internal and external pathogens if we are successful but contributes to the preservation of negative patterns in the case of failure. This gives outstanding health-psychological and psychobiological significance to the early mother–child relationship, which we are going to discuss in detail later, in the light of wider cultural correlations.

It is worth outlining a natural, social, technological, and cultural-cognitive dynamic space, which is built up of networked circular processes, in which the cultural-social-psychological-immune and immuno-neuro-psychosocial cultural flows and patterns of specific interactions can be drawn up. These environmental influences, which create dominant, symbiotic, parasitic, or saprophytic

ecological relationships with each other as well, are organized into tight circular processes with the human body.

The connections of early attachment systems with group-level regulation and cultural evolution

The conditions, legal regulations, and technical practices of birth are determined by the cultural and cognitive world and the social and institutional arrangements of the specific society; birth affects the mother–child relationship and has long-term developmental psychological consequences as well. We have already discussed mutual relationships in detail, such as the birth practices typical of the specific climate, how the following mother–child relationship can have effects on psychology, and even cultural and institutional characteristics. This is an important chapter of psychological anthropology; this problem takes an important place within the work of the proponents of cultural anthropology, Kardiner, Róheim or Devereux as well as in the anthropological oeuvre of Margaret Mead, Whiting and Child (1953) or LeVine. To us, it is the expanded human ecological interpretation of the phenomenon that serves as a framework for our evolutionary approach in this chapter.

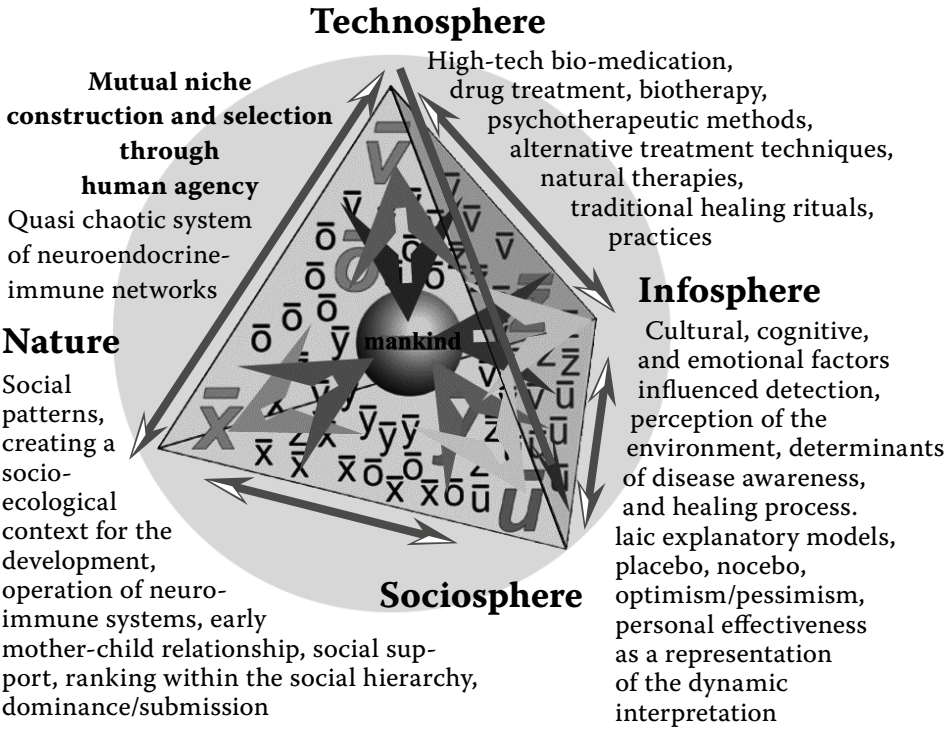


Figure 8. The human ecological context of psycho-immune patterns according to the M-E-O model

At the same time, but independently of the already-discussed Huether-model, we developed another evolutionary model (Lázár, 1994). The possible evolutionary selective consequences were assigned meaning within a social-psychoimmunological model, which was inspired by the animal experiments' findings on early-life trauma and was based on the developmental psychological interpretation model of attachment. This hypothesis has been confirmed by models of social epigenomics and cultural evolution at several points since then. We are going to detail the A/C developmental psychological model of early-life attachment together with the relevant psychophysiological consequences. We are only going to mention the evolutionary and selective patterns hidden in the model here.

I. Group defense mechanism with the characteristics of positive feedback
The increased social effectiveness and psycho-neuroimmune competence of a psychosocially 'fit' person (due to type B attachment organization, type B harmonic personality) increase their reproductive fitness.

Typical examples of increased personal and social effectiveness are increased attractiveness in the reproductive period and an improved mental and bodily health.

The individual's reproductive success also increases the reproduction of attachment organization and the fitness of social skills, harmonic social attachments, and group mechanisms, which represents an increased adaptive value in the framework of group selection.

The dominant attitude is a *harmonic attachment* in the value system of the given sociocultural and institutional system. The culture of reproduction is dominated by the secure mother–child relationship. The group creates a safe, harmonic, and ethical relationship with the sociocultural and natural environment.

II. Group-level eco-integrative self-regulation with adaptive potential
The behavior and adaptation modes exhibited by infants, traumatized in terms of the mother–child relationship develop due to the secondary type A or C attachment organization.

The unique type A or type C approach functions within the eco-contextual organizational framework of society and is connected to the sociocultural and socio-psychosomatic patterns of the majority with harmonic attachment.

The type A and type C behavioral and coping modes developed based on secondary attachment organization contribute to the development of the image of the culture in question and its maintenance across generations.

Society utilizes and takes advantage of the psycho(patho)logic characteristics, and it can address the negative psychobiological and somatic consequences on the level of biomedical industrial technology. Society and the relationship

developed with the environment is characterized by both changing normative attitudes and anomic contradictions.

III. Group-level group defense by negative feedback mechanism (kin selection)

The late social trauma (loss, sanctions) of a person damaged by trauma during an early-life relationship (due to type A or C secondary attachment organizations) can increase (in the case of genetic predisposition or accidental infection) the risk of developing depression, psychosomatic, or psychoimmunological disorders, proved by ACE studies.

This can reduce the reproductive fitness of the individual, which in turn reduces the likelihood of the reproduction of the secondary type C attachment organization, which is a factor that protects group-level fitness.

The population with harmonic attachment gains a selective advantage and the mechanisms maintaining the early-life attachment disorder fade out of the sociocultural system over time.

IV. Population-level shift with a maladaptive depopulation potential

Early-life social damage affects a significant portion of the entire group, which is expressed on the one hand in type A and type C attachment organizations, on the other hand, in the emergence of related behavioral disorders later in life.

In the case of a type A personality (A: psychopathy, addiction, avoidant or independent attachment in adulthood) or type C attachment organization, the personality traits predisposing the individual to psycho-immune-pathological disorders, such as allergy, autoimmune disorders, and cancer, are more common.

The values of adult attachment disorder, psycho-pathologization, and selfish negligence toward the environment can become dominant as a result of an early-life attachment disorder (Lasch: *Narcistic Society*, Fukuyama: *The Great Destruction*), anomy, a low rate of marriage, high rate of divorce, reduced reproduction, and a demographical crisis can be observed. The environmental and sociocultural crises bring about the decline of the entire society.

When borrowing from ecology, based on the work of MacArthur and Wilson (1967), and applying the so-called *r* and *K strategies* to the above correlations, we observe the r strategy more often in bad socioeconomic environments, among social groups in disadvantaged situations. The human ecological equivalent of r strategy and the uncontrolled, high reproductive rate, which does not follow the western practices of family planning, is characterized by a large number of offspring, which exceeds the resources and limits (carrying capacity) of the sociocultural and natural environment; therefore, an overpopulation crisis emerges if the environmental factors become unfavorable.

The increase in the number of traumatic childhood stressors, together with the unfavorable psychopathological and psychosomatic consequences, is characteristic of groups with a low socioeconomic status. This is expressed in lower life expectancy, worse health, often higher proinflammatory cytokine levels, and behavioral disorders that maintain an anomic social environment. This is true for a significant portion of the third world, the masses who fell victim to climate crises, the socioeconomic victims of globalization, and the cumulatively disadvantaged or unintegrated and poor social groups. Taking into account the fact that high technology, robotics, and automation exclude larger and larger masses from the world of (manual) labor, the situation of these masses is becoming more and more critical, which is further exasperated by the migration crisis.

The socialization experiences, which have long-term effects, are reinforced by poverty, the bearing of many children, the amount of care and attention they receive, the reduction in emotional support, abusive stress, and social epigenomics. They are communicated through generations, and leave a mark on social-psychoimmunological characteristics as well, and elevate r strategy among population-level maladaptive human-ecological risks. The social-psychoimmunological consequences discussed in this work (epidemics, inflammatory, cancerous, or immunopathological disorders with high healthcare costs, early-aging, and inflammaging) play an essential role in this.

On the other hand, the K strategy means fewer children from both a human ecological and attachment standpoint, with long-term, attentive care. The mortality rates of the population are low, and individuals live to old age in general. We would be forgiven for thinking that this is a guarantee for harmonic attachment, that is, welfare and the related K strategy guarantee the optimal state of the mother–child relationship and a harmonic developmental psychological path. However, the civilizational advancements, value and role system, and gender-cultural changes of industrialism and the following postmodern information society distorted the K strategy in a unique manner; lifestyle, career expectations, as well as the changes in female life strategies and gender image, resulted in childbearing being postponed further and further, and the damaged attachment patterns due to the early return to work of mothers, after just six weeks, resulted in an increase in the ratio of avoidant adult attachment patterns within the population, which was indicated by Csóka and Lázár (2013) in their Hungarostudy research. Therefore, due to the practice of technocratic birth, early return to work, and postponed childbearing as well as the cross-generational maintenance of the damaged attachments, K strategy has also taken an unfavorable developmental psychological path and could also contribute to the prevalence of the epigenetic consequences of the dysfunctional mother–child relationship.

A factor limiting the spread of the K strategy is the self-regulation of reproduction itself. The evolutionary scheme, the limitation of the increase in population, is caused by the characteristic of the K strategy that as the number of offspring increases, the amount of stress on the mother also grows, which could cause behavioral and physiological changes through the neurohormonal system, which restrict the number of offspring. In humans, the institutionalized cultural equivalent of this behavior is the single-child family pattern and the practice of abortion. However, it is present in numerous forms of family-sociological anomalies (cohabitation of partners, homosexuality, high rate of divorce) as well as in other tools of family planning.

Following a logic that disregards both health-psychological and moral values, Belsky (1991) interprets these phenomena from the point of view of the environment and identifies the r strategy as more favorable under chaotic, dangerous, and unpredictable social and environmental conditions, since he sees adaptive potential in the high number of offspring as well as the psychopathic, asocial, and anomalous social behaviors as well. In such cases, the uncertain attachment patterns, the avoidant and even anxious-ambivalent behavior can represent an adaptive value in an unpredictable environment. However, a safe and predictable environment favors the K strategy.

However, all of this affects the social-psychoimmunological correlations as well. A disadvantaged situation carries not only the risk of "downward" influence, such as the traumatic stress of the early-life mother–child relationship. Through perinatal infections due to an often bad hygienic environment (slums, shantytowns, and housing projects) or any irresponsible behavior of the mother that exposes the child to such risks, "upward", that is, long-term psychopathological and distorted stress-biological consequences can be observed, caused by immune-neural mechanisms. Such immune-neural stress factors also last a lifetime, and, based on the results of animal experiments, they have psychobiological and psychological risks, which become ingrained through epigenetic mechanisms and are exacerbated by the early-life developmental plasticity and vulnerability.

This is because, in the opinion of Sominsky et al. (2013), perinatal infections can cause anxious behavior as an adult trait due to the immune-neuropsychological effects, at least in animal experiments, and this can be carried forward across generations through epigenetic mechanisms. However, we can see an evolutionary limiting factor in this case as well, since the neonatally infected animals or those treated with LPS showed lower levels of fertility and thus produced less offspring than those not treated similarly. It is as if these selective mechanisms only checked the ratio of the changes.

If we examine the adaptive consequences of perinatal programming that increase survival rates, this is only true if the psychobiological and behavioral

consequences are actually adaptive. In a threatening, unpredictable environment, this can truly represent an advantage for avoidant attachment and even unempathetic, solitary, and uninhibited behavioral patterns; however, it is difficult to find a short-term advantage in stress-biological disadvantages, even under such circumstances. The harsh psychoenvironmental circumstances among those following r strategy – like childhood adversity such as maltreatment (Caspi et al., 2002), trauma (Weder et al., 2009) and sexual abuse (Beach et al., 2010) – are not infrequent. The risk of antisocial, violent, impulsive and aggressive behaviors in adulthood is higher among such children. Environmental stimuli can lead to epigenetic programming that influences life-long behavioral trajectories. Investigation of post-mortem brains proved that methylation and expression of the human *NR3C1* exon 1F gene showed altered profiles in the hippocampus of suicide victims exposed to child abuse (McGowan et al., 2009); and according to Labonté et al. (2012) genome-wide studies identified differential DNA methylation in many gene promoters in the hippocampus involved in cellular/neuronal plasticity in the case of people having suffered severe childhood abuse. Furthermore, adverse childhood experiences (ACE) showed correlations with ischaemic heart disease, cancer, chronic lung disease, skeletal fractures, and liver disease. Epigenetic modifications have been reported in patients with post-traumatic stress disorder (PTSD). Allelic-specific DNA demethylation of the FK506 binding protein 5 (FKBP5) gene, encoding an important regulator of the stress hormone system, is associated with long-term dysregulated response to stress and an increased risk for PTSD in individual victims of child abuse (Klengel et al., 2013). On the other hand, according to Barr et al. (2003) maternal deprivation might induce a high level of aggressive/impulsive behavior in the offspring with epigenetic alterations of the prefrontal cortex in the background.

Champagne et al. (2008) proved that animal offspring that developed with insufficient maternal care showed better cognitive abilities under stressful conditions in adulthood; however, they performed worse under ordinary circumstances than the control animals. In the case of rodents that provide regular maternal care, the researchers observed the opposite tendencies. All of this indicates that radical societal changes and unpredictable reorganization can benefit those who are damaged from a psychosocial point of view, including individuals with psychopathic, morally uninhibited tendencies or, on the contrary, individuals able to exhibit self-sacrificial and altruistic behavior, which goes against their own interests, while under consolidated social circumstances, the better problem-solving and norm-following ability of harmonic individuals provides them with a sociocultural and health-psychosocial advantage.

However, the "permanent revolution" of fast-paced technological, informational, and economic changes can have an opposing effect on adaptive behavioral-biological patterns. Therefore, over the course of evolution, experiencing perinatal stress implies an environment that is stressful and full of unpredictable adversity, which is accompanied by increased alertness, vegetative activation, and arousal or heightened anxiety when following the r strategy, based on the above. All of this can be advantageous during times of purely physical adversity; however, it is more often than not a source of disadvantage in the postmodern, high-tech information society. By the way, early-life traumas themselves increase phenotypical diversity on the population level, mediated by epigenetics, which changeability can be an advantage on the group-level, since during times of changing environmental adversity, it may "produce" the agents, extreme behaviors, habits, and solutions able to address ad-hoc challenges, even if at the expense of the health-psychological stress experienced by individuals.

This means that in spite of developmental psychological or psychoimmunological "cost", the group can utilize these irregular behavioral patterns, according to the above model described under the title "group-level ecointegrative self-regulation with adaptive potential". Therefore, for example, hyperactivity, lack of empathy, and a competitive attitude can be the source of high performance; however, the extreme behaviors and personality traits can be utilized by the group as a deterrent for maintaining their own sanctioned norms. Thus, the extreme behavior or illness can influence moral for the majority in adverse way, while the individual in question may be protected from risks by anxious behavior.

The developmental psychological correlations derived from attachment theory place the dramaturgical laws of the winner or loser personality dispositions as well as the ruthless restrictive and coercive ethology of social ranks within an evolutionary dynamic, creating a social psychobiological framework. As a result of early-life traumas and the epigenetic effects of childhood psychosocial traumatization, phenotypical variability increases within the population. From an evolutionary point of view, the increase of individual variability may have a beneficial effect on the survival of the group. What is disadvantageous for the individual, may be a unique resource for the group. On the other hand, the developmental psychological and neurovegetative developmental path, rooted in early-life traumatization, could cause susceptibility to certain immune-pathological or psychopathological disorders. The increased anxiety and reduced novelty-seeking could keep part of the group away from the increased risk as well. The appearance and transgenerational transmission of these phenotypes can have a context-dependent value in a continuously changing environment.

The anxious behavioral patterns, which are interesting from a psychoimmunological (and immune psychological) point of view as well, develop as a result of perinatal infection (perinatal LPS exposure) as an immune stressor, and can be detected in the animal in adulthood as well, are transmitted by these animals in a transgenerational manner. Since this is true to the paternal lineage as well, the epigenetic mechanisms, which we are going to discuss later, also play a role in their transmission. However, the newborn animals treated with LPS create a subpopulation with lower fertility in their adulthood, worse mothering and produce a lower number of offspring. This means that under unchanged conditions, the damaged subgroup is not able to proliferate; however, changes that are favorable to them and create an environment that selects for their traits can still increase the value of this subgroup. Thus, perinatal epigenetic programming ensures the development of population-level adaptation in a more flexible manner than in cases of the slower evolutionary pressures.

Through DNA methylation and histone modulation, the epigenetic mechanisms make changes in genetic expression possible without altering the nucleotide sequences. Thus, different phenotypes may appear while the genetic code remains the same. Maternal care as an environmental factor affects the genetic expression of the offspring, mediated by epigenetics. As a result of insufficient maternal care, which is harmful to the offspring, "tissue-specific" epigenetic modulation and methylation occur in the hippocampus, hypothalamus, and amygdala of the offspring. The epigenetically modulated structures can affect not only the stress-biological and immune processes, but they may influence behavior as well. Provençal et al. (2012) confirmed, using rhesus monkeys, that there are no changes in the case of the animals kept with their parents; however, they detected lower social skills in the case of the animals raised with peers but in the absence of the mother, and the adult female animals showed worse maternal behavior and were situated at the bottom of the social rank system. This is true not just for early life events. Human observations proved that a stressful, abusive childhood involving violence leaves an epigenetic mark through DNA methylation, which can be shown in adult T-cells as well. The trace of aggression can be shown in this manner through the examination of the so-called *protocadherin gene family* (PCDH8, PCDHB2, PCDHB8). This influence, which reflects different methylation processes in the hippocampus, can be observed in rats raised without their mothers as well as people who experienced abuse as children, as stated by Guillemin et al. (2014). This consequence, which creates an epigenetic imprint in T cells as well, is important since we know that persons experiencing early-life trauma, cold maternal behavior, or abuse can be characterized with an increased level of proinflammatory cytokines, which can be considered a morbidity marker. The animals

kept away from their mothers and "raised by their peers" showed a detrimental difference in the area of the prefrontal cortex as well as in the peripheral lymphocytes in terms of the methylation of the promoter gene section. The epigenetically modulated gene sections are connected to classic immune genes in the case of nine genes regulating interleukins and two MHC-II genes in the prefrontal cortex.

Whether we consider the neuroimmune communicational relationship a bidirectional "neuroimmune" discourse or a networked system that was shaped by evolutionary pressures and is in communication with its environment, the logic, dramaturgy, and experience-based heritage of environmental adaptations were built into the formation as information and became a structure. This is the evolutionary wisdom of our body.

ECOLOGY AND EVOLUTION OF PNI NETWORKS

Learning in a neuroimmune context

The brain and consciousness can be interpreted not only within the framework of evolutionary psychology, the ecological and evolutionary "epic" played out by the mind and the environment. The conceptual world of the infosphere itself is an evolutionary and ecological creation. It might be included in a general evolutionary theory (Csányi, 1988), like Popper's second world. The activity of the neurons creates stimulus patterns and structures. Csányi called these *concepts* based on Milner's work. They are created depending on the patterns already existing in their environment (such as memory impressions, mnemonic techniques, associations), which means that these concepts can influence other concepts' chances to develop, thus acquiring a function. Concepts are replicative structures, and as a result of repeated stimuli, the stimulus pattern states of "signal entries", create long-term memory traces, which can be thought of as the "resting state" of concepts. The existence of this state-dependent memory and state-dependent behavior implies that these concepts can be recalled, which are mobilized together with the entire behavioral pattern and the stimulus state related to the experience and reliving it in the case of the extensive activation of the concept, as we can often see during healing hypnosis. This could have significance in the case of the therapeutic resolution of the already discussed pathogenic traumatic experiences, which cannot be addressed in any other way.

The elimination of contradictions and the transformation of concepts into a convergent pattern resulting from conceptual development generate typical shifts from one state to another. The development of a worldview, religious conviction, or scientific paradigm can be considered a unique succession of concepts in an ecosystem.

Disadvantageous patterns can also become ingrained in the long term, which may be a burden for the individual and become pathogenic. There are specific patterns that are disadvantageous for the individual but are viewed as advantageous for society. These often serve the function of maintaining social control over the individual. Such a physiological concept pattern could be an exam, grief, abandonment, shame, or the pattern of voodoo death, in which

case a particular situation, rich in meaning, leads to a physiological reaction disadvantageous for the individual, maybe even immunosuppression.

The convergence of concepts often poses an obstacle to the acceptance of new theories or concept populations, as we see in worldviews, religious views, scientific paradigms and discourses, that is, in the world of socially accepted knowledge. A similarly resilient pattern may be created from social-psycho-immunological, mental, physiological, and behavioral concepts that had a function in the earlier periods of evolution but have become burdensome and pathogenic today.

If we think of the mind as an organ characterized by selective processes, we can interpret it as a consubstantial entity with an ecological environment. The *selective principle* of organizing the mind's operation is present in Thorndike's trial and error learning. The behavioral elements leading to the situation's solution are reinforced based on cause and effect and become part of the behavioral toolset. Karl Bühler interprets human development along three selective axes. He places the level of polygeny in the *Darwinian selection field*; the other level develops patterns during the lifetime of the individual through the selection of behavioral patterns, called the level of *habit development.* The third level is the level of the intellect, the *mind's level*, which also plays a role in selection and reproduction.

Edelman (1987) goes as far as to call his theory neural Darwinism, according to which competition and selection emerge between the various neural patterns during ontogeny, and even the nervous system's ontogeny creates a preliminary view of concepts and conscious logic. Perceptual learning processes reinforce the traces perceived more often, while the rarely-perceived ones deteriorate and degenerate. All of this is made possible by cell death and the degeneration of synapses. However, the *exaptational* explanation also has a meaning connected to evolution, since "ideas" and neural patterns selected without reason or for another reason may prove to be useful for survival following their selection.

Cosmides and Tooby (1996) developed the computational theory of mind based on Marr's work in order to explain the development of universal adaptive psychological patterns selected for during evolution. They interpreted the psychological mechanisms they called "Darwinian algorithms" as specialized learning mechanisms that organize experiences into schematics rich in meaning from an adaptational point of view, or phrases. These Darwinian algorithms concentrate attention, organize perception and memory simultaneously, and determine the operational knowledge controlling the decision-making behaviors.

It is difficult to imagine that in the case of behavior-organizing algorithms applied in existential situations that threaten self-preservation, such as infectious diseases or the processes related to wounds inflicted by a predator

becoming infected, learning processes memory, and the immune system could be separated from each other. On the contrary, the brain's cytokines play an essential role in neural and neuroendocrine processes and behavior regulation as neuromodulators, according to Vitkovic et al. (2000). The illness behaviors emerging as a result of interleukins, especially IL-1, IL-6, and TNF-α, affect and weaken the learning and memory processes based on Larson and Dunn (2001) research blocking cytokines, which promote inflammation, prevent such illness behaviors. Another illuminating piece of data is that according to Yamada et al. (2000), the emotional regulation and emotional behavior of IL-6 and TNF-alpha knock-out mice differ from the normal animals. Other cytokines were also measured. For example, a positive impact on cognitive functions was found in the case of the anti-inflammatory IL-4. Some researchers also reported a positive impact on brain functions generated by the proinflammatory cytokines IL-1, IL-6, and TNF-alpha, which was probably mediated by neurotrophic factors, such as BDNF, NGF, insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF). However, an excessive release of these cytokines in the event of severe stress may harm learning and memory processes, neuroplasticity and neurogenesis. The mast cells of the brain can influence emotional states. The immune system's activation has an effect on both the hippocampus and the connected cognitive functions. However, the cytokine effect is context-dependent; it may contribute to the mast cell's death and survival. IL-1 may have a neurotrophic effect on the immature neuron, but it may also contribute to the mature cells' death. During the therapeutic application of IL-2, confusion, and visual amnesia were detected. The paraventricular nucleus plays an essential role in integrating cognitive and emotional processes with the neuroendocrine and immune processes.

Memory and adaptation – cytokines and synapses

The immune system itself also plays a role in the processes of learning and memory. Pro-inflammatory cytokines contribute to the induction and maintenance of hippocampal retention processes (LTP), the production of neurotrophins, and neurogenesis.

In this context, it is essential to know that inflammatory cytokines are capable of influencing high-level cognitive functions as well. For example, the 12-week interferon-alpha treatment applied in the case of Hepatitis C activates the area of the brain responsible for conflict monitoring and cognitive control exercised during difficult intellectual tasks, the dorsal section of the anterior cingulate cortex to a significant extent. Therefore, IFN-alpha can play a role in stimulating the centers responsible for assessing danger and contributing to the resolution of dangerous situations and conflicts.

The effect of IL-1 follows a U shape, which means that normal physiological IL-1 levels are required for neuroplasticity, and the optimal functioning of the memory, and chronically high levels and the blocking of the IL-1 effect both lead to disorders of the memory functions. Its effect on neurogenesis is also crucial since the creation of memory traces also means creating new neurons. The synaptic plasticity of the hippocampus plays an essential role in the imprinting of memory traces. IL-1 influences other brain processes as well. For example, Ling et al. (1998) believe that it affects the differentiation of mesencephalic progenitor cells into dopaminergic neurons. The normal physiological levels of the corticosteroids influenced by IL-1 along the HPA axis is essential for the imprinting of spatial memory traces; however, increased steroid levels weaken the memory trace.

The receptors of the IL-1, IL-6, and TNF-alpha interleukins are present in some regions of the hippocampus as well, which is responsible for memory processes. Therefore, due to the induction of the LTP (long-term potentiation), an increase in the expression of the IL-6 gene can be detected in the hippocampus; however, blocking the IL-6 leads to an increase in the duration of LTP. Thus, the possibility of a negative feedback phenomenon emerges, which means that the IL-6 might have a physiological function to stop LTP. Tancredi et al. (1992) were among the first to prove *in vitro* the dosage-dependent blocking effect of TNF-alpha on LTP, which was later confirmed by others.

Under physiological and harmonic conditions, IL-1 is necessary and plays a physiological role in the consolidation of memory traces. It is confirmed by the fact that a low dosage of IL-1 improves the functioning of the memory, while the genetic or pharmacological blocking of the functions of IL-1 leads to memory disorders.

However, the increased level of IL-1 in the brain caused by stressors has an opposite effect, and in addition to its direct detrimental effect on memory, it also influences memory processes by activating the HPA axis. By the way, endogenic IL-1 activates the HPA axis not only as a result of infections but also due to psychological stressors, causing an increase in the level of IL-1 and the activation of the HPA axis, as stated by Goshen et al. (2003). Several other researchers have confirmed the role of psychological stressors in activating the brain's IL-1 system. If the effect of IL-1 is blocked using intrathecal IL-1ra before the application of the stressor, the detrimental effect of the stressor on memory is absent.

During nerve activity, the creation of IL-1 beta and TNF can be observed even without an inflammatory process, and these mediators play a role in regulating the intensity and strength of synaptic transfer. TNF influences synaptic activity through the TNF R1 receptors and affects the self-regulation of neurons concerning action potential, as stated by Stellwagen and Malenka (2006). However, TNF plays a role in hippocampal neurogenesis as well, and

increased secretion of IL-1 beta can be observed if LTP is injected into the hippocampus. LTP (long-term potentiation) may contribute to stabilizing memory traces, even if not as part of a homogenous mechanism. The cytokine secretion observed during increased neural activity influences the functioning of the synapses. IL-1 and IL-6 affect the brain's neural activity; however, the increased and uncontrolled presence of these cytokines may lead to a cognitive deficit, reduced memory function due to the level of activity in the hippocampus, and lower synaptic stability.

Therefore, the IL-1 and IL-6 cytokines may significantly influence the brain's physiological processes as well, and their increased level of expression may lead to cognitive disorders, the weakening of the function and strength of synapses, and the deterioration of memory processes. This is especially common in old age and becomes meaningful in the context of the so-called "inflamm-aging" phenomenon, which is characterized by an increase in IL-1 and IL-6 levels and an excess of TH1 highlights a connection between inflammatory tendencies and the deterioration of memory. In Godbout and Johnson's (2004) opinion, this is primarily caused by IL-1 and IL-6, while the role of TNF-alpha is less significant or could even be helpful. Therefore, the proinflammatory cytokines, especially IL-1 and IL-6, may play a role in developing dementia, which is especially important concerning the pathology of Alzheimer's disease pathology since memory loss can be one of its first symptoms. On the other hand, TNF-alpha could play a unique protective role in Alzheimer's disease. The IL-1 and TNF-alpha cytokines released during peripheric immune processes can influence brain processes through the afferent vagus nerves.

Chronic psychosocial stress could negatively affect the nervous system due to persistently increased levels of glucocorticoids. Sapolsky (1992) identified damage to the hippocampus in the case of animals exposed to intragroup conflict and significant distress, and Meaney (1996) asserted that the permanently high level of cortisol might have similar effects on the human hippocampus. However, burdensome psychosocial stressors or other permanent distress sources could influence different factors related to memory processes. For instance, the level of BDNF in the hippocampus might also decrease due to stress.

This observation could be just a mention of a miscellaneous side-effect; however, in this context, BDNF is a distinguished node of a network of effects, a molecular "hub" (including the receptors), for glucocorticoids, catecholamines, or even TLR4, IL-1, or IL-6. BDNF plays a crucial role in neuroplasticity, cell survival, the development of learning ability, and stress regulation. It affects stress-associated mood disorders, which places BDNF at a distinguished connection point between the social, narrative, and cognitive-emotional networks. Furthermore, physical activity makes the active muscles a source of peripheral BDNF secretion, playing a hidden health-protective agency. As we have

already mentioned, even moderate amounts of chronic stress can result in demonstrable changes in the level of BDNF in the hippocampus of lab animals, which is accompanied by significant long-term changes to the hippocampus based on the observations of Molteni et al. (2016). Fonken and Nelson (2013) experimentally proved that even low levels of light exposure at night (dLAN) can trigger depressive symptoms by reducing BDNF expression in the hippocampus. This is why many recommend the examination of BDNF levels in saliva in addition to saliva cortisol tests. The ability of mast cells to produce serotonin also contributes to adult neurogenesis in the hippocampus. Nautiyal et al. (2008) were able to eliminate the difference between mast cell-deficient mouse strains and standard animals' neurogenesis.

When looking at the body as a whole, we can say with certainty that the immune system's health is essential for the nervous system's normal operation. Damage to the immune system may lead to disorders of the neurogenetic processes and cognitive functions.

Synapses and immune synapses

The critical components of the information flow networks of social psychoimmunology are the information transfer interfaces; therefore, it is worth mentioning that the synapses that play a central role in the nervous system's information transfer are present in the immune system as well, in their own unique way.

The apparent similarity between the synapses between neurons and immune cells is caused by identical or related lipid and protein molecules. It should also be noted that short-term cell contact does not lead to an appropriate immune response in immune recognition. Only mature and permanent synaptic connections result in effective immune communication between APCs, equipped with MHC, and T cells, which possess TCR receptors.

This synapse-like connection is typical of B-lymphocytes and NK cells as well. B-lymphocytes create immune synapses with phagocytes, while NK cells do so with the recognized target cells. The part of the membranes of the APC (antigen presenter cell) and the T-lymphocyte that come into contact, where the activated TCRs (T-cell receptors) are concentrated, is also called the *supramolecular activation complex* (SMAC). The prolonged activation of the T-cell, which is an intracellular Ca2+ level lasting for more than 60 minutes, is necessary for appropriate IL-2 cytokine production levels to be observed 10–24 hours later. Such a stable neural synapse is required for the axodendritic, axo-somatic, or axo-axonic connections between nerve fibers. The two systems are directly connected through the so-called *tripartite synapse*

within the nervous system, which is a term that includes the astrocyte feeding the synapse of the two neurons as well.

In the case of immunological synapses, such as those created with thymic epithelial cells (TEC) or dendritic cells (DC), the strength and duration of the signal determines the fate of the T-cell, that is, whether it is transformed into a naive CD4 helper or a CD8+ cytotoxic T-cell during the maturation processes taking place in the thymus. Based on the signal's strength and duration, the contact with the antigen presenter (APC) dendritic cell can be short and fruitless or lead to T-cell priming. The differentiation of the Th cell lineage (in the direction of TH1/TH2/TH17) is determined by the created immune synapses. The startup of the antibody response is determined through the synaptic connection of the TH2/B cell.

Immune synapses are complex and dynamic contact structures mobilized by creating specific molecular connections, which provide an interface for information transfer coordinated in space and time and make the selection and integration of these signals possible.

Naturally, the differences are apparent when comparing the cells forming the synapses of the nervous and immune systems, since the development and connection of the nerve cells create a relatively unchanging and dynamic network. It does not show significant changes following its development, even if a certain amount of neuroplasticity is present in the central and peripheral nervous systems; significant changes only occur due to degenerative processes.

On the other hand, immune synapses are created and destroyed in an ever-changing, dynamic space in numbers as large as millions. The immune cells themselves are short-lived compared to nerve cells. Compared to the long life and locality of nerves, immune cells only live for a few days, and they travel vast distances within the body. However, a common characteristic of the nerve and immune synapses is that they are both made up of identical or related lipid and protein molecules, and the synapses of both the immune and nerve cells can only function if a so-called mature synaptic connection is established.

In addition to the immune synapses controlling T-cells' activation and differentiation, B-cells and NK cells can also create immune synapses. B-cells connect to the phagocytes carrying antigens on the cell's surface using immune synapses, and NK cells also create blocking or activating synapses with their target cells. The creation of synapses is a dynamic process that begins with scanning when the agile T-lymphocytes scan the potential partner cells found in their environment and if the suitable adhesive molecular pairs are present (DC-SIGN/ ICAM3), the T-cell stops moving and an immune synapse is created through the establishment of the TCR-pMHC connection.

Without this, the APC's connection with the T-cell are unstable, and the T-cell quickly detaches from the dendritic cell. If an immune synapse is established, the molecules (microclusters) in the interacting cells' plasma membranes

are reorganized and the number and affinity of adhesive molecules on the surface of the T-cells increases, resulting in an increased strength of the connection between the cells.

The TCR forms increasingly large clusters with the connected MHC-peptide in its synapse center (cSMAC – central supramolecular activation cluster). The cytoskeleton is also reorganized, and the cell changes its shape. The change in the structure on the molecular level leads to the formation of the so-called "membrane ripples", which ensure a high density of molecules, which is essential when presynaptic APCs and postsynaptic Th-cells come into contact with each other. Immune synapses are similar to nerve synapses in that they are also stabilized by an adhesive molecular ring around the synapse. The signalosome is created through the concentration of signaling molecules and so-called adaptor proteins in the synaptic center.

The neurohormonal effect can manifest at any of the attack points created by several "dramaturgical moments. These include the entry of an antigen through infection, injury or inflammation; the rallying of leukocytes by chemokines to the location where the antigen entered; the activation and migration of antigen-presenting dendritic cells of the tissue to the local lymphoid organs; the rallying and "trapping" of the circulated naive antigen-specific T-lymphocytes through the MHC-peptides and adhesive molecules presented by the APCs migrating to the local lymphoid organs; the polarization of the T-lymphocytes and the establishment of the immune synapse; the T-cell activation and differentiation depending on the bidirectional interaction of the dendritic cells and the T-lymphocytes; and finally the creation and migration of the effector T-cells.

Common language and lost memory

The central nervous system's resident immune and nerve cells understand each other's "speech", the language of cytokines, chemokines, and neurotransmitters, and the immune cells are also equipped with acetylcholine, adrenoceptors, glutamate, dopamine and serotonin receptors. The neuroimmune interactions are not all inflammatory; they also constitute part of the nervous system's homeostasis.

In the "depth" of intercellular space, the brain's maturation, learning, and memory processes are connected to certain aspects of immune communication by crucial factors such as NF-κB, an intracellular "hub" the network, which we are going to detail later on. The genes around which NF-κB binding points are located show increased expression during learning processes. All this shows how important a role the transcription targets of NF-κB play in neuroplasticity and learning and the fact that the growth factors (BDNF, NGF), cytokines

(TNF-alpha), and the kinases (PKAc) also contribute to this process. Besides, the transcriptional changes observable in astrocytes and other glial cells significantly influence the learning and memory processes.

Glia cells play an essential role in maintaining synaptic integrity through the neurotransmitters and immune proteins they excrete. In addition to their support and gatekeeper functions, they participate in the monitoring of synaptogenesis as well. Among glial cells, microglia cells can be considered immune-competent brain cells, which have a role in the normal functioning and homeostatic processes (sleep, metabolism, memory) of the brain, based on the work by Bilbo and Schwarz (2009). In the same vein, glial cells could play a part in psychiatric processes, such as the pathology of schizophrenia, anxiety, depression, or even cognitive dysfunction due to their cytokines. It is also possible that they participate in the brain's normal maturation processes or the survival and elimination of various reverberation patterns. The microglia cells continuously monitor the synapses in the central nervous system and contribute to the elimination/imprinting of synapse patterns during the developmental phase of the brain and probably during the entire lifetime of the individual. Microglia cells drive nerve apoptosis.

The functions of the microglia cells include the removal of the "waste material" of apoptosis and the trimming of synapses during the so-called pruning process, which is essential for the formation of neural networks. Microglia cells swallow presynaptic endings, thus promoting the development of the cortical architecture.

A chemokine, the so-called fractalkine signal present in the brain in larger numbers than in any other organ, plays a role in synapse selection and pruning. Microglia synapses are contact-activity-dependent; the smaller synapses that come into contact with the microglia cell disappear later. Paolicelli et al. (2011) assert that homeostatic communication between neurons and microglia cells is a prerequisite for the maintenance of the *neurogenic niche*.

However, based on new research, astrocytes' function is more critical in the brain's cognitive processes since they are capable of phagocytosis and interleukin production. The astrocytes themselves also participate in the reorganization of the nerves, and their patterns are plastic. They also play a role in learning processes, including the imprinting and retention of memory traces. Vasopressin, which reinforces memory traces, adrenaline, which plays a role in learning and memory, or the non-nervous cell structures, indicate that stress is adversity faced by the body as a whole, and memory traces are responsible for processes involving the whole body as well.

However, the learning processes can be extended to the context of the body as a whole. Therefore, learning and cognition cannot be restricted to the mind and brain processes; the body responding to the environment's challenges also

plays an essential role in these processes. Adrenaline, which is released from the adrenal medulla, and the increased glycogen degradation/producing function of the liver governed by adrenaline, also play an essential role.

Based on our ecology and concept of ecology metaphor, neurogenesis, the creation and selection of synaptic patterns, is performed in the neuroimmune unit.

Natural selection was also an essential factor in developing the adaptive neuroimmune system's structure and problem-solving capacity. In the interconnected functioning of the nervous and immune systems, the subsystems' adaptive algorithms can also be interpreted as social psychoimmune algorithms when looking at human life's cognitive and sociobiological characteristics. It is even more apparent if the *patho*logic of homeostatic imbalance is extended to the surrounding social environment. As a result of all this, we can use the *computational model* of nerve science developed by Cosmides and Tooby (1996) when examining the neuroimmune system.

The common ecological denominator: selection and succession in the "network of networks"

The above interpretation framework inevitably places psychoimmunology, the neuroimmunomodulation processes included in it, their pathogenicity, the logic of protective patterns, treatment options, and targets in an ecological and evolutionary context.

Various concepts are naturally not limited to merely conceptual thinking and abstract cortical activities, but the evolutionary layers of the brain's mode of operation are organized in them in an "ecosystemic" manner. Therefore, concept ecology has a "horizontal" plane as well, which provides an opportunity for competition between concepts, their selection, and "succession", but it also has a "vertical" plane, on which concepts acquire emotional quality and become associated with behavioral patterns and neuroimmune-biological, even psychosomatic consequences. These connections always emerge and organize themselves in a network-like manner. The location and competition of concepts take place in a typical ecodynamic system of relationships. We find dominant, symbiotic, subordinated, and exclusive ecodynamic relationships between thoughts as well.

The ecological descriptor of the world of ideas also implies that in the nervous system's organization processes, the layers are connected not only on an "instruction circuit" connected in series, but the network of mediator effects and receptors permeates the entire body. It is true when the *dominant* messenger factors of the information pathways typical of each layer are different, such as in the cerebral cortex and/or the midbrain and the limbic system.

Multiple reciprocal regulatory networks are created between different evolutionary layers, which is also apparent in excess of typical messengers. It is a result of the immunological self as well as psychological and ecological interactions. Identifying the immunological identity requires the simultaneous presence of a complex receptor and the interplay of numerous lymphocytes' functions; therefore, immunological identity is the result of immunological experience and a complex, interactive, and dynamic process.

The psychological "Self", the self-aware reflective cognition, results from integrating the social processes of teaching, learning, avoidance, and interpersonal experiences. The psychological "Self" results from many encounters and is correlated with the image others have of the individual.

In the opinion of Cohen and Young (1991), the immune system creates an image of its antigens, which the authors called an "immunological homunculus", similarly to the functional self-image in the central nervous system, wich also reinforces this analogy.

Following the emergence of clonal selection theory, the idea became more prevalent among neurobiologists to evaluate the *behavioral response's selective operating principle* instead of the instructional mode of operation. According to Jerne, selection targets a pattern already present in the system before the arrival of the signal; the perception of the signal only reinforces all this. The plasticity characteristic of the mind and the immune system ensures the appropriate response in a wide variety of adverse environmental conditions. These adverse environmental conditions maintain a constant dynamic relationship between cortical activity patterns, the "cognitive maps", and the environment. The key environmental stimulus triggers several pre-wired patterns, including "competing" behavioral responses and cognitive strategies. These are all assumptions supported by human ethological and behavioral ecology models. This analogy implies no less than the discovery that earned an immunological Nobel Prize for Sir Macfarlane Burnet: learning and memory are the results of selection in both the brain and the immune system, in the background of which ecological patterns play a dominant role.

These analogies apply in the case of pathological activity as well; for example, Cunningham (1981) states that the analogy of chronic infection and reactive depression implies that the network is unable to cope with the infection or tumor in one case and with a traumatic event resulting from a loss in the other. The DST (dexamethasone suppression test) probe's positivity and the permanent increase of cortisol could be shared factors in the informational exchange between the two systems. It could be the result of the unique nature, and bidirectional mutuality of psycho-immune networks. Keeping in mind that the depressed mood observed in the case of infectious diseases could be a consequence of immuno-psychological influences. On the other hand, we

can also observe depression in immune parameters and processes during endogenic depression.

We can outline a functional similarity between the immune and nervous systems but parallelism could also be observed between behavior and immunological behavior. Based on animal experiments' findings, fewer viral tumors were found in the experiment's aggressive female mice than in the passive animals. Fox's meta-analysis of several investigations had similar results; it found that aggressive, confrontational, and confident cancer patients tend to survive longer, and are more likely to recover than the resigned, repressive, overly-adaptive "peaceful" patients.

The dynamics of the effects of stress also imply an analogy. Acute natural stressors, triggering a fight-or-flight response, cause adaptive responses in the first-line immune processes, while prolonged subacute or chronic stressors have an immunosuppressive effect. Therefore, short-term exercise or mental stress increases NK cells' cytotoxic activity, while chronic stress reduces it.

However, the metaphor of aggression could also disguise harmful (psycho-) immune phenomena. Parallels can be drawn between the autoimmune syndromes that become more and more frequent with old age or the old-age inflammatory tendencies: "inflammaging" and depression, which can be thought of as aggression toward the individual. Early distorted attachment experiences are common in borderline autoaggressive, mutilating teenagers and are also frequent in patients suffering from autoimmune diseases.

Cunningham (1981) also drew parallels between phobias and allergies, which both involve an excessive response to a harmless stimulus. Schmidt-Traub (1991) proposed obvious relationship between allergic vascular reactivity (anaphylactic and collapse inclination) and psychological fear reactions, and described significant correlations in the case of allergy and panic diseases. Kennedy and Morris (2002) found allergy in 71.8% of their panic disorder patients. More subjects in the allergic group had comorbid anxiety disorders, but only the number with specific phobias was significantly higher than for the non-allergic. The analogy presents itself not only in pathologic processes; the treatment itself could also be subject to one. Desensitization is a well-known method for treating allergies, and for the behavioral treatment of phobias and the treatment touches on an ecological relationship, the heightened response to the environment, in both cases.

Immune depression and depression appear as comorbidities in 30% of psychiatric patients, with suppressed NK cell activity. On the other side, chronic low-grade inflammation with elevated proinflammatory cytokines like IL-6 might follow chronic social stress, marital conflicts, and lead to a depressive mood and an elevated risk of cardiovascular diseases.

In the case of immune diseases, we used to emphasize the predetermined nature of immunogenetics and the pathogen's attacking role. On the other hand, the psycho-neuroendocrine factor connected to personality, the psychosocial situation and the behavioral, functional characteristics of the patient might also call for attention. Evolutionarily ingrained ecological patterns play a role in both cases; just think of selection theory's ecological embeddedness. The neuroendocrine-immune adaptation patterns can be interpreted as phylogenetically developed, adaptive "eco-gestalts".

The concept of neuroimmune stress allows a broader interpretation of the stressful effects of triggering neuroimmune adaptation. Ottaviani and Franceschi (1998) draw up an evolutionary background for this expanded model when they assume a common evolutionary origin for natural immunity, inflammatory processes, and stress in their theory. All of this is supported by the *collaborative* nature and mutuality of these processes (ACTH, beta-endorphin, cytokine, biogenic amines, glucocorticoids, and NO).

Neuroendocrine-immune stress is an ongoing trial of evolution. In this sense, stress processes play the selective role of evolutional filters in the organization of human ecosystems. Animal experiment data and human observations confirm that prenatal physical stress and emotional or physical adversity experienced in the early stages of the mother–child relationship have a fundamental and permanent effect on the stress system's basic functioning and stress responses.

It means that the stress processes themselves are phylogenetic and act as evolutionary agents. Cosmides and Tooby's (1996) idea that the functional analysis of adaptive problems serves the discovery of new aspects of neurocognitive systems can also be applied to the interpretation of neuroimmune stress in a psychosocial context.

Besides the brain, the immune system can also be considered an *adaptive problem-solving system*, reflecting in its structure and mode of operation the antigenic adversity present in the primordial period of evolution, which occurred repeatedly and was stable for long periods. It is the result of the social determinants of human existence that a large portion of our cognitive programs was selected to solve adaptive social problems throughout our evolution. Therefore, following the computational theory's logic, we can interpret the neuroimmune organization within a social psycho-immune framework.

The complexity of adaptive information processing problems, the (psycho- and/or immune-) cognitive mechanism of problem-solving, which developed as a "product" of evolution, the high selectivity concerning specific cases of adversity, as well as the cognitive and "pre-wired" nature of adaptive problem management, can all be considered shared characteristics of the nervous and immune systems.

According to the interaction-based model, psychoimmunology is the science of the bidirectional communication between the central nervous system and the immune system. However, this communication happens not only between the nervous system and the immune system, but the two systems are part of a larger integrated regulatory mechanism of the body that serves adaptation and the protection of identity.

To sum it up briefly, the networked integration of the immune-, nervous-, and neuroendocrine systems is a necessary evolutionary development. This integration is a condition for the maintenance of homeostasis and the protection of cell and tissue integrity, but it also serves as regulatory redundancy. Therefore, in this model of these systems, the nervous and immune systems are communicating partners and creative components of the body in an organic relationship with a regulatory significance. These systems make up a (psycho) neuroimmune whole as parts integrated into neuroimmune processes, and this organic whole is the subject of neuroimmune adaptation.

Emotions as representations

From an evolutionary perspective, our emotions can be considered archaic environmental representations, close to our visceral processes. There are different bodily reactions associated with a grey, foggy November mood than with the spirit of a sunny May afternoon fragrant with flowers. The sensory and embodied experiences related to the complicated social dramaturgy of success and shameful failure are also different. In fact, the activated patterns are deep inner pictures of the situation and the environment, sometimes far from cognitive awareness. Situational assessment and evaluation are expressed in physical and emotional experiences. In the case of psychosomatic patients, emotions become pathogenic precisely because the patient themselves are unable to "read" their feelings (see alexithymia). Therefore, writing about trauma and therapeutic discussion can have a healing effect since these previously untouched, deeper representation layers become accessible for consciousness.

Thayer and Lane (2000) emphasized the cognitive content of emotions, in which case emotions can be considered integrative indices of adaptation to the environment, which make the quick mobilization of the various subsystems possible. Emotions, as self-organizing response mechanisms to environmental factors, make the evolutionary fixed, coordinated, and purposeful behavior-organization of the body possible. Emotions are specific to the stimulus patterns of the social and physical environment, which can have various meanings, can be threatening, attractive, repulsive, and have a mobilizing effect. Emotions can ensure flexible adaptation, stimulate specific response modes, and inhibit others.

The emotional representation of the environment can incorporate the patterns of several bodily reactions at the same time and inhibits all other alternative responses. It means that the body selects the suitable response to the environment from a set of paradigmatic patterns or creates a specific syntax in the given context, as modeled by the immuno-linguistic metaphor of Atlan and Cohen (1998).

Margaret Lyon, an anthropologist, called attention to the fact that emotions play a mediator role between the social environment and physiological processes. Emotions constitute an integral part of social semiosis. Social processes manifest themselves within the person through them, which triggers bodily reactions based on synchronization, empathy, mirror neurons, or in other cases, threatening but only imagined threats or ruminations. These processes are functions of a social and bodily disposition and permanent characteristics such as attachment or synchronization, which are factors that connect the phenomena of social, physical, and emotional existence. These psycho-biological connections form the basis of social psychoimmunology and connect bodily phenomena and social processes through a communicative informational bond. Emotions and, we should add, the personality structures closely connected to them tie together psychoimmunology and social phenomena.

Basic emotions are invariable from the human ethologic point of view, they have their roots in socio-biology and their expression is independent of culture. However, it is indisputable that the cultural regulation of emotions' meaning and expression places emotional socialization and the culturally constructed nature of emotions in the foreground of attention. The detection and assessment of emotions are placed in a varied context within the specific sociocultural medium. Emotions serve as a compass in the context of physical or even psychosomatic pathogenic processes and social relationships. The expressive and communicative nature of emotions that makes the relevant informational pathways and semiotics/semantics of social psychoimmunology revealed is exactly the expressive and communicative nature of emotions. Emotional attitude, coping mechanisms, the personality-shaping role of developmental psychological patterns, social relationships accessible for transaction analysis, social support and loss, and rank positions all gain meaning and interpretation within this social space interlaced with emotional expression and detection. And we should add that they all have psychoimmunological significance.

The communicative role and readability of emotions are apparent in Fonagy's mentalization model (theory of mind), where the mentalization ability is sensitive to early-life developmental psychological trauma. Emotions are time-sensitive. They can wear out or become charged by their relationship with the past, as in the case of nostalgia. However, grief and shame also concern our inability to change the past, which creates stress for the immune response due to their uncontrollable and unchangeable nature. In the social environment, there are several opportunities for social semiosis. Examples of this include

imitation, the spreading of behaviors like an "infection", the learning of habits, the imitation of tone and gestures, and all of these are motivated by empathy, the drive for cooperation, "identification" with others, synchronization, the need for attachment, and the intention and drive to become something.

Encounter training, sociodrama, psychodrama, ego drama, and other self-reflection methods make it possible to improve these embodiments of socio-semiotic phenomena. Their therapeutic potential comes exactly from the fact that emotions play the most crucial transmission role between the individual's physical and social layers of existence. Therefore, emotions can be considered an active representation of the environment, they play a role in modeling the individual *at a deep level of the body*, and this is exactly their social-psychoimmunological significance. However, these emotions not only model the environment but also allow the social environment to control the individual. Shame, remorse, and even the feeling of inferiority, which leads to a lowered self-esteem and a lack of control, play such an assessing and evaluating role. These feelings follow the social evaluating and controlling semiosis to the emotional and deep body and the socio-physiological levels. It is why it should not be surprising that shame has an immunosuppressive effect since the low self-esteem, the high level of anxiety, and the low self-evaluation create a negative stress-physiological situation. These emotions are triggered by social assessment and evaluating stressors. The actors in social situations transmit strong (reinforcing, threatening, excluding, judgmental, embarrassing, supporting, etc.) signals toward the individual, which evaluate their behavior, status, identity, or personality. The detection and assessment of these signals, which can have varied significance, value, and strength, depend on several personal characteristics. They depend on the life situation at hand, vulnerability, power structure, and the state of social relationships. All of this happens amidst a significant flow of information and communication processes, in which the *receiver themselves acts as an interpreter signal system* and is sensitive to changes. The behavior, with respect to which feedback is being given, and the social signals are organized into complicated dramaturgical patterns; games requiring transactional analysis might be played, fate-organizing scripts, symptom-maintaining traps, and deeper trauma might be encountered.

Amidst these social challenges, the examination of the *social self* uncovers unique mechanisms, the sociosomatic correlations of which are confirmed by psychoimmunology. According to the so-called *social self-preservation theory*, the stimuli threatening the social self, social self-evaluation, status, or social acceptance (SET: social-evaluative threat) trigger deep psychological and physical reactions. The already-mentioned shame inhibits the individual's urge for activity and indicates the experienced loss of social status and the reduction in acceptance itself. The social-semiotic expression of shame implies social reclusion (avoidance of gaze with the head tilted forward), which increases the level of cortisol in the

deep body. According to Stark et al. (2002), it increases the level of proinflammatory cytokines and the level of sympathetic activity as well. In addition to the increased cardiovascular response, we can observe an increase in the levels of TNF-alpha and IL-6 as well. In the case of a SET (social-evaluative threat), the role of cortisol in the reduction of inflammatory responses is also reduced.

Shame and social self-contempt lead to similar immunological consequences in the case of submissive test animals. The so-called SETs (social-evaluative threats) are the model of an examination situation, which means that it is about the emotions and physical reactions related to personal performance in front of a *judgmental public*. Such situations cause higher cortisol secretion, including all psychoimmunological consequences, and this is the case with the experience of shame as well.

Naturally, positive emotions have to be examined in a social context as well, since the expression of positive emotions is associated with socio-semiotic signals (smile, reinforcing positive gestures) with an affiliative, reinforcing or improving effect on social relationships, or it might indicate control, an advantage, dominance over the situation, and often a stable social rank. All of these are accompanied by advantageous immune indicators. A long-term positive mood or favorable disposition is often associated with a more favorable prognosis for HIV and cancer patients and with respect to immune indicators, we can observe that, compared to induced and natural situations, an examination following a few days or weeks of positive mood will find a larger amount of NK cells and more NK cell activity, more effective control of latent EBVs, and an increased cytokine response to the living influenza virus. Positive feelings can be associated with a reduction in allergic symptoms and, in the case of herpetic patients, with an increase in the number of circulating cytotoxic T cells and NK cells. A negative mood, brought about experimentally, inhibits chemotaxis and the inflammatory skin response to histamine. In contrast, a joyful mood increases chemotaxis and reduces the inflammation caused by histamine, according to the findings of Zachariae et al. (2001).

These feelings are born and expressed within the framework of personality, human relationships, and situations. The essence of social semiosis is that it depends on the person, the situation, and the dramaturgy. Franz Alexander considered the conflict specificity inherent to the fate of the patient, or in our interpretation framework, psychosocial adversity, stimuli, which renders the patient more sensitive to specific illnesses in the presence of certain genetic, biochemical, physiological factors, acting as a specific conflict exerting its influence within the black box of the body.

The effect of negative emotions on health and immune activity is expressed in increased mortality as well, while good mood, as well as physical and mental welfare, reduce the number of early deaths.

The peptidergic universe of emotions

If we consider emotions as total organismic responses to external and internal stimuli, then they manifest in the chemical signals permeating the body and the state changes of the vegetative nervous system. The receptor network able to receive the neuropeptides essential to us (e.g., opiate) permeates the body and many receptor carriers, such as the immune cells, are continuously on the move. The densest receptor area can be found in the center of emotional life, the limbic system. It is important to note that this same system is responsible for memory as well. Thoughts, memories, experiences and the multitude of messengers arriving from the deep body flow through the limbic filter of state-dependent memory. Maybe this is why they say that the root of the illness is memory. Depak Chopra states that the body itself is a structure of memory, the home of memory, which implies a relationship between information and formation. It is why emotional information processes manifest as somatic processes. The neuropeptides can be followed from the limbic system all the way to the visceral periphery. Pert (1985) considers their networked presence the bodily carrier of the behavior and mind understood within the framework of the psychosomatic whole as well as of emotional life. The neuropeptides create the basis, vocabulary and syntax for the language of the *unconscious*. The peptidergic patterns can be thought of as an organic whole of a network-like, purposefully operated, coordinated activity patterns.

Neuropeptides themselves also represent a complex experience pattern from a certain point of view. For example, orgasms and euphoric joy can be associated with opioids, oxytocin, while SP, among others, is responsible for the sensation of pain.

The endogenous opioids are the buffer hormones of stress; their high level simultaneously acts as an internal reward signal and in the case of significant trauma or pain (e.g., amputation), a painkiller that provides enough time for escape, but it also plays a role in internal defense mechanisms, immune stimulation, and the optimization of brain circulation.

As an example of the internal reward function, we can mention the "social mediator" role of the internal opioids, which presents itself during an undisturbed mother–child relationship but can be suspended by naltrexone. Thus, the opioid-antagonist can trigger the separation trauma even in the presence of the mother.

The stress hormone AVP plays a role in the development of aggressive behavior by connecting to the serotoninergic system, and it also exerts a complex influence on the immune system.

Another neuropeptide, angiotensin, relays the feeling of thirst to the brain to maintain the water balance of the body, promotes the retention of water by regulating the vascular tone in the kidney and increasing the production of

aldosterone, increases blood pressure on the artery-side, and participates in the redistribution of circulation as well. Curiously, a typical characteristic of the integration of immune-endocrine processes is that the immunocytes producing angiotensin II can also participate in it.

The neuropeptide network is comprised of restrictively hierarchic, partially coequal nodes. It is an essential fact of behavioral biology that the brain areas performing the emotional assessment of a situation are rich in IL-1, transferring, GF, and other neuropeptide receptors; therefore, the connection between immune processes and behavior is not surprising as the brain is aware of what is happening in the immune system.

The opioid, benzodiazepine and Substance P receptors responsible for emotional modalities receive mediators in the brain, which have a significant effect on immune cells. The immune-stimulant and pain-signaling SP shows the image of a classic "defense" reaction when entering the liquor cavity of the brain, including fidgeting, restlessness, and grooming. According to the findings of Culman and Unger (1995), SP is responsible for triggering the full range of behavioral, cardiovascular, and endocrine stress patterns. Considering the tightly intertwined nature of immune events, behavior, and mood, this phenomenon is not surprising at all. This all implies the economic coordination and holistic character of adaptive processes as well as their inclusion in a unique psychosomatic network. Whether we are talking about vasopressin, beta-endorphin, Substance P, or benzodiazepines, all of them affect immune cells' operation.

Syntax: the deep structure of experience

Alexithymia

The world of experiences is an inner mirror for the situations shaping the personality and its adaptive response mode. The psycho-physiological mapping of the processing of experience is a continuous challenge for psychoneuroimmunology as well; objective neurophysiological observations can help understand this disorder of "experience processing".

It is exactly the processing of experiences and the awareness and verbalization of emotions, the disorder of which the definition of alexithymia applies to. The patients cannot express their emotions or even put them into words; however, they list their sensations, especially somatic symptoms.

Sifneos stated that adversity presented by the dangers of the environment results in a disorder of the internal evaluation of the, perhaps adaptive, emotions in alexithymia patients, leading to a unique psycho-physiological escalation. The generation of symptoms might result from increased vegetative and neuroendocrine tones, which could cause organic symptoms, the reappearance

of ulcers, asthmatic attacks, heightened blood pressure, general anxiety, or diffuse symptoms in the case of an organ defect.

Alexithymia is also responsible for the case where psychosomatic patients, who experience somatic symptoms, often reject the explanation of their disorder with psychological causes, which makes the psychosomatic treatment of such patients impossible in the somatic ward. Although alexithymia is a characteristic of only about half of psychosomatic patients, it is more common in somatizing patients, who experience pain even in the absence of organ disorders. Solomon (1995) considered the association of the disorder of expressing emotions (alexithymia) and an insufficient response to immunological adversity (in the case of personalities prone to immunosuppression) analogous in nature.

Lateralization

Naturally, it requires a long list of research to establish how big a role a possible disorder of the cooperation between brain hemispheres could play in illnesses organized along a psycho-physiological logic, such as psychoimmunological syndromes. However, knowing the above, it is an interesting mystery whether the two hemispheres have different effects on immune parameters. The ablation of the left hemisphere causes immunosuppressive consequences concerning T-cell proliferation in experimental animals. In contrast, the removal of the right hemisphere results in a heightened T-cell response to lectin mitogens.

The results of Davidson and Fox's (1989) research, where increased EEG activity was detected in the frontal right hemisphere of children exhibiting depressive behavior and crying when their mother was not present, could imply a long-term (trait-like) characteristic of the neuroimmune organization.

The rLFA value of frontal EEG at 8–13 Hz reflects the ratio of left and right frontal hemispheric activity, where lower values proves a shift toward right frontal dominance. Since alpha activity has an inhibitory influence on cortical network activity, lower frontal asymmetry scores (right minus left alpha) reflect less left than right cortical activity (Allen, Coan, & Nazarian, 2004).

There is also some evidence that rLFA may serve as a moderator of the affective relationship between infant and mother. Forbes et al. (2008) found that for children with less rLFA at rest, mothers' depressive symptoms predicted negative affect in their children. This finding suggests that a mother's depressive symptoms predict a child's depressive symptoms only for those children who have less rLFA, in the case of right hemispheric bias. Less rLFA characterizes infants of depressed, withdrawn mothers more than infants of depressed, intrusive mothers (Field & Diego, 2008). Goldstein et al. (2016) also found that children with mothers with a history of depression had less rLFA from age 3

to age 6 but not children with mothers without a history of depression. Additionally, children aged 5-6 with low positive affect have been found to have less rLFA (Shankman et al., 2005).

Lewis, Weekes, and Wang (2007) showed that rLFA showing a shift towards right hemispheric dominance may reflect the relationship between environmental stress and negative health outcomes; the more an individual's rLFA is altered by periods of stress, the more negative health outcomes one is likely to experience. In their study, students' rLFA shifted from more rLFA during periods of low academic stress to less rLFA during periods of high academic stress, and a greater change in rLFA was related to increases in negative health from the low to high stress periods. rLFA might be seen as a predictor of anxiety (e.g., Mathersul et al., 2008), and children with anxiety disorders (Baving, Laucht, & Schmidt, 2002) and adults with panic disorder (Wiedemann et al., 1999) were found to have lower rLFA than healthy participants. In individuals with social anxiety, a state anxiety manipulation decreases rLFA, suggesting acute anxiety is related to lower rLFA, according to Davidson, Marshall, Tomarken, and Henriques (2000).

With their research conducted among adult women, Kang et al. (1991) confirmed that an expressed frontal right hemisphere activity is associated with reduced NK cell activity compared to subjects with frontal left hemisphere dominance. Davidson et al. (1999) found lower NK cell activity under exam stress and following the watching of videos with negative emotional content in university students with right frontal hemisphere dominance. All of this was confirmed by Gruzelier (1996), who found a similar correlation between active articulators, which implies the dominance of left-hemisphere activity, and heightened NK cell activity.

These findings are in line with the results of animal experiments performed by Neveu (1993) and others, based on which the ablation of the right cortex caused heightened immune activity, while the ablation of the left cortex led to a reduction in immune activity in the animals.

The consequences of early-life traumatization

The processing of experiences and biological stress characteristics are affected by early-life experiences and traumatic situations in a dominant manner. For example, corticosteroids administered in the first days following birth could influence behavioral responses in adulthood in experimental animals. This research of Elemér Endrőczy and Csaba Nyakas (1972, 1981) carried forward the legacy of the Grastyán school of thought and looked into the consequences of neonatal cortisol on behavior and stress physiology as early as the middle of the seventies. According to research, the corticoid administered

early, on day 3-5, did not cause changes in somatic development and decidedly reduced the defensive learning reactions in adulthood. The internal inhibitive processes, which are essential for the discrimination of environmental stimuli, participate in the development of primary relationships, and are so important for conditional reflex processes, were also reduced by the administration of corticoids. The authors stated that the point of attack of the corticoid administered to the newborn animals (or produced in increased amounts due to a stressor?!) was the nervous system; however, the fate of the catecholamine metabolism and probably other neurotransmitters can also be affected.

Based on the epigenetics research of Szyf, McGowan and Meaney (2008), the early-life emotional abuse sustained due to the absence of the mother leads to a reduction in the number of glucocorticoid receptors in the hippocampus as well as to an increased sensitivity to stress due to the methylation of certain gene sections.

The social epigenomics they outlined also serves as a good example for network levels of network medicine alongside the connections between social networks, psycho-vegetative, molecular, and genetic networks, which, when combined, create a network of networks due to their connections at important hubs.

According to the findings of Oberlander et al. (2008), it is a fact observed in humans as well that the prenatal experience of the depression or anxiety of the parent causes increased epigenetic changes in the embryo and leads to increased methylation of the DNA responsible for the production of glucocorticoid receptors, as expressed in the increased salivary cortisol production of three months old embryos as well. Based on the observations of Weaver et al. (2004), the early-life stress experiences, the abusive or negligent behavior of the mother results in the methylation of the GR17 promoter of the hippocampus, a reduction in the expression of glucocorticoid receptors, and dysfunctional cortisol feedback in the hypophyseal-adrenocortical system.

All of this indicates that the early-life mother–child relationship, which determines the logic of social existence, has a determining effect on the long-term psychological operation and the basic principles of the personal grammar of fate.

Socio-psychophysiological syntaxes

The social-psychoimmunological events, life events, mental patterns, the logic of response modes governed by personality, experiences, and the somatic consequences of all of this appear in front of us within the examined chain of responses as a piece of text to be deciphered and provides the basis for the approach of narrative medicine.

We associate life situations with a social context, personality patterns, response modes, and emotions, with their own PNI consequences in the spirit of the correlations in advance, which we have already learned through social psychoimmunology.

Table 6. Psychosocial PNI influence

INHIBITED PSYCHO-IMMUNOLOGICAL STATE	HARMONIOUS PSYCHOIMMUNOLOGICAL STATE
Avoidant behavior (BIS-behavioral inhibition system) the predominance of right frontal and hemispheric prefrontal activity depressive tendencies, decreased NK cell activity	**Approaching behavior** (BAS-behavioral activation the predominance of left frontal and prefrontal hemisphere, pride, motivational arousal, suppression of negative experiences low anxiety and depression results, lower cortisol level, higher NK activity
C-type personality inhibition of aggression increased need for competence, inhibition of emotional awareness, internal tensions increased psychoimmunological risk	**"Hardiness"** highly committed, tough personality, pertinacious attitude decreased psychoimmunological risk
Passive, repressive coping repressive coping, accompanied by immune dysregulation, typically with increased activity of the adrenal cortex.	**Active coping** an increased CD+4 T helper count for immunization is observed in aggressive animals after events of confrontation, with increased catecholaminergic activity
Loss of control unavoidable and uncontrolled shock reduces the T cell proliferation response to the mitogen, NK cell activity, and cytotoxicity; the tumor shows faster growth	**Control or presumption of control** control is associated with high noradrenaline, gonadotropin, testosterone, oxytocin and unchanged glucocorticoid levels
Submissive status an increase in suppressor (CD8 +) T cells, a decrease in IL2 production, a decrease in B lymphocytes, and a decrease in T cell cytotoxicity is observed in submissive animals typically chronic hypercortisolism and reduced immune response due to a disbalance in cortisol-CRF-HPA feedback occurs in animals with the subordinate status	**Dominant status** the dominant animal showed increased IL-2 production, significantly increased T helper/suppressor ratios, and significantly increased T cell responsiveness to mitogens (ConA, PHA) is identified

INHIBITED PSYCHO-IMMUNOLOGICAL STATE	HARMONIOUS PSYCHOIMMUNOLOGICAL STATE
Grief Bereavement causes 30% depression on PVM, PHA mitogens induced blast transformation for three months, decreased lymphocyte proliferation	**Social support** Adequate personal relationship and social support increased blast transformation in breast carcinoma higher NK cell activity in the case of a supporting spouse
Pessimistic state low self-esteem, hopelessness, decreased lymphocyte reactivity, decreased T-cell efficiency, decreased NK cell activity, lower CD4 / CD8 cell ratio	**Optimism** an effective response to the stress effect, predicting a positive outcome of the situation, and better immune response are typical among the tested law students
Exam stress decreased NK cell activity; decreased T cell count, decreased immune mediator level, increased susceptibility to herpes virus; decreased immunoglobulin A; increased Epstein-Barr virus levels	**Humor and laughter** increased IgA levels; increased lymphocyte count and activity, decreased NK cell activity, spontaneous lymphocyte blastogenesis, levels of cortisol, adrenaline, and dopamine catabolites (DOPAC)
Loneliness, solitude decreased NK cell activity	**Group-level intervention and support** increased NK cell number and activity; increased lymphocyte count; decreased helper T count
Chronic stress decreased T cell count; decreased NK cell count; decreased B cell count, increased Epstein-Barr virus levels	**Physical exercise and aerobic training** increased white blood cell count, increased production of endorphins and certain interleukins; increased NK cell count and activity, increased T cell count
Divorce/separation decline in the quality of family relationships, decreased lymphocyte function; increased Epstein-Barr virus levels; decreased T cell efficiency	**Discovering and sharing the traumatic spiritual experiences** increased lymphocyte response, decreased anti-EBV antibody titer, increased T cell proliferation response to Cona, decreased frequency of seeking medical help
Negativistic behavior when discussing family conflicts decreased NK activity; decreased macrophagic activity; increased Epstein-Barr virus levels; increased levels of certain T cells; decreased proliferation response to the mitogen	

Psychoimmunology offers a model for social semiosis in the wider sense. Puustinen (1999) was right to point out that the semiotic approach and with it, the extended text-based orientation supports diagnostics, patient instruction, and psychotherapeutic efforts. This approach also provides a good theoretical framework for analysts in addition to narrative analysis. The analysis of the polyphone, context-dependent, and open-ended nature of communication can help develop such medical skills as well. If we break down the texture of these "dramaturgic" associations into sentences, whether they are related to a psycho-physiological consequence of personality or conflict, we actually find the behaviorist basic formula of the S-O-R (stimulus–organism–response).

This work is also intended to improve the skill of socio-psycho-immune "signal sensitivity". This is important not only for the interpretation of illness but also expands the opportunities in medicine, in line with the concept of "doctor as medicine" by Mihály Bálint. This is because positive emotional disposition, optimism, humor, laughter, self-confidence, high self-esteem, the experience of the meaning of life, and the feeling of cohesion, all improve immune competence. In the healing "semiosis" of the doctor–patient relationship, with the help of the tools of the Rogersian person-centric psychotherapeutic attitude or suggestive communication, the patient as a (psycho-immune) interpreter is assisted in the recovery by the (verbal, metacommunicative, symbolic, maybe even ritualistic) signals sent out by the doctor. This means that the various cultural formations of medicine, the cognitive concepts about the world, and the signals included within them "operate as a force of creation", to quote Cassirer.

The dramatic unit of the body and the mind in psychoanalytic context

The history of psychosomatic medicine involves newer and newer attempts at the joint interpretation of the social, mental, and somatic phenomena. The decisive time in the life of analytical school of thought was between 1920 and 1955, the foundation of which was laid by excellent Hungarian psychoanalysts like Sándor Ferenczi, who made essential steps towards *self-psychology,* shortened the analytic psychotherapeutic process, and created an interpretation framework that allowed the symbolic interpretation of somatic symptoms, thus connecting the psychoanalytic approach with everyday, accessible medical practice. Ferenczi's psychosomatic approach is characterized by the concept of pathoneurosis, in addition to the psychological symbolism expressed in somatic symptoms. The intellectual cooperation between Ferenczi and Georg Groddeck, a proponent of the psychoanalytical approach to understanding internal medical disorders, also enriched the history of European psychosomatics. Ferenczi's transference/countertransference concept, which concerns the

doctor–patient relationship, culminated in the theoretical and practical work of Mihály Bálint, and the so-called Bálint group practice based on it offered significant help in the psychosomatic interpretation of disorders, which is used even today during the everyday work of general practitioners.

The idea of psychological symbolism manifesting in somatic symptoms was further developed by the also Hungarian-born Alexander into his conflict-specificity concept. In the center of Alexander's work was this exciting *semantic* problem, the question of specificity, based on which a series of proofs indicate that similar to the organ-specific microorganisms, certain emotional conflicts can have such specificity, and thus be limited to certain organs.

Alexander modified the concept of transference this way: "The patient, in order to be helped, must undergo a corrective emotional experience suitable to repair the traumatic influence of previous experiences. It is of secondary importance whether this corrective experience takes place during treatment in the transference relationship, or parallel with the treatment in the daily life of the patient." In the concept of corrective emotional experience, we might reveal the holistic phenomenology of illness and healing as social semiosis.

With his psychosomatic pathological model, connecting the yin-yang poles of the sympathetic and parasympathetic systems, Alexander attempted to integrate dynamic psychiatry and the pathophysiological approach to the fullest extent possible.

Social-psychological patterns are created by typical, specific life situations, to which the patient has already become sensitive earlier as a result of a typical key conflict. This experienced, "activated" conflict is accompanied by strong emotions, which change the function and the structure through vegetative, hormonal, and neuromuscular ways. Alexander described several such conflicts, which we can also call "narrative patterns", and connected them to the triggered somatic events. He connected suppressed anger to the response of the circulatory system, dependent behavior, and asking for help with the dysfunction of the gastrointestinal system, and the conflict between dependence and sexual attraction with the dysfunction of the respiratory system. Within his own psychoanalytical interpretation framework, he connected stomach ulcers to the explanatory model of infantile oral addiction and fixation. If the patient is unable to process his/her deep conflict, the production of stomach acid increases and the vasoconstriction of the gastric mucosa offers an explanation for the development of peptic ulcers in Alexander's model. Based on this, Alexander interpreted psychosomatic syndromes within a social-psycho-physiological framework as a result of the interactions between psychological, physiological, and social factors. These unresolved inner conflicts, which are activated in certain emotional situations, lead to psychosomatic disorders together with the physiological pattern that offers a point of attack with their vulnerability.

In his summative work on psychosomatic medicine, Wolman (1988) collected patterns interpreted in the spirit of conflict-specificity from several authors. The illness interpretation following this almost "key and keyhole" logic dominated the psychosomatic approach for a long time.

Such patterns: asthma and the fear of the child of losing their mother, hypertension as a response mode accompanying difficulties with controlling the patient's own aggression, arthritis as a protest against the rule of parents and restrictions on movement, the correlation between peptic ulcers and dependence or the desire to become independent. In truth, we are talking about a response reaction with chronic consequences to a traumatizing psychosocial environmental stimulus, interpreted as having been made more sensitive (being "pre-patterned") by the key conflict, which leads to meaningful symptoms; therefore, the theory of Alexander and his followers fits within the category of psychosomatic semiosis even without this being explicitly stated.

However, Eysenck (1987) asserts that even neurosis is the consequence of the interaction between personal disposition and an environmental stressor. Personality and its own coping mechanisms, psycho-physiological characteristics, and response modes are present in this personal attitude as well, and stress should be interpreted within its personal framework, embedded in the given social and cultural context.

At the same time as Alexander's pioneering work, another system of correlations was also defined, which is also an important part of the history of social psychoimmunology. Its emphasis was on the psychological system incorporating emotional balance, that is, personality. Personality is also an interpretative, complex signal processing, and response behavior organizing signal system, which operates as the interface of the internal and external worlds. Inwardly, it manifests and organizes into a somatic reality the changes of the external world through its emotions but outwardly, it "represents" the person together with all of its prior somatic, psychological, and social experiences through the expression of emotions.

Helen Flanders Dunbar was the first to look for a connection between individual personality profiles and individual illnesses in the middle of the forties. In her work titled *Psychosomatic Diagnostics* (1943), she describes the psychological structure imprinted during the individual's life history, which is not inherited and is not dependent on predisposing factors but is a result of personal experiences, relationships, and life history. The personality type thus outlined can be described by mapping out the life history of the individual, and it reflects their value system, way of thinking, approach to the questions of existence, and relationships with their family, society, and professional environment. This approach converts fate into a piece of text to be deciphered and this text considers the somatic events of illnesses a deep layer, which means

it screens the bidirectional system of correlations of texts written on top of each other.

Dunbar described the relationship between the so-called "top-dogs" and "would-be-top-dogs" and coronary artery disease. With this personality profile, she described a workaholic person who does not take out any holidays, demands authority, and seeks out opportunities to express dominance in conversation. We may recognize this type of person who is unable to relax, skeptical toward religion, living on stimulants but still ascetic when we look at the personality pattern threatening managers with cardiovascular disorders.

Dunbar believed that somatic changes could be triggered by mental or emotional stimuli as well. If the expressive behavior is not suitable, the physiological accompanying symptoms of the emotion can cause permanent stress, which can, in turn, result in the long-term or repeated dysfunction of the organs.

The research of typical "disease-prone" personalities predisposing individuals to illnesses left a mark on the early decades of psychoimmunology. The personality patterns predisposing to cancer, the Grossarth-Maticek type I personality model, the Temoshok type C personality type, the shyness of allergy patients, or Solomon's immunosuppression-prone personality category indicate that the legacy of Helen Flanders Dunbar has forever determined the course of social-psychoimmunological thinking. This work is going to accept this fact, despite acknowledging the legitimate critical opinions, and makes an attempt at finding answers to the still open questions around the topics of developmental psychology and epigenetics.

In fact, Alexander (1950) himself did not reject this approach to interpreting personality patterns; however, he placed conflict-specificity in place of personality-specificity. He placed interactive, dynamic factors in place of static dispositions and put emphasis on the physiological mechanisms that allow the given personality to exert and influence the pathological process from the beginning to the end of the illness.

Instead of personality types, he emphasized the emotional state and adaptation characteristics of the challenging individual adapting to the environment. In connection with the personality pattern with a cardiological risk, he thought that a certain kind of lifestyle or mental response mode leads to the development of somatic circumstances that cause lesions in the circulatory system and thus coronary heart disease. However, the real correlation is not between personality and atherosclerosis of the coronary arteries but between lifestyle and illness. For example, permanent adversary impulses are accompanied by increased blood pressure, while in the case of a dependent or help-seeking disposition, an increased production of gastric acid can be observed.

Based on Alexander's work (1950), these emotional conditions are present in persons with varying personalities; therefore, he concluded that the

uncertain and vague correlation between personality and illness does not exist; however, it does exist between certain emotional constellations and certain vegetative nervous system patterns. Whatever interaction we find between personality types and somatic disorders, it can only have a relative statistical significance, and it is often incidental... The real psychosomatic correlations are found between emotional patterns and the changes of the vegetative nervous system.

However, it is difficult to argue with the strong and tendentious connection between temperament, personality, habits, that is between learned and imprinted emotional response modes, the ethological basis of which can be observed in animal experiments. This means that the personality reflects the deep genetic and hormonal deep patterns that make one individual dominant and aggressive, but another one shy and submissive. Koolhaas considered the ecological and evolutionary biological background of the given species to be dominant with respect to the response to the adversity in question. Others called attention to the wider biosocial context of the relationship between personality and illness, which determines behavior in terms of prevention and avoiding or seeking out situations with a risk of developing an illness. However, this biosocial context is inseparable from personality, temperament, and life history if take into consideration genetic factors, especially epigenetic processes. The idea of a personality predisposing the individual to illness does not contradict conflict-specificity either but supplements it.

The true opposite of conflict-specificity is the non-specificity of Selye's stress theory. It was exactly the power of the shearing forces of *nonspecific factors* to deplete reserves that Selye saw as an explanation for many illnesses.

Pavlov's reflex theory also played a large role in the interpretation of the so-called functional internal medical disorders. The internal medical oeuvres created in the Hungarian branch of *nervism* were also built on this. In Hetényi's works, the autonomous nervous processes were paid exemplary amounts of attention; however, this school of thought was not continued in a worthy manner either.

Contemporary psychosomatic medicine broke with the psychoanalytic foundations, and its research directions reflect a turn in behavioral medicine, which reflects cohesion between the approaches of psychosomatics and psychoimmunology.

1. The role of psychosocial variables in the development of illness (etiology).
2. The examination of the causative connections between the changes of psychosocial variables and physiological parameters (psycho-endocrinology, psychoimmunology).
3. The basic psychological changes accompanying illness (illness behavior).
4. The psychological and mental concomitants of specific somatic processes.

5. The effect of therapeutic methods affecting behavior on somatic conditions and somatic variables.

Although Lipowsky only pinpointed one of the above five areas as the place of psychoimmunology, it essentially pertains to all of them. Actually, if we compare the wider history of psychoimmunology, the roots of these two disciplines can be placed in the 1920s, together with the development of the modern concepts of psychosomatics. In Metalnikov and Chorin's work in 1926, they already discuss the conditionability of immune phenomena. This is related to Speransky's work, a former colleague of Pavlov, which summarized the influence of the central nervous system over the immune system. However, other early observations also connected the nervous system, which exerts mental and emotional influence, and its effects on the inflammatory process. As early as at the end of the 19th century, we see data about the effect of damaging the nervous system on the loss of protection against anthrax; at the beginning of the 20th century, Salomondsen and Mandsen already connected vagotomy and the atopic and anaphylactic reactions; Hatiegan first described the effect of adrenaline on increasing the number of lymphocytes in 1925, which was confirmed by Frey and Tonietty in 1927. The general immunological influence of emotions was described by Erich Wittkower, when he detected an increase in the number of white blood cells in the states of anxiety, anger, grief, and heightened mood. He coined the term *Affektleukocytose* to describe this phenomenon, which he explained as the stimulation of the sympathetic nervous system. A group of physiologists from Kolozsvár (Cluj), Csaba Hadnagy, and the Romanian researcher Baciu also joined this trend when they examined the effects of the vegetative nervous system on the number of white blood cells at the beginning of the forties.

To tell the truth, immunology itself cannot boast of a longer history either. If we follow its developmental path backward, we can perhaps call the animal-experiments of von Behring and Kitasato to confirm the existence of antibodies that neutralize the toxins of diphtheria and tetanus as its starting point, dated 1890. However, the specific cellular background of this phenomenon remained undiscovered; they believed that all cells were able to produce antibodies. The role of lymphocytes in antibody production was only confirmed in the 1950s. Our understanding exploded in the following 20 years, but research was mostly indicating the autonomy of the immune system, and this idea was undoubtedly solidified by the fact that the immune competence of immune cell cultures experimentally kept alive remains unharmed. Perhaps this was one of the reasons why in the immunological textbooks written at the beginning of the 1980s, which served as benchmarks for the discipline, the results of psychoimmunology, which had been around for the lifetime of a whole generation at that point, were not even mentioned.

However, Locke prepared a bibliography of more than 1500 articles as early as in 1983 under the title *Behavioral Immunology*. If we take into account the names given to the scientific field discussed in these articles, the first "christening" took place in 1974 and is connected to Robert Ader, who used the term *psychoimmunology* and in 1981 coined *psychoneuroimmunology*. The term neuroimmune modulation is connected to Herbert Spector. Despite the English-speaking name-givers, the pioneers of the field were Central and Eastern European researchers. This is where we should mention the early results of Speransky, Metalnikov, and Chorin, which founded the paradigm, and the significance of Selye, who recognized the joint significance of the hormonal and hypothalamo-hypophyseal systems and in 1936, deduced from the three symptoms of the General Adaptation Syndrome that during the alarm reaction to a stressor, the size-reduction of the thymus and the lymphatic organs only takes place in intact animals but not in their adrenalectomized counterparts. Later, Selye confirmed the effect of the adrenocortical extract on inducing thymus atrophy in rats in 1943, and he called attention to the role of corticosteroids in regulating the inflammatory response in 1949. This resulted in the development of the medication that is so important for autoimmune and allergic patients, or those requiring organ transplants. However, Selye's Hungarian students also achieved important results in the field of endocrine immunology. István Berczi became a student of Selye in the sixties, and he was researching the immunological effects of hypophysis hormones together with Éva Nagy. They were among the first to confirm that not only cortisol but other stress hormones, such as the growth hormone or prolactin, also participate in the regulation of the hemo-lymphopoietic system and the immune functions. Lóránd Bertók, who also first met with Selye in the sixties, can be considered one of the pioneers of natural immunity research. He examined the protective role of bile acids against bacterial lipopolysaccharides. The toxic effect of the lipopolysaccharide endotoxins released by bacteria is an important motif of inflammation since their membrane disrupting, capillary-penetrating, shock- and fever-inducing effects provide dramatic components of the illness. During endotoxic shock, the levels of ACTH, corticoids, and beta-endorphin increase; however, the levels of prolactin, TSH, T3, and T4 are reduced. These effects are mediated by immune mediators such as IL-1, IL-6, and TNF, which are secreted by the macrophages activated by endotoxins and monocytes. Lóránd Bertók's research also confirmed that the radiotherapeutic treatment of the endotoxins reduces their toxic effect; however, the endotoxins turned to be harmless, can increase the natural immune reaction and mobilize stem cells.

Hungarian researchers played a pioneering role in the discovery of another system of connections, the "neuroimmune syntax". Beside István Berczi, Andor Szetinványi also played a role in discovering the nature of the connections

between neuroendocrine-immune networks when he managed to prevent the anaphylactic response, which results in the fall of blood pressure, through lesions created in the tubular area of the hypothalamus. The work of Miklós Jancsó Jr. is also important: he investigated the effect of histamine on the endothelial vascular cells and the reticuloendothelial system as early as in the 40s and identified histamine as the physiological activator of the reticuloendothelial system. However, he also identified another neuroimmune network, which played a large role in the understanding of the neuroimmune processes taking place on the internal and external surfaces of the body. By researching sensor neurons in the forties, Miklós Jancsó Jr. arrived at a conclusion among the first that *a neuroimmune network must exist*, in which the sensory fibers play an important role. The antidromic electric excitation of the sensory nerves triggered an inflammatory response, which the researcher was able to prevent with capsaicin treatment and the selective destruction of C-fibers. Since on the internal surfaces, such as on the surface of the gut or joints, sensory fibers and the increase in Substance P plays an important role in inflammatory processes, the discovery of Miklós Jancsó Jr. still provides a paradigmatic interpretation framework for psycho-immune research today.

In addition to the adrenal and lymphoid tissue correlations of the triad of symptoms discovered by Selye, István Berczi's endocrine-immune research, the research done by Lóránd Bertók even before the term natural immunity was coined, and the pioneering work of Szentiványi and Miklós Jancsó Jr. in examining the neuroimmune connection network, Béla Bohus also brought a new slice of reality into the interpretation range of PNI. As we have already mentioned above, the ethological and physiological correlations connect the internal and external, social informational patterns into an informational continuity; therefore, the former student of Endre Grastyán, who was able to examine the correlations between social interactions, dominance, subordination, behavioral traits, and physiological indicators and also confirmed the correlation between the ethological factors, the social rank of the rat, and its immunocompetence in The Netherlands, occupies a special place within this context. We should mention several Hungarian think tanks as well, such as the works of Elemér Endrőczy, Csaba Nyakas and Lajos Korányi, or the research performed by Szilveszter Vizy, to which Ilia Elenkov's or Judit Szelényi's internationally significant immune modulation and signal research is connected. In the field of applied psychoimmunology, we have to mention the pioneering role of György Németh, and in the context of neuroimmunology, the neuroimmunological research of András Guseo and Zsolt Illés.

Towards behavioral network medicine

Issues in psychoimmunology

In the network approach of psychoimmunology, the network of causal relationships of psychoimmunological phenomena is assessed by considering the biological, psychological, and social mechanisms. If these causal relationships are sufficiently strong and persistent, and with the fixation of the feedback pattern, they can become a modified self-sustaining network characterized by abnormal secondary homeostasis. Thus, chronic disease states in psychoimmunology can also be interpreted as alternative stable states of strongly related symptom networks. This person has a modified state of M-E-O. The technospheric needs and aptitudes, knowledge and constraints, social status, and relationship system of the individual involved are permanently changing. Indicators of the status of people with the psychoimmunological disease, quality of life, mental health, resilience, compliance and adherence, vulnerability, and responsibility appear in the network model in a multidimensional reference system.

As comorbidity data are common in psychoimmunology, the causal relationship is unclear, and, as accidental co-movement is possible, network analysis of disease associations may be critical. Mental disorders can be associated with physical illness, and conversely, people diagnosed with physical illnesses have a higher risk of developing mental illnesses. Significant correlations can be observed between immunological/inflammatory conditions and mood disorders. The most basic empirical network studies have found that symptoms are strongly correlated. Using cross-sectional analyses, the researchers examined the hypothesis that more excellent connectivity (also known as network density or global strength), is associated with the persistence of anomalies from several perspectives. Examination of the patient's social networks is also essential. Family, civic and workplace participation and social support should also be examined when examining biopsychosocial protective factors or risk and harm factors. The "real structure" of interpersonal, networks and the different causal systems can be tested. In the mass processing of a large amount of data, the network of symptoms can also be outlined. Thus, symptoms of central and peripheral importance emerge on the network map of connections. Its central role is positively correlated with the strength of the relationship and the rest of the network. Examination of network structures may help study intra- and inter-diagnostic syndromes. A networked approach makes the boundaries between mental and physical disorders permeable through networks and helps map the pathways through which they interact.

Therefore, the network approach follows the decades-long logic of the information anatomy of psychoimmunology. Furthermore, network images

emerging from large amounts of data processing allow for multidimensional analysis, which can also be used in the M-E-O model. Thus, a network spanning many symptoms and health-related dimensions can encompass a wide range of phenomena, from general psychopathology to behavioral disorders, health psychological characteristics to chronic physical conditions, and functional and health-related quality of life (HRQoL) data.

For example, Isvoranu et al. (2017) provided a picture of depression as a mediator between socioeconomic factors and the number of days spent in the patient population, similar to the results of Hungarostudy research. In their study, the element measuring anxiety and depression appears as a link between two domains in the middle of the network. All of this was strongly associated with psychopathological items, panic attacks, loss of interest, anxiety, obsolescence when separated from family members (adulthood), physical health, movement, pain/discomfort, and mental health. Correlations between other "provinces" included hypertension, which was visibly and strongly associated with gambling, asthma, restless mood, and social phobia. Migraine headaches were associated with psychosis and were very weak with mood restlessness and blood sugar levels. Diabetes was mostly, albeit weakly, negatively associated with ODD and alcohol consumption.

The network approach explores the networked relationships between a wide range of psychopathological conditions, chronic illness, and individual functions. Several elements connect and bridge the blurring boundaries between the two domains. Such may be the performance that can link chronic diseases and psychopathology. Thus, chronic disease processes are associated with a decrease in individual performance and function and a deterioration in psychopathological symptoms. Conversely, chronic psychopathological phenomena affecting daily life are also associated with chronic physical symptoms. Centrality analyses show that functional and depressive elements appear to be central to the network structure.

Life-long and current diagnosis of asthma has been associated with many mental disorders, including social phobia and affective disorders, as confirmed by relevant psychoallergic research. On the other hand, some groups of psychopathological symptoms showed a weaker association with others (e.g., specific phobic complaints) than other symptoms (e.g., depression, anxiety, childhood disorders), suggesting that the latter have more pronounced comorbid network connections. It is well-reflected in the results of psychoimmunological research (the inflammatory theory of depression and the effects of stress-biology.

Intra-provincial and intra-cluster associations, depression, anxiety, and childhood disorders as related clusters also receive reinforcements from psychoimmunological disease models.

The network approach interprets symptoms as interacting as a complex network that mutually reinforces symptoms. Networks of causally related symptoms are composed of strongly correlated elements, where comorbidity reflects pathways of causal relationships between symptoms that can link different disorders through bridging symptoms. An objective or "real" point where the symptom network could be split in two, with each part representing a separate disorder. In the network approach, disorders should be interpreted as a set of more closely related symptoms, intertwined and synchronized. The M-E-O model connects disease networks as an extended network with only social, knowledge, and technological networks. Thus, an individual's symptom network interacts with the networks of others and leads to a change in that person's social network. Networks (social support, patient base, network of helpers). Exploration of layered network structures and simultaneous analysis of social, symptomatic, and physiological networks can help in modeling M-E-O.

Neuroimmune networks

Networks are stand-alone factors in themselves, displayed by graphs depicting symmetrical or asymmetrical relations between cells, molecules, or possibly organs as hubs. The network-type depiction is also warranted by the need to present regulatory cycles in block schematics, system theory modeling, and the communication and information paths and logical relationships. In fact, the neuroimmune networks are graphs, and the task is to identify the hubs connected by them and the system of relations between them.

However, in context of the socio-psychoimmunological approach, the limits of the graph's validity exceed the levels of the systems of molecules, organs and organic systems and bypass the individual and personal as well. This approach includes the cultural and social spheres, economy, politics, and macrosocial environment too. It includes partnerships, social support, control, power, the territorial principle, dominance and submission, and social ranking. They are all presented in a set of relationships that can be outlined by graphs, edges and hubs. But connections over time are also aligned with the psychoimmunological interpretation of diseases as a graph and network, in the narrative framework of psychosomatics. Therefore, the particular 'metagraph network' of socio-psychoimmunology lies across several layers of graphs.

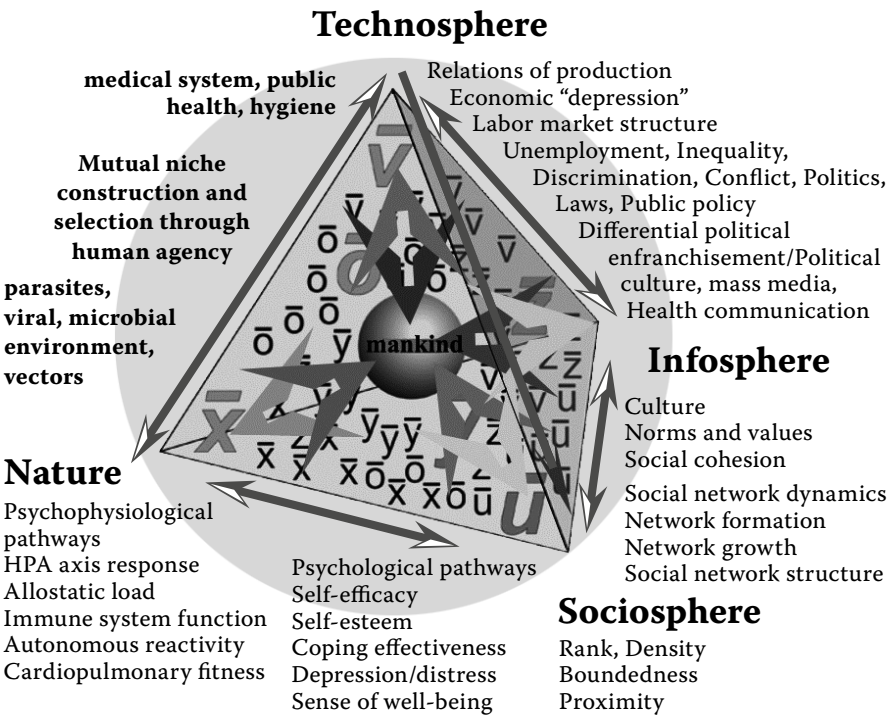


Figure 9. Biopsycho-sociocultural networks

The anamnesis and history disclosed by the patient, the writing or conversation therapy for disclosing traumas, the research for early traumas or the investigation of infection chains, learning about the dramatic dynamics underlying sociosomatic relations are all possible using the toolset of narrative network analysis.

This is the anatomy of experience embodied in the psychosomatic self, the crystallography of the petrified personal suffering time. Identifying the persons and events included in the text of personal fate and exploring the system of their relations pose the same kind of challenge for network theory as the comparison of neural, endocrine, and immune networks, locating the hubs that connect them and drawing the graph lines of the relationships in them, just as analyzing big data of different "omics".

The identification of key players, dominant communities, groups and the system of relationships between them based on the personal narrative, with the help of ranking by or after eliminating the obstacles obscuring memory, is an inevitable part of 'decoding' the socio-psychoimmune network. This is how actual dramatic hubs, traumas, frustrations, dominance relations and the nature of relationships between objects are explored. As it is the person who does all this in the therapeutic process, this also means a rearrangement of

the representations of the external set of relations and the set of relations generated in the mind hidden by time. This means that a network analysis immersed in psychosomatic psychotherapy may reveal revelatory rearrangements between the related set of life events, personality and psychological network patterns, and the narrative *re*-presentation of these networks may reach even the neuroimmune networks in the deep. This is why social networks and their narrative reflection in life history should be analyzed together with biological networks in socio-psychoimmunology's network model.

Assessment of perceptions, cognitions, situations, and the psychophysiological and neuroendocrine networks helps to explore this extended metanetwork, including neuroendocrine and neuropeptide patterns, cytokine networks, extracellular messengers, and intracellular molecular paths genetic programs and transcription processes. Overrepresented hubs and edges that determine the dynamics and types of physiological and pathological events, as well as possible therapies, are also outlined here.

Therefore, socio-psychoimmunology is part of the network medicine already outlined. The 'upward/downward' dichotomy already mentioned is present here as well. However, the networks interpreted along the lines of upward causality and the system of relationships interpreted along the lines of downward causality, approaching from the environmental effects, comprise bi-directional (often ominous) circuits. This genetic background determining the 'upward' causality in the depths of molecular networks peg out systems of genotype-phenotype relations, which are incorporated into the 'downward' causality networks by epigenetic mechanisms working from the 'top-outside', and environmental impacts enforced by methylation and acetylation. Relations between transactional events that carry psychological meaning are explored in the networks of the socio-psyche layer, which create traumas, feelings of submission or loss of control that are difficult to understand for the person and operate as chronic psychosocial stressors. Traumatic life events, alexithymia, or social inhibition, the psychological network patterns of a type C personality convert all this into increased HPA activity, high arousal, increased LC/NAergic activity, so that all this is eventually embodied in the disruptions of the immune cell network controlled by cytokines. Then, by virtue of the IL-1 and IL-6 produced pursuant to the modified protein synthesis in the cell core, the causal chain reversed in somatic depths reaches the central nervous system, and the change detected in the molecular network is transcribed into psychological network patterns, and depression, experienced in sensing, experiences and behaviors, emerges. This motivational, mood and behavior pattern vibrates on in the disturbances of the dynamic position experienced in social networks (micromanic contents, reduced motivation, lack of adequacy in the workplace, family conflicts, loss of socioeconomic status).

In network medicine, identification of networks, hubs and edges represents a true 'big data' challenge, as the protein synthesis is determined by nearly 25,000 genes, and the network hubs of "interactomes" are created by numerous proteins and functional RNS molecules as cell builders, on a scale of thousands. The number of network interactions with functional relevance is even higher. Learning about these interactions and identifying biological networks are the tasks of network medicine. However, the logic of network pathology is followed by research on the connections between the brain, hormone organs and the immune system, on physiological networks, the exploration of which is also a mapping task for interactomes of different levels. Such a map, comprising nearly 7,000 interactions, is drawn by the protein–protein interaction network map of Venkatesan et al. (2009), the metabolic network summary by Duarte et al. (2007), as well as the cytokine map playing a part in neuroimmunomodulation. However, the concept of a personality susceptible to disease, or Berne's transaction analysis, also strives to draw up such maps. Exploring the connection between anamnesis data and disease progression is also a similar effort at representation.

The task is to identify interactomes as networks, within which the network patterns and relevant connection paths associated with the disease should be identified. Probably, the analysis of the socio-psychoimmunology path is necessary as well, given that the 'interactomes' of this mappable system of network relations can be identified.

The sovereign network of hubs of all layers of socio-psychophysiological networks also needs to be identified, which may be molecules, metabolites, illnesses, narrative elements, life events, early trauma and late loss of object or persons, symbolic or physical stressors that may be identified in a post-traumatic stress experience. The edges and hubs consist of the deeper, multilayered neuroimmune network of organs, nerve fibers, receptors, and kinases.

The edges are outlined by the intracellular signal paths connecting neurotransmitters (the nervous system), cytokines (immune cells) with the DNA carrying genetic codes for the cell core or, in relationships between organs, the pathways connecting the HPA axis, limbic system and immunocytes.

It is possible to explore the relationships between these factors, causal relations, and multi-directional pathways of influence, the network characteristics of the personality and the body, the dynamics of the evolution and progression of diseases. Low socioeconomic status, discrimination, the subordination are accompanied by an increased level of proinflammatory cytokines influencing the HPA axis, through the mediation of neurohumoral pathways, as demonstrated by Dickerson et al. (2009), for instance. Anxiety, depression, and post-traumatic stress disease, along with the accompanying social and behavioral phenomena, are connected to neurohumoral and immune network anomalies, such as increased inflammatory cytokines (e.g. IL-6) or the

activation of the NF-kappa B path, which has central significance in the activity of inflammatory networks, according to Haroon et al. (2011).

The combined interpretation of genetic, molecular, inflammatory physiological, and behavioral social networks is, in fact, nothing more than a consistent application of the English bio-psycho-social interpretive frameworks. Genetic factors for mild inflammatory (CRP, IL-6) responses to psychosocial stressors and transcriptional responses affecting the genome span the above range of bio-psycho-social interpretations.

In the case of genetic bases, we can identify genetic variants and analyze the nucleotide-level polymorphism (SNP), which may predict the intensity of inflammatory responses to social stress. One target of such interest is the polymorphism of the regulatory region of the promoter gene responsible for IL6 (rs1800795; Fishman et al., 1998). Fishman found a genetically determined difference in IL-6 response to psychosocial stressors. Of particular importance is the fact that a person's IL-6 genotype may thus influence the role of IL-6, which is overproduced by psychosocial factors, in the development of ISZB. A similar network marker may be rs1800795 G, which is associated with increased mortality and a 2.8-year lower life expectancy in homozygous patients, whereas there is no such risk in carriers carrying the C allele according to Cole et al. (2010).

Thus, genetic networks and social, environmental, and psychosocial networks are interconnected. However, genetic polymorphism plays a role only in the case of expressed genes, i.e., transcriptomes play a critical, hub-like role in the interaction of genetic and molecular networks. An essential point of attack is the level of mRNA activity responsible for NF-kappa B. According to Chen et al. (2009) and Miller, Rohleder, and Cole (2009), the number of genes on the order of different psychosocial stressors can play a mediating role due to social isolation, status differences, and high interpersonal stressors. According to Slavich and Cole, an entire genetic pattern, an actual genetic program, can be activated in the wake of adverse psychosocial effects. An example of such a pattern is the so-called CTRA (conserved transcriptional response to adversity), an evolutionarily fixed response to a threatening environmental stressor, an allostatic pattern. Similar attention is paid to the genome-level transcriptional changes observed in asthma, post-traumatic stress disorder, and certain cancers such as breast and ovarian cancer.

This system of relationships within the paradigmatic framework of network medicine has been called social genomics, which calls for the study of gene segments in a regulatory relationship with the social environment and the neural and molecular mechanisms that mediate their influence on gene expression. The aforementioned genetic polymorphism thus has an explanatory meaning in genomics when interpreted in the social context. Thus, the effects

of neural and molecular networks linking social and genetic networks on complex behavioral phenotypes and susceptibility to disease are also revealed. This dynamic network approach initiates the entrenched misconception that our molecular genetic characteristics are independent of the environment. The network effect of psychosocial stressors induces several multilevel network changes, proinflammatory cytokines are elevated at the molecular level, transcription factors show a change intracellularly, and several genes are affected by such an influence.

Among the psychosocial variables, those with a social threat, such as social conflicts, exam situations, assessment, rejection, exclusion, or isolation, are critical. The overlapping nature of these networks is indicated by the fact that the neural patterns responsible for physical pain mediate the emotional pain of social origin caused by rejection and loss.

But conversely, inflammatory mediators and cytokines such as IL-1, TNF alpha, or bacterial endotoxins, can elicit a depressive-like pattern of behavior. Disease behavior can also be considered a unique adaptation with evolutionary roots, which organizes a pattern of behavior favorable for healing through the cytokine system mobilized by bacteria and viruses (avoidance of physical exertion, sleep, inhibition of food intake).

In the brain, proinflammatory cytokines produced by microglia and astrocytes bind to several sites and promote the production of norepinephrine, dopamine, and serotonin, which induce behavioral changes and, additional neuroendocrine-immune processes in the patient. Thus, disease behavior, and in many respects, analogous depression, may result from a change in the state of an integer immune network, and the network of cytokines can induce evolutionarily patterned states of the neural network simultaneously affecting mood regulation, patient cognitive status, and behavior. For example, inflammatory mediators, proinflammatory cytokines, IL-1, IL-6, TNF alpha induce somnolence, fatigue, anorexia, psychomotor retardation, decreased sociality, and exploratory behavior.

Identifying the degree of distribution and the identification of hubs characterized by several connections are needed to find the characteristics of these networks. At the molecular level, these can be TLR4, Nfkappa B, caspase, or at the cellular level, macrophages or the nodular cellular elements of the HPA axis. More abstract network modeling is necessary to find hubs in neurological structures participating in the assessment of controllability, the psychological processes of social perception and assessment, and neurophysiological structures that organize the personality. This way, the early mother–child relationship, which is important for the development of personality, xneurobiological structures, and carries permanent immunobiological consequences, might become a network hub.

In fact, the network itself is held together by a few hubs that have many connections. This is why socio-psychoimmunology researches point in so many directions: lifetime hubs (mother–child relationship, separation, loss of the object, loss of control), positive or negative traits that are sensitive in immunology terms (pessimism, type C personality, active or passive coping), pathologic network patterns (HPA activity, regulation of glucocorticoid receptors, TH1/TH2 shift), allergic or autoimmune disease patterns in patient narratives at the social level. These various key *hubs* may connect several types of networks of correlations. These small worlds are features of complex networks. The interconnected molecular networks are surrounded by relatively short path connections where a large portion of the component proteins are responsible for a low number of interactions, while they may be along main routes affecting the entire body, influencing the entire network.

Therefore, the hubs responsible for specific local cellular processes may be deemed to be *party* hubs, while they may also be *date* hubs interconnecting different processes and associating relationships that organize the interactome. Further characteristics of the network are the 'subgraphs' having motif power and in charge of biological functions such as negative or positive feedback, or the oscillator function. These subgraphs are the totality of the interconnected hubs that make up a subnetwork within the network.

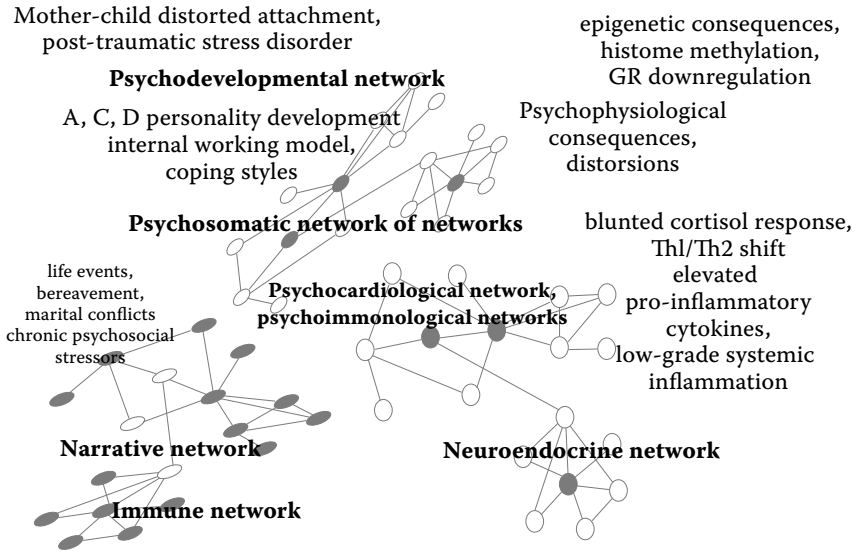


Figure 10. Psychoimmunological network of networks

Most networks may be described by the substantial creation of beams and are accompanied by the generation of topology modules characterized by the emergence of a high local regions with mutual connections. Hubs are characterized by a high betweenness centrality that describes the number of the shortest paths running through the hub, otherwise referred to as *'bottleneck'*. This is the nature of regulatory networks with vector edges.

An important part of network analysis is link analysis, which looks primarily at the relationships between factors, hubs, and objects. Psychoimmunology itself offers a good example for the analysis of key relationships and links between the various objects, as it identifies and maps relations between networks of different characters (wired neural, endocrine propagated by blood flow, immune moving via tissues). Socio-psychoimmunology allocates the anamnestic narrative network relations and the social and symbolic, cultural hub networks leading to stress to these networks, exposing their mutual interactions.

This network approach provides a new framework of cognitive mapping for anamnesis, diagnosis, and therapy. The result is, in fact, a transversal metanetwork appearing through a series of information transcripts and translation mechanisms, which weave a psychosomatic disease pattern through the network layers with its own heteronomous hubs.

Network features of Solomon postulates

George Freeman Solomon was one of those pioneers who established the scientific paradigm of psychoimmunology in the 1960s and 1970s, pointing to the connections between brain, behavior, and immunity. He gathered the psychoimmunological revelations in a corpus of postulates. We can test these postulates from the network perspective.

Graph of neuroendocrine-immune networks might be seen as real *small-world networks* in which most nodes are not neighbors of one another, but the neighbors of any given node are likely to be neighbors of each other, and most nodes can be reached from every other node by a small number of hops or steps.

Neuroendocrine-immune pathways

1. IL-1-paraventricular NA secretion-CRH-ACTH-adrenocortical cortisol (sickness behavior, neuroendocrine-immune feedback, inflammation theory of depression based on depletion of dopamine, or diminishing serotonin secretion).
2. Immunological abnormalities may be accompanied by psychological or mental disorders.

3. Activation of the immune system can lead to changes in the activity of the central nervous system.
4. Immune signaling can also affect the central nervous system.
5. Cytokines of the immune system, as part of the neuroimmune endocrine axis, play a role in endocrine regulation, including stress-induced endocrine processes.
6. Cytokines influence psychological processes and cause psychiatric symptoms. Immunity influences behavior, and behavior can aid in immune regulatory functions.

Psychoneuro-endocrine-immune pathways

1. Psychological states/traits-neural networks-stress hormones-immune system (C-type personality, right frontal hemispheric dominance, chronic stress, depression, shame, submissive status).
2. Adaptive coping styles and enduring characteristics can improve the prognosis of immune diseases and protect susceptible patients from the disease.
3. Stress coping and traits, including personality traits that influence stress management, may influence the immune response to exogenous antigenic stimuli.
4. Emotional changes and distress (state characteristics) can influence the onset, severity, and course of disorders controlled by immune processes or resulting from disturbed immune processes (allergies, autoimmune, diseases, AIDS).
5. Severe emotional and mental disorders can cause immunological disorders.
6. Immune functions may also be affected by altered states of consciousness.
7. Experimental behavioral effects may lead to immunological changes.
8. Damage to and stimulation of some regions of the central nervous system may lead to immunological changes.
9. Substances produced and regulated by the central nervous system (neurotransmitters, neuropeptides, other neuroendocrine factors) must influence immune processes.

Social-psychoneuroimmune network pathways
(social rank, social-evaluative theory, shame, bereavement, social losses, social exclusion, voodoo, cultural nocebos)

1. In extensive prospective studies, specific patterns of psychological risk should be associated with a higher incidence of immune disease.
2. Genetic, gender, and behavioral factors influence the immunological effects of stress.
3. In addition to the influence on the adult psyche, early injury and the traumatic mother–child relationship can affect the adult immune system.

4. Therapeutic influences on behavior (psychotherapy, relaxation, biofeedback, and hypnosis) may also affect immune function.
5. Positive emotions stimulate immune function.

Bridges in the network

1. Immunocompetent cells have receptors for receiving neuropeptides, neurotransmitters, and endocrine signals.
2. Central nervous and hormonal factors may play a role in the regulation of feedback processes in the immune system.
3. Lymphocyte receptors are also affected by changes in transducer sensitivities that are characteristic of mental disorders and cells of the central nervous system.

Hubs in the network

1. Thymic hormones that regulate immune function may be under central nervous system influence.
2. CRH plays a role in the processes and symptoms of depression and immunosuppression associated with depression.
3. Certain cell groups of the nervous and immune systems occur together.
4. The prenatal hormonal environment has an effect on the CNS and the development of the immune system, which can have lasting effects on both behavioral and immune functions.
5. Sleep affects both the CNS and immune processes.
6. Immunological processes and specific personality characteristics (coping style, "hardiness") may play a role in longevity.
7. Enzymes for the synthesis of brain neurotransmitters are found in immunocompetent cells and neurons.
8. Melatonin, a neuronal hormone involved in the regulation of circadian rhythmicity and affected by stress, affects immune function.
9. Mitogens, potent, non-specific immunostimulants, also act on the nervous system.
10. Immune cells influence the development and function of the surrounding nervous system.
11. Lymphokines may affect pituitary hormones directly and via the central nervous system.
12. Some cells of the central nervous system are capable of lymphokine production.
13. Cytokines of the immune system, as part of the neuroimmune endocrine axis, play a role in endocrine regulation, including stress-induced endocrine processes.

These psychoimmunological facts support the profound relevance of social and psychological network changes exerting deep visceral influence through psychophysiological networks. It also supports the connection between psychosomatics and broad areas of internal medicine.

Social networks and neuro-immunobiological networks are linked with psycho developmental hubs. Common, hub-like narrative foci are the early mother–child relationships and the adverse childhood experiences, just like the syndrome of post-traumatic stress. Distorted early mother–child attachment organizations have an impact on the so-called internal working model and other personality features, creating enhanced risks for some somatic diseases. A-type anxious avoidant secondary attachment organization might diminish empathy and hypothetically create a tendency toward A-type personality development, striving for dominance, competition, hostility and tendencies for cardiovascular vulnerability. In contrast, C-type secondary anxious/ambivalent attachment organization creates lower self-esteem, behavioral inhibition of aggression, and expression of emotions, high anxiety, and psychophysiological arousal.

Epigenetic consequences of distorted mother–child attachment, like downregulation of hippocampal GR receptors via histone methylation, distorted HPA feedback, and distorted estrogen regulation with consequences for adult maternal behavior also prove the hub-like role of the mother–child relationship between socio-psychological and developmental personality networks, stress physiological networks, and neuroimmune network.

Relations between transactional events, traumas, feelings of submission, and loss of control, just as chronic psychosocial stressors that carry psychological meaning are explored in the networks of the socio-psychological layer. Alexithymia or social inhibition and the psychological network patterns of the C-type personality convert all this into increased HPA activity, high arousal, and increased LC/NAergic activity, so that all this is eventually embodied in the disruptions of the immune cell network controlled by cytokines. Then, IL-1 and IL-6 as result of modified protein synthesis in the cell reach the central nervous system, and via modified dopaminergic and serotoninergic molecular network changes are transcribed into psychological network patterns and depression. The disturbances of rank position experienced in social networks (reduced motivation, lack of adequacy in the workplace, family conflicts, loss of socioeconomic status) are also embodied this way (via neural networks and proinflammatory cytokines).

SOCIAL PSYCHOIMMUNOLOGY

Traits and states

Research results, which have a history of half a century, have yet to be able to give an unambiguous answer to the question of whether there exists a personality structure that is susceptible to immunopathological and/or tumor diseases. Though inhibited power motivated (IPM – McLelland) personality prone to immune suppression or cancer, the Type C behavioral pattern (TCBP – Temoshok, Baltrusch) as well as Grossarth-Maticek and Eysenck's Type I personality model are all indicators of efforts to come up with such a theory, it is a wasted effort to set up reassuring statistical classifications in these complex systems and processes, which remain quasi-chaotic even when regulated, and are highly volatile in their function subject to context. Nevertheless, in a remarkable part of the diseases concerned, phenomena and characteristics that may be classified in the above categories are indeed outlined, as indicated in Herbert Weiner's summary (1977) with readers well-versed in psychosomatics. From this point on, we wish to shed light on the logic underlying these characteristics with an eye to socio-psychoimmunology.

The question or dilemma of 'nature vs. nurture' arises here as well. Kang et al. (1991) raise the question of whether the depressive trends noted in children that may be characterized by an increased dominance of right frontal activity excess and the reduced NK cell activity are innate personality traits; a dysfunctional adaptation pattern may form a part of this kind of character. This is particularly important because, in contrast with persons with an increased right frontal activity, significantly higher NK cell activity was measured in persons with increased left frontal activity, albeit none of them showed anxiety or depression symptoms. In the repeated test, Davidson et al. (1999) state that the resting NK activity of persons characterized by increased left anterior cortex activity was higher, and they reported on the enhanced positive experience in response to films with positive contents, whereas it was persons with excess right anterior activity who responded to a clip evoking sorrow or a natural stressor with a greater reduction of NK cell activity and an increased negative response to the experience.

Applying the PANAS psychological scale to persons with increased left frontal activity, Tomarken et al. (1992, 1994) found a markedly increased rapprochement, increased scale values for enthusiasm, pride, and motivated elation. Persons with an extreme dominance of left frontal activity are characterized by the suppression of negative experiences and low anxiety and depression values on the Marlowe-Crowne scale. The pattern of aversive conditioning 'wears off' faster in the case of persons with a dominant left hemisphere, meaning that the body also forgets the associations of aversive learning that may even have bodily manifestations more readily.

The repressive coping style is frequent in type C persons, who show immunosuppressive trends and have increased affiliation tendencies, and are susceptible to immune suppression. Solomon's (1987) proposal also expands this circle, offering a new personality pattern to add to the increasing number of risk characters, which is the 'immune-suppression-prone personality pattern'. In this case, the method of processing stress is what plays a role, and the term is related to both the type C and the alexithymia personality, while the particular method of stress processing is accompanied by an enhanced susceptibility to immune suppression.

The repressive coping style is a permanent personality trait in which the person does not report significant stress, yet their vegetative responsiveness is elevated and shows greater internal tension. According to Schwarz (1984), this is coupled with increased lateralization and physiological features implying an increased activity in the right hemisphere, as confirmed by EEG tests by Tomarken and Davidson (1994). The right frontal cortex plays a role in organizing evasive behavior that is responsible for passive coping, and ACTH secretion is also controlled by processes of the right hemisphere to a considerable extent. To the contrary, the left hemisphere's role is conspicuous when it comes to organizing experience factors that assist objective and reward-oriented behavior. According to the dominant assumptions, the left-side dorsolateral prefrontal cortex plays an especially significant role in this, and the ganglion basalis associates the expression of the abstract goal in the action plan to this function, whereas the amygdala mobilizes the vegetative nervous system through hypothalamic connections in organizing an experience. The parietal and prefrontal cortex sections, as well as the gyrus cingulatus, also play a role in organizing selective attention, so important for target-oriented approach behavior. This system of nervous connections, which organizes rapprochement, and this activity pattern organize the positive nature of the experience before the result is achieved, forming a part of the motivation. The underactive functioning or muting of this mechanism is parallel to the condition of giving up, of losing control, and may presumably also lead to the development of such situations.

Withdrawal, which serves to protect against threats from the environment in an adaptive manner, has a negative role in qualifying situations and organizing experience. Fright and disgust are experiences of this type, in which the amygdala and the polar region of the temporal lobe play a role, and Davidson et al. have detected increased EEG activity of the right frontal region in negative experience situations that prompted withdrawal (1990). The organization of the negative experience accompanying evasive behavior also extends to changes in the activity of the ganglion basalis and the hypothalamus and to changes in the accompanying autonomous processes in the tests done by Smith et al. (1990).

The differences in frontal activity variations between the hemispheres pursuant to social and non-social positive and negative stimuli may show further asymmetrical shifts, enhancing the typical difference in the basic asymmetry of frontal activity.

In depression patients, alpha activity is increased in the left-side (central) frontal cortical areas, meaning a decrease in the activity of the given cortical region. Targeted, encouraged behavioral response was weaker in depression patients, which may also be associated with the reduced left frontal activity, according to Henriques (1994). The above difference also exists between the group that is momentarily normothymic but has a history of depression and the normal control free of depression antecedents, which also implies that the differences in the frontal hemisphere may be a permanent trait.

Animal test results also imply a trait-type difference in immune character in highly lateralized animals. Fride et al. (1990) investigated immune indicators of animals selected on the basis of highly or weakly lateralized behavioral tendencies (limb preference), and compared them to each other as well as an unselected control group. In the highly 'lateralized' animal stock, reduced immunity was detected in respect of both NK cell activity and cytotoxic cell response.

The investigation by Pettito et al. (1993) linked the genetic characteristics of social behavior to NK cell activity and tumor development. Animals that could be described by low aggression were raised separately from those with high aggression indicators. As a result of the selective process, behavior patterns have evolved that did not show the aggression triggered by isolation otherwise typical for the species, but appeared to be socially inhibited in the presence of a strange mouse. The tumor triggered by 3-methylcholanthrene evolved in each of these socially inhibited animals, in contrast with aggressive animals, where tumors appeared only in 44%. The basal level of NK cell activity was also lower in the socially inhibited animals. The aggressive group and the control group displayed no difference in basal NK cell activity. No difference between the three groups was found for non-social emotional reactivity and

in respect of serum cortisol. Based on the findings, the authors assumed a correlation to exist between permanent social characteristics, immunology indicators and tumor susceptibility.

Personality traits and immune vulnerability

The relationships between psychological and immune characteristics may also be investigated from the perspective of classic personality traits. The Big Five, the five groups of factors developed pursuant to the factor analysis of the various personality traits, offer trait-like characteristics such as *extraversion, friendliness, conscientiousness, emotional stability* and *culture/intellect.* There may also be traits difficult to fit in this palette, such as neuroticism, optimism as a typical positive emotional attitude, hostility and social inhibition. In fact, it is the underlying arousal, the activation levels, and the accompanying autonomic nervous characteristics that should be investigated for these traits. Of course, a responsible person apt to moderation, who is conscientious and may be characterized by emotional stability, is more protected in health psychology respects than an unbalanced, hostile, irresponsible person with unstable passions. The stress physiology characteristics of neurotic persons are also unbalanced and extreme, while the factors influencing immune response are adaptive and favorable in immunology respects in people with an optimistic disposition.

The dynamics are similar for hostility as well, where the arousal level and stress reflect extreme dynamics pursuant to the aggressive or conflict-seeking hostility. Naturally, all this may be interpreted only in a socio-psychological, transactional context.

An important dimension of the Big Five is 'extraversion'. This dimension of the personality is easy to involve in the context of socio-psychoimmunology, because – as interpreted by Eysenck (1967) – an extrovert seeks the challenges of social transactions and social activities because their arousal level is low by default, as opposed to introverts, who avoid social interaction due to the initial high arousal level. In fact, the early immunologic effects of virus exposure causing upper respiratory symptoms – provoked mostly by rhinovirus – were measured in extroverts and introverts, as can be seen in Cohen's et al. (2003) summary; and all tests have signaled a reverse correlation between the psychological indicator of extraversion and the symptoms triggered, meaning that extraversion (and, presumably, the low arousal typical for it) defends against respiratory infections by strengthening local immune protection. In these tests, higher extraversion scores were coupled with weaker symptoms, or the authors found no correlation between the symptom and extraversion. Gonzales-Quijano et al. (1998) detected higher lymphocyte proliferation in

case of higher extraversion, and Miller et al. (1999) measured higher NK cell cytotoxicity, while Bouhuys et al. (2004) demonstrated a positive correlation between extraversion and NK cell number, and a reverse relationship between CD4+/CD8+ cell proportions. Ironson et al. found a positive correlation between CD4+ T cells and extraversion in people who have AIDS. Overall, the tests imply that extraversion helps to maintain defense and resistance against infections.

Cohen et al. (2012) have demonstrated a link between the indicators of the Big Five and immunity in chronic patients as well; extraversion, conscientiousness, openness, and positive emotional attitude all showed a positive correlation with immunity. Ožura et al. (2012) also confirmed the connection between the Big Five indicators and the number of NK cells and B cells.

Neuroticism may also be important for psychoimmunology due to the underlying neurovegetative dynamics. Eysenck (1967) connected neuroticism to a low stimulus threshold, permanent arousal with large amplitudes, and Miller et al. (1999) also connected this to increased catecholaminergic and HPA activity. According to Costa and McCrae (1992), this trait makes people vulnerable to frequent negative emotions, such as anxiety anger, and depression, which is why it can be interpreted as a negative emotional style or a trait-type negative affection. People with this personality see the world as a threat, a source of distress, the challenges of which are hard to overcome. Persons who may be described as having low neuroticism are calm, emotionally stable, and find it easy to cope with ambient challenges. Higher neuroticism values are coupled with lower antibody titer, according to Phillips et al. (2005). In parallel with higher neuroticism, Arrantz et al. (2007) found increased TNF alpha and higher IL-6 values. On the other hand, higher neuroticism is coupled with lower NK cell cytotoxicity, lymphocyte proliferation, phagocytosis and chemotaxis. According to Borella et al. (1999), stress and neuroticism have a synergic effect on immune regulation.

The indicator for hostility is also characterized by increased neurovegetative arousal, considered the 'toxic' factor of the type A personality model. The applicable psychoimmunological tests allow for finding that higher hostility is accompanied by increased proinflammatory cytokine production. Marsland et al. (2008) and Stewart et al. (2008) found the level of IL-6 out of interleukins to be higher at higher hostility. By the way, IL-t may be deemed to be an unfavorable psychological marker for health.

Social inhibition as a trait covers a feature well-known in psychoimmunology and psychosomatics. The aggression inhibition, the disturbance in expressing negative emotions, emphasized by Lawrence LeShan, Temoshok, and others, may be part of this characteristic. According to Asendorp's (1993) definition, the suppression of emotions during social interactions increased

sensitivity and vulnerability to criticism from the environment, and withdrawal expressed in uncertain or defiant chapters are typical features of social inhibition.

In agreement with Eysenck, who emphasizes the role of the activation of the vegetative nervous system, which plays a central role in stress physiological and neuroimmune processes in the background of extraversion or neuroticism, the above moments of personality are reasonable to set into a model based on the evolution and fixation of early neurovegetative patterns that have consequences in evolutionary psychology.

Early traumas

Importance of early traumas in human ecology and psychoimmunological consequences

Psychoanalytic theories, human ethology and the psychobiological approach all attribute predominant importance to early psychological injuries, disturbances in the mother–child relationship (attachment, bonding). Disturbances caused by medicalized, 'technocratic' hospital births, separation for hygienic reasons and baby blues play a role in the early stage of the mother–child relationship. The involuntarily early return to work, the rise in the ratio of single-parent families, the atomization of society and the increase in the number of teenage mothers intensify this and turn the issue into a public health problem.

Whether the newborn baby is 'functionally premature' is a decisive factor as regards the potential for early traumatization. 'Psychological birth', the appearance of the ego is a complicated process realized in the processes of separation and individuation. The factors that force this prematurely, or act in a disturbing manner in respect of Mahler's stages in the phases of normal autism and the normal symbiotic phase, which have increased importance, may develop serious psychobiological maladaptive mechanisms influencing the maturing processes of neuroendocrine organizations or fix these mechanisms by condition-dependent learning.

The disorder thus created, which impacts the development of the personality, the emergence of the ability to cope and social competences, and may even point towards psychopathic personality development, may play a role in the background of permanent adaptation problems in respect of psychosocial stressors.

In Rhesus monkeys, prenatal stress has permanent effects that last after birth as well and may accompany the animal in the period of adolescence. Behavior is inhibited, exhibitionist behavior is reduced, they play less and act disturbed in new situations pursuant to prenatal stress. According to Clarke and Schneider (1997), this can be extended to children subjected to prenatal stress.

The mother's dominant role is confirmed by the fact that a part of the monkeys raised without a mother in the colony responds with extreme cortisol and NA activity hikes already in a short separation process. These animals find it hard to adapt to new situations.

Bowlby interpreted the mother–child relationship, attachment, as a homeostatic external ring, which is aligned to the internal physiological homeostatic system in adaptation to the environment. This homeostatic mechanism changes the child's explorative behavior after a while. However, in case of danger, the child retreats into the attachment that means safety.

A sure foundation, accessibility, shelter from ambient dangers and nurture are important elements of the attachment system. Attachment behavior is characterized by seeking the gaze maintaining closeness, and contact. Damage in the attachment may lead to childhood depression, anxiety disorders, difficulties in adaptation and disturbances in the parental role, which may be transcribed between generations. In Bowlby's theory (1988), the strength of attachment is proportional to the probability of survival. Naturally, a trauma caused by rupturing the attachment to the nurturer is also proportional to the intensity of the attachment. It is surprising, however, that separation from incompetent parents (ensuring lower survival success) causes even greater trauma, indicated by Kraemer (1992) based on observations of Rhesus monkeys.

In contrast with specimens raised under normal circumstances, Rhesus monkeys raised in social isolation are characterized by different thermal regulation, immune functions, body weight regulation, polydipsia, hyperphagia, self-hazardous behavior, motor stereotypes, hyper- or hypoemotionality and aggression. Animals raised in social isolation are unable to receive facial expressions as discriminative stimuli during learning processes, which indicates injury to the social communication competence. In addition, these animals are characterized by disturbed sexual and maternal behavior.

Studying Rhesus monkeys that grew up with peers but were raised with no mother, Kraemer (1977) confirmed that the absence of the mother had a negative impact on the development of interactions between various neuroendocrine systems and influenced basic cognitive processes. Thus, in the absence of the mother's regulatory effect, the behavior of animals growing up among peers proved to be chaotic instead of patterned and orderly. The investigations imply the disconnection of behavior from the biogenic amine system. This also indicates that the functional maturation of these systems requires the mother's regulatory presence. Adult animals who grew up among peers only turned out to typically neglect or abuse their offspring. Therefore, attachment systems make up a joint homeostatic regulation system of the mother and the child, where the mother makes up for the regulatory functions that are insufficient in children with her presence, an external regulatory mechanism.

However, psychophysiological harmonization is not restricted to the mother–child relationship. Separation of the monkey offsprings raised together may have deep immune consequences. According to observations by Reite and Field (1985), the elder child often responds to the absence and return of the mother with depression symptoms when a younger sibling is born. Reite and Snyder (1982) state that there is an increase in vulnerability to diseases after an involuntary separation from parents and/or peers in small children.

Considering that close and intimate relationships develop in later phases of a lifetime as well, Field (1985) proposes an extended attachment model. In this model, attachment is a relationship involving the mutual psychophysiological harmonization of two or more persons. Thus, attachment systems may be considered a behavioral and biological system that plays a role in creating and regulating psychobiological harmony between organisms, which has its foundations in and is transmitted by neurobiology, according to Reite and Capitanio (1985). This is true not only for the relationship between mother and child; based on investigations by Levenson and Gottman (1983), synchronization of behavior and heart rate can be seen between spouses, as well as the harmonization of cortisol level cycles according to Lundberg (1979). When such a deep attachment evolves, the loss of the significant other person has just as in-depth psychobiological consequences as mother–child separation. This is why adult attachment attains crucial psychoimmunological significance in the grieving process.

Maternal behavior may be reassuring (sensitive, accepting, cooperative, and always accessible), while maternal behavior that is kept in limbo is characterized by inconsistent behavior, the lack of behavioral response, or rejection. The latter type of mother–child attachment increases the likelihood of maladaptive behavior. Internal regulatory processes are ensured to mature pursuant to maternal stimuli, but if the mother nurtures the baby or primate investigated insufficiently, and with a lack of empathy, the offspring's regulatory processes will also develop in a disturbed manner. This may have serious consequences in the event of separation from the mother.

In families living in economic misery, childcare lacking in empathy is more frequent, and the mother–child relationship gets disorganized. The internal working model thus fixed, which organizes expectations and behaviors of social attachment later, is very solid over the course of life, and the personality is pushed towards a new basic stance concerning relationships only by poignant events in most cases.

Attachment organizations in adulthood may also reflect the logic of early relationships, as reflected by the increasing number of divorces and the rate of alienation, loneliness, and psychopathic or addictive behavior.

In the wake of nurture without empathy, factors so important in socio-psychoimmunology such as control, confidence, ego strength, self-esteem, social competence and social support are weakened or even inhibited.

Persons who may be described by a safe mother–child attachment are resistant to psychosocial stress also in adulthood, according to Fonagy (1994). This has great significance for public health, because the inadequacy of parental behavior and the most frequent occurrence of uncertain attachment patterns can be seen in economically and socially desperate groups of society.

The pathological psychobiological aspects of this may be monitored in human observations as well. In the event of insufficient empathy in nurture, babies may be observed to show hypo- and hyper-condition indicators in lieu of harmonic behavioral responses, ranging from kinetic features to visceral phenomena such as GBR, reactions of the gastrointestinal tract, or circulatory responses. These responses may also be fixated as condition-dependent traces of memories and behaviors and may become the basis for generating psychosomatic symptoms. The endogenous opioid system and hypothalamic NA-erg processes may also mirror a mother–child relationship lacking in empathy.

The intensive occurrence of an early attachment trauma is also a model for multi-stage grief dynamics. The behavioral response to mother–child separation consists of two phases; 'protest' and 'despondency' follow one another. The protest stage is characterized by increased activity, agitation, a typical vocalization, while despondency is characterized by inactivity, withdrawal, thumb sucking, negative approach to eating, and an embryonic pose. The second stage reflects a depressed situation and implies experiencing a severe loss.

Neuroendocrine consequences of early traumatic experiences

Tight attachment to the mother is an indispensable prerequisite for cerebral maturation in babies, and basic emotional regulatory processes that strengthen or weaken the 'experience expectant neural processes', in the words of Collins and Depue (1992), take shape at this stage. It should be seen that the crucial factor in the baby's development is the mother's empathic behavior tuned to the baby's needs, and her mere and often frustrated presence is not sufficient.

In psychophysiological terms, this means that the baby may feel safe because it experiences understanding and reassuring behavior from the mother in response to danger signals. The baby experiences that the psychophysiological arousal experienced does not lead to disorganization when the danger is beyond the baby's possibilities for coping, because the mother is able to restore the

balance. This trust and safety are also the basic formula for the belief that the situation can be resolved, accompanied by the sprouting experience of self-confidence and competence.

In the wake of early separation and empathy-deficient nurture, the reduction in the number and activity of hypothalamic opioid receptors generates the neurophysiological foundations for joylessness according to Belluzzi and Stein (1977), while the noradrenergic system's chronic reciprocal activation reflects the psychobiological background of the distress experienced in Van den Kolk's investigations (1987). In the case of infant monkeys separated from their mothers and raised among peers, Kraemer and Clarke (1990) found the basic activity of the noradrenergic and dopaminergic systems to be reduced, which may explain both oversensitivity at the post-receptor level and the excessive responsivity to social stressors that increase catecholaminergic activity and to drugs.

Early (traumatic) influence from the environment has an impact on the expression of the glucocorticosteroid receptor gene of the hippocampus and the frontal cortex, which play an important role in regulating the negative feedback for CRH and arg-vasopressin. Pursuant to the repeated separation of the mother from the offspring for 180 minutes, the level of glucocorticoid receptor decreases in the hypothalamus, the hippocampus and the frontal cortex, which become characteristics valid in adulthood as well, according to an early study by Meaney (1988). This effect is prevalent primarily in the first three weeks of the baby rat's life but may resonate all throughout life. The system, which has grown insensitive to the inhibitive effects of glucocorticoids, may react to the given social and other stressors by increased HPA activity and vasopressin secretion, which may be a permanent neuroendocrine trait of the traumatized person according to Francis (1996). Elevated HPA activity may have immune suppression consequences, while increased AVP secretion may result in the development of aggressive behavior trends. Understandably, the mother's presence and body contact have the opposite effect, which underlines the psychobiological significance of the early and undisturbed mother–child relationship. 'Handling' increases the expression of the glucocorticoid receptor gene in the above areas and enhances the efficiency of negative feedback.

Epigenetic research sheds new light on the determination of early trauma and stress response in developmental psychology, the issue of individual vulnerability, and the socio-psychoimmunological aspects of certain traits.

Epigenetics of early trauma

The concept of epigenetics surfaced in the middle of the last century and is a combination of the concept of 'epigenesis' used in the discipline dealing with embryonic development with the concept of genetics. According to

Waddington (1968), the founder of this field, epigenetics deals with factors and mechanisms mediating between genes and the creation of the phenotype. A similar idea is expressed in Erik Erikson's developmental model, who borrows the key thought of his developmental model from embryonic epigenesis, namely that the unfolding of the program for human development depends on certain critical factors, and each of the eight development stages described by him depends on the success of the maturation processes taking place in the preceding stage.

Peedicayil also emphasized the parallel between Erikson's developmental concept understood in the analog sense and epigenetics when suggesting research into the connections between (pheno)genetic and psychobiological mechanisms responsible for the different changes under pathologic and normal conditions. The psychoimmunological aspects of this correlation were investigated by Meaney et al. in the late 1990s, which also offered confirmation of the correlations between the A/C distorted secondary attachment systems hypothesized by us and their hypothetic psychological and psychoimmunological consequences to be detailed later.

Meaney and his team confirmed the phenomenon that has already been exposed by neuroimmune research based on behavioral principles to a significant extent, namely that pursuant to traumatizing maternal behavior, the HPA axis feedback mechanism of the progeny goes out of tune and stress-biological vulnerability increases, and McGowan et al. (2009) have been able to confirm this in the case of suicides involving persons subjected to childhood abuse. In 2004, Meaney and Szyf confirmed that in contrast with this, the mother's caring behavior (licking, scratching) enhances the expression of the glucocorticoid receptor in the hypothalamus and improves stress-biological response. It should also be mentioned that adults may also respond to environmental stressors by an epigenetic mechanism, which may affect behavior, physiological processes, and disease risks, according to Handel et al. (2010).

Thus, the stress process becomes inalienable from the socio-psychological embedding in terms of its development, nature, and events. Therefore, individual psychosomatic events cannot be interpreted without their developmental background, and the frequency and dissemination of diseases also acquire a socio-cultural context. The multi-tiered complex causal chain of epigenetic epidemiology also models the multi-factor effect paths and 'transcriptions' of our 'palimpsest' metaphor. Epigenetic patterns are influenced by genetic variations, epigenetic inheritance mechanisms, random processes, and the psychosocial environmental effect. Research provides ample data to show that unfavorable, abusive early life experiences increase the incidence of adult psychiatric conditions.

Epigenetic inheritance takes place in a non-genome way, meaning that the ambient influence – in our case, trauma caused by perinatal infection or

abusive or negligent maternal behavior – is capable of influencing gene activation without changing the DNA itself. This effect occurs at the level of gene expression, at the histone level, and these changes may be transmitted mitotic or meiotic ways, according to Meaney and Ferguson-Smith (2010). Epigenetic processes influence gene transcription and ensure phenotypical plasticity that may be transmitted between generations and subject to experience by way of the methylation of DNA sections and the acetylation of histone. Methylation and acetylation exert an effect on the N terminal section of histone by influencing the chromatin structure. Methylation inhibits gene expression by affecting the chromatin section, while histone acetylation promotes gene expression by way of the histone acetyltransferase, which remodels the chromatin. This process is particularly sensitive to stress, according to Hinwood et al. (2011).

The reduced HPA feedback and increased stress sensitivity in the wake of reduced glucocorticoid receptor expression that may be observed in rat progeny pursuant to abusive and/or negligent maternal care may have central importance for our theory. Monitoring rats, Weaver et al. (2004) observed that increased licking and grooming increased GR expression in the hippocampus, while chromatin methylation at the GR promoter exon1 attack point resulted in increased HPA responsiveness and reduced hippocampal GR expression and restless behavior in negligent animals that neglected their offspring. It is important to know that according to research by Weaver et al. (2006), the variations in glucocorticoid receptor density are accompanied by increasingly anxious behavior so that early traumatization leaves a trace in the pattern of social behavior as well. The increased activity of the HPA axis and anxious behavior may be suspended by administering a histone deacetylase (HDAC) inhibitor.

Early trauma and aggressive behavior

Separating rat babies from their mothers also results in a reduction of oxytocin receptors in the hippocampus, according to Noonan et al. (1994). The affinity of serotonin receptors in the frontal cortex, the striatum, the hippocampus, and the hypothalamus may decrease pursuant to early isolation. In isolated non-aggressive animals, 5-HT1 receptor affinity and the number of receptors decreased only in the hypothalamus, while this typically occurred in the hippocampus as well in aggressive animals. Substance P depletion in the developing brain also influences the development of the brain's serotonin system in mice. All this may explain the relationship between early trauma and subsequent aggressive behavior. However, Kraemer emphasizes that the low activity of the serotonin system in itself fails to explain the emergence of aggressive behavior trends, which may be better explained by the disintegration of a number of

neurochemical systems, which may be detected in the course of mother–child separation. The deficit of attachment behavior may be associated with changes in the oxytocin system and the opioid system. Panksepp's (1985) observation confirmed on a number of species including dogs and guinea pigs implies a role of the opiate system; according to this, the state of social separation is similar to opiate deprivation conditions, and administering opiate receptor agonists reduces separation stress condition, while naloxone as an opiate antagonist increases the separation distress experience. Only clonidine, which may be applied in opiate deprivation, offers an effect of reducing distress similar to that of opiates.

An important element of the separation trauma is that the most important source of confirmation is gone with the departure of the mother, the partner, the Significant Other, along which the control stemming from interactions, the experience of being able to predict a situation, and feedback are also reduced.

Rutter (1979) lists acute distress syndrome, intellectual retardation, conductive troubles, and the state of emotionless and empathy-deficient psychopathy as the consequences of maternal deprivation. The most dangerous aspect of maternal deprivation is that its effect may survive generations as a transferable 'internal working model'. Thus, the acquired basic social attitude that organizes the logic of human social relations will be transmitted when the child who is the victim of the disturbed attachment system becomes a parent.

A lower arousal level is typical among aggressive, uninhibited, and antisocial psychopaths. The social experience generating early trauma may have a role in the development of reduced autonomous neural arousal. Theories state that the psychophysiological response developed for maternal separation may be considered to be a particular form of stress inoculation. The animal tests offer a background to this, as the prenatal stress on rodents reduces emotional reactions to the stressor after birth, according to an early study by Keeley (1962). Similarly, a lower heart rate response may be observed in antisocial persons in burdensome situations.

Sapolsky and Meaney raise the proposition that during early development, the levels of corticoid receptor and CBG (corticosterone-binding globulin), so important for the functioning of the HPA axis, are reduced, and the activity of the axis itself is inhibited, which indicates reduced ACTH production during stress effects. This reduced stress response period (SHRP) is typical in rats during the first two weeks after birth. This period may be deemed to be a vulnerable and risk-generating period that promotes the emergence of aggressive behavior.

In addition to the reduced activity of the serotonin system, vasopressin should also be considered to play a role in organizing aggressive behavior. Ferris (1997) reports that vasopressin administered to the hypothalamus of

hamsters increased their aggression toward intruders, while a blockade of hypothalamic vasopressin receptors inhibited aggressive behavior. All this raises a number of questions in socio-psychoimmunology. The nature of early traumas, which reduces glucocorticoid feedback and, therefore, probably increases AVP activity, may play a role in respect of psychopathic personality development as well.

Vasopressin increases aggression and plays a role in shaping dominant behavior, countermanding the role of the serotoninergic system. Fluoxetine reduces the vasopressin system's activity, thereby reducing aggression. Ferris proposes that the reduced sensitivity of the serotoninergic system is coupled with increased vasopressin level and aggression (Ferris 1997). The other question concerns the partly favorable immunological effect of vasopressin, which may play a role in the development of aggressive behavior. All this is revealed in a particular light when thinking about Fox's meta-analytical data (1988), according to which aggressive, contesting, confrontative cancer patients with a fighter disposition have a better outlook for survival. At the same time, aggressive behavior may be interpreted as the extreme or disorganized form of an active, coping psychological functioning.

Early traumas and the "suffering way of existence"

Children setting out in life with the drawback of an uncertain attachment between mother and child are characterized by low self-esteem, low motivation and performance capacity, integration problems, and a weakened sense of danger. The temporary or final loss of the mother represents an even greater, traumatic danger. The initial stage of loud protest followed by the inactive phase of withdrawal, ending in detachment when the baby treats the mother as a stranger, make up the dynamics of separation. Separated babies may become negativistic and die. In certain test animals (Rhesus monkeys), their death in spite of appropriate parenteral nutrition was noted, which appears to support the possibility of psychological death.

Animal tests support the hypothesis of the late psychoimmunological risk of early social trauma. Ader and Friedmann (1965) found the mortality of carcinosarcoma to be higher in rat progeny weaned early. In a test by Santisteban and Henry, mammal tumors showed a higher occurrence in animals held in isolation during the period of 4 to 12 weeks of age.

The "growing out of tune" of the hippocampal glucoreceptor–CRH feedback interpreted by Francis and Meaney (1999), leading to a permanently increased CRH secretion, seen in melancholic and depressed patients, may play a role in this. In addition to the varied neuroendocrine response in the wake of early mother–offspring separation and increased anxiety, Plotsky et al. (2005)

detected an increased CRH level in paraventricular cores, in the amygdala and the locus coeruleus in adult progeny. The behavioral consequences of insufficient maternal care include elements of increased defense and anxiety, which Weaver et al. (2004) attribute to the changed activity of serotonin on the 5-HT7 receptor, and the GR reduced expression detected in the wake of the epigenetic effects mentioned earlier.

However, this pattern is likely to have several other factors as well. Separation, the grieving situation is also a basic situation of loss of control, an unbeatable state of desolation and helplessness for the progeny, accompanied by the stress reaction of destitution that mobilizes the HPA axis. Given up/giving up, the situation of acquired helplessness, a serious challenge that cannot be controlled by activity, may mobilize immune suppressive mechanisms with opioid-noradrenergic mediation. The event with the highest score on the Holmes-Rahe scale cited as an example for uncontrollable and unescapable stress, is the loss of a life partner or of a child. Based on the above model, the issue of being able to control early trauma is important for the internal classification of the situation. Sensations of loss and separation that cannot be influenced by the child may be precursors to future tragedies. According to Forsen (1990), injuries suffered in early childhood, perinatal separation traumas, the death or divorce of parents may lay the foundations for immunosuppressive processes, and this trend was confirmed by investigations of breast cancer patients. The occurrence rate of early trauma was also higher in testicular and gastrointestinal tumors. The early loss of a parent is frequent in other diseases with an immunopathological background, such as IBD (inflammatory bowel disease): Crohn's disease, and ulcerative colitis. Both the results of animal tests and those of epidemiologic research conducted on a deduction basis support the psychoimmunological significance of a leitmotif of dynamic psychiatry, that is, early trauma, as discussed above.

Narrative context of early trauma and immune processes

Before starting the analysis of the hypothesis concerning the developmental consequences of perinatal events and early mother–child relations, we need to take a look at the evolution of psychoimmunological risk factors of personality as an ongoing, open-ended story. Therefore, the neurophysiological foundations of the permanent trait-like elements of psychological resilience are not burdened only by traumatic perinatal experience; the order of neuroendocrine-immune regulation may be disturbed by the aggregate of stress experience accompanying life, which, of course, is not independent from personality traits and physiological type. In other words, a loaded life story in itself leads to 'allostatic load', overwriting and distorting psychophysiological

registers. This allostatic load develops due to chronic stress, repeated and elongated stressor effects. It is possible to detect a circular logic; in other words, permanent interpersonal troubles, a transactive relationship with damaged attachment, games and traps that create uncertainty, the experience of social inadequacy, exclusion, and low pecking ranking, reduced self-esteem may be interconnected. These turn into recurring stories and have an indubitable effect on shaping the personality. "Whoever has will be given more, and they will have an abundance. Whoever does not have, even what they have will be taken from them." – also true in health psychology. The perception, assessment and behavior schemes set out in the stories that become part of the ego turn into emotional and neurohumoral representations in the deep, and affect events at the immune periphery as well.

However, the opposite immuno-neuropsychic direction can lead to somatopsychic phenomena in psychoimmunologic context, too. The models looking at the inflammatory origins of depression and aging shed light on this reverse immunopsychological load. This immuno-neural influence is part of the allostatic stress load and leads to chronic inflammatory processes pursuant to the increased use or allostasis of the connected 'intrinsic networks', which is also reflected by the permanently higher level of proinflammatory cytokines, particularly IL-6 and CRP. For the reasons already explained, this phenomenon is typical in old age, but may also be observed in young adults in the event of a loaded, traumatizing childhood. In the case of abusive childhood experiences, Danese et al. (2007) found latent inflammatory phenomena coupled with increased CRP to be more frequent in young adulthood, controlled by other risk factors in the sample investigated. Carpenter et al. (2010) noted a permanently higher IL-6 level in the sample of subjects complaining about a 'difficult childhood' compared to the sample raised under harmonic conditions in the course of the social stress test. This measured result was confirmed by Kiecolt-Glaser et al., because IL-6 and TNF alpha levels were higher in young adults who had suffered childhood abuse. These chronic stressors that exist in the long run and work as a shear force play a role in the development of poor health.

The developmental consequences of traumatizing life events and the psychological suffering in early childhood may be elements of a permanent psychopathological nature, traits and forms of behavior. In the personal history of psychopaths and drug addicts, Weil (1992) attributes a special role to low-empathy parental and carer behavior. Zanarini (1989) confirmed that 89% of persons investigated due to antisocial personality disorders had been separated for a long time from the parent or carer as children. The insensitive and emotionally deprived behavior of mothers and the deviance of fathers lead to shiftiness, irresponsible behavior, and inability to feel regret or guilt, according to McCord

(1979). According to Heim et al. (2004), it is proven by epidemiology data that the frequency and weight of sexual, physical, or emotional trauma suffered in childhood correlate with the degree or early occurrence of depression. Childhood abuse is frequent among those living in a miserable socioeconomic environment, which makes distress nearly permanent for both parents and children, and make the parent–child relationship unstable, and this traumatizing family context causes the occurrence of depression to increase in later phases of life, according to McLoyd (1998) and Rapetti et al. (2002). Baby blues, and/or depression symptoms or anxiety occurring in the mother later on may also lead to poor empathy, negligent or abusive maternal behavior, causing distress and reduced immune competence in the offspring, according to Davis and Sandman (2010). The neural and developmental consequences occurring in progeny, the physical and mental risks increase the risk of generating damaged parenteral patterns and of making the children anxious and unstable parents themselves.

Miller and Chen (2010) monitored girls living under family conditions burdened by chronic stress for one and a half years and measured permanently elevated IL-6 levels and glucocorticoid resistance. Miller et al. (2009) measured elevated inflammatory cytokines in respect of APC cells, monocytes and plasmacytoid dendritic cells, along with the reduction of glucocorticoid receptor expression. In the meta-analysis of the relevant investigations, Wegman and Stetler (2009) found that childhood abuse is accompanied by health and psychological risks to the same extent, and this correlation was conspicuous in the fields of neurological, motor, respiratory, cardiovascular, and gastrointestinal diseases. In respect to this paper, it is important that the consequences concerned inflammatory and immunologic pathological processes.

In a family environment full of stress during childhood, the mother's warmth and support and the child's cognitive abilities may mitigate the immunological consequences of childhood stress, i.e. may play a protective role as regards health psychology. Caserta et al. (2011) indicated that the greater self-efficacy of the children investigated was coupled with lower IL-6 levels.

Primary and secondary mother–child attachment organizations and personality theories

Bowlby interprets the mother–child attachment organization, which is featured as a dual union in the analytical school, as a homeostatic system that is continuously active and sensitive to the context of the environment. The unavoidable foundation of social neural studies is the research on attachment organization because many 'lifetime' elements of character, response types and even personality components are decided by the events and development of this socio-psychophysiological organization.

The selection advantage of cooperative groups, which may be described by altruistic behavior within the group, needs no explanation. However, progeny with an uncertain attachment situation needs to compensate for parental negligence with a secondary behavior strategy.

The offspring's strategy in the secondary mother–child attachment organization is to be handled as a behavior to optimize survival. The optimum is the mother's adequate behavior that offers security. If this is not in place, the child may attempt to reduce the distress that arises with changes in the environment by ignoring threatening situations and using an independent, avoidant strategy (type A). On the other hand, the child may attempt to sensitize the mother by extreme attachment, danger signals and displaying signals to retain the connection, when prompted by even slight stimuli (aggression inhibition, superficial oversocialization, that is, hypothetically, by behavior elements that imply a type C personality later on!). Such children strive to maintain the mother's attention with danger signals even in an unthreatening environment. The sensitivity of these secondary mother–child attachment organizations to context may be considered to be subject to culture, and different climatic, ambient conditions or civilizational conditions may result in different frequencies of these compensating attachment organizations that actually cover maladaptive personality development trends.

Comparing the fundamental behavior modes (type A – type C, independence–dependence; avoidance – increased attachment; active coping – repressive coping; assertiveness, hostility – inhibition of aggression, disturbance of the expression of negative emotions; lack of empathy, inhibited empathy – increased compassion, affiliation) may make the trends classified in these dyadic opposites as typical domains that become the dominant elements of personality development.

The two poles of the personality pattern of type A personality versus type C personality (cancer-prone or CTBP: C-type behavior pattern, C-type coping style) that may be discovered in the pairs of opposites recall James Henry's (1997) psychobiological model relying on ethologic grounds. Approaching and evading behavior patterns may also be given a different ethology interpretation. In addition to the active and passive modes of coping, Henry determines two different ethologic strategies, and identifies the two cerebral hemispheres as their settings. Active left-hemisphere coping is accompanied by the activation of the sympathetic nervous system, and entails the mobilization of emotional, cognitive activity for the purpose of self-sustenance. In this pattern, Henry emphasizes rationality and the withdrawal of empathy.

Coping processes localized in the right hemisphere serve the survival of the species, according to Henry's theory. This is coupled with increased empathy, affiliation, aggression inhibition and self-suppression, accompanied by an increase in HPA axis activity. Henry thinks that in normal cases, the

integrated functioning of the two hemispheres ensures highly adaptive dynamics in behavior organization. At the same time, traumas in life history (early separation trauma, PTDS) may bring about disturbed communication between the hemispheres, as a result of which an independent dominance by the activity of the left or right hemisphere may evolve. All this may be compared with the research results on the dominance of left and right frontal cortex activity. This binary polarity is closed to the *phylogenetic perspective of social engagement and attachment (Porges) proposing* a dynamic balance between social aversion tendencies maintained by sympathetic fight-or-flight circuits, and social approach tendencies that promote a sense of safety through close social interactions. Based on this consideration, the attachment system includes two different motivational components. The avoidant, independent strategy is about preventing risks of threats or stressors, and the other includes an approach-oriented motivation to foster closeness to others and the attainment of felt security.

By the way, disruption of information exchange between the hemispheres is a feature of alexithymia, which is frequent in psychosomatic diseases. Henry's theory coincides with our hypothesis that connects secondary attachment organizations with type A and C personality patterns and the personality theories analogous with those on the grounds of learning theory. This is how the introjective, self-defining and the anaclitic, dependent personality patterns formulated by Blatt's et al. (1993) terminology, and the egoistic-altruistic typology outlined by Freud may be arranged into the poles that emerge along the lines of secondary attachment organizations. The introjective personality may be characterized by the need for self-control, identity, autonomy and strength, and is sensitive to loss of control and injuries to autonomy, whereas the anaclitic-dependent personality lingers on emotional ties and human relations and is especially sensitive to rejection and loss.

The assumption is that babies responding with a secondary, compensative attachment system of type A or C develop in these two extreme directions (A vs. C, independent vs. anxious, overly dependent). On the other hand, it should be seen that these trends make up the dialectic system of a normal, integrated personality in a reciprocal balance. However, when the reciprocity between the two systems is upset – and this is where Henry's theory gains emphasis – one of the hemispheres or trends may come to dominate without counterbalancing.

The question regarding the traumatic experience and neuroendocrine development variations of babies may influence the neurobiological background of the personality-based of coping mechanisms, which requires further research. The dominance of right frontal activity suggests itself to be underlying the behavior pattern of a baby of type C, with inhibited aggression and repressive behavior features with anxious attachment.

The question is whether the depression experienced by a baby left to its own devices may promote the emergence of a relative reduction of left frontal activity on a permanent basis, which may have a late psychoimmunological risk due to the related reduction of activity in NK cells.

Based on the data from animal tests conducted by Fride and Weinstock (1988), prenatal stress effects enhance anxious behavior, and prompt increased dopamine turnover in the right prefrontal cortex and reduced dopaminergic activity in the right nucleus accumbens, a permanent change in the dopaminergic system, leaving a permanent mark in the offspring's cerebral lateralization.

Based on the effects of pre- and perinatal stressors that shape neurotransmitter asymmetries and influence the generation and destruction of synapses, Davidson considers it likely that early environmental processes have an influence on cerebral function and structure that have a permanent effect on behavior, and this may play a role in the development of prefrontal asymmetry as well. Therefore, the socio-psychophysiological effects on the highly plastic brain in the early stage may be predominant in the background of the nature of permanent cerebral activity.

Fox and Davidson (1988) detected increased left frontal EEG activity in ten-month-old babies when their mother was approaching, whereas those babies that responded to the departure of the mother with crying and experienced separation anxiety showed increased right frontal activity. Rapprochement entails left frontal, while passive evasive behavior entails increased right EEG activity. Cloninger (1994) attributes great importance to the serotoninergic system showing dominance of the right hemisphere in the background of the inhibited behavior.

Kagan et al. (1991) found separation fears to be typical of the inhibited temperament, and the rapprochement and unfolding driven by the left frontal hemisphere to be reduced. Davidson (1994) found increased right frontal and reduced left frontal EEG activity among inhibited individual and observed that NK cell activity had a reverse correlation with right frontal dominance. The asymmetry of the anterior frontal lobes may explain the increased and differentiated susceptibility of the individual to certain emotions and/or psychopathologic tendencies. Reduced left prefrontal activation is coupled with increased sadness and reduced rapprochement, while motivation for recognition of the responses given to challenges is also lower.

The autonomy, assertiveness, control, anger, mistrust, and readiness of social isolation that characterize the type labelled as *introjective* by Blatt, which focuses on defining the Self, may be explained by the uncertain-evasive dyad of the early mother–child disorder, while the repressive defense reactions, the aptness to experience hopelessness and helplessness and the emotional instability and dependency of the anaclitic (type C) personality may develop from the secondary type C mother–child attachment organization.

While the former is typically susceptible to cardiovascular diseases, the latter undergoes stress-biological processes making them prone to the inhibition of immune processes (see active vs. passive coping).

Naturally, it is possible to interpret type B, the harmonic personality in this system of coordinates. Blatt and Blass (1990) say that in the course of normal personality development, the two development trends play a role in personality development in an interactive and reciprocal balance, in encouraging interaction, from the beginning to the end. The dependent personality type seeks different coping strategies for different stressors (increasingly sensitive to rejection, loss, and responds to conflict situations by repressive coping and suppression), and even selects environments characterized by different stressors.

Table 7. Psychodevelopmental hypothesis of A and C type personalities based on attachment organizations

Primary mother–child attachment organization		
A type insecure-avoidant	**B type harmonic secondary mother–child attachment organization**	**C type insecure-ambivalent dyadic relationship**
diminished response to environmental challenge, independency		exaggerated response to minor challenge dependence
Personality models		
Type A, introjective egoistic phylobat sensitizer psychopathic development		Type C (cancer-prone) anaclitic (Blatt) altruistic (Freud) ocnophyl (Bálint) repressor (Byrne)
decreased sense of danger, increased independence, reduced empathy, low arousal, low anxiety		conflict avoidance, inhibition of aggression decreased self-esteem, high anxiety, high arousal
aggressiveness, hostility		inhibition of the expression of negative emotions, increased affiliation
Coping		
left hemispheric dominance, BAS active (sympatherg dominance)		right hemispheric dominance, altruist, affiliative passive (parasympatherg)

Reaction-forming, overcompensation, intellectualization	**Protective mechanism**	repression, rejection, denial, projection,
autonomy, prestige, assertivity, power	**Aims**	intimacy, affiliation, support affectivity, fusion, harmony, integration
low empathy, difficulty of social integration, competition, dominant and subdominant social position		self-sacrificing, self-suppressive, inhibited behavior
IPM (inhibited power motivation) higher arousal catecholaminergic reaction, testosterone	**Immunosuppression**	higher arousal (cortisol) separation trauma, enduring passive coping,

The A and C type secondary attachment organizations as the cradle of the proper internal working model may be basis of development of A and C type personalities. A similar polarization, a cardiovascular-prone and an immunosuppression-prone personality type were made by Blatt, Cornell and Eshkol (1993), where the self-critical (introjective) and the dependent (anaclitic) personality styles were opposed (Blatt & Shichman, 1983). This dichotomy provided a theoretical model for integrating a diversity of findings linking personality factors to the onset and clinical course of immunological and cardiovascular disease.

In their model, the self-critical (introjective) personality style may provide a conceptual structure for integrating personality factors of social isolation and mistrust, along with preoccupations with anger, autonomy, assertion, control, and self-worth (e.g., failure and achievement), are important in cardiovascular disease.

The so-called *self-critical individuals* are primarily responsive to loss of self-control and self-worth, and generally react to these stressors with heightened behavioral and autonomic arousal. These features are characteristic of the independent and competitive personality with a need of dominance and sensitive for his/her position in the social rank resembling C type personality.

On the other side, dependent, anaclitic personality pattern may fit the C type anxious attachment organization implying dependence, the use of repressive defenses, feelings of helplessness, emotional lability, and preoccupations with interpersonal relationships. These features have been found to be predictive factors in neoplastic disease, and may be re-formulated in the so-called C type or immunosuppression-prone personality.

Table 8. Personality configurations and attachment styles

Attachment style (Ainsworth's typology) **Adult Attachment style** (Hazan and Shaver)	**Avoidant Attachment Style** Little affective sharing in play, little or no distress on mother's departure. *Lack of empathy* is reflected in little or no response to distressed child. *Independence* suppression of needs due to repeated rejection and difficulties in forming intimate relationships	**Secure Attachment Style** *Trust* without concerns for abandonment, feeling self-worth and being liked better developmental outcomes than non-secure patterns in areas that include self-reliance, self-efficacy, empathy and social competence.	**Anxious/Ambivalent Attachment Style** worrying that others will not reciprocate intimacy.
Type A versus Type C (Friedman, Greer, Miller, Temoshok)	**Type A** behavior is a stress-producing behavior, aggressiveness, perfectionism, unwillingness to relinquish control, and a sense of urgency. **Type A** personality, competitive, impatient, aggressive, dominant with difficulties giving up control or sharing power.		**Type C** They do not express emotion and are unaware of any feelings of anger, past or present. Aggression is inhibited, and they do not experience of express other negative emotions such as fear, anxiety or sadness. They are patient, unassertive, cooperative and appeasing with work, social and family relationships and also compliant with external authority. They are overly concerned with meeting others' needs and insufficiently engaged in meeting their own needs; self-sacrificing to an extreme.
Typology of Grossarth-Maticek and Eysenck	Type II cardiovascular-prone (chronic irritation, anger)		Type I cancer-prone (submissive, non-aggressive, self-derogative and susceptible for repressive cues from dominant persons, hopelessness, depression)

Blatt's typology self-critical, introjective *versus* dependent, anaclitic personality	Social isolation and mistrust, along with preoccupations with anger, autonomy, assertion, control, and self-worth (e.g., failure and achievement), are important in cardiovascular disease.		Dependence, the use of repressive defenses, feelings of helplessness, emotional lability, and preoccupations with interpersonal relationships
James Henry's typology	Left-hemispheric-based coping self-sustaining functions sympathetic nervous system and emotional and cognitive activity providing *self-sustaining* functions. Rationality and diminished empathy	Balanced, reciprocal and context-based left/right activity	Right-hemispheric-based coping interest of the species enhanced empathy, affiliation, inhibition of aggression, suppression of self-interest accompanied with higher arousal, and activity of HPA system.
Timothy Leary's typology	Competitive-narcistic, autocratic, sadistic		Hyper-conventional, dependent, submissive masochistic

The formulation of these two personality styles also contributes to understanding the role of personality factors in vulnerability, suggesting that dependent individuals are more responsive to interpersonal disruption and generally respond to this type of stressor with passivity and resignation. Similar observation were made by LeShan, who emphasized the importance of dependence and losses with meaning of *raison d'etre* in developing cancer; Grossarth-Maticek, Siegrist and Vetter (1982) described 'cancer-prone personality' as "submissive, non-aggressive, self-derogative and susceptible for repressive cues from dominant persons based on observations made in the mid-sixties in Crvenka, Yugoslavia; while Lydia Temoshok's *Type C personality* with low self-esteem, inhibition of aggression, enhanced drive for affiliation and high internal psycho-physiologic anxiety and tension also offer a parallel. If we compare the content of these personality configurations with attachment styles in the given bipolar way, the result is tempting.

Vrtička proposes another binary polar balance between the affective evaluation and cognitive control networks beyond the balance of social approach and aversion tendencies. Fonagy and Luyten refer to this second equilibrium as a balance between emotional and cognitive *mentalization* and a state where stress/saliency importantly determines whether information is processed. This way, the attachment behavioral system relies not only on the mental

representations of the self and others but on the individual differences in attachment influence the degree of the dependence on the cognitive control network and the affective evaluation network.

Table 9. Psychophysiological patterns of different attachment styles in frame of a double balance (Vrtička et al., 2017)

		Attachment avoidance	**Attachment anxiety**
Affective evaluation	Social approach	Decreased neural representation of social reward in several contexts. Likely mediated through dopamine, oxytocin, and/or endogenous opioids	Probably increased neural representation of social reward per se and likely also reward prediction errors
	Social aversion	Activation decreases and increases reported in different contexts. Probably a combination of deactivating secondary attachment strategies and emotion regulation capacities (i.e., deactivation is applied but can only be maintained up to a certain degree)	Activation increases as well as modulation of structural integrity likely related to hyperactivating secondary attachment strategies. Probably mediated through stress/arousal (HPA axis and cortisol/glucocorticoid signaling)
Cognitive control	Emotion regulation	"Impaired" emotion regulation (concomitantly high activity in emotion regulation and affective evaluation areas). Evidence for preferential use of suppression for both positive and negative emotions. Relative efficiency but high emotionality if preferential emotion regulation strategy cannot be employed or fails	"Impaired" emotion regulation (concomitantly high activity in emotion regulation and affective evaluation areas). Mainly associated with increased activity during natural viewing when no emotion regulation strategy is employed. However, preliminary evidence that emotion regulation can be efficient if properly instructed
	Mental state representation	No clear evidence so far	Increased positive and negative self-representation as well as decreased negative other-representation (in adolescents). However, no clear evidence regarding theory of mind (ToM) during exposure to external information so far

James Henry, who interpreted the psychobiological background of attachment disorders, called attention to the fact that traumatic experiences from early childhood can also be fitted into the palette of post-traumatic stress disorder (PTSD), and the consequences of mother–child separation, empathy deficient, punitive and negligent maternal behavior may also be classified here. The traumatic childhood of criminal psychopaths is a tragic factor that forms their fate, and traumatic early social experience plays a role in the development of narcissistic and borderline personalities as well. In describing the borderline personality, van der Kolk (1987) highlights the damage to the attachment. Others, such as Gunderson, Person or Bursten (cited by Henry 1997) emphasize the manipulative, demanding, cold, merciless nature of the borderline personality, incapable of loyalty and guilt. All this might be classified in the consequential nature of type A secondary attachment. What is common within this character, between these personality and behavior patterns and the post-traumatic stress disorder is the disturbance of social emotions. Muller assumes disturbances in the communication between hemispheres to be behind the emotional disorders associated with PTSD. Henry suspects the dominance of the left hemisphere in self-sustenance to be underlying egotistic behavior, while sociality, the affiliative, self-sacrificing, caring, and attaching emotions and disposition required for the survival of the species are weak. Behavior traits dominated by the right hemisphere, such as the striving for intimacy, affiliative behavior, and self-subordination are related to type C secondary attachment and type C personality. Therefore, the malfunction between hemispheres, the loss of balance in hemisphere integration expressed in alexithymia, which can be observed in PTSD, may explain the emergence of personality traits, and psychosomatic tendencies.

Bahnson thinks tumor patients describe their parents as emotionally distant, negligent and rejective persons. Based on reports of tumor patients, the family environment in their childhood, the so-called centrifugal family model also indicates attachment disorders. In such families, the person is isolated, left to themselves, and fail to receive adequate social support.

Other authors found the loss of parents below the age of 17 to be more frequent for tumor patients. Early traumas also affect the development of mental working methods. In the long run, early traumas may lead to low self-esteem, insufficient response to challenges and insufficient mental work methods in Kraemer's (1992) model. The above psychobiological and psychoimmunological data are examples that show that the codes of psychosocial information acquired in the course of early learning are transcribed into neurohumoral patterns that affect how the given experience is qualified, the endocrine system of the body (e.g. growth hormone) and immune protection. Therefore, systems that transmit psychosocial influence appear to have central significance in the interaction between the neural, the endocrine, and the

immune systems. The success of adaptation depends on mental working methods, the quality of coping. The early fixation of passive, dysfunctional responses may entail not only a loss for the psyche but also psychophysiological, bodily consequences, and disadvantages. To carry on with the train of thought, the mental method of coping that evolves in the wake of early trauma is characterized by the suppression of emotions and fundamental psychological needs, which may be coupled with the inhibition of cognitive processes and underestimating the person's own response capacity when facing challenges, low self-esteem, and a consequential disturbance in social support in addition to the need for external control, which may create a socio-psychoimmunological trap to which the person may easily fall victim also at a late stage of life.

While the suppression of emotions and the oppression of own needs with overly social behavior may be considered to be unreasonable forms of adaptation, the state of learned helplessness generated by repeated encounters with uncontrollable external stressors also leads to the failure of coping.

It is remarkable that separation trauma, or a directive, authoritarian, emotion deficient maternal behavior are frequent in the anamnesis of diseases that may be explained by the role of psychoimmunological factors, such as tumor diseases, rheumatoid arthritis, Crohn's disease, ulcerative colitis, Boeck sarcoidosis, and autoimmune hyperthyreosis. In fact, the double bind-like mother–child relationship problems raised in schizophrenia are also shown in a different light by connecting the socio-psychiatric model and the explanation that links schizophrenia to autoimmune etiology.

Based on the results of a large number of personality tests conducted since the 1940s, a significant part of patients suffering from tumor and autoimmune diseases may be characterized by aggression inhibition, the inhibition of expressing negative emotions, superficial sociability accompanied by considerable inner tension and high arousal, leniency and submission. In a smaller part of these patient groups, psychopathic aggressive personality structures develop that are not capable of empathy. As regards the childhood environment of the 'cancer-prone personality', most researchers agree that the parent's behavior is cold, controlling and distant. Similar data were found in the analysis of families of Crohn's disease and colitis ulcerosa as well as rheumatoid arthritis patients, where the mother's overly controlling, emotion-deficient and punitive disposition also implies a disturbance in early attachment. An interesting bit of epidemiology information for Crohn's disease patients is the North–South, West–East gradient of the disease's cultural-climatic frequency, which also corresponds to the differences in the cultural code for mother–child relationships inherent in the given civilization. The protective role of the close mother–child, adult–workplace attachment also arises in respect of the low occurrence detected in Japan. In Hungary, the occurrence of Morbus Crohn is one magnitude lower among the Roma population, which may be characterized by

a much more natural and closer physical contact between mother and child. The data on the difference of occurrence between babies who were breastfed and those who were not is similar, in favor of those living in a closer mother–child contact due to breastfeeding. Changes in the mother–child relationship also need to be interpreted when investigated as the factor underlying the relationship between tumor diseases and the development of civilization.

Type A personality via hostility, competitiveness exaggerating catecholaminergic nervous activation states is thought to be accompanied by cardiovascular risks. One of the earliest studies of Grossarth-Maticek showed similar results. The so-called Type I is close to the Type C behavioral pattern while type II is close to the Type A personality with its critical factor of hostility (anger). Although the Grossarth-Maticek and Eysenck's studies had become subject of a serious and deconstructive professional debate (Eysenck and Vetter, 1991), we have to recognize its place among the other personality theories.

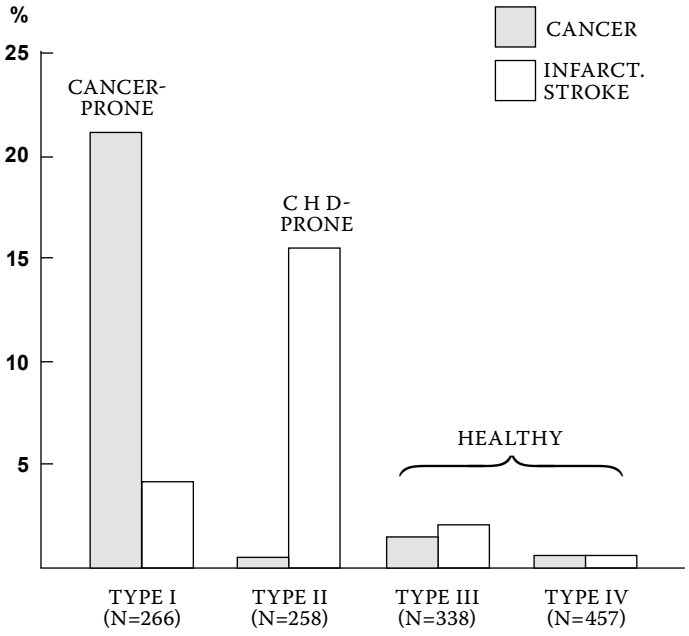


Figure 11. Mortality of different personality types from cancer and CHD, 1982 to 1986 (Eysenck and Vetter, 1991)

Although there are few evidence-based and clinically relevant data proving connection between early distorted attachment and their late psychopathological consequences, they seem to be convincing. Warren showed that children with C type attachment style (*anxious-resistant insecure attachment*) experiencing high distress when the mother departs, and showing ambivalence when she returns were significantly more likely to be diagnosed with anxiety

disorders as adolescents (Warren et al., 1997). Similarly, in patients of agoraphobia (Faravelli et al., 1985), and panic disorder (Brown and Harris, 1993) early separation trauma and inadequate caregiving were more frequently reported. Generalized anxiety patients (Cassidy, 1995) and patients with other anxiety disorders reported more rejections, and frequently describe their parents as unloving and controlling. Persons with borderline personality disorder report very high rates of prolonged separations from caregivers during their childhoods (Zanarini et al., 1989). It is more serious if the missing caregiver is the mother (Soloff and Millward, 1983). The babies' emotional neglect observable in presence of the returning caregiver (Patrick, 1994) points towards the A type attachment organization in cases of frequent separation traumas.

In a large study of 9,508 patients in primary care practice, a graded relationship was found between the number of retrospectively reported childhood family risk factors and adult diseases. One might see these adverse childhood experiences (ACE) as precursors of attachment insecurity, including psychological, physical, or sexual abuse, violence against mother, and living with family members who were substance abusers, mentally ill, suicidal, or imprisoned which showed correlations with ischaemic heart disease, cancer, chronic lung disease, skeletal fractures, and liver disease (Felitti et al., 1998).

In the case of insecure-ambivalent maternal behavior, the personality consequences can be summarized in the so-called C (cancer-prone behavior) personality trend (inhibition of aggression, pathological niceness, high anxiety, enhanced affiliation with less success, denial, extreme vulnerability to the loss of the significant other, etc.) (Baltrusch et al., 1988).

The protective role of secure attachment is reflected by the result of a 50-year prospective study of a cohort of men recruited at university age (Vaillant & Vaillant, 1990), where several indirect parameters showed that secure attachment might be a predictor of physical health. Cohesiveness of the home before the age of 20, harmonic parenteral relationships, trust, autonomy, and initiative were predictors of the man's health at the age of 50.

Maunder and Hunter (2001) list three possible ways in which insecure attachment might influence psychosomatic processes. First, insecure attachment may affect stress regulation. The epigenetic consequences of early trauma is good example for this. Furthermore, attachment insecurity may increase perceived stress and in preoccupied attachment personal vulnerability and vigilance might be so intense that interoceptive sensation (normal perception of physiological operations) is perceived as a potential threat, according to Stuart et al. (1990).

Social support might be important stress buffer, and in the case of avoidant attachment or fearful attachment interpersonal distrust might inhibit these health resources. Attachment patterns may also determine the success of social support in buffering stress. Maunder (2001) emphasizes that secure

attachment is thought to be associated with a greater willingness to seek support and a related expectation that support will be available and effective. According to West et al. (1994), avoidant attachment is associated with a desire for interpersonal distance and self-reliance, whereas preoccupied attachment may be associated with less support-seeking because of a fear of unavailability or rejection. Among healthy volunteers, clear differences arose in perception of available support, in 81 healthy young adults dismissing and fearful attachment styles were associated with much less support seeking than secure and preoccupied styles (Ognibene and Collins, 1998).

Perception of stress also causes different responses in insecure attachment. In a retrospective study of student retrieval of military experiences were supported of difference in stress perception, as insecure subjects reported higher levels of hostility and somatization than secure subjects, while ambivalently attached (preoccupied) subjects also reported more anxiety, depression and distress according to Mikulincer et al. (1993).

Attachment insecurity may affect the intensity or duration of the physiological stress response, which is crucial in psychoimmunological consequences, too. Ambivalently attached infants show exaggerated HPA reactivity to the Strange Situation challenge, while secure or avoidant infants do not show alterations.

Self-report of childhood bereavement exerted influence on the cardiovascular response to a laboratory stressor compared to a student with a harmonic family background. When a film depicting the death of a boy's mother was recalling personal memories, it predicted an enhanced cortisol response to the stress of viewing a movie (Luecken, 1998).

The insecure attachment might cause psychosomatic dysregulation by altered use of external regulators of affect, as a distorted coping mechanism. Childhood abuse and trauma predict adult smoking, alcohol consumption, alcoholism, and drug abuse. Drug use in young adults is also related to parent–child attachment according to Brook et al. (1998).

Insecure Attachment may also alter the use of protective factors like treatment adherence, and symptom reporting. Attitude may distort the need for access of the health service. Subjects with avoidant attachment had significantly higher levels of HbA1c than those with secure or preoccupied attachment, according to Ciechanowski et al. (1999).

The attachment is a core element of human ecological model of personal social, psychological and bodily adaptation, and therefore we might see attachment patterns as one of the core hubs of network medicine.

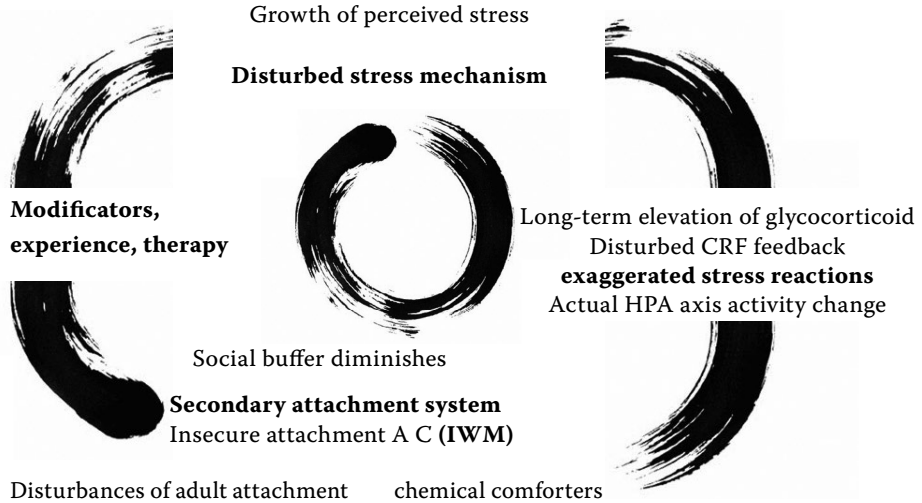


Figure 12. Attachment systems and its attached systems

Coping, attachment and emotions

The differences between the HPA axis and the sympathetic autonomic nervous system due to early traumas do not necessarily appear immediately when facing environmental challenges. The so-called double hit model suggests that the vulnerable adaptation pattern, altered as a result of either a psychotraumatic or perinatal infection effect, becomes dominant, that is, the maladaptive phenotype occurs, only when a second powerful traumatic effect decompensates it. Immune effects (infections) experienced during critical phases of the development of the limbic and neuroendocrine system may cause neuroendocrine dysfunction and anxiety behavior, but it is truly exacerbated and appears in its full severity in adult animals after a second traumatizing effect, according to Walker et al. (2009). Mostly, the cumulative effect of the stresses associated with our way of life develops the anxiety or depressive disorder associated with immune vulnerability, but the origin of it is the epigenetic substructure burdened with the early injury, which only 'exposes' our life story. However, these specific personality traits, attitudes and the vulnerabilities and responses

determined by our inner spiritual workings determine our exposure to stress and our coping methods.

The effectiveness of adaptation depends on the nature of our spiritual workings and coping methods. A wide range of passive and dysfunctional responses can be associated not only with a decrease in mental capacity, but also with psychophysiological and physical consequences and disadvantages. Brown et al. have proven that early separation and loss are major triggers for adult depressive disorders. If we learn that our behavior cannot influence the outcome of events, then a state of learned helplessness sets in. This is important because the low-motivation negative-experience status thus created can persist in a new environment with more opportunities, and this is the 'result' of the previous learning process – according to Seligman. Therefore, due to the 'non-contingency' and inconsistency between the behavioral response and the outcome of the situation, a loss of control can be experienced, through which a person becoming more and more passive may become a victim of other, avoidable stress situations.

The psychological struggle of early traumas is characterized by the extremes of active coping, either with hostility, aggressive attitudes and lack of empathy or, at the other extreme, may also be a suppression of emotions and basic spiritual needs. The latter may result in cognitive impairment, which is influenced by the controllability of the stressor.

Endogenous opioids also play a part in the development of selective attention and search and exploratory behavior, just as they play a part in the development of learned helplessness. The latter is particularly important if the experimental stress leading to the condition of learned helplessness causes a temporary decrease in NK cell activity with naloxone (opioid antagonist). In this case, we talk about the central effect of the opioid.

As discussed earlier, the impact of disrupted attachment systems due to early injuries can result in damage to coping processes. The coping processes are also characterized by a psychophysiological binarism: active/passive, approximating/avoiding, self-sustaining/self-submitting reproductive. James Henry outlines a dualistic stress concept. According to him, the individual cognitive, behavioral characteristics determine whether the active coping sympathetic-adrenal neuroendocrine response or the passive coping HPA (hypothalamic-pituitary-adrenal) neuroendocrine subsystem is activated.

Bohus et al. (1987) also recognize the role of hereditary tendencies within the background of active and passive immobilization response selection. Aggressive animals are characterized by choice of fight/flight, accompanied by the activation of the sympathetic nervous system, while non-aggressive animals exhibit an avoidance or immobilization response associated with sympathetic and parasympathetic nervous system activation, high HPA activity, and cortisol separation.

Bohus acknowledges the important role played by the central nucleus of the amygdala in developing the passive immobilization response observed in test animals. At the same time, the amygdala has a general modulating role in the development of the neuroendocrine response to acute stressors. Amygdala is a peptidergic influence under differentiated control and plays an integral role in coping and adapting, in which we must include the integration of cognitive and emotional expression.

Type A secondary attachment system favors an independent, empathy-deficient response. If we assume that there is a developmental psychology link between type A secondary attachment and psychopathic tendencies, then we may observe a predominance of the approximating behavior associated with predominant left hemisphere activity. Here, when applying James Henry's ethology-based concept, we are confronted with the predominance of self-sustaining, approximating aggressive behavior patterns. The neuroendocrine pattern that forms during acute stress is a key element in the learning processes related to the situation. Learning processes reinforce and record the coping behaviors that develop during dominance situations, therefore, the group hierarchy structures are partly formed from elements of coping patterns.

The psychobiology of a loss of control cannot be understood without the raphe nuclei of the brainstem. The animal unable to embody passive activity, even in the absence of the dominant animal, is characterized by increased attention and passivity. According to Charney et al. (1996), the passive coping response develops as a result of the communication between the hippocampus and amygdala. Henry also emphasizes the importance of hemispheric differences here. Literature offers us many models in relation to hemispheric differences of emotionality. Sackeim et al. (1982) suggested that negative emotions are processed by the right hemisphere, while the left hemisphere is responsible for the development of positive emotions. According to Davidson's (1990) model, the prefrontal cortex of the left hemisphere is responsible for the approaching behavior, while the prefrontal cortex of the right hemisphere is responsible for reserved, avoidance behavior. PET scans of brain processes that induce recalled or film-induced emotions indicated that different areas of the brain are involved in different ways in the neurophysiological events that form emotions. Some areas (prefrontal cortex, thalamus) play an equal role in the processing of three emotions – happiness, sorrow and disgust –, while in other cases, like when happy experiences were recalled via film, the PET scan showed activity in the left amygdala, in the areas close to the nucleus accumbens and bilaterally in the globus pallidus, while for the film-induced disgust it showed increased activity on both sides of the amygdala. In general, however, the scan did not prove any significant lateralization of the above emotions, according to Lane et al. (1997).

The suppression of emotions and the suppression of one's own needs by overly social behavior can be regarded as an inappropriate form of adaptation. The state of learned helplessness that arises from repeated encounters with uncontrollable external stressors is also a failure of coping. In fact, addictive illnesses with immunosuppressive consequences such as alcoholism or drug abuse can be classified as distorted spiritual workings.

According to the definition of Lazarus, coping is a reality-based, targeted, problem-solving activity that in addition to data collection, concentration, reflection, learning, attention, etc., is needed for the provision of an appropriate response, includes, where appropriate, walking, relaxation and other stress-reducing activities, together with laughter, crying and even conversing. Social engagement or persistent activity with distant goals also falls within the category of coping. According to Kobasa (1982), self-confident, socially committed, and so-called hard people ('hardiness') are more protected from psychoimmunology risks.

Against traumatic experiences trapped in our subconscious, the Freudian analytical approach is likely to provide anti-anxiety control modes that use a serious amount self-energy to keep our subconsciousness and consciousness away from this threatening content. These include repression, sublimation, alienation, rejection, reaction coaching, intellectualization, and projection.

Of these, repression or suppression can be attributed to psychoimmunological significance if the concepts are convertible into the concepts of dynamic psychiatry and health psychology. Bahnson considers the repressive personality trait, suppression, and dissociation to be decisive factors in cancer patients. Others consider it a personality trait, an element of the type C personality.

Based on the experiences of Baltrusch, Temoshok, McClelland, and others, there is a threat of reduced immune function with passive or repressive coping methods.

Karen Horney, who is one of the heretics of the analytical tradition, explains in her psychosocial, ecological model that neurotic symptoms require interpretation in interpersonal frameworks not only for their causes but also for their consequences and symptoms.

According to her, the neurotic behaviors indicate three directions. The compulsive power of the experienced helplessness is working in the background of the pathological dependency towards the other person, which is in line with the dynamics of the C type, i.e. 'cancer-prone personality'.

The other two directions show reclusive behavior with the avoidance of others, or a confrontational, clash-seeking, a kind of 'fight-or-flight' alternative, with appropriate physiological responses. Belligerent, competing behavior is a characteristic of the type A personality.

Psychoimmunological studies of successful, mature coping techniques, such as humor or sublimation, have shown an increase in humoral immunity and

IgA levels responsible for the protection of mucosal surfaces, an increase in NK cells, and a decrease in serum cortisol levels.

The psychoimmunology of social conflict and dysfunctional relationships

Human social relationships are not only supportive but occasionally the source of severe conflict as well. In the light of social exchange theory, it is apparent that the individual is often exposed to serious distress in the high-cost medium of the temporal, monetary, and emotional strain of social interactions. This can mean symbolic, detected or assumed, and sometimes even prolonged psychosocial adversity for the individual, which can lead to the development of learned helplessness. Similar to social support, plenty of evidence is available for presenting the social-psycho-immune consequences of distorted human relationships.

Negative or ambivalent social relationships, and the resulting conflicts and associated negative emotions can influence immune processes. Hostility, which we primarily know as a cardiovascular risk factor of psychosomatics, has a negative effect on inflammatory processes as well, which is indicated by CRP and IL-6 differences, according to the work of Suarez (2004) and the increased level of the proinflammatory cytokines typical of depression as well, such as IL-6. Taking into account the inverse correlation between depression and social integration, as well as the relationship conflicts caused by depression and its negative effect on social perception, depression highlights a distinguished area of research within social psychoimmunology.

Depression is thought to be the dominant mediator between psychosocial factors and somatic diseases (Kopp, 2004). Even mood dispositions may contribute to accelerate cardiovascular problems, growing evidence indicates that negative emotions may influence the development of CHD (Kubzhansky et al., 2000). Negative affect and hopelessness predicted mortality in a 19.4-year follow-up study after controlling the data according to the other confounding factors (Barefoot and Schroll, 1996). Depression and enduring negative emotions can make the course of other disorders, such as cancer, diabetes, immunological abnormalities, osteoporosis and the aging process more serious.

The attitudes and emotions increasing the stress of social interaction and interpersonal emotional relationships, such as anger or the hardships caused by depression, are also reflected in the differences in the immune response. Social conflict influences the course of rheumatoid arthritis, in which case catecholamine plays an important role among the neurohumoral factors mediating psychosocial distress. In the social network of ambivalent individuals (those who exert positive and negative influence as well), the ambivalent

persons cause increased adrenergic reactions based on the work of Uchino et al. (2001), and the contact and conflict with ambivalent persons can provoke an increase in systolic blood pressure. Long-term tight, ambivalent and conflict-rich human relationships are common in bad marriages, where worse health indicators are also often observed, according to the findings of Kiecolt-Glaser and Newton (2001). The dissatisfaction indicator of marriage is accompanied by worse immune indicators, as seen in the case of the ratio of anti-EBV antibodies, CD4+, or CD8+ cells. The hostile behavior typical of bad marriage, impulsivity resulting in cutting each other off when speaking, as well as critical and judgmental impatience, can be indicators of physiological differences and increased blood pressure and endocrine values, based on the work of Malarkey et al. (1994). Among newly-wed couples, those who are more prone to negative, hostile reactions, and this is recalled during a short, 30-minute discussion, suppressed immune function was shown in samples taken 24 hours later. Kiecolt-Glaser et al. (1997) stated that the discrepancy indicating dysfunction of the endocrine-immune regulation was true to older couples as well during discussions where they had to recall their conflicts. The amount of negativistic behavior was in direct correlation with the weakening of the immune response. Mayne et al. (1997) confirmed that as much as 45 minutes of trauma and conflict disclosing discussion was enough to reduce lymphocyte proliferation in the examined women. During prospective research, Levenstein et al. (1999) found a connection between ulcerative inflammation of the oral cavity and marital stress, while Kiecolt-Glaser et al. observed significantly, approximately 60% longer wound-healing in the case of couples exhibiting hostile behavior.

Trait-like hostility, characterized by aggression, anger, and cynicism, causes an even clearer immune-regulatory disorder in the event of family conflicts, in the opinion of Mayne et al. (1997). Miller et al. (1999) found a distinct correlation between hostile and cynical attitudes and behaviors during conflict management and the cardiovascular response, cortisol, and immune discrepancies. Social stressors stimulate the inflammatory mediators as well and cause systematic inflammation in the body, based on the work of Steptoe et al. (2007). Partnership conflicts, rejection, and exclusion have significant proinflammatory effects even compared to depression and various life events, according to the findings of Denson et al. (2009).

The so-called TSST (Trier Social Stress Test) consists of an improvised performance and solving complicated mathematical problems in front of a negative, critical audience as well as in a control situation. In front of the negative, critical audience, the tested persons showed higher proinflammatory TNF-alpha levels and glucocorticoid resistance during the experiments of Dickerson et al. (2009).

The stressors that are least controllable but carry a high social-evaluative threat are the ones that trigger the largest increase in cortisol, which is restored at the slowest pace. How we experience such situations is naturally dependent on personality and experiences; therefore, the inflammatory neuro-immune response to physical and social stress depends on the individual. In the case of the persons exhibiting more fear during the TSST, higher inflammatory indicators (TNF-RII) were detected, while during another test, a proportionality was detected between the level of circulated IL-1 beta cytokine and the controlled social stressor created by the TSST. During a test by Carroll et al. (2011), public speaking caused the subjects to become anxious and angry, which also increased the level of circulated IL-6.

Table 10. Emotional stress and its psychobiological consequences

	EMOTIONAL STRESSOR	
Direct or internally induced stressor	Stressors derived from endangered social status	Stressors demanding high efforts
Associated interpretation and emotions Surprise Projection Worry Disgust Danger	**Associated interpretation and emotions** Subjection Fear of losing social competence Threat Rumination Self-centered thoughts	**Associated interpretation and emotions** Challenge Danger Intensity Novelty Rumination Surprise Projection
	Physiological consequences Cortisol secretion alteration Adaptive changes in the native and adaptive immune response	

Since perceived social stressors increase the level of inflammatory mediators, anxiety, therefore recall and imagination, rumination and the prevalently repeated thoughts connected to the stressor should also be examined. In this sense, persevering cognition is a trap that can keep the person in a maladaptive state, even without an actual stress situation. This means that one network-level represents both networks.

Worrying about the uncertainty and unpredictability of the future is a cognitive state that considers the possible negative outcomes, while rumination involves an uncontrollable and undecided state that repeatedly fills the mind

of the subject. All of this creates true psychophysiological stress with psychoimmunological consequences. Additionally, rumination is a component of several psychiatric syndromes, including anxiety, depression, and post-traumatic stress disorder, so it may also have an impact on the psychoimmunological changes seen in these cases. During a meta-analysis performed by Brosschot et al. (2006), increased cortisol levels and other discrepancies were identified in the case of six experiments during anxious and ruminating states.

For example, McCullogh et al. asked their experimental subjects to recall an earlier interpersonal conflict (being cheated on, argument, offense) or above-average grievance, and the ruminative recollection resulted in higher cortisol levels on the day of the experiment. The research confirmed that the stimuli constituting social threats and the associated thoughts also increase cortisol levels. Naturally, the cytotoxic activity of the NK cell was significantly reduced in the case of individuals who described their lives as full of stress and who suffered from intrusive thoughts.

From an evolutionary psychological point of view, the elimination of tight social connections recalls the dispositions of vulnerability and loneliness with their ecological depth and can be considered one of the most severe social stressors. This is especially true if all of this is coupled with social rejection or loss of status since the loss is considered an especially severe stressor if accompanied by an existential trap or humiliating situation. Naturally, the weight of the loss and the inherent "contextual threat" and the other psychological and social-ecological circumstances (e.g. social support) create unique differences. Such life events involving personal loss are behind 44% of all reactive depression cases, based on the work of Farmer and McGuffin (2003). Divorce already involves loss and increases the risk of depression tenfold in itself; however, if it is initiated by the other party, which is a qualifying example of social rejection, the risk of depression further doubles, as it was detected by the experiments of Kendler et al. (2003).

The threatening of the social self has to be listed among the severe social dangers. Such is the threat of loss of status, rejection, and negative social judgment as well. The individual may become reclusive after such trauma, feel shame and guilt, and act submissively to gain the acceptance of the group. Taking into the fact that this behavior has evolutionary psychological roots, these are ancient and intense feelings. With respect to psychoimmunology, this is all-important since Dickerson et al. (2004) measured increased proinflammatory cytokines following feelings of guilt. The fear of losing social acceptance also affects cortisol levels.

Status and identity

The question of the Self, the identity interpreted in the framework of social psychology and immunology, is a central issue in both psychology and immunology. However, in a multi-actor, multi-situational world, in which individuals are constantly changing their roles and hold various ranks and statuses in different situations, this identity becomes multi-faceted and context-dependent. Identities form a systemic, state-dependent network amidst the struggles of role experiences faced by the individual. Socioeconomic mobility also means that the individual's identity is under constant attack. Part of this is subtle and often subconscious.

In the context of sociology, social mobility often means leaving behind the former social class culture and embarking on an upward, status-changing journey, which requires changes to the values, habits, and approaches of the individual. Such a path full of changes and often bidirectional adaptive pressure involves a high amount of social stress experiences, during which the inherited values and those acquired in the early life of the individual become clear, while the world to be "conquered" often treats the individual in subordinating, excluding, humiliating, and "socially critical and judgmental" ways. These acute and chronic stressors often only reach the individual in a hidden manner. Socialization trials and accultural effects often force environmental requirements on the individual that exceed their adaptive reserves, and this carries pathogenic biological risks as well. The proinflammatory cytokines, which are important from a psychoimmunological point of view, could indicate the psychobiological requirements of social stress. Subject of social mobility often begin their career as a child with low social status, and we have already discussed the stressors associated with this elsewhere. However, Lewis et al. (2010) found that discrimination also increases the CRP level of the inflammatory indicator, and they proved this connection in the case of 296 elderly Afro-American people. The connection between discrimination and identity is tight and often painful in a discriminatory social environment. Social mobility does not reduce but instead increases the number of negative experiences, since the person discriminated against leaves their own society, which results in its supportive social and protective role becoming weaker, and the receiving society can often remind the individual of their alienation and the lower-class background even if this is done unintentionally.

Such a prejudiced and stereotype-driven social environment means a serious threat and social stressor, according to John-Henderson et al. (2015). The low SES in childhood was coupled with high levels of inflammatory cytokine (IL-6) in a prejudiced environment; however, the same authors confirmed that

in a supportive environment, the level of IL-6 was restored in individuals with low socioeconomic backgrounds, even in a trial situation.

Several personality traits influence the increased level of proinflammatory cytokines, such as hostility, aggression, and depression. Marsland (2008) found a connection between negative feelings, hostility, and increased proinflammatory cytokines in nearly 800 of the tested subjects. Ranjit (2007) confirmed a connection between chronic stress, distrustfulness, depression, and an increased level of proinflammatory cytokines in a sample of nearly 7000 individuals. Such emotional patterns often accompany integration issues. Rejected identity is true social stress even in and of itself. The adversity faced by identity becomes a chronic social stressor, often because of chronic stress and often insufficient social support, which leads to an increase in the number of inflammatory cytokines (IL-6, IL-8, and CRP). Since proinflammatory cytokines are indicators of an increased risk of cardiovascular disorders, stroke, and cancer according to the findings of Kaptoge et al. (2010), the phenomenon has clinical significance.

The social network, mental representations, identity, self-image, and group-awareness, the psychological representation of the internal social ranking, and the neuroendocrine-immune networks are well-defined examples of network medicine. This is why social support, the self-organizing autonomy of the student hostel environment, and democratic student clubs, which all have several-hundred-year histories in Hungary, are important components of social mobility for students with poorer backgrounds. Rheinschmidt-Same et al. (2017) found that there were lower levels of IL-6 in students living in student hostels with social and cultural programs than in students living in traditional student housing.

The study by Antonucci and Jackson (1987) also supported the idea that social support can be considered a key factor in reducing chronic stress effects affecting the identity, which was reflected by immunological consequences as well. Loucks et al. (2006) found that a higher level of social integration was accompanied by a lower level of inflammatory mediators in the tested sample.

Chen et al. (2009) did not find increased levels of IL-6 or NfkappaB, which are responsible for transcription, in individuals with a low socioeconomic background that experienced childhood maternal warmth and supporting empathetic care.

Social support from a psychoimmunological perspective

Psychobiology of love and attachment

The range in between the empathy-deficient type A and the pathological, i.e., the extremely attached (and alienating) type C personality and the experience of a harmonious mother–child attachment system can provide a solid basis for the development of a loving personality.

The medium of love and attachment – as James Henry's ethical suggestion suggests – serves the purpose of reproduction, providing anxiety relief and stress-reducing environment that provides security. Selective social attachment and love have a neuroendocrine substructure. Positive social behavior reduces HPA activity. Oxytocin plays a major role in the formation of social attachment behavior, also involving the vasopressin system, with the same neuropeptides also playing a role in the control of the HPA axis. Both parental love and love are very deep and characteristic psychophysiological states of selective social attachment. The neurobiology of love is phylogenetically and ontogenically closely related to reproduction and the concept of homeostasis, according to Uvnas-Moberg (1997). There is no romantic affection and love without attachment. The need for proximity and allogrooming is typical attachment behaviors. Reunification following a temporary separation is characterized by a normalization of the temporarily increased HPA activity, according to the research of Levine et al. (1997). The activity of the oxytocin's peptidergic system reduces the defensive behavior associated with stress, anxiety, and fear, and strengthens affectionate behavior and social attachment while rendering aggression incompatible with it, according to Porges (1998).

The condition for creating social bonds is the overcoming of neophobia. According to Witt (1990), oxytocin treatment in prairie dogs reduces aggression and increases social behavior. Oxytocin in rats also reduces anxiety and restlessness and increases explorative behavior. In relation to only the two amino acids, the two different oligopeptides, oxytocin, and vasopressin, play an equal part in social attachment. However, this is a bit like the combination of love and hate; while oxytocin clearly activates a gentle behavioral program, vasopressin can also play a role in shaping aggressive behavior. Vasopressin synthesis is enhanced by androgens in the medial amygdala, and this is confirmed by the fact that castration reduces male aggression, as vasopressin levels decrease after the castration procedure. Vasopressin has a unique role in attachment behavior, strongly associated with spatial protection and the protection of one's mate, according to Winslow et al. (1993). In prairie dogs, aggressive behavior against strangers dosed with vasopressin is accompanied by an increased attachment to their mate and even mating behavior. Vasopressin can be used to increase partner preference. Vasopressin, as part of the HPA

axis enhances ACTH secretion but also enhances the activity of the 'smart' vagus, which promotes social communication and social behavior. When vasopressin is involved in the stress process, oxytocin is a stress-relieving hormone that reduces ACTH secretion. Endogenous opioids also play a role in the modulation of social attachment. The isolated animal becomes more quiet; the separation signals cease if the animal receives opiates or oxytocin.

The stimulus of oxytocin secretion is dopamine, and inhibition of dopaminergic activity in prairie dogs reduces mating. Some suggest that endogenous opioids and monoamines can affect social attachment through the central separation of oxytocin and vasopressin. On the other hand, they also influence social interactions through arousal, attention, motivation, and reward.

The development of social attachment can be considered a state-dependent process, as it occurs or deepens, either after the extreme physiological event of pregnancy and childbirth (mother–child attachment) or extreme physical stress (companionship) or sexual activity (love). High levels of opioids, oxytocin and/or vasopressin and steroids increase the number of social interactions in test animals.

Positive social interactions are associated with an increase in oxytocin levels and a decrease in HPA axis activity and anxiety and fear, all of which have psychoimmunological consequences. However, traumatic, severely threatening experiences inhibit the subsequent attachment formation and instead lead to avoidance behavior. At the same time, we are familiar with the concept of 'traumatic attachment', in which the extreme levels of CRH, vasopressin or catecholamines, may play a role.

Oxytocin secretion is enhanced not only by breastfeeding but also by allogrooming. Oxytocin thus acts as an important neurotransmitter not only for the role it plays in the erasure of traumatic birth pain memories but also in the process of forming attachments. Its secretion is stimulated by the sight and scent of the baby, by sucking, breastfeeding and touching the breast, while, based on the increasing level of oxytocin, maternal instinct and lactation increase, with the sensation of pain decreasing. Similar to opiate antagonists, with oxytocin inhibition, we can also interfere in the development of a safe attachment experience. After delivery, biochemical inhibition of oxytocin secretion results in a lack of maternal instinct. Similarly, separation from the offspring reduces or even minimizes the oxytocin secretion in the long run, based on research conducted by Ågren et al. (1995). However, anxiety, insecurity, pain and chronic stress reduce oxytocin production in both mother and infant.

Due to its maternal behavior forming effects, oxytocin is worthy of the name attachment hormone. Oxytocin inhalation enhances the emotional content of the relationship, the caring attitude and motivation, as well as acceptance, and increases the sense of security, the effectiveness of social memory, and

attention to the needs and emotional requirements of others as part of empathy, according to Buchheim et al. (2009). It is important to know that oxytocin secretion in mothers and infants is closely intertwined during joint games, touching, and cradling, while in the case of children entering childcare institutions early, this does not occur or only occurs at decreased levels between the adoptive parents and the infant (Kállai, 2013).

In mothers with safe attachment, higher levels of oxytocin can be measured after caring for the child. When following personal development based on safe, harmonious attachment experiences, adult attachment is also more harmonious, with higher levels of oxytocin and testosterone, an increased parasympathetic baseline and a more relaxed state, showing approximating social behavior, while in the case of early (e.g. institutional) foster care relationships lacking support CSF oxytocin levels are lower.

Actually, the intimate marital bond should be addressed in the social support chapter; however, the psychobiology of love cannot be interpreted without it. The marital bond is the strongest and in most cases, the most intense source of social support, lasting for a lifetime. The socio-psychoimmunological significance of NK cell activity in breast cancer patients correlates with the emotional support received and observed from the spouse by Levy et al. (1990). According to a prospective study by Zautra et al. (1999), on the basis of self-reports of married patients living with rheumatoid arthritis, in addition to positive emotional relationships, the symptoms of the disease and recurrent episodes were milder compared to those of patients who were in an indifferent or confrontational relationship.

According to Wu et al. (2003), the partnership of unmarried individuals who are in a loving relationship also provides significant psychological support, in the same way as close relationships with relatives, such as parents and siblings, and close friends. Of course, the content of the intimate Of course, the according to age: at an early age friendships, then love, and finally, the family play a central role.

The true test of the psychoimmunology of loving relationships is hopeless or burdensome caring activity. In this case, a high-ranking positive feeling, altruism, self-giving and self-sacrificing care become sources of stress. Such is the chronic care of a child with an incurable illness or relatives with Alzheimer's disease. Such a caring task can often be accompanied by a great emotional, physical, time, and financial burden, and very often a fundamental rearrangement of the family structure. Those bearing the burden of chronic nursing complain of more respiratory infections compared to the norm have a worse immune response during viral exposure or vaccination and prolonged wound healing. However, according to Esterling et al. (1996), during long-term patient care (and even directly afterward) their NK cell response (recombinant) to

IL-2 and gamma interferon was also lower, while in another study, Kiecolt-Glaser et al. (2003) measured significantly higher levels of IL-6, compared to those not in such a situation.

Loneliness can also be seen as the absence of a loving relationship. In this case, the immune consequences of loneliness should also be interpreted in a social context. Kiecolt-Glaser et al. (1984) found an inverse correlation among psychiatric patients between loneliness and the number of NK cells and proliferation to PHA. A study among medical students also found an inverse relationship between loneliness, NK cell activity and a weaker immune response to the vaccine.

The neuroanatomical basics and aspects of attachment

We touched on the correlation between attachment and behavioral aspects and oxytocin, and also mentioned the role of endogenous opioids. However, many other neurological structures play a role in the development and continuance of attachment. Attachment as a psychophysiological structure is a set of neurobiological sub-systems that form affective, cognitive, behavioral and adaptive physiological processes, in which the infant plays an active, shaping role with their specific temperament and with their constantly expanding behavioral elements in the transactive system of the attachment circle and the broader social environment. This also broadens the scope of attachment structures.

An important element in maintaining physical proximity is the cognitive arousal mechanism that activates the feeling of a threat of separation from deep stress-biology mechanisms, which plays a central role in this process by activating the classic emergency response, as well as the HPA axis and sympathetic nervous system. Continuous and/or intense exertion of this system (including peripheral strain on the immune system, e.g., infections) with epigenetic mediation may lead to sustained disharmony of the sub-system due to the decrease in hippocampal GR expression and the feedback disruption of the HPA axis.

The connecting parts of the olfactory lobe and the limbic system are important for the development of social attachment in mammals, especially rodents. These brain areas are closely linked to the amygdala. The amygdala and hippocampus, important in terms of psychoimmunology, also play a key role in social interactions and in the forming of attachments. Damage to the amygdala is associated with a decline in social interactions and a loss of social attachment, according to Brothers (1995). Kling and Brothers (1992) suggest that the amygdala is directly involved in the coding of social events and in the development of adequate motor-automatic behavioral sequences in social

interactions. Oxytocin and opioids are important mediators and 'representative' neurotransmitters of the mother–child relationship, with dopamine also playing a role, according to Nagasawa et al. (2012). The role of sex hormones in enhancing the long-term effects of early contact is particularly important if, in animal studies, in the case of negligent maternal care and maternal deficiency, estrogen-dependent behavior can suffer long-term disruption as a result of the referenced epigenetic and methylation processes.

In the process of influencing social behavior, one of the targets of oxytocin and vasopressin is undoubtedly the amygdala. Damage to the medial amygdala reduces the interest in the familiar female partner in prairie dogs, while the hippocampus plays an important role in the learning and memory processes associated with social recognition.

The emotional experiences experienced in the parent–child attachment system influence the development of neurophysiological regulatory systems, automatic affective response patterns, the representation of social relationships, and the cognitive models and attention strategies, and emotional and experiencing modes that color them, formed by the anticipation of the other's behavior.

In the state of persistent separation threat, deep adaptive neurobiological, cognitive and behavioral systems may fall out of tune, such as the structures responsible for the memory-learning ability, for sensing pain or for spatial orientation, and the neural formations responsible for the setting and maintaining of the vegetative nervous system tone and dynamic balance.

As we already studied, in relation to the dialectics of the avoidance and approximation behavior, the fixed patterns resulting from damaged attachments can permanently influence these rewarding or aversive neurobiological systems.

The correlation between rewarding motivational systems and attachment is indicated by the fact that in the case of parents with safe attachment and avoidance behavior, the visual image of children triggered changes in different brain centers shown by the functional MRI image. With harmonious attachments, the ventral striatum and the orbitofrontal cortex showed a change in activity in the study of Kim et al. (2010), while in the case of avoidance type parents, lower ventral tegmentum activity and decreased orbitofrontal activity were observed in a similar situation during the study of Vrtička (2008). The ventral tegmentum, hypothalamus, striatum, and the orbitofrontal cortex can be considered part of the rewarding system, while structures sensitive to aversive stimuli (amygdala, hippocampus, insula, anterior cingulate cortex) generate different response patterns in different attachment systems.

It is worth mentioning that Kim et al. (2017) found mothers with addictions showing reduced activation of reward regions when shown reward – related cues of their own infants. In their research thirty – six mothers receiving inpatient treatment for substance addiction were scanned at 6 months

postpartum, while viewing happy and sad face images of their own infant compared to those of a matched unknown infant. When viewing happy face images of their own infant, mothers with addictions showed a striking pattern of decreased activation in dopamine and oxytocin in brain regions, including the hypothalamus, ventral striatum, and ventromedial prefrontal cortex regions in which increased activation has previously been observed in mothers without addictions.

In addition to the low-intensity reward system activity associated with avoidant attachment, it is also relevant to mention the structures involved in the assessment of threat or emergency situation. For a person with attachment issues, the structures playing a role in the experiencing social rejection, emotional conflict, and grief and sadness are also significant. As described in the summary of Kállai (2013), risk perception and evaluation are related to the amygdala, with the hippocampus playing a role in the experiencing of distress, just as the insula and cingulate cortex play a role in the psychological trauma of social rejection and the anterior temporal lobe plays a role in grief and sadness.

Hemispheric deviations play a major role in the cortical development of social behavior, according to Davidson and Hugdahl (1996). The left temporal limbic system and amygdala areas are responsible for displaying behavior related to social emotions, which are independent of cognitive processes. An individual with avoidance behavior shows reduced sensitivity in emotionally loaded social situations and avoids or minimizes attachment behavior, communication, and experience schemes. However, in a strong and deep relationship, this pattern of otherwise reduced amygdala activity can radically intensify, which does not improve the situation. Thus, the avoidance behavior pattern is characterized by inhibited emotional sensitivity, which also negatively affects the activity of the orbitofrontal and anterior insular cortex, which otherwise indicates reciprocal inhibition. In contrast, anxiety attachment types exhibit an increased amygdala response to rejection, increased sensitivity to negative social feedback and increased activity in the insula and anterior cingulate cortex. In emotional emergencies, they show increased hippocampal activity, higher arousal levels, and unstable HPA axis activity.

According to Vrtička's NAMA model (a functional neuroanatomical model of human attachment) inter-individual differences in attachment associate with brain anatomy and activity across the lifespan forming a neural attachment system composed of two emotional mentalization modules (aversion and approach) and two cognitive mentalization modules (emotion regulation and mental state representation).

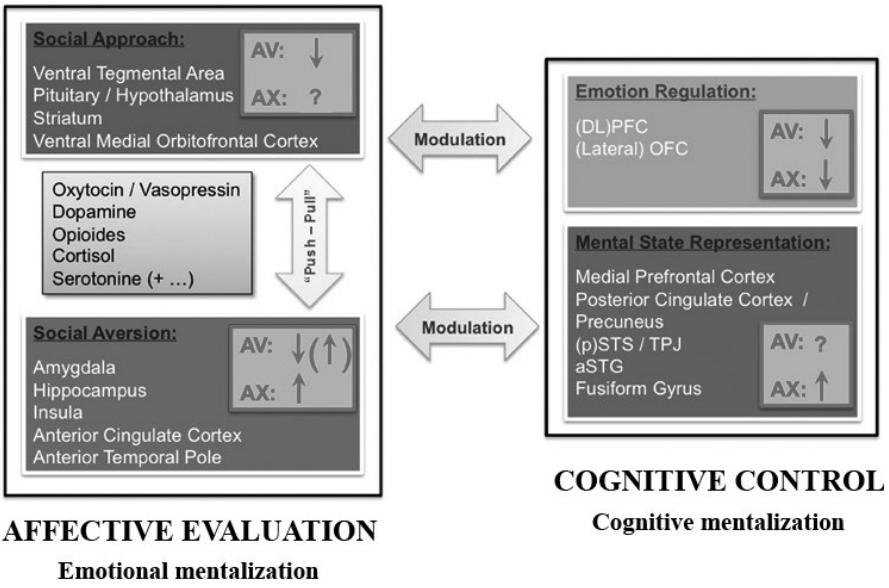


Figure 13. Neuroanatomical basis of attachment (after Vrtička and Vuilleumier 2012)

The human attachment system comprises an affective evaluation network made up of a social approach and a social aversion component that are in dynamic balance. The social approach component encodes (mutual) social interactions as innately rewarding – and thus counteracting fear tendencies – in a neural reward-related, primarily dopaminergic network including the ventral tegmental area (VTA), the substantia nigra (SN), the ventral striatum (VS), and the ventromedial orbitofrontal cortex (vmOFC) according to Vrtička and Vuilleumier (2012) This social approach network (including dopaminergic reward circuits under the influence of the oxytocin and vasopressin, endogenous opioids, and serotonin) is activated by social interactions with beloved ones (children, parents, partners), friends, or any "significant" (e.g., contextually relevant) other person with a cooperative relationship (e.g., joint task), which are all associated with the experience of positive emotions. This activated network implies VTA ventral tegmental area, SN substantia nigra, PFC prefrontal cortex, OFC orbitofrontal cortex, (p)STS (posterior) superior temporal sulcus, TPJ temporoparietal junction, and STG superior temporal gyrus.

Aversive social responses induced by social exclusion/ rejection, social stress, social conflict, loss are mediated by the amygdala and the hippocampus closely connected to the hypothalamic-pituitary-adrenal (HPA) axis, the insula, the anterior cingulate cortex (ACC), and the anterior temporal pole (ATP).

The emotional representation and affective evaluation of others have an emotional cognitive frame comprising elements of emotion contagion/mirroring, empathy, and compassion. The attachment system includes conscious representations about others assessing socially relevant dangers in the context of attachment. This cognitive control network has a regulatory function involved in the volitional control of emotions and social behaviors based on neural network activity in the lateral ventral, middle, and dorsal prefrontal and orbitofrontal cortex (PFC/OFC). The cognitive control network also maintains the representation of internally focused information about others through processes related to theory of mind (ToM) based on rational inferences about the mental states and intentions of others. These processes are encoded by an array of cortical midline areas such as the medial OFC and PFC, the posterior cingulate cortex (PCC), and the precuneus, as well as lateral temporal regions like the superior temporal sulcus (STS), the temporoparietal junction (TPJ), the anterior superior temporal gyrus (aSTG), and the fusiform gyrus (FG) according to Vrtička (2016). There is dynamic balance between social approach and aversion tendencies as part of the affective evaluation network of attachment, but Vrtička extends this dynamics to a "push-pull" mechanism arising between the affective evaluation and cognitive control networks, too. Vrtička (2016) sees attachment as drawing upon the functions of at least two distinct networks, generally maintaining affective versus cognitive processes – the latter being further differentiable into social approach versus aversion and emotion regulation versus mental state representation components, respectively – and that individual differences in attachment orientations and/or AWMs generally influence which network and component are preferentially activated and how the networks relate to each other in terms of a dynamic balance.

Empathy, imitation, mimicry, and emotional contagion

An important element of social relationships is sensitive openness and the ability to adapt to the other person's emotions. With a slight exaggeration, the alexithymia mentioned among psychosomatic risk factors is a disorder of this ability. The difference is 'only' that the alexithymic person is blind and insensitive to their own emotions as if alexithymia was a lack of empathy towards ourselves.

An optimal position for the development of empathy is provided by the secure attachment system, which helps to safely predict and have an interpreted mental representation of the behavior and emotional attitude of the 'significant other' in the fabric of optimal sensory, motor, emotional and social stimuli.

We will first review the phenomenon of empathy and the related neurobiological structures in relation to socio-psychoimmunology. Empathy at the same time means recognition (cognitive empathy), experiencing-feeling (affective empathy) of the other person's emotions, and the responsive behavior they trigger. In this sense, it includes the so-called "theory of mind" ability and mentalization and is a prerequisite for pro-social behavior. Other related behavioral phenomena, such as imitation, mimicry, emotional contagion, sympathy, or compassion, can also be classified as pro-social behaviors.

An important step in the theory of empathy was the study conducted by Ekman, who asked university students to participate in a memory test based on the reviewing of portrait photos. He placed EEG electrodes on their heads (to mislead them), but he was actually interested in the indications of myographs attached as ground electrodes, reflecting the movements of facial muscles. The result indicated that the muscle movements of the students reflected the specific emotional expressions of the portraits viewed.

That is, in the involuntary sensorimotor process of empathy, the observed mimicry, gesture, or movement is turned into a motor response process through the mirror neurons of the brain, and through limbic and prelimbic activation, it also develops parallel inhibiting processes. Facial expressions of negative and positive emotions result in the activation of the anterior insular cortex. Because this area is rich in connections both in the thalamus, the sensorimotor cortex, and in the dorsal posterior insula, here perception and prediction of the emotions that are currently being experienced are integrated with the prediction of personal interoceptive experiences. This ensures the ability to experience the displayed feelings of the other person or the (expected or presumed) feelings related to the situation of the other person. The perception and 'reading difficulties' of social stimuli also depend on the behavior of mirror neurons.

Thus, to experience the feelings of the other, the integration of several systems is necessary, the situational assessment of the other person, the perception of emotional expressions, meta-communication, the stimulus pattern of the current vegetative state of the body, and the recalled experiences, physical, emotional and cognitive memories all contribute to the development of empathic sentiment.

Social support

The importance of social support is very high with regard to health, as confirmed by many public health studies. The findings of the Alameda County Study, which also looks at social networks, as well as those of the Tecumseh Study, the Durham County Study, and the Evans County Study carried out in the State of Michigan, all support this.

According to Cohen et al. (1985), the concept of social support refers to a broader set of instruments that include instrumental (economic, institutional, financial) support, emotional support, and the support from information and social impact protection, as well as self-esteem strengthening support. When examining social support, we have to take into account the structure of the personal social network, its integration, and the quality and functionality of the support provided by the people involved. The degree of social integration is reflected by the number of participants in the social network, the type of relationships, and the number of contacts, while functional support is dependent on emotional attention, empathy, and the perceived availability and quality of support. In this sense, in the functional examination of perceived social support, we need to pay attention to emotional, information-based, technical support and personal support.

Holt-Lunstad et al. (2010) conducted a meta-analysis of 148 studies involving a total of more than three hundred thousand subjects and showed a 50% lower morbidity risk among those with good social support. This correlation also existed when examining the samples based on age, gender, health status, deaths, and follow-up duration. However, the main lesson was that the importance of social support and social relationships proved to be an independent factor, which could be compared with the risk factors of smoking, exercise, and obesity. This may be reflected in the higher risk of cardiovascular mortality associated with low social support and lower risk of cancer associated with social support, especially in the prognosis of breast cancer, and the inverse correlation between infectious diseases and social support.

Changes in the current state of social support, such as mourning or lone challenges (exam stress), are also psycho-immune stressors. Nevertheless, the misidentified and evaluated lack of support is sufficient for the development of health risks and immunosuppressive consequences. Although the integration of social networks seems to be beneficial regardless of the level of stress, it is primarily perceived social support that shows an inverse relationship with psychological stress, according to Uchino et al. (1996). The degree to which social support's assistance meets the needs related to the stressor and its prevention determines the extent to which social support serves as a stress-buffer. This also depends on the broader socioeconomic status and the context it creates, depending on social rankings and earnings, according to the studies conducted by Krause and Borawski-Clark (1995). People with lower social standings or marginalized individuals (homeless, unemployed, migrant) are less able to support others, and therefore reciprocal support is lower. However, personal well-being is most likely linked to recognized and perceived social support.

In the study of Thomas et al. (1985), according to the stress buffer theory, social support mitigates the effect of daily stressors on the lymphocyte count

and the mitogen-induced proliferative response. According to Kang et al. (1998), the effect of exam stress on NK cell activity is diminished by significant social support. Based on multiple studies, such as Ell et al. (1992) and Levy et al. (1992), in cancer patients who do not experience adequate social support, mood disorders are more frequent, with reduced NK cell activity and shorter survival rates are observed. As part of their active coping process, breast cancer patients actively promoting social support show greater NK cell activity. Social support extends the lives of terminally ill patients by 80 days, according to research conducted by Damm and Kulik (2005).

In the case of higher levels of perceived social support, Glaser et al. (1992) measured an increased antibody response to the hepatitis B vaccine. In relation to the widowed spouses of cancer patients, Baron et al. (1990) found that greater perceived support had a positive effect on both the NK cell activity and the proliferative response to mitogens compared to depressed coping. Social support was measured with the Social Provisions Scale (Cutrona and Russell, 1987), all indicators of which showed this correlation. Levy et al. (1990) investigated the correlation between immune competence and social support in 120 breast cancer patients and found that strong social support was associated with higher NK cell activity and improved tumor status.

Thomas et al. (1985), during the study of 256 older people, observed a higher lymphocyte count and mitogenic responsiveness in individuals with strong social bonds.

In the case of healthy men, the key factor was not the size of the personal network of contacts or even the actual use of the requested support, but, instead, it was the perceived control that showed a positive correlation with the activity of NK cells according to Miyazaki et al. (2003).

When examining gender differences in this field, it is noticeable that relationships based on trust have led to a stronger proliferative response in women than in men. Social support experienced as a resource helps the burdened immune responses during stressful situations with its stress easing effect.

The psychoimmunology significance of social support is mainly defined by its absence. Loneliness, divorce and mourning, and the lack of supportive social media have a negative impact on immune functions, according to Gerra et al. (2003) and Pressman et al. (2005). Problematic and stressful social conditions, as a source of distress, can interfere with the regulation of immune processes. Kiecolt-Glaser et al. (1984) examined the quality of social support among psychiatric patients and found that a group of patients suffering from loneliness showed lower NK cell activity and a blastic transformation response to PHA mitogen. Kiecolt-Glaser (1988) achieved a similar result when studying individuals living alone after a divorce, finding those lonely individuals have a higher incidence of infectious diseases and a higher antibody count induced by latent EBV and HSV-1 viruses, which indicated a weakened state of cellular immunity.

If we consider loneliness to be a unique situation of isolation, then researchers are also capable of providing animal studies that shed light on the phenomenon. In the case of isolated animals, Fauman (1987) found a lower antibody titer compared to those living in groups. Salvin et al. (1990), on the other hand, observed a higher antibody response and better macrophage functions in an isolated mouse than in animals living in groups.

The previously mentioned early maternal separation studies have shown that early maternal deprivation decreases the antibody response at later stages. Ackerman et al. (1988) observed a lower T-cell proliferation response to RBC and PHA mitogens as a result of the premature separation. A similar phenomenon was observed in pigs and monkeys. The low perceived support was also associated with reduced protection against infections, which was also indicated by the presence of more frequent upper respiratory complaints.

The degree to which social support's assistance meets the needs related to the stressor and its prevention determines the extent to which social support serves as a stress-buffer. We must also take into account that alcoholism, depression, or drug use also undermine the individual's social support, burden the family, and thus increase the psychoimmunology threat to the individual. Kiecolt-Glaser et al. (1993), when investigating marital conflict, found that couples, or individuals, with negative or hostile problem solving, have lower NK cell activity and lower blastogenic activity, together with a higher antibody titer resulting from latent EBV. Women who complained about a family conflict were more likely to have reduced immune responsiveness.

Social support models

The health protection role of social support is explained by two models. One is the 'main effect model', according to which social support, which stimulates healthy behavior and the discussion of psychological problems, exerts its effect independently of the stressor. On the other hand, social support increases the sense of identity, positive self-esteem, and sense of control while also reducing anxiety.

The other interpretation is provided by the 'stress-buffering' model, according to which social support can have an impact on the health-damaging effects of stress. The consequences of stress can be mitigated if the social environment helps to re-evaluate the situation or develop other coping strategies. We have to mention social support among the factors that change the stress experience. This is provided by relatives (nuclear or extended family), a circle of friends, a circle of acquaintances, and a wider social network. The relaxation offered by social life and the relationships offering instrumental support is important in

relation to the stress experienced. The other buffer option lies in solving the already existing consequence, which can be manifested in reassuring the stressed individual, providing medical assistance, or solving financial difficulties.

The same background factors, e.g., personality factors, can also contribute to unfavorable changes in the state of psychoimmunology and social support. Instead of demonstrating a clear causality, it may be more appropriate to look for patterns or the logic of circular interaction in the ecological approach.

Special mention should be made to regular physical exercise, which affects coping reserves and can also increase social competence by increasing self-sufficiency and self-confidence.

Laboratory experiments have also shown that individuals exercising regularly were less exposed to the unpleasant physiological consequences of the stressor, providing a stronger but quicker hormonal response to the challenge. Physical exercise and depression showed an inverse relationship. Women with a high-stress burden, who did not regularly exercise, were more likely to have a stress-related illness than those who trained regularly.

A decrease in anxiety and excitement was observed in the test subjects after the introduction of exercise programs. It should also be mentioned here that regular exercise involves an increase in NK cell activity in the elderly, with the phenomenon attributed by some researchers to the opioid system and by others to the adrenergic effect. According to Pedersen et al. (1997), the cytokine response is mainly due to catecholamines and growth hormone, and the NK cell activity enhancement due to exercise can be associated with the activity of released B endorphins, although the role of endorphins is far from clear. According to Jonsdottir (1997), prolactin released after physical activity may also play a role, and beta-adrenergic mediated catecholamine effects should also be considered. However, extreme physical exercise causes a decrease in NK cell activity. McIntosh, Kaplan et al. (1993) examined the psychological adaptation and social support effects of approaching life events in 192 older people, taking into consideration nutrition, income, and the potential side effects of drugs. Based on the results, supportive family and close friendship relationships increase the lymphocyte count in the elderly.

On the basis of all these, it is not surprising that the self-help groups, which also implement regular exercise in their programs, have a greater role in health psychology and behavioral medicine. The joint interpretation of the social learning theory and the psychoneuroimmunological model allows these groups to play a role in replacing the lack of natural social support and in maintaining immune competence. Social support covers not only families but also the self-help and sports communities, which can also provide a mixture of immune competence, improving remedial effects. This option should be used by public health professionals in social diagnosis, planning, intervention, and evaluation.

Socio-psychoimmunological significance of control

Separation traumas and mourning can be seen as the polarized situation of a loss of control due to a sense of irreversibility. However, the question of control can also be examined from the aspects of dominance-submissiveness, attachment disorders, and loss of subject status, social support, or in other words, in terms of social psychoimmunology problems.

The Skinner box makes it possible to compare a test animal with the capability to control the situation to another animal excluded from monitoring the situation, while they are simultaneously shocked with the same amount of electric shocks. In one of the partitioned cages, for one of the rats, the control pedal eliminates the electric shock in the common circuit-fed floor for both animals. Naturally, the other animal experiences it passively. The results of the psychophysiological 'mood' of the actor and the sufferer were compared on a dissection table. Following the experiment, the neurotransmitter levels in the rat brains showed a difference in every respect, therefore, the sense of control provides an advantage in the internal qualification of the same circumstances of experimental reality.

The hypothalamic noradrenaline level in the brain of the rat controlling the situation with the pedal does not show any significant variation compared to the significantly reduced levels observed in the hypothalamus of the animal condemned to helplessness. Dilman considers this phenomenon to be part of passive coping, a characteristic of type C spiritual workings.

Control and the sense or illusion of control are therefore crucial. In general, people tend to overestimate their control over a situation, and this also becomes a central element of the system of self-esteem and expectations until it is limited by the formative influence of negative experiences. A frequent lack of control or traumatic events can reverse this. The sense of control over aversive events is also reflected in the decrease in arousal.

So if we find a causal link between our behavior and the outcome of the situation, that is, there is a response-outcome contingency in behavioral psychology, then a sense of control occurs. If this contingency is not created, it is hard to imagine that we are dominating the situation.

Predicting the occurrence of an aversive event with regard to psychophysiological consequences is important, so the administration of an unforeseen electrical shock will have more serious consequences than the uncontrollable suffering of regular shocks.

If the work schedule of a worker is not tied to their own position, but is determined in an ever-changing and unpredictable manner, e.g., determined by a machine, then, in this uncertain and unpredictable case, the serum noradrenaline, adrenaline, and cortisol levels of the individual shall also be elevated.

In animals exposed to an inescapable and unpredictable shock a greater amount and slower settling cortisol secretion was detected compared to animals subjected to controllable stress. Recognition of the uncontrollability of the situation involves opioid secretion. Undoubtedly, in animal studies, an inevitable stress (electrical shock) could induce opioid-mediated analgesia in test animals, which can be inhibited by naloxone.

The unpredictable and uncontrollable shock also reduces the mitogenic T-cell proliferation response. The activity and cytotoxicity of the natural killer (NK) cells are also inhibited more by uncontrollable stress than by controlled or avoidable shock. According to the study by Seligman and Visintainer, when tumor cells are injected into test animals, the adherence of the tumor and the mortality rate in animals subjected to the uncontrollable stressor are much higher: 73% compared to 50% observed in animals under controlled stress or stress-free conditions. A study by Sklar and Anisman (1981) shows that in an animal exposed to an uncontrollable stressor, the tumor shows faster growth.

The study examining early traumas in terms of controllability and late consequences is also informative. In the first month after birth, rats were exposed to electrical shock stress in three groups, the first to avoidable and the second to uncontrollable stress, against the control group left undisturbed. Animals were inoculated with tumor cells at 9 days of age, and uncontrolled stress and avoidable shock were reintroduced in one-third of 'adult' animals.

The condition of early helplessness alone did not have a greater effect on tumor rejection. Animals exposed to early controllable stress increased their immune competence against the tumor regardless of the nature of the late trauma. If the early uncontrollable trauma was followed by late avoidable or uncontrollable trauma, the immune response proved to be inadequate compared to other animals. This was also observed in animals that had not been subjected to stress in their early life, but the late stress they were subjected to was uncontrollable.

So, early traumatization can be decisive, and its negative influence will only cease if we succeed in protecting the individual from stress in adulthood. Early controllable stress experience provides special protection, which can also be called the formula of experienced safety, which is manifested in the increase in tumor rejection observed in the animal, even if the adult individual is exposed to an uncontrollable stressor.

So, if we learn that we cannot influence the outcome of events with our behavior, then the state of learned helplessness sets in. This is important because the low-motivation negative-experience status thus created can persist in a new environment with more opportunities, and this is the 'result' of the previous learning process – according to Seligman.

The relationship between learned helplessness and the psychoimmunology consequences of early trauma

The refinement of the model of learned helplessness is attributed to Abramson (attributional models of learned helplessness), who observed in regard to the source of helplessness that attributing the experience of helplessness to external reason does not cause such a profound change as when the test subject attributes it to the inadequacy of their own resources (skills, intelligence).

The constant or changing nature of the causes of the condition is also important. Thus, the obstacle arising from the level of intelligence that can be considered a stable feature is greater than the difficulty caused by the variability of motivation. When examining the background between the reduced immune response to uncontrollable stressors in animal studies and the immune changes observed during depression, the noradrenergic transmission of the central opioid activity should be evaluated first. In animal studies, this effect is suspendible by naloxone entering the central nervous system and the denervation of the spleen. The uncontrollable stress can inhibit the cytotoxicity of the NK cells of the spleen, which is also a specific state of learned helplessness. However, a persistent, uncontrollable situation can also constitute chronic stress; therefore, the role of the overactivity of the CRH-ACTH-cortisol axis in the immunosuppressive event also arises. The abnormal shift of CRH-cortisol activity in depression, more frequent ACTH spikes, and the abnormal shift of the DST (dexamethasone suppression test) suggest that this hidden stress reaction may play a role in the development of the immune risk situation. Ostroumova and Dilman based their concept of hyper-cancrosis on the model of this persistently out-of-tune cortisol feedback loop. This is not the only model. Sapolsky et al. (1986) mention the adverse effect of sustained glucocorticoid secretion on the hippocampus as a result of the so-called "dysregulation cascade", resulting in damage to the glucocorticoid negative feedback effect. McEwen (1998), when describing the concept of allostasis, points out that chronic stress leads to damage to the hippocampus, which is rich in glucocorticoid receptors. Severe stress leads to a decrease in the volume of the hippocampus, according to Stein et al. (1997), while post-traumatic stress disorder (PTSD) is associated with hippocampal damage and hypercortisolemia, based on studies by Bremner et al. (2008).

The passive coping attitude, the tendency to suppress, and the frequency of uncontrollable stressors in life-history data typical of a C-type personality cause suppressed immunity, which appears during depression, even without experiencing depression. Thus, the perception of control and the presumption of helplessness can play a decisive role in social situations.

Psychoimmunology of social conflicts and relational disorders

Human social relationships are not only supportive but can also be sources of serious conflicts. In the light of social exchange theory, we can see that in the quite costly environment of the utilization of time, money, and emotional social transactions, a person is often exposed to severe distress, which can sometimes be a symbolic, observed or perceived situation, or a lasting psychosocial affliction for the person, a situation of learned helplessness. Similarly to social support, there is also much evidence to show the social-psycho-immune consequences of distorted human relationships.

Negative or ambivalent social relationships, and the resulting conflicts and negative emotions can affect immune processes. Hostility, which is mainly known as the cardiovascular risk factor of psychosomatics, also has an adverse effect on inflammatory processes, as evidenced by differences in CRP and IL-6, according to Suarez (2004). Elevated proinflammatory cytokines such as IL-6, also typical in depression. Because of the relationship between depression and social integration, and the negative impact of depression on relationship conflicts and social perception, depression is a central research area in social psychoimmunology.

The attitudes and emotions that are burdensome to social interactions, interpersonal emotional relationships – think of stress caused by anger or depression – are also reflected in the immune response's differences. Social conflicts affect the course of rheumatoid arthritis, where catecholamine influence plays a vital role among the neurohumoral factors mediating psychosocial distress. In the social network of ambivalent people (of both good and bad social influences), ambivalent persons trigger an increased adrenergic response during stress, according to Uchino et al. (2001). Contact and conflict with ambivalent individuals can provoke a rise in systolic blood pressure. Close, persistent ambivalent and conflicting human relationships are common in bad marriages, where a bad marriage is often associated with worse health indicators, according to Kiecolt-Glaser and Newton (2001). The marriage related dissatisfaction indicator is associated with worse immune indicators, as shown by the ratio of antibodies or CD4+ and CD8+ cells against EBV. The hostile behavior in family relationships, the impulse to interrupt other, are critical judgmental impatience can be a prediction of physiological abnormalities, elevated blood pressure and endocrine values, according to Malarkey et al. (1994). Among newlyweds, those who were more susceptible to negative, hostile reactions and recalled them in a short, half-hour conversation showed a suppressed immune function in the samples taken during the next 24 hours. In older couples, a difference is also indicated, suggesting an endocrine-immune

regulatory disorder that occurs during conversations that recall their conflicts, according to Kiecolt-Glaser et al. (1997). The extent of negativistic behavior correlated with the weakening of the immune response. Mayne et al. (1997) proved that a 45-minute conflict-exploratory discussion also reduced lymphocyte proliferation in women involved in the study. In prospective studies, Levenstein et al. (1999) found a correlation between oral ulcerative inflammation and spousal stress, while Kiecolt-Glaser et al. observed an about 66% longer, i.e. a significantly more extended wound healing period in the case of hostile spouses.

In the case of family conflicts with a hostile character trait, characterized by aggression, anger, and cynicism alike, a more pronounced immune disorder develops, according to Mayne et al. (1997). Miller et al. (1999) found a strong correlation between hostile and cynical attitude and behavior in conflict management and cardiovascular response, cortisol, and immune defects.

Hierarchy and interactions: results of animal studies

Sociality does not only signify support. The social existence of animals living in complex social structures can also be a severe source of stress. In the study of Vessey (1964), incorporating an otherwise isolated animal into a group for 4 hours resulted in a reduction in antibody response to bovine serum.

In the test group, the highest antibody titer was observed in the dominant animal. A decrease in antibodies was also observed in rats and mice exposed to congestion.

In the case of guinea pigs, the physiological indicators of social existence can also be thoroughly studied. According to Henry and Stephens (1977), the organization of a given social system affects the neuroendocrine processes that organize social behavior and social experiences that have accumulated after receiving social support from companion animals and earlier stages of development. All this indicates that, besides early social learning, the social structure also plays an essential role in social-psychophysiological processes.

The researchers also investigated the role of the social structure in terms of immunology. Research carried out by Vessey, Bohus and others has shown that there is a correlation between humoral and cellular immunity in both immune indicators and social rankings. Immunosuppression and low helper/suppressor T cell ratios are observed in submissive and exiled animals.

Bohus (1991) examined the rat population divided by control positions in an ethological animal study in a rat community formed in 6 m^2 and found that specific social physiology patterns were associated with social positions. Frequent and victorious interactions characterize the dominant male animal. In such an animal, blood pressure is normal, there is no stomach ulcer, and the

immune indicators are within normal levels. In another study of social rankings and psycho-immune signs of chronic social stress, Bohus found that the dominant animals had a higher number of B cells, a lower number of T cells, more IL-2 production, a much higher ratio of T helpers to T suppressors, and increased T cell responsiveness to mitogens (ConA, PHA).

Males with a subdominant status are also characterized by social activity and combat skills, although the number of interactions resulting in defeat is high, as there is no chance of victory over the dominant male, and they may be defeated by an animal with a similar position.

Among these animals are dominantly high blood pressure, thymic involution can be detected, together with a lower number of peripheral lymphocytes, but with a high T4/T8 ratio. In another study, Bohus observed an increased cytotoxic T cell response in this group, increased responsiveness to mitogens, and increased IL-2 production.

The third class includes subordinate, submissive animals, which demonstrate very little social activity. They are passive, and the other animals also pay little attention to rats of this status. Their blood pressure is normal, the peripheral lymphocyte count and thymus are normal, but the T4/T8 ratio is low, and the spleen lymphocytes' proliferation ability is also reduced.

In the other study, IL-2 production was reduced in this group, the number of T lymphocytes increased, and the decrease in B lymphocytes and T cell cytotoxicity was also common. There was also an increase in the suppressor T cell fraction.

The fourth class is the class of socially excluded animals. Such an animal may also be a previous dominant male who has lost his position. Those animals, characterized by stomach ulcers, are subject to frequent attacks, and both dominant and subdominant animals are among their enemies.

Here, a decrease in mitogenic responsiveness, an increase in the T suppressor ratio, a decrease in the T helper/suppressor ratio, and a decrease in mitogenic T cell response are also visible.

Alperina et al. (1996) compared the consequences of aggressive and submissive behaviors of C57B1/6J mice. Following 'collisions' observed for about twenty days, aggressive animals experienced an increase in CD+4 T helper response to immunization with control, while in the case of the submissive animals, researchers observed an increase in the number of suppressor (CD8+) T cells in response to SRBC immunization during the bone marrow testing of the animals, with the plaque and rosette-forming activity decreasing.

In the case of aggressive animals, Alperina attributed the phenomenon to the activation of the dopaminergic system, which also increased immune activity, while concerning the submissive response, the activation of the serotonergic system exerting an immunosuppressive effect by activating the CD8+ suppressor cell line, was provided as an explanation.

According to Padgett et al. in the midst of a continuous social conflict, and the collapse of social conditions, the mortality of influenza A virus in the C57BL/6 mouse strain tripled. According to the study's surprising result, dominant animals were more likely to fall victim to influenza than their submissive counterparts. Simultaneously, cortisol levels were less pronounced in dominant animals, even if their baseline cortisol levels were higher than those of submissive animals. However, on the seventh day of the stress caused by the overthrow of the social order, the peak value of cortisol elevation in the dominant animals was only one-fifth of the levels measured in the submissive subjects. However, this indicates that in hierarchical groups, the dominant individuals also bear the burden of social change.

Presumably, the position occupied in this social environment is indicated by the differences in the control of the situation, i.e., the successful coping. Coping strategies can be divided into two variants: active, fighting, or suffering way, accompanied by different neuroendocrine patterns.

The hierarchy within the group and the risk of disease correlating with it are not limited to rodents. On the contrary, the bite order and hierarchy status in the studies of Sapolsky and Mott (1987) also influenced the disease risk physiological indicators of the observed baboons (Cercopithecidae monkeys), thus indicating the low levels of HDL cholesterol in submissive animals. In another study, the authors demonstrated the relationship between social rankings and cortisol levels and immune function.

Examining more physiological stress dimensions, we found the following:

1. HPA axis: in dominant animals, basal cortisol levels are lower, higher, and faster stress responses are detectable with rapid alignment, and sensitivity to negative feedback is more pronounced.
2. Testicular effects: Stress in dominant males does not reduce testosterone levels.
3. Cholesterol metabolism: In dominant animals, HDL cholesterol levels are higher than in submissive animals.
4. Autonomous nervous system: dominant animals are more sensitive to catecholamines.
5. Cardiovascular functions: The baseline blood pressure of dominant animals is lower, but the blood pressure response is higher and resolves faster together with the heart rate response.
6. Immune profile: the number of circulating lymphocytes is higher in dominant animals (Sapolsky, 1995)

Social subjection means a lack of control over the situation and predictability, and at the same time, it often involves the obstruction of frustration relief, grooming or the interruption of sexual behavior by the dominant individuals.

It is therefore not surprising that socially subjected animals show higher basal cortisol levels, which are often associated with a decrease in pituitary CRH sensitivity. This can be explained by the persistently high level of CRH. A common phenomenon of depression is the dexamethasone test's insensitivity, which is justified by chronic hypercortisolemia with decreasing neural receptor density.

In addition, social insecurity, social change, and socially conflicted relationships cause increased HPA activation in both dominant monkeys and submissive animals. It also indicates that the lower cortisol levels in the dominant individuals are due to the control feeling and the perception of a predictable and accepted higher status. However, this sense of control is disrupted by the situation of social uncertainty. Otherwise, the price of dominance is a more sensitive, faster, and more labile stress response. Although base cortisol levels are lower in dominant animals, the response to acute stress may be more intense, according to Sapolsky (1983). This difference may be explained by the fact that chronic HPA activation and chronically elevated levels of cortisol, due to chronic stress experienced through social interactions, have a reduced response to acute stressors. The number of glucocorticoid receptors also shows a change along the feedback loop due to persistent cortisol. Sapolsky explains the psychoendocrinological character of submissiveness with the cortisol-CRH-HPA feedback, which is a high level of CRH activity even at high cortisol levels.

However, the social stress experienced is also dependent on affiliated behavior, which is partly personality-dependent and can affect the occupied status itself and the stress perception and the status response of HPA. Sapolsky (1992) identified specific animal behavioral features in dominant animals, such as the ability to create an alliance, affiliative behavior, and a lower number of provoked aggression events.

Psychoimmunological dynamics of uncertain social situations

High social status is only a stable factor in a stable situation and may become a risk factor if it becomes unstable. In this case, the dominance struggles of 8:2, 9:1, which are typically observed in monkey communities, change to 5:5 in fighting pairs. The death of the dominant animal and the rearrangements in the hierarchy are accompanied by significant psychological stress. In such a situation, the baseline cortisol level observed in the dominant and subdominant animals doubles. The cortisol level is similarly high during the struggle for position among dominant individuals striving for the normalization of the status quo. In monkeys, the change in rank is a stressor itself, and the rise in the bite order is accompanied by a rise in cortisol, as observed by

Sapolsky (1992). Ranking differences also affect the characteristics of cardiovascular reactivity. For example, the heart rhythm of senior animals recovers faster.

It is just as exciting to see a new combative male appear in the baboon congress. Alberts (1992) observes that cortisol levels are doubled in both the aggressive intruder and the 'indigenous' dominant animals, while the lymphocyte count decreased.

In dominant animals placed in an uncertain situation, increased atherogenesis was observed compared to the situation of the submissive animals, and this vegetative arousal was prevented by the administration of propranolol reducing cardiovascular reactivity in the macaque monkey population. The stability of a given social environment and the interactive relationship system protect against the harmful effects of social stress on the immune system. Studies in primates showed that male animals randomly selected and placed in an unstable environment for 26 months already showed a reduced immune response within the first three months of the study and reduced T cell proliferation to mitogen.

During the observations of Manogue (1975) and Sapolsky (1983), the dominant animals were also more sensitive to submissive individuals and were more labile, faster, and had a higher amplitude response to acute stressors such as the restriction of movement or the detection of a snake. Of course, this can also be explained by the responsiveness of the less stressed, harmonious stress axis, which is less 'drained' by chronic stress. Hypercortisolism in submissive animals is explained by Sapolsky (2005) with disrupted HPA feedback control, i.e., the hypothalamic negative feedback in dominant animals provides a more sensitive and faster inhibitory response through the CRH-HPA axis.

Chronically elevated levels of glucocorticoids damage hippocampal GR receptors (Sapolsky and Plotsky, 1990), and this recognition precedes the epigenetically mediated downregulation theory of GR receptors and is in line with Dilman's concept. They explain the disharmony of hippocampal regulation of the HPA axis, and the decreased response to acute stressors, by hippocampal neural damage caused by persistent cortisol elevation. Thus, primate studies also confirm that chronic psychosocial distress is associated with hippocampal GR deregulation.

However, in an environment characterized by changing, conflicting, and unstable social rankings and 'organization', an increase in HPA axis activity can be observed in both dominant and submissive animals, resulting in lower cortisol levels associated with control sensitivity and the predictability of the situation. Sapolsky (1995) studied baboons and confirmed that social affiliations affect both social stress and HPA responsiveness alike. It is also true about Cercopithecidae that the ranking of adult animals is variable, and the personality traits can be compared to status-dependent stress characteristics. Those

more skilled in creating alliances preserve their dominant position more easily, are subject to less aggression, and are characterized by affiliative behavior. Sapolsky's (1995) observations of the 50–150-member community of the Serengeti baboons (Papio Anubis) indicated that social rankings and the personality derived from behavioral patterns contributed to the sensitivity to social stress.

The permanent enclosure of two rat pairs by Stefanski (2000) also created a serious chronic social stress situation in which dominant and submissive behavior patterns quickly developed. At the end of the first week, the number of CD4+ cells declined in both the non-biting winner and the submissive loser animals, but there was no change in the number of CD4+ T lymphocytes in the biting winner, while a decrease in the CD8+ cell count was observed only in the loser, who did not suffer any bites. At the same time, repeated social disruption, rapid and radical transformation of social relationships lead to faster wound-healing than repeated use of restraint-based stress, according to Sheridan et al. (2004). Seven-day social disruption stress also increases basal proliferation of splenocytes and the proliferation to lipopolysaccharides, but the proliferation to ConA is reduced. When Stefanski (1998) studied the rankings with his colleagues, only submissive animals showed a reduced proliferative response to ConA. No such deviation was observed in the subdominant, competing animals.

The psychophysiological protective role of the social hierarchy, which reduces intra-group aggression, occurs in the case of food scarcity and the presence of a sufficient amount of food under laboratory conditions. The ranking position within the group is also 'coded' into the group member's behavior and, as a guarantee of group-level survival, it can even be a detriment to the individual, i.e., the hierarchical position has a direct effect on physiological processes, which in turn affect the individual's disease risk.

Of course, this can only be interpreted in the stable or labile social context of the group and by taking into account the personality determinants. In dyadic relationships, ranking uncertainty only raises cortisol levels if the individual below the person in rankings starts to elevate themselves. If an individual can 'move up', it will not increase the cortisol level despite uncertainty.

The 'personality' of the examined animal can be inferred from its social behavior. In male-male rivalry, cortisol levels were elevated in those animals that were able to maintain a higher social position only for a short time, demonstrating less fighting skills, and unable to show the outcome, victory, or defeat of their interaction in their behavior. Both in maintaining social control and predicting interactions, these animals proved to be inadequate.

The playful, grooming association behavior was another indicator. According to Kaplan et al. (1991), the highest cortisol levels were observed in solitary

animals with low-association and less playful tendencies. The social grooming, proximity-seeking monkeys show a greater cytotoxicity and proliferation response to mitogen at the time of group reorganization.

Simultaneously, in a stable social situation, affiliative or aggressive behavior did not show any correlation with in vitro immune parameters, according to Cohen et al. (1992). However, in competition for scarce resources, the competition itself triggered increased cytotoxic activation irrespective of social rank. In an unstable situation, social status itself can be dangerous to the dominant animal. In the case of a submissive animal, the unfavorable psychophysiological effect of the ranked position is clear. All this proves that social life is both a source of protection and a source of risk. Individuals who emerge victorious from the rivalry within the group are in a dominant position, and their degree of dominance shows an inverse correlation with baseline HPA activation and immunosuppression. Animals that lose these fights as submissive animals within the group and have more difficulty accessing resources and food exhibit higher stress mediator levels and immunosuppression proportionate to the experience of chronic stress.

Territory defense and control

The social structure is made up of dyadic relationships. The resident–intruder relationship forms a test-like framework. The majority of studies indicate that the losing animal is characterized by a lower antibody titer in both mice and rats. However, Hardy et al. (1990) found a suppressed antibody response in the dominant, territory defending animal. The cellular immunity of the dominant vs. submissive 'newly arrived' animals were compared, where the proliferation of the dominant animal to ConA mitogen and its IL-2 level was lower than that of the submissive animal and the control.

In Stefanski and Engler's (1998) study, the indigenous native who is vulnerable against the intruding animal shows social insecurity and stress, which is rank dependent according to immune indicators. The lymphocyte and white blood cell counts of the intruding animal finding themselves in a submissive position are reduced, while the granulocyte count increases two hours after the conflict. The leukocyte increase in the defeated is explained by increased glucocorticoids and IL-6 levels in injured animals (Merlot et al., 2003).

Raab, Dantzer et al. (1985) examined animals in pairs for 11 days. Animals that were previously found to be aggressive were also examined as residents and 'intruders'. In the study, non-aggressive animals were found to have a smaller thymus in both resident and intruder roles and reduced in vitro T cell proliferation to PWM, PHA mitogens.

Active territory defense against the intruder and active avoidance behavior against the dominant animal are physiologically associated with high testosterone and plasma noradrenaline levels, followed by increased catecholamine responsiveness and blood pressure response.

The observations made among baboons indicate that the activity of the intruder is above the average, and the contact initiation attempts are mainly directed at females. When immobilizing males of the host animal community, the base cortisol value is higher, and the lymphocyte count is lower than that of the control animals, which is more pronounced in females. The lymphocyte count of the 'indigenous' subjects challenged by the intruding animal was lower than that of animals that avoided aggression. It is peculiar that intruding animals also had high basal cortisol levels, and their testosterone levels were three times the average of other animals.

So, the disruption of or threat to the social order is a serious source of distress that raises cortisol levels in the studied animal community, where the most intense effect occurs on the first occasion in the case of such repeated 'intrusions'. After that, an adaptive process, the creation of a new ranking begins, according to Avitsur et al. (2001). There is no 'absolute' cortisol level change in submissive animals. However, the level of CBG (corticosterone binding globulin) decreased on the second day of social conflict, the consequence of which is an increase in the bioactive free cortisol level together with all its associated effects, according to Fleshner et al. (1995). In this phase, elevated levels of catecholamines are also observed in submissive animals. A quarter of an hour after the initial social confrontation, non-aggressive 'indigenous' (resident) animals and the submissive animals show elevated levels of ACTH, while there is no such change in aggressive, dominant intruders. Freezing behavior also correlates with circulating ACTH levels. On the seventh day of the social 'collapse' of the transforming mixed (BLB/c mice) animal population, in contrast to the dominant, aggressive intruder, we see an equal increase in glucocorticoid levels in all defeated animals, regardless of their rank, according to Merlot et al. (2004). Due to the neurohumoral consequences of this process, we can see the development of TH2 immune obesity according to the previously referenced stressed-induced TH1/TH2 shift model.

Possible alternative responses to repetitive social intrusions and aggressive intrusions are retaliation and surrender. The antibody titer response to KLH (Keyhole Limpet Haemocyanin) antigen was the lowest in surrendering animals, while in the case of fighting and defensive animals, the results observed were similar to those of the control animals kept in optimal environments. The anti-KLH antibody likewise showed a decrease in repeatedly (on five occasions) defeated, submissive Syrian hamsters, according to Jasnow et al. (2001). Incidentally, the access to social assistance reduces the elevation of the cortisol level resulting from the submissive situation.

Submissive animals are losers in competitive situations and are characterized by 'repressive' coping styles. Their behavior is submissive, and their posture is defensive. They flee from aggressive animals and do not demonstrate explorative behavior. In subdominant animals, the tyrosine hydroxylase level of the adrenal gland is higher, while the same is true for glucocorticoid levels in submissive animals in the studies of Koolhaas et al. (1999). All this is accompanied by increased weight loss in submissive animals, which researchers associate with increased glucocorticoid levels, while the fighting skills of subdominant animals is associated with an increased sympathetic tone.

In a social context, the most passive animals show the most submissive behavior, and they exhibit significant glucocorticoid resistance in a social disruption situation, according to Avitsur et al. (2001). Glucocorticoid insensitivity due to persistent abuse is likely to be the result of disharmony or insensitivity of the periphery of the HPA axis due to prolonged use, which indicates reduced allostasis, but may also have adaptive values (e.g., reduces the adverse effect of cortisol on wound healing). The social environment exposed to unstable and continuous reorganization favors the intensification of aggressive behavior because of the arrival of newer and newer intruding animals. We can achieve a recurring reorganization status in the examined animal community every 4-6 weeks. This creates long-lasting social instability and profound neuroendocrine implications, is accompanied by accelerated atherosclerosis, and can form gonadal or ovarian disorders resulting in reproductive problems, according to Kaplan and Manuck (2004).

We have already touched on the beneficial effect of active agonistic behavior on tumor growth, and this can also be observed in the individuals of the AK mouse strain exposed to leukemia, where we found significantly prolonged survival in the subjects demonstrating dominant, active behavior compared to the isolated, submissive animals.

The positive immune effect of agonistic behavior is manifested in the slower growth and smaller dimensions of the implanted tumor (Maloney sarcoma). According to Rozing et al. (1982), dyadic social stress has been shown to affect the course of implantable pre-B cell leukemia in animals. The survival period proved to be longer for intruders. The 'indigenous' animals with tumors who encountered aggressive 'intruding animals' showed a lower survival rate. Of course, active behavior alone is not a guarantee; therefore, in repeated defeats, the loss of control may also occur in the case of active behavior.

According to Stefanski (1996), the nature of intruder–resident interactions significantly influences tumor metastasis in the lung, a process that is significantly influenced by NK cell activity even from the first day. Among the factors that mediate the effect of social confrontation, adrenergic influence on NK cells was substantial, significantly altered by the butaxamine beta-adrenergic antagonist. According to another study by Stefanski (1996), the effect of

psychosocial stressors in guinea pigs, depending on previous social experiences, leaves a mark on the increased indicator of the detectable cortisol level and the activity of the complement system, in the event of social confrontations.

The passive strategy is expressed in reduced social activity and freezing in the presence of the dominant male. Here, the physiological characteristics are characterized by lower testosterone levels, decreased parasympathetic activity, and the increased operation of the HPA (hypothalamic-pituitary-adrenal) axis.

The personality tests of tumor patients reviewed by Fox (1988) show a unique parallel with the above data. In patients with long-term survival, Stavraky found hostility while maintaining emotional control, Greer found a fighting spirit and rejection, Visintainer observed problem-solving behavior, Derogatis distinguished aggressive, non-compliant and complaining behavior and Ikemi found committed religiosity to be common, while Reynolds linked social isolation, Greer stoic acceptance, and helpless-hopeless attitude, Temoshok the accepting, aggression inhibited, abnormally kind type C personality, Jensen the suppression of emotions and Schonfield social introversion with the worse prognosis.

Psychoimmunology of social conflicts and tension zones

Cultural factors affect both the experience of a social ranking position and the symbolic meanings within it, the status structure itself, and the changing relationship attached to it.

The community of values and social solidarity can be considered a protective factor in terms of social psychoimmunology. This relieves the stress slightly by experiencing social support, as it has already been discussed. Psychosomatic medical anthropology fieldwork performed by Decker et al. (2003) may also provide an opportunity to observe social cohesion, congruent, and coherent relationships in the field. The authors' observations made during the study of 30 males in a Dominican rural community confirm that the measured salivary cortisol was much lower for reliable, cooperative, helpful, and influential group members than for group members without such virtues.

The authors interpreted the value system examined along cultural anthropological emphases between the poles of religious values and anomalous behavior. The values of the inhabitants of the village of Bwa Mawego are determined by the Christian values mediated by former missionaries, the monogamous, peaceful, labor-loving, merciful behavior that follows the harmonious family values. This set of values condemns abusive behaviors, aggression, drunkenness, looting, gambling. There are other religions, including Rastafari, among the inhabitants, but they are a minority. Decker et al. studied

the father's presence as an important socialization factor in upbringing and family socialization.

The authors linked cultural anthropological field observation with stress-biology studies. According to their experience, congruent social behavior with the prevailing cultural model negatively correlates with stress and is especially true of well-respected people. It is important to note here that for those identifying with internalized community values, self-contemplation and failures, shame, low self-esteem and depression resulting from so-called social evaluation processes, due to the sense of inadequacy, have immunosuppressive effects, while social support experiences, a sense of coherence, and socially rewarded personal efficacy work as a stress buffer and improve immune responses. All this must always be interpreted in the given sociocultural space. Observations from the above Dominican fieldwork indicated that low cortisol levels are mainly associated with those who are respected by the community and rewarded for their behavior. At the same time, neither income nor education, nor wealth or institutional position, showed any correlation with stress and the chronic HPA axis activity in this study. During their observations of culture, Brandstadter et al. (1991) found a link between socioeconomic status indicators and chronic variations in saliva. Therefore, it seems that prestige of status, wealth, and other attributes differ by community. In western industrial societies, education, income, and material wealth are associated with increased competition and individualism, but according to Decker, recognition and respect are conducted through more altruistic strategies in Dominican families' studies. Therefore, the authors consider the relationship between status and stress to be culturally dependent and variable. Thus, the status position does not correlate with dominance, aggressive, hostile superiority, or with an anti-social or hostile personality, but with the appropriate social skills, according to Spangler (1995); even in case of a temporary loss of status, such persons are more protected.

The status-affiliated social relationships of human society, embedded in symbolic interactions, can also be the source of many social-psychoimmunological risk factors. We also need to weigh up situations burdened by rapid cultural changes and the serious loss of subject status associated with cultural bereavement. Of course, a large part of the migrant workers and economic migrants are outside this circle, because for many, migration is a real liberation as an element of active coping, while others do not emigrate voluntarily but are forced to leave their country or relatives because of war or persecution. Eisenbruch compares this to individual mourning, and therefore the associated pathological or atypical mourning reactions can also affect migrants. Especially when migration or acculturation itself is often associated with post-traumatic stress, it also carries the consequences of severe stress, which

is exacerbated by the conditions of escape and migration, poor hygiene, and the risk of infection.

Since migration can be considered a special loss of subject, the loss of birthplace, the supportive social network, and the linguistic-cultural environment are in some respects analogous to mourning, so the psychoimmunological consequences must be weighed.

Simultaneously, the cultural 'rise' brought about by economic migration can also pose a psychophysiological burden, just as Dressler considered the competition for upward social mobility and the large wage differences as distress causing factor among Caribbeans living in the United States.

The effect of migration and acculturation on blood pressure is well known. In Cassel's summary work, we can see that in the case of the population of the Cape Verde Islands to the west of Africa and migrants who had already migrated to the eastern parts of the United States, the blood pressure measurements taken were higher, in all age groups, in those who had migrated to America. Similarly, higher rates of hypertension (32%) were found among Irish immigrants living in the United States than among their counterparts living in Ireland (21%). According to Cassel, the disappearance of a coherent set of values among psychosocial factors and its substitution with different values and situations are of great importance.

Brown (1982) studied Philippine immigrants and already settled Filipinos in Hawaii and found that, among the immigrants, going through the acculturation process, the level of catecholamine derivatives collected over 24 hours was significantly higher than the values found in newly arrived immigrants. Thus, the mixing of traditional values and new values derived from the Americanized lifestyle has become a source of increased stress. However, the value of affiliations and social congruence also plays a role in every aspect, which clearly deteriorates due to the shift and change of the socio-cultural environment. This value harmony, congruence actually measures the consensus, the lack or deterioration of which is a serious source of social stress, according to Dressler and Bindon (2000). The tension so experienced can lead to greater stress or even immunosuppression.

According to Bindon et al. (1997), the expectations and hopes of control over resources are important regarding the stress experienced in relation to the status. Inequality in the use of resources, which is also reflected in the tools available, plays a role in this. Status creates incongruity when someone has higher status expectations than they can achieve.

Modernization processes, technological change, generational change, or alternate management of political power networks can all lead to social and status uncertainty that can lead to increased social distress. In this respect, the situation of the migrant is even more serious, as, for them, their perception and evaluation of their fundamental status already hide uncertainties. This is

the case even if the migrant arrives in the elite strata of society due to having a highly-skilled scientific or artistic career or transferred into another cultural-social environment within the context of the so-called "brain drain". Part of the process is the so-called cultural shock, which, despite the equilibrium gained after early euphoria, uncertainty, and then realistic assessment of the situation, does not guarantee congruence between the expected and the real social status. Even in seemingly successful integration, the discerning and experiencing the hidden discriminatory tone of social status and ranking positions causing psychological difficulty can be a great burden.

Evolutionary psychology also confronts us with the fact that even with great efforts, the status position and the cultural standards and symbolic values associated with it (e.g. obligations for well-paid economic leaders or professors – performance, professional social life, time, home, car, social life responsibilities) may exceed evolutionary psychological capacities and equilibrium, according to Cosmides and Tooby (1992). All this is true for the members of the given culture. Moreover, Bourne et al. (1968), or later in a study, Brandstadter et al. (1991) found a positive correlation between HPA activity and military rank, and socioeconomic ranking. The higher power or status position is accompanied by increased arousal, which can be seen as a symptom of increased adaptive arousal. Knowing the inner intensity and distress of professions and roles with high social status, material, and symbolic recognition, it may not be such a big surprise after all. This is suggested by Győrffy's (2009) research that in certain age groups of male and female doctors, deaths related to cancer are more common than in other similar age groups, and according to Guseo (2014) more than two-thirds of retired chief physicians die of malignant cancers. Incidentally, the more competitive lifestyle and attitudes of individuals striving for institutional power and living with it might be associated with higher vegetative arousal and a greater risk of coronary artery disease. An old and well-known psychosomatic risk behavior pattern is the Flanders-type 'top dog', or as it became known later, the type A personality, 'a success-oriented, challenge-seeking, hostility-tinted, emotionally engaged, time crunch fighting and result-oriented' personality.

Strangely enough, Sapolsky saw the dominant entities in the monkey communities as having B type personalities, and in many societies, the source of social success and evolutionary fitness is the harmonic type B character, and not the type A personality pattern characteristic of the dominant forms of modern industrial societies, transnational companies or violent organizations.

Thus, individualistic and competitive social behaviors and their associated social formations have already separated from the social frameworks on which our social-psycho-physiological adaptive patterns have evolved, and which also limit our allosteric load capacity. Thus, the conformity or tension between the

prevailing cultural and social model of the individual and the surrounding society determines a significant part of the socio-emotional stress experienced.

Of course, all the early circumstances that can put a burden on an early mother–child relationship, such as technocratic childbirth with early separation trauma, the mothers' early return to work, single-parent families, cultural changes in gender roles burden the foundations of this traditional relationship map woven from social transactions. The importance of sociocultural determinants of developmental psychological characteristics, early traumas, burdensome childhood, and other social experiences has been confirmed by many researchers, such as Rohner et al. (1991), LeVine (1990), or Rutter (1979). The inadequacy of maternal care often comes from the father's absence. The consequent psychopathological and developmental psychological consequences predestine increased stress sensitivity and presumably expose the person to psychoimmunological risks. In this social-psychological context, we also need to interpret personality traits such as disturbed self-esteem, personal effectiveness, and the often damaged cognitive social relationships model.

Culture, hierarchy, and control

In Julian Rotter's theory of social learning of personality, the center of control has an important role regarding general expectancies. According to Rotter, people are on the scale between complete internal and complete external control. People with internal control feel that they can bring events under their control in most cases, while the lived of those with an external control consciousness depends on external factors. It seems that the health of individuals with 'internal control' attitudes prove to be better.

The challenge of bio-cultural adaptation is to control the situation; therefore, the control experience can be rewarding in itself from a psychobiological perspective. Control may vary from culture to culture, especially if it results from competition, in which cultural change (colonization, acculturation processes, minority existence) puts the oppressed, submissive losers under a definitive biological disadvantage. A group that does not command its own destiny is not in a state of autonomy. Even in the case of existential guarantees (see reservations, social insurance), it is subject to social anomalies, acculturation, and psychophysiological consequences. This defect manifests itself in the absence of control and entails the threat of inadequate social support and self-sufficiency, and ultimately leading to a state of learned helplessness. This, in the case of minorities, results in the dynamics of emigration, self-annihilation, and assimilation, with which they aim to avoid control-deficient psychobiological 'self-punishment' processes. At the same time, this puts the logic of social life forms on a socio-psychoimmunology scale. Anxiety mechanisms,

such as retention of information and inequalities that make it impossible to share control, can create a socio-psychoimmunology situation that can gain public health significance according to the above logic.

Thus, the permanent loss of control and passive behavior will sooner or later lead to the state of learned helplessness, which in the same sense also classifies the individual into the less adaptive class concerning their physiological chances. Human studies suggest that people characterized by so-called external control are more likely to suffer from a state of learned helplessness than those demonstrating strong internal control.

It can be true for all communities if, in a colonial situation or a minority existence, they have to passively experience their values, undermining the dominance of the other culture, both in the use of symbols and the moral code system of everyday existential frameworks. It might also be true for the majority who have lost their attachment capability and their values.

That is why we need to take the signals seriously from the extensive behavioral, epidemiological study of Mária Kopp and her colleagues, which should be considered from a social psychoimmunology point of view, as 24% of the population surveyed complained of depressive symptoms, of which nearly 3% complained of severe depression, which, according to the repeated surveys carried out, has significantly increased over the past twenty years. Thus, in the 2002 Hungarostudy study, almost 40% of those who did not complete eight classes and 22% of those who graduated elementary school, so almost every fifth person suffers from such a condition, while the depression indicator shows only 4% among college graduates and only 6% among high-school graduates. That is, depression reflects the social rank of education and the different socioeconomic control over circumstances.

Social support indicators are even more alarming, as 11% of the population is not in contact with their neighbors, 12% have no friends, and 88% do not rely on official support. In a difficult life situation, 42% of the Hungarian population cannot count on the help of their neighbors, 29% cannot count on the help of their staff, 18% cannot count on the help of friends, with 15% are even unable to count on their relatives. 32% of 60-year-olds exposed to immune risk have no friends, and 72% cannot count on their colleagues. Maybe the early traumatization, often the forced mother–child relationship with a lack of empathy, may explain the fact that one-fifth of the interviewed young people cannot count on their parents when they are in trouble, according to Kopp and Skrabski (1995). It relates to the sense of control that 35% of citizens are moderately able to influence what happens within their working group, while 29% are less able to do so, with 17% having no influence at all.

Behind all this, Hungarian society bears a heavy burden affecting several generations. The forced return to work of mothers only six weeks after giving birth, forcing a lot of young children to be banished to nurseries, apart from

their mothers, which resulted on many occasions in a psychological wall being built between the mother and the child due to distrust. It burdened the lives of newborn babies for two and a half decades. It is apparent from Weil's (1992) work that this traumatizing early experience can be decisive in the context of psycho-pathological or behavioral disorders in adulthood.

Thus, the morbidity, migration, and depopulation tendencies of communities going through forced cultural loss and acculturation can also be interpreted from a psychobiological perspective. According to Kopp and Skrabski, self-identity and its components: coherence, faith in the meaning of life, psychological defense, social relationships, trust, cooperation skills, tolerance, useful coping skills, and abilities provide psychological health protection. Faith in the meaning of life has a close relationship with community efficiency, the strength of neighborhood relations, the practice of religion, the importance of religion, and the membership of a civil organization, which, according to numerous studies, are significant health protection factors. Furthermore, faith has an inverse relationship with mistrust, rivalry, and anomie, according to Skrabski, Kopp et al. (2003).

In this process, the crisis of autonomy becomes simultaneously a deconstruction of culture and, among other things, an embodied crisis of physical existence through psychoimmunological processes. The social-psychological crisis of society and psychoimmunology, forming part of the unfavorable morbidity data (such as allergic or cancerous diseases), as an interpretative model of socio-psychosomatic processes provides an approach.

The psychoimmunological effect of unstable social situations – the study of impending unemployment

As an example of social instability, threatening unemployment can be considered serious social stress. According to studies by Cobb and Kasl (1977), this condition is characterized by increased cortisol levels, GH, and prolactin, i.e., increased separation of stress hormones.

The social-psychoimmunological facts presented in this chapter can shed light on the social-psycho-immune status of workers in a precarious social situation, threatened by the break-up of their social relationships, and who are living in a socially deprived situation in a society living in a transition phase in the nineties of Hungary. The immunological consequences of the threat of the breaking of social bonds and impending unemployment were examined within a group of employees of a firm under privatization.

The majority were in the 40 to 50 years' age group with limited ability to find new work and with a long record of employment and attachment to the plant. They were compared with 15 controls with stable worksite conditions.

None of the subjects had immune disorders or habits (drug, alcohol, smoking) that could modify their immune status. The experimental group was divided into subgroups according to a social hierarchy: six subordinates, seven foremen, five plant managers, eight department heads, and four board members.

We assume that the threat of unemployment may have different psychobiological effects at different local social ranking levels, measured by the immunobiological (NK cell activity) and vegetative nervous system (RR, GBR) indicators of the worksite hierarchy in the group of employees. Personality factors, psychological variables were measured by the CPI 5 test with 480 items including shortened MMPI test and the Big Five questionaire.

Based on our assumptions, the loss of workplace attachment as a human niche in ecological terms is the prime example of the threatening loss of subject status.

When comparing the average results of those under threat of unemployment and the control group, the NK cell activity showed a significant difference, but we also found a difference within the studied group. When we classified the individuals into dominant and submissive groups according to their social rank (white-collar or blue-collar leaders), NK cell activity showed a significant difference during the labile institutional situation of impending unemployment. There was no discrepancy among the top managers having safe employee status, while there was a significant difference between the lower and middle managers and the control group.

The NK cell average decreased gradually in accordance with organizational ranking positions, and the skin resistance increased, with a significant correlation being shown between the indicators.

The lowest NK cell activity was found in the group of blue-collar foremen as compared with department heads or subordinates. The correlation analysis showed a linear trend between social rank and electrodermal activity in the skin resistance study. Results showed that the threatened group did have lower NK cell activity than the controls ($p < 0.05$). This was paralleled by high skin resistance, indicative of low sympathetic arousal in the subordinate groups, such that there was a linear trend with social rank that approached significance ($p < 0.07$). This relation was endorsed by correlations between NK cell activity and skin resistance ($r = -0.33$, $p < 0.05$ for each hand). Blood pressure also correlated with NK cell activity in the direction of lower pressure and immune compromise: systolic ($r = 0.31$, $p < 0.06$); diastolic ($r = 0.33$, $p < 0.05$). Additionally, there was a highly significant linear trend with diastolic blood pressure and social rank position ($p < 0.006$), indicating hypertonia in those with a higher social rank with higher responsibility (CEO-s).

The blood pressure test results showed a significant linear relationship between diastolic blood pressure and social rank, but there was no such significant correlation with systolic blood pressure.

We found no correlation between the values of the NK activity of the subgroups and the values of coping, social support, insecurity, and workplace attachment-related self-esteem. A significant inverse correlation was found between NK cell activity and Autonomy, Maniform behavior, and Hysteria values. The only relations with the psychological ratings were negative correlations with NK cell activity and the California Personality Inventory subscales: autonomy ($r = -0.40$, $p < 0.40$), maniform behavior ($r = -0.34$, $p < 0.03$), psychopathy ($r = -0.33$, $p < 0.04$) and hysteria ($r = -0.32$, $p < 0.04$), interpreted as reflecting the role of inhibited power motivation. The Autonomy scale value showed a positive correlation with the Maniform and Psychopathia scale values. However, there was no correlation between the Depression, ES, (self-sufficiency), and An (anxiety) scale values and NK cell activity.

The suppression of NK cell activity, which corresponds to the ethological-psychobiological tendencies observed in lower and higher mammalian populations, shows a fitting picture of the group leaders' social hierarchy. Strengthens epidemiological research initiatives, according to which multi-dimensional examination of health levels (gradients) correlating with socioeconomic status and the interaction of variables and the coexistence of variables (education, income, employment, indicators at the individual level: depression, hostility, sense of control, health risk behavior) are needed in the relationship between disease risk and socioeconomic status. Social rankings must also be included in this, as the social class position is one of the most important predictors of the disease health issue. All this can explain the gradual-type correlation between mortality and social status in diseases such as malignant tumors, infectious and parasitic diseases, respiratory, digestive, and circulatory diseases.

The labile social structures affect not only those in a submissive position, but also those in dominant positions based on observations, which are reflected in cardiovascular maladaptation. In our study, hypertensive blood pressure values in the upper manager and director group showed this significant group difference. In two cases, hypertension was discovered on the site, and in all four cases, blood pressure was higher than expected, which also should be evaluated in conjunction with the white coat hypertension phenomenon.

The trend, shown by the GSR (galvanic skin response) test, initiated further measurement, as it implies the balanced or right hemispheric dominance in submissive groups.

NK cell activity shows an inverse correlation with the more A-type personality pattern and the indicators (Au, Ma, Pp, Hy) following psychopathic personality development. Surprisingly, it did not show any correlation with self-sufficiency, depression, or anxiety (Es, D, An) in the current test sample. A seemingly surprising personality diagnostic image revealed that we did not see any change in the parameters indicating type C response in the background

of the observed immunosuppression, we did not detect reduced self-sufficiency or depression, but, on the contrary, our assumed model shows that the personality image induced by the type A secondary mother–child attachment system correlates (negatively) with the activity of NK cells, i.e. the more intensive these indicators (Pp, Au, Ma, Hy), the more NK cell activity decreases.

In summary, the immunosuppression found in the subordinate employees is consistent with social hierarchy studies in animals. In contrast, cardiovascular overactivity was a characteristic of social dominance, in keeping with those reports that find such an association with people in competitive social positions. The reduced electrodermal activity of the subordinate employees signified low sympathetic activity, a known accompaniment of depression and social inhibition. Impending unemployment against a background of work stability, when compared with controls in safe employment, appears in this preliminary study to be a significant psychophysiological risk factor.

Further research is needed to assess whether the submissive situation and the immunosuppressive response are causal, or both are the consequence of a hidden variable, perhaps the personality, which also plays a decisive role in social engagement, and where the psychophysiological indicators found may reflect this interaction between physical determination and the labile social situation.

Considering the values measured in a control group with a secure workplace, job insecurity, as a threatening separation trauma, appears to be a significant psychophysiological hazard, differentiated according to social rankings.

Retirement

The workplace is an integral part of the social environment, where much of human life takes place. This medium can be a source of recognition, a self-sufficiency boost effect, and a source of security and control, while on the contrary, it can also be a source of chronic social distress. The workplace can be a prerequisite for social prestige and appropriate income. A good workplace environment from social perspective is one of the key conditions for spiritual well-being and health. However, redundancy or retirement can easily lead to marginalization, social isolation, and a sense of worthlessness. A worse prognosis characterizes the chronic illness of the unemployed individuals excluded from the workplace social network. Earlier studies, such as Lazarsfeld and Jahoda (1933), have shown that cardiovascular disease and rheumatoid arthritis, which develop following redundancy and the subsequent period, threaten the unemployed. The wives of unemployed men are also characterized by weaker health and increased morbidity, which alludes to unemployment's familial consequences. Arnetz et al. (1991) demonstrated the immune

competence-reducing effect of prolonged unemployment on unemployed women who had been without a job for more than six months. The researchers found a reduction in the proliferation response to mitogens. In 9 months of unemployment, the study showed decreased T cell proliferation to PHA even in secure socioeconomic conditions (unemployment benefit).

The social psychoimmunology of bereavement

Bartrop (1977) pointed out that the worst event of life, the spouse's death, may be associated with immune suppression, which occurs six weeks after the event and may last for months. Real bereavement may increase the ratio of both morbidity and mortality. The mortality rate of widows aged over 55 is 40% higher than that of the control individuals of the same age group but free of any loss event. Clayton et al. (1990) detected health deterioration and increased frequency of internal and psychiatric diseases in two-thirds of the widows in the first year of bereavement, and Parkes et al. (1969, 1984) detected severe depression in 45% of the widows. The unavoidable loss of bereavement makes us recall the powerlessness relating to giving up life and being beaten, which is the cradle of a wide range of diseases according to the assumption of Engel and Schmale. Engel dedicates outstanding importance to the bereavement in his psychosomatic disease model, which he interprets as an adaptive failure model triggering psychological incapacity. The earliest threat experience of personal development, the threat of any break in the early infant-age attachment may give an interpretative emphasis to that condition. While assessing the immunologic consequences and psychophysiological features of bereavement, we must also consider that such an event in life usually occurs at a later age and that most of the subjects of the studies belong to that age group.

Weiner also warns about that in his summary. According to Engel, the complex psychological response to bereavement may be described with reduced self-power, the loss of meaning of company and pleasant leisure activity or essential work, detachment from the personal past-present-future experience and the revival of such memories. Naturally, coping with a loss also influences physiological consequences according to the subjective assessment versions. According to Engel, the classic bereavement, where the 'giving up/given up' complex may be justified, triggers a series of diseases in 70%-80% of the cases. Psychosomatic research also presumes that such threats or actual losses are a triggering factor for cancer (Bahnson 1969, Kissen 1964, LeShan 1966), tuberculosis (Day 1951) diabetes mellitus (Hinkle and Wolf, 1952), lymphoma, leukemia (Greene and Miller, 1958), and heart failure (Perlmann, 1971).

The HPA axis also shows a change in the DST (dexamethasone suppression test) in those bereaved. In 15% of mourners, dexamethasone does not suppress

cortisol secretion one month after the bereavement. Tests have confirmed that if a mourner cannot psychologically cope with the awareness of loss, in their state the measured hormonal (cortisol) levels are elevated, and the 24-hour secretion profile also changes. The same has also been confirmed for the parents of children who have leukemia. The more efficiently the parents coped psychologically, the lower was the 17-OHCS content of urine. Given the immunosuppressive impact of cortisol on the mediators escalating the immune events (IL-1, IL-2) it is not surprising that the first psychoimmunology test in this context was based on the correlation between bereavement and the T-cell response to lectin. Bartrop (1977) examined the immune mirror or bereavement by monitoring 26 widows for six weeks. Compared to the 26-member control group, among the in vitro immune parameters, the response to Con A and PHA mitogens was significant in week 6 (it could not be detected until week 2), yet no change was detected in the number of T and B cells, the autoantibody level or the plasma TSH, GH, cortisol or prolactin level.

Irwin, Daniels and Weiner (1987) compared the changes in lymphocyte populations, NK activity, and cortisol secretion in the mourners. The T suppressor-cytotoxic cell line was present in a reduced number, and the ratio T helper cells increased during bereavement. According to the authors, for mourners, the reduced NK cell activity is independent of the adrenal cortex's influence and may be caused by some other neuro-hormone, transmitter or neuro-peptide mediator, according to Weiner. The same seems to be confirmed by the NA in vitro NK cell activity reduction. In addition to ACTH, beta endorphins are also mediators controlled by CRH. Opioids are believed to reduce NK activity in rats observed in the 'foot-shock' experimental stress situation. This way, the NK cell activity reduction following the release of CRH may be due not only to the cortisol effect but also to NA and endorphins or other, so far undetected mechanisms. Therefore, despite the unchanged cortisol level as observed by Bartrop, neuroendocrine factors' mediation role in the psycho-immune consequences of bereavement is likely.

Schleifer et al. repeated the test in partners of advanced breast tumor patients in longitudinal prospective examinations (15 persons). During the immunological examination of partners prior to and following the death of tumor patients, the studies of the immune response to Con A; PHA and PWM mitogens repeatedly proved significant suppression of lymphocyte proliferation 1-2 months after the bereavement event. In the period of 4–14 months after bereavement, the values did not show any significant changes. There was no change in the quantity of T or B cells either. Schleifer, Keller, and Stein (1987) confirmed that, in fact, it was the bereavement event itself that triggered immune suppression, in which the previous chronic stress caused by the spouse's disease has no relevant influence. However, the impact of bereavement is not clear at all, because for some people, any previously occurring immune

suppression disappears in a few months, while for others initially there is no significant immune suppression, but the lymph proliferation values induced by mitogens reduce in the second six-month period following the bereavement event. The person's coping style, the patients' age or the surrounding family conditions may play a role in that difference. Psychological and medical symptoms increase in widows with low-income family status and lack of social support, which points to psychological care's preventive role. A wider range of immune indicators is affected in bereavement, not only the T cells. Irwin (1988) also found NK cell activity reduced in mourners, and he observed the same in projected potential bereavement.

The sociosomatic context

The quality, emotional, and cognitive content of social relations are crucial for psychosomatics. The break-up of crucial relations that often give meaning to life (*raison d'etre* – LeSahn) and the closest person's irreversible loss may cause severe trauma. The hidden symbolic content of experienced life events and everyday stress also appears in this semantic scope, yet its roots are narrative. As this meaning context colors and influences the weight of stress experience and the more profound process of psychological/pathological events, the narrative focus is essential and useful in diagnostics and therapeutic patient control as well as in psychotherapy efforts.

The situation semantic content developing based on social relations influences the patient's cognitive efforts in dissonance reduction and cause-and-effect explanations. The patient's intellectualization tools, the closed or open interpretative formulations, beliefs and fears as well as hidden basic assumptions are all important. The coherence feeling depends on the person's fundamental values as well as their intellectual flexibility, personal inventiveness, as well as the adaptive reorganization of the status analysis. The experience of affective contents have an essential role, and the level of social performative abilities may also be determining factors. All this appears in the person's expressing ability, rhetoric, expressive or artistic elaborative toolset and is reflected in conflicts, frustrating situations.

The animal experiments revealed the neurovisceral costs of aggressive, position fighting, subdominant conduct and submissive behavior. They showed that real dominance, an ideal situation in psychoimmunology, depends on a habit and attitude that are rich in social skills and are strongly self-confident. People with such social characteristics and habits more often reach higher status positions than aggressive, anti-social and hostile or competing people, according to Spangler (1995). It also applies to the sociocultural stress that the stress effect depends not only on the stressor's objective factors; the subjective

assessment of the effect itself can be decisive. In other words, the interpretation of social psycho-immune stress strongly depends on the meaning of the given culture, the values, challenges, and threats of the co-existing sub-cultures and layer cultures and the cooperative or competitive, suppressive or inspirative social dynamism. For an idyllic setup and lifestyles driven by competitive and deadline-based forced performance, success and social dignity depend on different standards. This is the case with the roles of genders, different assessments of motherhood, the mother and child relationship, early and adult attachment issues, i.e., the images associated with a large number of determinants of psychosocial immune stress and related attitudes.

However, in terms of health psychology, this variety is not indifferent because, according to Cosmides and Tooby and other evolution psychology researchers, during the long history of humankind, social success and evolution fitness has not been the reward of the present competitive, A-type hostile, success and performance-oriented (at any price) behavior, as suggested by the media in our days. As previously described in the previous chapters concerning the surrounding psychosomatic and psychological costs, it may rather be regarded as a special civilization evodeviation that, concerning the environmental risks created by it, led to a new social-cultural situation, which Ulrich Beck describes as a risk society. All this closely relates to the accelerated technocultural development analyzed critically by Spengler, Heidegger and Mumford and many others, with which the inherited (evolved) adaptive mode of life of man can maintain a balance only with many efforts, corrections and a technological toolset according to Cosmides and Tooby (1992).

Culture itself was also a source of distress and variable psychoimmunological risks in relation to the former historic existential situations, cosmologies and related semantic worlds. Without a highly advanced curative technology (vaccinations, operation, hygiene, antibiotic treatment or biological therapy options), the pathogens, epidemics and the infection of wounds caused by predators or the enemy were the main sources of death and represented a demographic balance until the twentieth century.

These days the inflammatory diseases and other immune protection disorders (insufficient or wrongly aimed activity) are the 'main predators' that require a psychosocial approach due to the sociosomatic background factors and consequences. On the other hand, the narrative approach also requires cultural emphasis in detecting personal psycho-neuro-immune vulnerabilities.

With this approach, the micro and macro correlations of people and society integrate into the dynamism of diseases. The social integration of individuals and the degree of agreement with the given dominant or hegemonic values could be another important determinant of the stress experienced, according to Dressler and Bindon (2000). The psychoimmunological consequences of the different life logic must always be reinterpreted in the individual context of

the individual even if the considerations of developmental psychology and ethology-based psychobiological processes create a solid basis of interpretation. Narrative medicine helps understand the 'accounting' of personal costs and benefits of fate and helps the healer in therapy in the spirit of respect for fragile balances. For the sufferers of social deep layers, social distress is inseparable from the early development psychology traumas, also interpreted by behavioral, social epigenomics, and from the socialization space in which the psychological and stress-biological disadvantages may burden an individual from childhood due to miserable social circumstances. The detection of the civilization paradox, known as the "hygiene hypothesis", believed to be in the background of allergy and autoimmune diseases, also demands a sociosomatic perspective. According to the above, in the interpretation of social psychoimmunology, the suppressive ranking position, migration, segregation and exclusion, anxiety or hostile competition caused by unstable positions in society, unemployment, uncertain employment are all systemic dramaturgy traps that should also be examined from the perspective of social psychoimmunology.

CULTURAL PSYCHOIMMUNOLOGY

The natural extension of the system of correlations in social psychoimmunology is cultural psychoimmunology because the environmental challenges and the assessment of the threats leading to distress are culture-dependent. The assessment of the threat and the awareness of the tools available for overcoming it depend on the given culture, the culture, which, according to Clifford Geertz, is the "web of meanings" created by the given community. Threat perception and assessment and fighting behavior are psychological phenomena integrated into that web of meanings and into the fringe science of intercultural psychology. The field could also be named *cultural psychophysiology* or *sociocultural neurosciences*. The conference held in the Teleki Mansion of Szirák in 1990 was organized under the title 'Cultural Psychophysiology'. The conference was attended by excellent physiologists, cultural anthropologists, intercultural psychiatrists, human ethologists, and psychosomatic researchers, including Karl Pribram, Mária Kopp, Nico T. Malan, Péter Molnár, Joseph Kovács, Béla Buda, Gordon Claridge, Zsuzsa Kulcsár and many others. In the same year, also as a satellite symposium of the 5th International Congress of Psychophysiology held in Budapest, we organized a European meeting of Psychoneuroimmunology, too. The abstracts of both symposia are added to this book as a supplement at the end of the volume.

Psychoimmunology may not be taken out of the stress research interpretation framework – psychoimmunology does not wish to separate stress as an 'adaptive allostasis' and its neurohumoral, cardiovascular and immunology impacts from the sociocultural conditions that trigger the stress effect and embed the individual's stress response. This behavioral science focuses on the human ecology nature of stress. Consequently, social psychoimmunology greatly overlaps with cultural anthropology itself. Medical anthropology offers that overlap with its multilateral interpretation framework, as described in previous chapters.

A number of branches of medical anthropology have an interest in psychoimmunology. It is true for medical anthropology dedicated to co-evolution and focusing on ecological aspects, just as for another discipline that uses cultural phenomena as an explanatory model of psychoimmunology based on biopsychological functionalism.

Medical anthropology itself is a biocultural discipline and as such is a special coalition of different scientific approaches, including fieldwork-based

ethnographic and emic qualitative social science practice and may use the etic interpretative tool of biological processes hidden in the depth of the thus recognized beliefs, habits, and phenomena. The critical direction revealing the political power and economic background of the world of diseases and curing is also a separate field. Medical anthropology also contains an interpretative branch that focuses on rites, habits and symbolic meanings and an approach that interprets the entire semantic world in an ecological system. All this offers a multi-dimensional interpretation framework for social psychoimmunology. That service is mutual because the application of psychoneuroimmunology as an explanatory model offers a special blueprint for rationalizing 'etic' ways, structuralist-functional evolutionary and ecological approach, which is a characteristic of medical anthropology. Thus, psychoneuroimmunology can be used as an 'etic' (meta)explanatory model that interprets the explanatory models of cultures of different traditions and diseases, facilitating the joint examination and interpretation of biological and cultural adaptation through mechanism-level understanding.

The social psycho-immune processes outline the core processes of becoming ill and recovering, thus covering the psychophysiological center of the mechanism of adaptation stemming from biological and cultural sources. Medical anthropology investigates correlation between physical and cultural anthropology by discussing these phenomena in the framework of biological and cultural evolution in an eco-systematic and adaptation framework. (Alland, 1970). Adaptation is a phenomenon among the individual population and the environment, making the application of the ecological system theory important for our subject. Biocultural adaptation as a way of coping depends on cognition, which includes culture, knowledge, beliefs, skills, technologies and behavior and therefore, it is also part of the behavioral sciences.

Medical anthropology as a biocultural science

The medicine of a particular society is the totality of the value set, traditions, beliefs and cultural practice methods: techniques and toolset embedded in ecological adaptation, it is what ensures health and eliminates diseases and injuries of the members of society. The medical system of a given society is the total organization of all social structures, technologies, personnel, and role frameworks relating to medicine and used for practicing and maintaining medicine as well as responding to intra-, and extra-cultural challenges.

Medical anthropology, as a discipline, intended to research and interpret medicine and medical systems embedded in the given culture is, in fact, a special meta-medicine, i.e., a science studying different types of medicine

according to their characteristics, yet looking for the common features at the bottom of diversity. This is where psychoimmunology it is what working mechanisms.

The different cultural qualities, such as medicine, the medical system and the disease concepts of a given culture, are selected and evolve through biological and cultural evolution. Cultural characteristics may be inherited through imitation and learning. Although cultural evolution is mostly subject to deliberate institutional control and power; natural (biological) selection, which equally depends on the adaptive value of biocultural processes in the given population in an ecological sense and the condition of health and reproductivity of the given population, also have an important role in its regulation. In such a sense, culture is a system of learned beliefs, technological knowledge, values and behaviors accepted by the group members. A given culture integrates the special and selective modes of behavior, thinking, emotions, communication, and technology accepted by the given group as their own and include the special logic of organization of the given culture.

One of the keys to human genders is social relations, and therefore that social context is in the focus of attention also in its cultural psychoimmunological interpretation. The wide dissemination of humankind affecting all biomes was the result of the neuroanatomical and neurophysiological development of the brain, facilitating complex learning processes and speech, manipulation and tool preparation as well as the ability to build social relations, which together constitute the basis of biocultural adaptability. The adaptability of man, deemed premature in self-supply despite congenital sociality, is determined by the early period, spent as mother–child binding.

The reparative, instrumental and institutional structures of medicine as biocultural adaptability included in discussions is an inalienable element of culture and has a close correlation with social, cultural and economic subsystems.

Culture is a tool of adaptation against environmental challenges, but culture can also be the source of inadequate adaptation (female circumcision as an example, the baby's separation and cot death syndrome [SIDS] [McKenna, 1986)], *kuru* [Gibbs et al., 1980]). Clothing can protect against strong solar radiation and may also contribute to the development of rachitis, shortage of D vitamin (Tuaregs, Bedouins). According to the allergy hygiene theory (Strachan 1989), otherwise known as 'biome depletion' of 'lost friends' (Rook 2003) theory, if a child is raised in an environment which is poor in antigens, it weakens the ideal operation of the network of Treg cells. It impedes the development of ideal antigen tolerance toward the surrounding environment. The technological development of our culture added a global paradox of biocultural adaptation to the environment-man interrelationship, in which it also

partially became a pathogen against which *man does not have* any evolutionary protective capacity.

This includes background radiation, carcinogenic substances, transportation, lack of exercise and physical activities, CO2 emission, greenhouse effect, climate change; industrial acid rain, terrain poor in Se, Mg, ozone issue, air pollution, agriculture, DDT, pesticides. Most of them affect our immune processes and their psychophysiological embeddedness. Any damage to social attachments should also need to be included in these civilization paradoxes as deep down it may often be related to an adaptive technology intention, such as mother and baby separation for hygiene purposes after a medicalized childbirth in hospital or the development of contemporary, gender philosophy and politically correct genderscape in conflict with traditional motherhood also be added as a risk to be assessed.

The need to identify the functionality of seemingly irrational healing practices, magico-religious or other beliefs are the main features of functionalist anthropological traditions. The descendants maintain the adaptive value of practice preserved in the cultural and behavioral canon and the related beliefs during evolution by the selective retention resulting from positive biological feedback. An example of such behavioral instruction could be the sex taboo after pregnancy (postpartum), which protects the baby's lactation and the mother–baby relationship. Lactation is also known as a contraceptive method. For pregnant women, the prohibition of leaving their settlement is a similar behavioral canon, which may protect against the increased vector threat in territories affected by malaria.

The early return of mothers to employment six weeks after birth, which was the effective practice in Hungary between 1948 and 1966, reflected ideology and power considerations and was a feature of the communist gender ideology. Its health psychological consequences were revealed during research concentrating on the psychoimmunology of stress-biology consequences and its inter-generation importance.

Also, a thorough critical medical anthropology analysis is needed if the lactation period is cut short too soon because of an underlying economic and industrial interest. This could be done through media influence to come up with a solution.

In the process of biocultural adaptation, diseases appear as mechanisms reflecting the failure of biocultural adaptation, in which the psychoimmunology processes play the selection role described above. The assessment of the selection mechanisms of culturally transmittable maladaptive behaviors that entail an inclination to disease also relates to the subject of cultural psychoimmunology. A genetically coded disease itself could also be adaptive, as shown by the heterozygotic form of sickle-cell anemia protecting against malaria (Weisenfeld, 1971).

In the medical anthropology approach, culture offers an inclusive framework (matrix) for disease ideas and concepts reflecting society's social structure and its symbols and beliefs, modeling and presenting reality. This creates a shared view similar to a common agreement, a mythical world concept that functions as a special cultural system. This regularity becomes especially important if we think of the hidden social regulatory role of ideas and experiences, emotions, and psychophysiological conditions relating to disease (nocebo phenomenon, exclusion, spell, curse, magic disease, psychosomatic types of disease) or if we look at the group of diseases resulting from a particular, culturally determined lifestyle (agriculture, infectious diseases, urbanization-civilization diseases, etc.).

Thus, regardless of whether the internal cognitive psychophysiology mediated psychosocial regulation or the systemic consequences of ecological and cultural adaptation to the environment are examined, the disease concepts of the particular culture can be seen credibly only amidst the basic assumptions of the cultural world and may be interpreted based on the ecocultural adaptive practice of the given culture.

As Farmer and Good (1991) wrote, we must see that for the anthropological approach, culture is not only one of many variables or some modifying impact but is a densely woven medium of social and psychological processes, which is also the basis of human experience and action. That is why disease concepts and assumptions about diseases are fundamentally cultural constructions. On the other hand, it is a phenomenon that may be interpreted at the level of disease as a process in the medium of culture.

This recognition is not new, as Rivers saw the healing practices of natural people as rational, as the thinking of contemporary healers, following the logic of the system of beliefs inspired by ideas about the causes of diseases.

Rivers interpreted the beliefs, practices, and roles of medicine as social institutions, According to him, primitive cultures' medical practice was a consistent practice resulting from the basic cosmological assumptions and the system of beliefs, an organic part of the given culture and was practically institutionalized in that culture.

According to his concept, the observable types and features of behavior are dependent variables and the bases considered independent variables are the attitude and world concept of the given community about the world, according to Rivers. Naturally, all this affects the healing practice the interpretation and qualification of phenomena, the perception and evaluation of the environment, and, ultimately, the cognitive side of the disease forming distress processes.

Rivers partially follows Frazer when he establishes the 'magic', 'religious' and 'natural' categories in the three distinguished paradigms.

1. In the magic model, the individual can influence the cosmos' events with their own will.
2. In the religious model, the individual believes that the outcome of events depends on the power of supernatural forces, which also determine the forms of behavior influencing the disease and the allocation of roles.
3. In the natural model, the forces and laws of nature dominate how the world of health and disease are subordinated; the healing theory and practice consider such forces recognizable and rationally influenceable.

Consequently, in order to deal with ideas and images of disease, we need a dual aspect of interpretation developed based on participating and co-habiting observation *(emic)* within the world concept of the given culture and a rationalizing interpretation reflecting the world concept of our own culture and allowing for intercultural comparisons *(etic)*. Psychoneuroimmunology could be of great help in the latter.

Disease theories and beliefs

In every given culture, its special etiological beliefs – which are difficult to interpret rationally yet are culturally adequate or organically adapted to – determine how a sick person interprets the disease, how they relate to it, and how they place it in the interpretation of their fate. Naturally, this is affected by knowledge stemming from a more remote information environment and medical practice of a different culture, which are in contact with the given culture.

The individual may look for the source of impacts causing disease in the supernatural world, in society as a medium, in the impacts of nature and themselves.

According to the nature of inclusive world concepts, the contrast between the healing practice of natural people and traditional cultures vs. the modern world concept comes easily where primitive medicine is primarily of magical and religious nature with very few rational components. In contrast, modern medicine is predominantly rational with a few magical components (Ackerknecht, 1942).

Ackerknecht describes the medicine of natural cultures in the categories of contemporary medicine (obstetrics, surgery, psychotherapy), which may be understood in an *etic* approach but contributes very little to interpretation within the particular culture. However, the value judgment included in such an approach easily violates the researcher's consistent loyalty to cultural relativism. It may keep readers away from the understanding of the functionality

of seemingly only magical-religious phenomena and their rationality, which applies to a certain extent.

There are several approaches in the interpretation of a disease concept (disease representation, disease conception). Practical life confronted public health experts of the third world with the fact that either considerable objections and resistance developed against the public health practice to be implemented (vaccination, screening, contraception, etc.) in the particular traditional culture or the rational measures went through a semantic modification in the awareness of patients and was integrated into the given system of beliefs. The concept of belief may be confronted with the category of rational knowledge, where belief, i.e., a certain 'pre-science' form of knowledge, i.e., a set of uncontrolled and uncertain assumptions, drives the progress of the individual.

But it is not enough to apply disease concepts as a 'protoscientific' form of knowledge to merely rational biomedical knowledge because the disease concepts are socially and culturally defined realities. Naturally, the culturally defined reality concept includes a special compound of objective and subjective elements, which is equally influenced by cultural traditions, direct and indirect experience obtained about the environment, the interactive relationship with the environment, the role and status system of society, and the psychological, intellectual and psychophysiological characteristics of the person. The belief that the researcher's own knowledge is to be placed above the system of knowledge of the data communicator of the examined culture on an authoritative basis is heavily criticized by epistemology.

According to the 'meaning oriented' medical anthropology approach, the disease concept is a culturally created clinical reality (Kleinman, 1980). This theory is associated with the name of Arthur Kleinman. Kleinman studied the medical system as a cultural system and believed that the disease concept itself was also simply an explanatory model. This scheme made the experienced process of disease understandable for the suffering patient, the family, or the popular healer or professional physician.

That Explanatory Model includes (1) etiology (2) the occurrence and continuation of symptoms in time (3) and a pathology model (e.g., the problem in the flow of qi, the vital inadequacy of vis, rational models, etc.), (4) the dynamism of the course of the disease and (5) adequate treatment.

Despite their contradictory and imperfect knowledge, patients have a disease concept that reflects their social status, cultural beliefs, education, occupation, religion, and prior experience and ideas about the disease and the healing system.

So contrary to the cognitive school, here the emphasis is not only on how they manage and store the information on the disease in a particular culture but also on how the individuals living in that culture, interpret and treat the somatic, psychological and social experiences included in the disease.

It is important to note that this framework looks at a disease not only as a set of its distinguishing signs but as a system of meanings of the disease, i.e., a systemic set of special experiences, cognitions and emotions (a semantic network) expressed in a special discursive manner as the disease concept, the disease perception and a talk about the disease.

This semantic network concept is different from the one used in cognitive psychology, where it intends to describe the association samples of ideas and memory contents in cognitive storage. In Kleinman's and Good's view, this semantic network appears as the *cultural set of symbols* in the deeper layers of culture as an association that evolves during historical experience and practice and can explain the bad experiences. This historical process of clinical thought is studied in the history of medicine, and explored brilliantly by Michel Foucault in his *Naissance de la Clinique*.

Psychoneuroimmunology as an explanatory model

Disease concepts may be different not only by culture but also by different medical branches. The differences in the emphasis of the trends within Western medicine also carry important differences reflected in the different applied frameworks on the disease and the collection of information about the patient, the doctor–patient relationship, and the compilation of the therapy to be applied. The following quotation from *Current Medical Diagnosis and Treatment* (Tierney, 1989) illustrates the changes in emphasis of the dialogue between the explanatory models (somatic technicist versus psychosomatic) and its identification boundaries.

"A patient will be more satisfied if we also discuss psychosocial issues with them and ease the physician's dominant role during the conversation."

This shift in the approach, which is still distant from the Rogersian view of therapeutic relationship, or the biography analysis, yet pointing towards them, indicates the dialogue between the explanatory models.

The language of clinical medicine is the language of controlled experience. It is a semantic network built on the nodes of correlations based on the dual code system of complaints and symptoms, and the examination data (physical, instrumental, laboratory, and pathological) disclosed in their background. This historically evolved and culturally structured disease model and disease representation scheme can hardly be applied to the etic-type interpretative analysis of traditional etiological beliefs and healing practices despite the fact that,according to the comparative epistemology assessment of natural people, the cognitive and recognition system, of ethnomedicine is also characterized by inductive epistemology frameworks. However, their generalization effect

and predictive success are rather small. The theoretical assumptions are accidental and coincidental. When concepts of high predictive certainty are associated with the causal data and treatment of a given disease, the belief will last longer and will continue to exist.

As an example, according to the data collected in a Transylvanian village, Kalotaszentkirály, *the red currant reduces fever better than penicillin;* this meets the belief that *preserved plums reduce fever,* gathered in a distant village Kárpátalja (Subcarpathian region). In both cases, fruit preserved in Salicyl was applied, the efficiency of which can naturally be proved convincingly only with a drug efficacy test.

However, based on controlled knowledge and neuroendocrine-immune laboratory research, beliefs can also satisfy the epistemological requirements of biomedical, clinical philosophy. It is a question of whether psychoneuroimmunology ensures only a mechanism-level understanding. PNI diseases can be fully modeled according to the five criteria defined by Kleinman. However, psychoneuroimmunology has a special feature: when interpreting signal transmission and signal processing processes, it integrates the two adaptive systems serving the adaptability of an individual, the neuroendocrine and immune adaptation processes. Cultural adaptation also has a close two-way correlation in the frame of learning, memory and behavior with the above systems and the common psychoneuroimmunological adaptation system. The thus evolved complex biocultural system is the subject of medical anthropology, *biocultural adaptation* itself. In his medical anthropology theory, Kleinman focuses on the importance of the biological anthropology component primarily in relation to stress and culture and urges the extension of the medical anthropology theories with a biological dimension. It supports further the medical anthropology function that makes the object a bridging interdisciplinary science between biomedical and social sciences referred to by many but practiced by a few (Kleinman, 1980). The social-psychoimmune interpretation as a field of social psychophysiology also functions as a special *hermeneutic interface*, with which the mechanism of action of the healing practice interpreted in the context of the given culture may also be made understandable for the biomedical tradition.

Often the examined medical anthropology phenomena reveal the psychobiological channels of regulatory and adaptive functions serving the group's interest in the depth of the processes that violate Sahlins' principle of personal usefulness. Naturally, the interpretation of these processes also impacts biomedical medicinal knowledge (doctor–patient relationship, family therapy aspects of the disease process, culture, and disease, etc.).

Medical anthropology and psychoimmunology

The holistic nature and interdisciplinarity, alien to the increasingly specializing trends and tendencies, are watermarks of cultural psychoimmunology. What is disturbing in this 'between genres' approach is that it matches the facts of molecular biology to the results and recognitions of epigenetics, personal psychology, clinics, behavioral epidemiology and, as this study proves, also with social sciences. If we use the medical network paradigm or the biopsychosocial behaviorist framework, we gain discursive legitimation. If not, we might soon become the object of scientific suspicion.

Psychoanalytically informed medical anthropology might create proper interface to understand psychoimmunology of early mother–child detachment. The talkative, psychoimmunological body image matches Scheper-Hughes and Lock's 'mindful body'. *Embodiment*, a basic "cultural phenomenological" paradigm of cultural anthropology, offers a key perspective for psychoimmunology. The cultural practice turning into a bodily practice, the rituals and emotions, the thoughts and the phenomenology of perceived and evaluated social relations constitute the central components of social psychoimmunology.

One of the key texts that describes this is 'Flexible Bodies' by Emily Martin, which draws a parallel between the dominant ideas and world concepts of a time and changes in the image formed about the immune system. The traditional immunology metaphor is military, as this is also shown by immunologist András Falus (1999) in his book *Adj király katonát* [King, Provide Soldiers]. In his book a fabulous intertextuality brings the reader in and out of analogic social and narrative textures describing the survival strategies in the world of microbes. We learn about the dirty tricks of cancer cells, sticky crabs, and Ali Baba's immunological tales. Falus introduces the double agents in the immune system and the services of a corrupt immune policeman. He also shows how the Immune Empire strikes back. The immune system and our contemporary cinema mythology allows an analogous paradigm transfer between different evolutionary system levels. The immune system is the army that protects the organism from alien intruders and the own anarchist cells, just as the police and border guards protect a regime. The same is the same, and the alien is an alien.

However, Emily Martin sees a change: with a friendly co-passenger and flexibly held back immune response, a network closely co-operating with other systems is rising as a different system image, where the immune system becomes a field, where any disturbance, in contact with other systems, may cause a disturbance to the organism. It also appears in front of us in its complexity of everything relating to everything, as a whole unit in constant dynamic change instead of having solid internal boundaries where the key value is not its closeness or limits but, as also emphasized in the title of Martin's book, its open flexibility. These are age metaphors and the book is not only

about the unlimited information flow between networks, it is also about fast and adaptive changes. In its knowledge archaeology, Martin follows the changes of immunology, disease, and health concepts from the forties to the current days in America's health culture. Emily Martin discovers the postmodern approach in the complex interpretation of the human body as an open system. The organism's sub-systems are shown as flexible, open, overlapping and attached networks, as was also proved by neuro-immunomodulation in relation to the interfacing networks of the immuno-neuro-endocrine sub-systems. According to Martin, this model is different from the militant metaphor that dominated the period of the Cold War both in society and in immunology. On the contrary, the traditional biomedical approach still focuses on closed disciplines, which is especially true in the clinical science. This network model also pushes the individual's boundaries into the background because the sociocultural systems, including the individual, also come to the forefront and the individual's sub-systems, including the psychological and immunological selves, are also 'doubled' variable contexts. An alien microbe becomes a tolerated or useful co-passenger, as the microbiota of the intestinal flora – Martin also points out the analogy, the identifiable self-erosion of the postmodern times. All this is manifested in the metaphors of cancerous diseases and autoimmune diseases and HIV considered the source of a similar metaphor. Martin thinks that the former xenophobic-militant metaphor may no longer be sustained in the AIDS (or cancer) 'war without borders' situation.

Martin is not alone in the examination of the political metaphors of immunology and psychoimmunology. In her study *Illness as Metaphor*, Susan Sontag (1977) is very critical about the social metaphors of cancer, TBC, or AIDS and rejects the psychologization of these diseases. She believes that the concept of a personality inclined to develop a disease entails the risk of *blaming the victim.* According to her, the most conspicuous similarity between TB and cancer is that both are considered a disease of temper, where both psychologizing disease theories emphasize the reduction and decline of life energies. Sontag follows the change of illness sanction logic, writing that it seems less of a moralization if the disease is seen as an expression of the human inner self, rather than a penalty imposed on objective human morals.

Modern diseases (TB earlier, cancer today) are not only expressions of character any longer, like in Romanticism: the theory has been expanded, stating that the character itself has become the cause of the disease as it has not found any other form of manifestation.

In her fundamentally incredulous work, Susan Sontag stigmatized the tumor theory of a psychosocial approach of psycho-oncological tumor theory as a residue of mythical thinking. This critical objectivity is perhaps a bold gesture towards literature and forms part of critical medical anthropological inquiries, as written earlier; however, her skepticism may only become a rightful judgment

if the facts are brought up to defend the approach brought before her tribunal are insufficient.

Returning to Martin, she also discovers the rebirth of Darwinian emphasis and also believes that a new social Darwinism approach may also evolve. The biotechnology development, biological therapy indicate a new strategic concept within immunology. A new strategy is revived because vaccinations also use pathogens. Retroviruses may become part of the curative strategy and weakened pathogens (e.g., fowl pest, Newcastle virus) may mobilize anti-tumor immune activity. According to Martin, it is not accidental that disease metaphors and social metaphors match as they reflect the spirit of their time, civilization changes, i.e., in this case globalization and the postmodern shift in attitude. Hence, the bodily metaphors change together with the 'body politic', contemporary 'political body' images. Martin states no less than that scientific objectivity may not be separated from the contemporary socio-political ideology and that "Zeitgeist", the spirit of the time also affects the sterile laboratory.

Another important element of psychoimmunology, described as neurohumoral signals across the body, the neuropeptides, form the language of the "Unconscious". In other words, the mind crosses the body, the body is a 'mindful body'.

As mourning, social hierarchy, unemployment, examination situations, pride and shame, success and failure, social support and solitude all have meaning and vary by culture or social layer, we must approach biological and evolutionary essentialism very carefully, as there is still a need for the particularistic approach of cultural anthropology here as well.

It is especially important to see that our evolutionary adapted neuro-endocrine patterns may become contradictory in a different evolutionary environment and may even cause a disease. More specifically, the development of our civilization may attract us into the traps of evolutionary paradoxes, where the basic phenomena of psychoimmunology also reflect these contradictions. This is the case in the early mother–child relationship and the conflict of the modern, postmodern woman and mother's role, in relation to which Bowlby stressed that *each system functions well only in the environment to which it has adapted* (Bowlby, 1969), indicating that the cultural gender changes occurring as a result of the development of (post)industrial society and the differences between the traditional female roles, e.g., early return to employment six weeks after childbirth, may cause a problem in the system of attachments. The intercultural differences between the stress and immune consequences of ranking, experienced by a Dominican country farmer (Decker et al., 2003), an officer in a military hierarchy or a Western citizen with a higher socioeconomic status, were already indicated in relation to the social ranking and its psychoimmunology consequences.

The placebo and nocebo issues cannot be alienated from the cultural semantic network, either, and bear consequences, affect the body and reach the immune events. This is the case with the cultural embeddedness of early socialization (and potentially traumatic experiences), in the mentioned field research in Dominica or among the youth of Samoa, in Hungary or anywhere in the world.

The only difference between cultural psychosomatics and experimental research is that cultural psychosomatics examines biological indicators in the field and questionnaire-based and qualitative social research data. This field expression indicates that the researcher needs holistic attention with an ecological emphasis. In the field, the report of the party providing information about their health or illness, cold or other infectious diseases and their course and biological indicators, such as blood pressure, the cortisol level of saliva, and the catecholamine derivatives of urine, all reflect the correlations between sociocultural phenomena/factors and the stress responses to them. The psychoimmunology extension of the cultural anthropology interpretation puts the naturalistic stress model into a semantic sociocultural context and creates a human ecological interpretation framework for it. The paradigmatic work edited by Wilce under the title of Social and Cultural Lives of Immune Systems, includes chapters, where health-hazards of emotional and social pressure on psychoimmunological adaptation are presented in cultural and political context based on field work data.

New social neuroscience insights offer a renewal for biological anthropology and its methodology urging 'field friendly' research ways (McDade et al., 2000). These include salivary cortisol measurement and there may also be a need for developing simple blood drop kits. The development of the immuno-essay techniques of saliva offers a practical and useful instrument because the collection of saliva samples is not invasive, and they can be stored simply even under poor field conditions. The observation of the daily activities of 'index persons' selected in the field, the monitoring of their health and psychological conditions, and the stress hormone and immune indicators (e.g., saliva cortisol, IgA) together may also provide a good resolution image for a cultural psychoimmunology field worker. As the anti-test levels excellently reflect immune competence, EBV anti-test kits or a CRP definition may be very helpful.

Similarly, the definition of certain interleukins (e.g., IL-6) can also bring fieldwork closer to the mainstream of PNI research. We must be very careful during the evaluation of the cortisol samples taken in the field because of the individual variations, difficulties, and circadian differences resulting from the time of the sampling. One must also understand that the saliva's cortisol level depends on peripheral inflammatory events through cytokines and affected

by changes in a number of neuroendocrine factors, such as catecholamines, melatonin, testosterone, serotonin, β-endorphins, and encephalins.

The psychosocial meaning of cortisol is as particular and context-dependent as the local meaning of cultural symbols. The same can also be said about cortisol's immunological effect because we understand the immunosuppressive effect of cortisol, mainly when it mediates the impact of chronic stress. We also have several data about the permissive immunological effect of cortisol, as was described in detail above. The immune regulatory influence of cortisol-mediated stress impact is often incidental. The variable activity of a durably elevated CRH or ACTH-cortisol axis may change the receptor density of the periphery or certain areas of the center, receptors may be regulated, and the regulatory circles may become unsuitable for perception. That may lead to an inadequate response, an increased affinity for disease or chronic inflammation, and recurrence. In relation to psychosocial stress, a theoretical consideration also arises that during stress, the organism reorganizes its energy dynamism and mobilizes the resources for the challenges (central nervous system, muscles, etc.), pushing the permanent strategic mechanisms (metabolism, growth or immune protection) into the background or they may also be impeded.

On the other hand, social ties and personal relations are conveyed by oxytocin or endorphins, but their field measurement is expensive and illusory. That is how the narrative method and registration and analysis of behavioral forms remain at the forefront of research, but it also affects the human ethology depth besides culture-specific aspects.

There is no need to stress the practical importance of sociocultural stress models because from employment-related psychosomatics to public health issues such as globalization, modernization, migration or social transformation caused by an environmental crisis or family sociology and gender changes may all affect the stress-biological characteristics with special regard to the transformation of the evolutionary adapted human environment and the impacts on our inherited adaptive mechanisms. We see a new aspect of the old nature/nurture issue when the human organism confronts the sociocultural human ecological environment's pressure and the traditional natural (microbial, tumor) ecological environment in the neuro-immune allostasis process.

In the previously described human ecology framework and the M-E-O tetrahedron model illustrate well, how the stressors of social existence (social ranking, social support, loss of an object, dominance, subordination, socioeconomic status) or phenomena interpreted from the infosphere (placebo, nocebo, explanatory models, symbolic medical mythical system) have an impact on the neuroimmune/immune-neural patterns. Naturally, in this space, technosphere, the world of knowledge and the circular processes of social

relations influence each other on the basis of a circular logic. New curative technologies push out the old treatments, replace beliefs functioning as placebo or create a new nocebo effect through media technology. Technosphere itself can also have a direct immunomodulating effect, as seen in relation to biological therapies, and may cause primary damage, as experienced in the case of chemical haptens, by molecular mimicry or chemical/radiology damage. At the same time, social changes and the pluralization of medicine may open the way to ancient healing ideologies and cosmology in alternative/complementary medicine that may result in a confusing competition with the high-technicized methods of biomedicine (Lázár, 2012).

The immunological risks of intercultural contact, and the behavioral immunological system (BIS)

The shared catastrophic history of cultures and epidemics is history itself, the power drama of conquerors and the conquered, the rise and fall, and often permanent disappearance of peoples are milestones of civilization. The Spanish flu claimed more victims than the first world war, which was carried over from the United States, and it decimated the European continent weakened by destitution.

It was not necessarily armed conflict or social subjugation that caused the shrinkage of the population of the small Siberian peoples (Yukagirs, Kets, Selkups, Evenks) during the expansion of the Russian Empire; the main role was often played by epidemics brought along by the subjugators. We find several chapters of death by pandemics in the history of North and South American natives as well.

Due to the history- and population-shaping power of epidemics, it is worth considering what role do evolutionary behavioral patterns with ethologic depths as well as the instinctual behavioral elements play in the immune protection of the individual from a cultural, social immunological, and behavioral point of view.

Encountering pathogens is necessary ("old friend hypothesis") but at the same time, full of threats, as we saw during the above-mentioned historical pandemics. However, we do not have to think of large epidemics since families with a high number of children lost the majority of them to diphtheria, scarlet fever, or pneumonia in local settings before the age of antibiotics. Certain illnesses, such as TBC, acquired such telling names as *Morbus Hungaricus*. The main cause of death used to be illnesses carried by pathogens; however, there are still unsolved issues today, such as malaria, which claims a hundred million lives annually, AIDS, which can be thought of as a pandemic in many African countries, or Ebola, H1N1, COVID-19 and we could go on listing all

the new global epidemics that appear with the spread of global tourism and the destruction of natural environments.

The ethological bases of behavioral immunology are the instinctive behavioral elements serving to avoid illness. Schaller et al. (2011) interpreted the behavioral, immunological system as a complex defensive mechanism based on the detection of pathogens in the direct environment and the mobilization of the cognitive and emotional responses to illness as well as the behavioral elements aiming to avoid illness. In this sense, the BIS (behavioral immunology system) is the first, behavior-level preventative line of defense against illness; although the second line of defense, the so-called illness behavior, also exhibits the elements of secondary prevention, since the individual is reclusive and socially inhibited due to being prone to sleep, anhedonia, and lack of appetite, which at the same time limits the risk of further infection: the ill individual does not mingle with the community, and they are isolated by their own conflict-avoiding and weakened state. This is why the process of BIS (behavioral immunity) cannot be separated from the process of CIS (classic immunity). This indicates that even the sight of the infectious disease induces a psychoimmunological response, an increase in the level of proinflammatory cytokines. Following a sensory experience eliciting disgust, Stevenson et al. (2012) detected the activation of the immune markers of the oral cavity, while Rubio-Godoy (2007) found that the connection between biological immune events and the avoidant behavior is the serotonin system. Murray et al. (2019) explained the behavioral immunological and molecular patterns with the pleiotropy of the cytokine regulatory genes. Such is the IFNG_874 A allele, which is responsible for gamma-IFN transcription and regulates serotoninergic activity, which is a change that organizes behaviors and psychological patterns with a behavioral, immunological purpose. The activation of the IFNG_874 A allele increases danger avoidance and reduces exploratory and extroverted behavior. The joint mapping of the behavioral, psychological neuroendocrine-immune, molecular, and genetic networks is a true network medicinal task. For example, Murray (2019) believes that increased feeling of affection selectively increases the transcription response responsible for interferon production, while loneliness, which otherwise also reduces the risk of infection due to restricted socialization, is accompanied by the lowering of the transcriptomes responsible for the antiviral response and increases proinflammatory transcription factors at the same time, as stated by Cacioppo et al. (2015).

Another thought-provoking phenomenon that should be interpreted in the context of network medicine is the fact that those possessing the IFNG +874 gene allele, who are therefore more susceptible to several infectious diseases (malaria, TBC, leprosy, etc.) are inherently more introverted and cautious, as found by MacMurray (2014).

In fact, behavioral immunity is a joint pattern of network activities with various levels, since the cognitive-neural detection of the pathogen elicits the feeling of disgust, stereotypical behavior, the prejudiced attitude, and an increase in the number of inflammatory markers of the oral cavity and blood (e.g., the TNF-alpha level of the saliva, increased IL-6 secretion following mitogenic stimulation) at the same time. These data indicate the mobilization of the proactive behavioral and neuroimmune patterns in the case of the detection of danger, which manifests on the transcriptome-level. We saw the hub-like role of IL-6 in connecting psychosocial stress, neural and immunological networks. Behavioral immunity is a typical network model of adaptation patterns. However, Murray et al. (2019) point to the correlational insights, which suggest that in the absence of an immediate pathogen threat, the relationship between the BIS and the physiological immune system may not always be additive. According to Gassen et al. (2018) stimulated release of proinflammatory cytokines (IL-6, IL-1β, TNF-alpha) from blood collected from healthy subjects were not related to self-reported germ aversion, and the spontaneously released proinflammatory cytokines (IL-6, IL-1β, TNF-a) and *in-vivo* proinflammatory cytokine (IL-6) levels were *negatively* related to germ aversion and perceived longevity. Based upon these results, Murray concludes that in addition to short-term pathogen management, the BIS may also function to promote long-term health by lowering levels of basal inflammation and cellular oxidation. Relatedly, while IL-6 has traditionally been highlighted for its proinflammatory (i.e., defense) qualities, it also serves downstream anti-inflammatory tissue maintenance functions, according to Del Giudice and Gangestad (2018).

What behavioral immunology (BIS) examines in cultures and instinctive human behaviors may become interesting for social psychoimmunology as well, the patterns of revulsion, instinctive avoidance, selective social behavioral patterns, and the so-called assortative socialization, in which ethnocentrism, xenophobia, and philopatry could be rooted, which have all become antipathic ideals in our globalized world. Assortative socialization incorporates cognitive and behavioral patterns that help keep intra-group infections at bay and the avoidance of threatening infections brought in by individuals outside the group. All of this developed based on values and cultural patterns imprinted in the past, which influenced the inclusive fitness of the ancestors of these individuals.

Faulkner et al. (2004) found that philopatry prevents migration and dispersion, increases the interactions of local group members with similar immune experiences, and reduces social interaction with individuals carrying different parasites and biomatter. Xenophobia is a negative sentiment towards individuals outside one's group, and it is also a component of avoidant behavior at the same time, which keeps away the microbial flora carried by the outsider. This social-cognitive set also includes neophobia, the behavior of observing

traditions, which elicits the fear of anything new or novel, including ideas, methods, and values. Ethnocentrism is the preference for members of the same group and altruism towards those with identical ideological and immunological characteristics.

Navarrete and Fessler (2006) found that ethnocentrism serves the embedded network of intragroup individuals and, at the same time, protection against the parasitic pathogens carried by those outside the group. Fincher et al. (2008) established that the pattern consisting of all of the above and constituting part of behavioral immunology is stronger in an environment higher in pathogenic risk and is less typical in an environment devoid of such threats. This system of correlations implies that if the treatability of the pathogen increases and the epidemiologic risk of migration, mixing, and contact with foreign groups is reduced, openness and the frequency of contact, the number of alliances, and the rate of exchange of goods, ideas, and services increase. In such cases, the size of the social network increases, and the frequency of intergroup contact and mating increases, too, based on the interpretation of Fincher et al. (2008). If an individual is informed of a risk of infection under experimental conditions, their behavioral, immunological system (BIS) is activated, and their emotions, personality traits, and behavior reflect this change; they become reserved and avoid strangers, as found by Curtis et al. (2004).

Fincher and Thornhill (2012) found that the intensity and prevalence of the pathogenic threat affect other social attitudes as well. Such attitudes are collectivism versus individualism and the psychological mechanisms mediating these dispositions, extraversion, or introversion. Therefore, the behavioral, immunological system itself becomes a structural factor that influences the structure of society and intergroup relationships. The authors called this correlation *the parasite-stress theory of sociality* (PSTS). Cremer et al. (2007) stated that personal behavioral, immunological patterns and the PSTS create the social immune system together.

Social psychoimmunology of COVID-19

The COVID-19 pandemic rewrote the social and cultural patterns of our lives. Lockdown, social isolation, telecommunication by internet, home office type work, suspension of travel, theater life and communal cultural life, restaurant and hotel business in an age of the sensual culture of services and entertainment proved to be a radical socio-cultural transformation moved by behavioral immunity considerations and policy.

The critical medical anthropological approach of De Ver Dye and Muir (2020) offer proper perspective to explore the influence of SARS-CoV-2 pandemic on the structures and relationships of adaptive/maladaptive human

agency in context of ecological processes that create, shape, and sustain people in their multidimensional, intersecting environments. This approach is very close to the hybridizing concept of M-E-O tetrahedron model (Lázár, 2015).

The COVID-19 pandemic is accompanied by socio-behaviorally-oriented public health efforts aimed at reducing exposure and preventing morbidity/mortality once infected. De Ver Dyes' Critical Medical Ecology model comprehensively balances social scientist and biological frameworks rooted simultaneously in microbiology and in anthropology including conceptual contexts of evolution, stress paradigm, issue of homeostasis, adaptation, and power relationships.

COVID-19 is equally – if not more – a socially-driven disease as much as a biomedical disease, where primary prevention of transmission rests upon social and behavioral interventions, and at last but not at least, the local, national differences in COVID-19 hospitalization/death rates is not expected to significantly be attributable to a more virulent and rapidly-evolving virus, but rather to differences in social, technological, political and behavioral factors. Globalization and long chains of production, transfer of preventive and therapeutical tools, and competitive market conflicts in availability of masks, respirators, drugs like remdesivir, favipiravir, and vaccines with different East–West cultural-political connotations (AstraZeneca, Pfizer-BioNTech versus Sputnik V, Sinovac) generated infodynamic tension at level of health politics and media, just as among members of health services and the people of diverse sociocultural orientation and shared fear of COVID-19. The new normal of lockdown, the exchange of personal freedom for perceived security, mass media exposition to the mortal dangers of the COVID-19 epidemic exerted deep influence on social-psychoimmunological status of the subjects, too. Social isolation, loss of social support, learned helplessness, the enduring and hardly controllable process extending well beyond a year of experience, pessimism because of the new mutants and preventive and interventive efforts questioned by mass media for background power interests – are social-psychoimmunological risk factors.

The local health ecological patterns are shaped by the logistics and volume of patients in the given city or neighborhood, where lack of access to sustaining products and services for many residents living in isolation create an adverse sociocultural context for optimal health behavior.

Even effective vaccination programs with the aim of reaching herd immunity is prone to personal psychoimmunological dispositions. The so-called "coronaphobia", induces generalized anxiety and depression (Lee et al., 2020). The prevalence of psychiatric symptoms and clinical diagnoses have increased during the worldwide pandemic. The number of depressive disorders, anxiety disorders, or both was tripled compared with adults surveyed in one year before during the pandemic (Twenge and Joiner, 2020). Similarly, in China the

prevalence rates for clinically significant generalized anxiety symptoms, depressive symptoms, and poor sleep quality among the general population were elevated to as high as 35%, 20%, and 18% (Huang and Zhao, 2020). Low socioeconomic status is related to COVID-19 severity (Raifman and Raifman 2020). The network approach of understanding the COVID-19 pandemic must include age, comorbidity, SES, and the personal psychological dispositions like elevated stress, depression, and anxiety, insomnia, fear of COVID-19 as important variables in the dynamics and outcomes of COVID-19 pandemic.

According to the excellent review of Madison et al. (2021), stress, depression, loneliness immersed in or caused by adverse sociocultural environment of the COVID-19 pandemic might also affect the efficacy of several types of the SARS-CoV-2 vaccine, which might call for psychoimmunological ways of help, like meditation/mindfulness, expressive writing, stress management, and exercise interventions, and enhancing quality of sleep. The COVID-19 pandemic itself has aggravated many of the risk factors for poor vaccine responses, such as stress and sedentariness and lack of social support, loneliness, and we can add socioeconomic threats, like impending unemployment, the delayed social uncertainty, loss of self-confidence, perceived declining value of competencies, social status, pessimism.

The social networks assessed during the pandemic proved to be smaller than a pre-pandemic cohort of students, which predicted worsening mental-health trajectories according to Elmer et al. (2020). COVID-19-related stress exerts a distorting effect on depth and quality of relationships, inducing increasing rates of loneliness. This is an aggravating factor as the lonely or socially isolated persons have higher risk of insufficient vaccine responses. From a network medicine point of view, it is a relevant cultural-psychosomatic network hub in the case of COVID-19 pandemic as social ties, networking and social support can be protective or a source of burden.

Another key feature of COVID-19 induced behavioral changes is the aggravation of sedentarism, lack of physical activity. The American company Fitbit reflected sedentarist changes in everyday physical training based on their wide database including 30 million users, showing 7% to 38% reductions in average step counts in many countries. It is worth noting that physically active older men who had done regular aerobic exercise at least three times per week had more intensive antibody responses to antigen challenge (Smith et al., 2004). If we want to understand these correlations, we have to outline the deep connections between socio-cultural and physiological networks. The skeletal muscle communicates with other organs such as adipose tissue, liver, pancreas, bone, immune system, or brain. The action of myokines is mediated by the presence of receptors on muscle cells, fat cells, liver and pancreatic cells, bone, heart, immune, and brain cells. Myokines like myostatin, IL-6, IL-8, IL-15, FGF21, Follistatin-like 1, BDNF, hepatocyte growth factor, fibroblast growth factor,

insulin-like growth factor play a role in metabolism, tissue regeneration, IL-15 reduces abdominal adipose tissue, while in heavy physical exercise, the secreted Il-6 as myokine rises to 100 fold of resting level, and increases IL-1, a source anti-inflammatory mediator. Brain-derived neurotrophic factor (BDNF) might be secreted as a myokine, and muscle-derived BDNF enhances fat oxidation. Physical training of skeletal muscle enhances cerebral BDNF secretion. Irisin is another neuroactive mediator secreted by active muscle cells, which helps maintain a healthy weight, improves cognitive processes, and increases brain-derived neurotrophic factor (BDNF) production. Therefore, physical activity might modulate the dopamine/serotoninergic balance, the increased plasma serotonin and decreased level of dopamine in young girls suffering mild depression (Jeong et al., 2005). Physical activity exerts deep psychoimmunological influence, as walking 3-4 hours a week reduces the risk of someone dying of breast cancer by 50% based on an overview of 3000 women's cases. Exercise activates the immune system through myokines, which are produced in the active muscles, inhibit the proliferation of cancer cells in the breast. This reveals the importance why children should spend at least 60 minutes each day exercising.

The COVID-19 pandemic exerted *further* sedentarist pressure during the lockdown. Sedentarism has become a silent killer in our society. Our artificial, technological environment enables us to reach our aims with a minimal physical effort, cars, elevators and escalators keep us away from the minimal bodily exertion. People spent 55%–75% of the daily wakefulness in a sitting position. An average of six hours of continuous sitting per day shortens even the lives of otherwise active and seemingly fit people by five years. Continuous sitting and inactivity are harmful even if someone exercises regularly. In 2010, a research team from the American Cancer Society processed a 14-year follow-up study including 123,000 middle-aged adults, led by Patel et al. (2010). Researchers compared the mortality rate of those who sat six hours or more a day to those who spent less than three hours in a sitting position. Extra time spent in the armchair increased the mortality rate of women by 37% and that of men by 17%. The WHO estimations connect 3.2 million deaths to sedentarism annually. Type 2 diabetes, cardiovascular disease, colon cancer, postmenopausal breast cancer, dementia, and depression are a group of diseases in which physical inactivity is involved.

The lifestyle shift caused by COVID-19 pandemic does not seem to be an exceptional situation, rather a sociocultural transformation towards something new way of more "cyberized" lifestyle. In the near future, the internet of things, artificial intelligence robotize and destroy the physical work activity of hundreds of millions. In this dystopia of the coming brave new world of volatility, uncertainty, complexity, and ambiguity (VUCA world) high cognitive strain, the challenge of high and permanent psychosocial-cultural adaptation load

create strains, and this expanding sedentarism diminishes the personal stress resilience weakening the bodily resources. Less physical activity is frequently accompanied by insomnia. Sleep quality is also a focus of lifestyle medicine. Physical activity and sleep are both important elements of health behavior, and they are under sociocultural influence. Sleep also exerts a significant influence on immune function. People who are regularly sleep deprived are at great risk for vaccine non-responsiveness, perhaps in the case of COVID-19, too. Burns et al. (2002) showed a significant relationship between disturbed sleep and lower antibody responses.

Sport, growing leisure time offer proper balance and resistance. Health industry reified the sense of health and translated it to the daily number of steps, kilometers, calories, summed on the microscreen of smartwatches and smartphones, which help us to correct the consequences of our laziness and sedentary lifestyle. This inevitable progress can be a blessing and a curse, bringing solutions and challenges at the same time, as always. However, the rational insights do not help or do not change human nature purely on their rational offers. Intensive health promotion at the Millennial turn in the US did not change the health behavior of the US citizens at all, King and colleagues (2009) showed how lifestyle choices and adherence to healthy lifestyle habits associated with cardiovascular disease and mortality were changing between 1988 and 2006. In the COVID-19 crisis, the physical inactivity also played an important role based on the consequences of the above-described sedentary lifestyle turn. Staying attached to the screens of virtual reality, locked to cyberized social withdrawal minimized spontaneous physical activity, creating another dimension of health deficits, especially in the overpopulated world, where artificial intelligence, (humanized) robotics free people of the traditional professions and traditional lifestyles.

The mass media pressure regarding the threatening consequences of COVID-19, the personal information mediated by uncontrolled gossip and contradictory information from social media exerted serious psychological pressure. As Madison et al. (2021) summarize in their review, distressed individuals show poorer vaccine responses, which might persist long after the vaccine administration (e.g., Glaser et al., 2000) and long after the end of the stressor (e.g., Glaser et al., 1998), and stress can affect the primary immune response. Long-term stressors (e.g., caregiving) and short-term stressors (e.g., an academic examination) can impair vaccine responses, and it is certainly true for the case of COVID-19, too.

Enduring, pessimistic psychical dispositions, chronic distress with uncertain or negative outlooks can be modeled by caregivers of Alzheimer or end-stage cancer patients, relatives.

Kiecolt-Glaser et al. compared the influenza virus vaccine responses of caregivers of spouses with long-term dementia and the responses of

non-caregivers, matched according to age, sex and socioeconomic status (Kiecolt-Glaser et al., 1996). The more intensive, almost permanent care as a chronic stressor, similarly to COVID lockdown, leads to a reduced social network, narrowing everyday engagements, leisure activities and elevating the risk of anxiety and depressive disorders. They found that only 38% of caregivers had a clinically significant antibody response to the vaccine, whereas 66% of non-caregivers responded. This difference was more pronounced among subjects of older age. Depression induces or reflects the disregulation of the immune system, and this might play a disturbing role during vaccination, as evidenced by heightened levels of inflammation (Kiecolt-Glaser et al., 2015). Social-cultural and psychophysiological considerations might emerge from such psychological burden of caregiving, which beyond the practice of positive social support, act of agape, self-sacrificing love includes a state of helplessness, painful attachment and the pessimistic elements, because of the inescapable, and uncontrollable outlook. The newer and newer waves of mutant versions of COVID-19 can trigger similar chronic stress, themselves.

The PNI network model includes a net of trait and state personality factors, too, which all affect the shorter-term innate immune response to COVID-19 vaccination. Low self-esteem and high neuroticism (Morag et al., 1999), high trait negative affect and low trait positive affect (Marsland et al., 2006), all seem to influence the success of vaccination predicting lower antibody responses to vaccination. Subjects with elevated COVID-19 fearfulness have a higher risk of clinically significant depressive symptoms (Fitzpatrick et al., 2020) and based upon the above considerations, fear of COVID-19 itself may lessen a vaccine's ability to confer immunity against the virus. There is another form of COVID-19 fear, avoiding or denying the vaccination. According to Cornwall (2020), half of US citizens may refuse to receive a SARS-CoV-2 vaccine, which is also influenced by psychological factors. These data, summarized by the review of Madison et al. (2021), clearly support the importance of sociocultural and psychological network approach of public health issues.

Stress related to COVID-19 promotes poor health behaviors and lifestyle, worsening mental and physical health, and lowering the efficacy of a SARS-CoV-2 vaccine. Therefore, complex intervention program is needed, with psychotherapy, efforts of stress management, cognitive behavioral interventions, meditation/mindfulness, expressive writing completed with recreative elements like massage, tai chi, walking, jogging or other physical activity and according to Vedhara (2019) even short-duration psychological and behavioral interventions can modify the immune system's vaccine response.

Returning to the issue of physical activity, it offers beneficial health behavioral response to the above-mentioned difficulties in handling the COVID-19 pandemic. Keylock et al. (2007) showed that physically fit elderly people had better antibody immune responses to tetanus and influenza virus vaccines

compared with their less-fit peers. The somatic gains are obvious, as regular exercise enhances the performance of the heart and lungs. Blood fat levels are dropping; blood pressure tends to normalize even at the beginning of essential hypertension disease. Muscle work lowers blood sugar levels, helps to maintain body weight, and thus has a particularly beneficial effect, for example, for people with diabetes mellitus who are at increased risk of cardiovascular disease. Insomnia gets better, as those who exercise regularly can sleep better, wake up fresher, be more lively, and concentrate more permanently. It helps to increase endurance in working capacity and perseverance, and greater burden improves both physical and mental performance. Recent research has shown that regular physical exertion may also play a role in preventing and attenuating minor depressions, which also seems to be a risk factor in handling COVID-19. The active muscles are part of the neuroendocrine-immune network of the human organism, they exert significant influence on the metabolic system, the immune system, the brain, and the abdominal fat, which also part of the complex information network. Exercise induces endorphin secretion and anandamide crossing the blood-brain barrier during physical efforts.

The tetrahedron model of these M-E-O shifts induced by SARS-COVID-19 pandemic illustrates the holistic human ecological, medical anthropological understanding of these socio-cultural psychoimmunological networks.

The sociosomatic approach in anthropology

Kleinman (1998) replaced the term psychosomatic with sociosomatic. That extension of the term may help extending the body/soul dualism of diseases with the social context. That triadic model helps understand the regularity of disease generating and healing interactions between individuals and the social micro- and macro-environment and also allows for a somato-social perspective. Life events and psychophysiological consequences may not be separated from the cultural context. The internal contradictions of lifestyle (lifestyle incongruity) may also become a source of stress because the tension between socioeconomic status and lifestyle itself leads to psychophysiological tension and higher blood pressure and also has an impact on the immune system. Of particular importance for the medical anthropological approach are diseases that are difficult to integrate into the nosological web of biomedicine, such as the so-called culture-specific syndromes, such as *latah*, *koro*, *windigo*, *hsieh-ping* or *amok*. However, the issues of sociocultural or voodoo death, lay disease models (curse, evil eye, loss of soul, magic and other folk or popular, lay etiologies), illness as sanction model, nocebo, and placebo cannot be interpreted beyond the context of a particular culture. In a broader sense, all healing practices are characterized by cultural, economic, political, and technological

determination. Not only in the case of exotic cultures can we talk about culture-dependent diseases, but we must also mention culture-related disorders related to the Western way of life, such as behavioral and drug addictions, shopping seizures, or violent conflict between motorists, the so-called "road rage". Many people consider work alcoholism, burnout, and even the concept of stress itself to be Western culture-bound syndromes. Special attention may be paid to the sociocultural determinants of body image disorders and eating disorders. A particular local, cultural aspect repaints every physical, psychological, or social syndrome. In this sense, the sociosomatic processes studied by medical anthropologists are phenomena of interactions between the physical body and the social body. Thus, the given diseases can be subjected to multidimensional analysis at the sociological, epidemiological, anthropological, psychological, biomedical, and physiological levels. This behavioral science approach has also created an interdisciplinary sociosomatic framework for co-interpreting socioeconomic and cultural characteristics, health psychology, and somatic relationships.

Considering the Westernized consumerist value orientation of the Hungarian society and the different economic conditions dominated by a severe debt, globalization and the dominant power of multinational companies as well as the deconstruction of the one-time national industry, this tension was also present in Hungary at the turn of the Millennium. Essentially, the developments of globalization (multinational companies, Hungarian offshore companies) led to low-profit operations, tax evasion and low wages driven by the international labor competition in Hungary, without even mentioning the foreign currency loan crisis that affected masses and pushed many people into despair. All this results in strong tension in the duality of personal expectations and reality, SES and desired and forced lifestyles. Mária Kopp et al. (2004) published a summary study on this special Central and Eastern European health paradox. Their behavioral epidemiology study conducted on a large population sample of more than 12,000 respondents under the title of Hungarostudy showed that the increased morbidity and mortality of Hungarian men were also the result of the prestige-driven self-exploiting lifestyle (Kopp et al., 2004; Lázár, 2007).

Considering the favorable psycho-immune effects of control, success, self-esteem and optimism and, in the case of an individual internalizing the value set of a given culture, the immunosuppressive effects of failure, shame, surrender, and learned helplessness, it is difficult or impossible to separate the social context from the cultural context. In the historical experience of the Hungarian society, the psychoimmunology of the loss of objects, mourning, and unemployment are connected with either the experience of forced formation of "kolhoz" (Soviet-type agrarian associations) and the expropriation of private property, or the drama of unemployment and mass emigration that

followed the closure of factories (many times the elimination of various industries), or the threat to families in relation to the currency loan crisis. The social ranking, the radical historic changes in social hierarchy, exclusion based on origin, B-listing, class alienation, and promotion difficulties have become *cultural psychophysiology* disadvantage factors, which were even aggravated by the frequent shift in values in power aiming at total power, usually also associated with the transformation of power groups and social networks. On this basis, it is understandable that types of behavior with a health risk, death from tumors and high frequency of allergy diseases combined with psycho-immune factors, and a high suicide rate evolved in the 1990s, and the life expectancy also reduced. As a phenomenon affecting the stress-biology foundation of society, we must also see the almost human ethology depth damage which was caused by the early return to employment of mothers after six weeks of maternity leave between 1948 and 1966. Consequently, for a considerable part of a generation, the harmonic attachment between mother and child and the at least six-week harmonic mother–baby symbiosis was broken. This injury may deteriorate the stress-biological competencies during the entire lives, as also confirmed by epigenetic information, and may have an important distorting psychological effect on adult relationships which may be passed on to the next generations in a special way.

Sociocultural transition, acculturational consequences of compliance with the Western value set appear in psychophysiology and numerous intercultural research. The psychophysiology costs of migration were already covered, and urbanization got people to pay a similar price for those arriving in the industrial cities from a rural environment. Among the psychoimmunological stress effects, lifestyle, and unfulfilled expectations for social support must also be considered.

Very often, culture itself becomes the source of stress effects. A psychosomatic phenomenon from Ecuador, when *colerín* is made responsible for the death of an individual, is an interesting example of it. *Colerín* is the consequence of frequently expressed anger, i.e., the Ecuadorian people can grasp interpersonal tension and conflict in it. Thus, an assumption blaming *colerín* in fact blames an angry, irritated, and hostile social behavior and protects not only the individual but also the social body. Thus, the protection of 'body politic', the community becomes important.

According to Wikan's (1990) example from Bali, the body is exposed to others' social emotions and anger, but that effect is conveyed by witchcraft. Even symbolic anger can have that effect and, therefore, that belief is a warning about social interaction. Prevention and therapy do not allow for the expression or release of emotions. All this requires internal work, introspection. This coping strategy is known as sociosomatic suppression due to the assumed supernatural problem, causing the transcendental importance of anger and fury.

Sansom's (1982) fieldwork among the Australian aborigines is also a sociosomatic example, in which the correlation between a diseases, narratives, and society was reviewed. Disease is the narrative expression of distress, which makes social ties closer and is a story of suffering, which builds cohesion. Here, disease and healing are public expressions of a cry for help, which mobilizes the community. The above examples simultaneously indicate the validity of sociosomatic interpretation and its particular differences, the variability of social contexts in terms of witchcraft, the suppression of anger, the harmful effect of emotions on others or, on the contrary, the narrative role and social cohesion triggering effect of an illness.

Cultural psychoimmunology not only offers a common denominator as a special etic explanatory model in the background of particular different phenomena (Lázár, 1994) but, as a field of science, it is also a cultural construction. Psychoimmunology has a number of dialects with different modes of speech and accents. The extended model of neuro-immunomodulation, psychoimmunology, endocrine-immunology, behavioral immunology and social psychoimmunology is different, and each stresses different terms.

The psychological consequences of immune processes result in social consequences, as the inflammatory theory of depression also makes it clear. Such a bottom-up process, manifested in disease-related behavior or inflammation caused mood disturbance or experience behavior role changes accompanying chronic diseases, can significantly influence social-psychological transactions, spiritual states, ability to work or a social role in the family and the wider community. It changes the place of the person in their smaller and wider environment and the experienced bodily change might also gain a social interpretation or meaning in the light of beliefs or scientific knowledge.

The psychoimmunology of the same phenomenon, i.e., depression, is different from a 'downward' direction and is different in the inflammatory theory of depression following it from the bottom to the top. Early stress experience might root in behavioral factors and might have an inflammatory background, like in the perinatal infection. Cultural psychoimmunology is sensitive to metaphors and symbols collected on the field, which offer a key to the disease interpretation, set of beliefs, and even biology of the given culture. These keys are indispensable for the interpretation of symbolic healing because, in that case, the mythical world concept mutually accepted by the patient and the healer is the key to the therapy. Suppose we decide to criticize psychoimmunology, as Susan Sontag (1977) did. In that case, we can criticize the connection between disease and personality and the adequacy of the 'blaming the victim' or the correlation between cancer and other diseases and personal characteristics, a personal failure or lack of success (Sontag 1977, Martin 1994). On the other hand, the disease concept of psychoimmunology helps to escape from

the statistical fate and opens the way to hope by appreciating personal healing factors.

It is difficult not to see the particularist or context-sensitive, personalized tuning of psychoimmunology. The personality factors involved in healing, the possibility of psychotherapy and social support, the appreciation of beliefs and the placebo phenomenon, and a certain degree of openness to alternative therapies together also create a discursive position for psychoimmunology. Social and psycho-immunology itself also builds stories and narrative terms of the discourses of mind, society, and healing in which the anthropological approach of the critical physician also has a role. The fate, place, and drama of psychoimmunology in the versatile world of medical sciences can be seen through that medical anthropology approach. Critical, economic-political analysis can consider the financial and institutional aspects that reveal the dominant power of the Big Pharma, the pharmaceutical industry approach, high-tech medicine, and the financial weakness of holistic psychoimmunology. At the same time, clinically applied medical anthropology can discover and strengthen the personal resources of this approach among the patients in the field itself.

We can also see the competition of the discourses of hope (del Vecchio Good et al., 1990) in everything because the belief in technology and belief in personal resources face each other there, but in the interpretation scale of cultural psychoimmunology, other sources of belief triggering hopes are also interesting provided that their impact on the immune system and stress-biological processes can be certified. It is clear, therefore, that the overlap between social psychoimmunology and medical anthropology offers mutual benefits, self-reflection, and a wider outlook.

The identification of social psychophysiology processes helps medical anthropology in the "etic" explanation of rites and beliefs observed on the field, while medical anthropology offers a reflexive framework for the "self-assessment" of psychoimmunology and, in the field, it helps the practical evaluation of theoretically clarified processes in the given context. It helps practice human ecology science in a human ecology medium.

At the same time, it would be a mistake to attach an underlying sociocultural or psychological meaning to each occasional immuno-pathology case. Therefore, psychoimmunology must assess its own discourse in a self-reflexive way, in which evidence-based medicine helps.

Culture and stress

Like the endurance of pain, enduring stress effects depend a great deal on the given culture, and in fact, the beliefs of the given culture could also become a

source of stress through the cognitive processes and status assessments defined by it.

Kiev (1964) refers to the culture-bound diseases, emotional states and stress syndromes as 'exotic syndromes'. It explains these syndromes' cultural determination that the beliefs and social structure of the given culture and the values included in it contribute to the development of the psychopathology process. A psychogenic or voodoo death is, in fact, very rare, but 'malign anxiety' in Africa, or *amok* in the Philippines, *latah* in Thailand or Burma, or *koro* in the given culture may not be considered exceptional at all.

Before going into details of these disorders, we must also note that there is also a previously described assumption in anthropology, according to which the term of stress, at least post-traumatic stress disorder itself is a *culture-bound syndrome* and can only be used accordingly. According to Allan Young (1980, 1996), from the perspective of Euro-American biomedical interpretation, the stress phenomena fit in the model system built from the vocabulary of personality motivations, coping and neuroendocrine factors. This assumption only confirms the dual nature and cultural determination of our explanatory model and its meta-explanatory role as controlled knowledge. Among the culture-related emotional disorders, *koro* and *susto* are the diseases that entail an emotional disorder the most. In *koro*, where diminution of the penis is accompanied by panic-like sexual anxiety and inadequacy, the patient feels extreme guilt. Hallowell described a similar pathological fear reaction among the Saulteaux Indians who have extreme anxiety fits when they see snakes and other animals. *Susto* or *espanto* begins with sudden fear and the loss of soul, triggered by a stressor in the highland of the Andes (strike of lightning, fall, meeting a predatory animal) and leads to insomnia, anorexia, and apathy. Psychotherapy cannot or sedatives cannot 'bring back the soul', it can only be achieved by a specialist, known as 'curandero'.

Nocebo and sociocultural death

Poisoning without poison, harmful effects without an effective agent, the expectation and attribution of decay – this is nocebo, an injury without an effective agent. In contrast with the well-known placebo effect, here the meaning of the Latin verb *noceo, nocere* ('cause harm') indicates the phenomenon's essence.

Among the anthropologists, Marcell Mauss was the first to describe sociocultural death and, according to his title, the impact of the idea of a community implied death on the individual. This phenomenon was treated as evidence of the 'direct correlation among physical, psychological and moral, i.e., social factors' (Mauss, 1924). His examples were taken from the phenomena observed

among the Austrian aborigines, New Zealand Maoris and Polynesian people. For Mauss, the essence of this phenomenon is that "a dying person does not believe or does not know that they are ill and believes that they are dying only for specific collective reasons". This phenomenon's power relates to supernatural beliefs because such cases coincide with the assumption that the relationship between the individual and the sacral powers controlling their fate is broken due to transgressive sin, magic or other guilt. Thus, for Mauss, the sociocultural death is not only an impact on the physical body due to a collective factor but is also a sacral tragedy. That could be a violation of a totem or the consumption of a totem animal. "If a young vakelbure (boy or girl) eats a prohibited game and falls ill and probably dies, they will die by producing the cries of the animal concerned." So according to a collective assumption also shared by the individual, the spirit of the animal moved into them and killed them.

Mauss recalls several other cases about superstitious individuals who died because of their imagination, i.e., individuals who imagined being victims to magic, spells, or witchcraft and died soon after losing their spiritual and physical power. As Mauss writes, for such patients, "the European medicine will not create any trust. It cannot do anything because it does not fall in the same category as magic." Mauss quotes a medical study by Dr. Goldie, who deems this phenomenon a fast and fatal case of melancholy where people sentence themselves to death. The physician summarizes the phenomenon as follows: "The individual completely closes down and is unable to get rid of the idea of the terrible nature of their sin and the hopelessness of their case and will fall a hopeless victim to imagined melancholy. An overwhelming illusion fully takes them over that they have hurt the gods and they would die."

The bodily phenomenology of this case is as follows: "Nervous depression and great bodily loss of energy occur and that secondary depression gradually extends to each organ; the vital functions reduce, the heart does not function properly, the muscles relax involuntarily and in the end total 'anergy', i.e., death occurs. A spirit that has lost its balance falls from the severity of the shock of superstitious fear that conquers them." (Goldie in Mauss, 1924).

One could read ideas that rhyme with the theory of psychoimmunology about the immunosuppressive aspects of shame; these rows are similar to the social self-evaluation theory (SET). Why does Mauss consider this a social and sociological phenomenon? He wrote: "The consideration of psychic or rather psycho-organic here is not even sufficient to describe the complex. Society must be taken into account […], these phenomena belong where social nature very directly relates to the biological nature of man." This social scientist declared the need for social neurosciences before their times. However, a precise biological explanation was provided later by the pioneer of psycho-philosophy and the forerunner of the stress theory, Cannon. According to Cannon's

explanation, a psychogenic magical death, also known as thanatomania, is a threat to the individual through the neuro-vegetative consequences of the stress effect. His theory is that extreme sympathetic neural system activation, consequential general vasoconstriction, and the collapse of circulation are due to the redistribution changes caused by the triggered capillary anoxia (Cannon, 1942). According to Richter's theory, based on animal experiment observations, voodoo death results from the opposite, i.e., extreme parasympathetic stimulation. This theory's phenomenology is based on bradycardia, radical reduction of the number of breaths, and body temperature, which Richter explains with the parasympathetic dominance that results from the experience of powerlessness and hopelessness (Richter, 1957). Barnett explains the crisis caused by the damaging situation with the loss of balance between the sympathetic and parasympathetic nervous systems. According to Barbara Lex's theory, this phenomenon is due to the total dysfunction of the vegetative nervous system and the oversensitivity of the centers. The phenomenon consists of three phases. The first is dominated by sympathetic, parasympathetic reciprocity, in the second, sympathetic activation reduces, and extreme parasympathetic dominance develops, followed by the joint activation of the two systems in the critical third phase. The condition is 'tuning', during which altered consciousness and extreme suggestibility develop, making the individual susceptible to the reality of magic death (Lex, 1974).

Wolff describes a Papua New Guinea case where his tribe and family had excommunicated a person due to breaking a taboo and he was taken to hospital where he showed depression and apathy and a negativist conduct towards drugs and food. The doctors were unable to identify any definite illness of the patient, and he was found dead on the ninth day after admission. The autopsy revealed arteriosclerosis and hepatic cirrhosis, but the direct cause of death was missing. According to a case described by Lambo (1956), an African patient may develop malignant anxiety from a spell unless the tribal healing therapist can help in time.

The social attachments are restored and confirmed through the public shamanistic healing, which is associated with the patient's confession. Lola Romanucci Ross describes something similar in her book concerning the healing practice of the shamans of the Island of Manus, where a public confession of the committed sins was also a precondition, and therefore in addition to the confirmation of the community attachments, the socio-psychophysiology experience of forgiveness and readmission and restoration of attachment is also ensured.

Recalling the fact that a close relationship with the mother gives adaptive security to the baby through the activation of the endogenous opioid system, among others with its favorable psycho-neuroimmune effect, we can also understand the psychophysiology and psycho-immune significance of any

violation to attachment and the culturally and cognitively strengthened stress condition caused by social exclusion. At this point, we must also mention anomic depression, which is typical of the Indians of the West Coast whose culture has been transformed, i.e., they have lost their own tribal culture. For them, the loss of their roots and cultural alienation leads to apathy, anorexia, insomnia, neurotic/reactive symptomatology, and suicidal tendencies or alcoholism. It is typical that while these symptoms are often inaccessible in Western psychiatry, they can be remedied through tribal healing rituals in an altered state of conscience, through the reorganization of personality.

As for hospitalized children, the self-induction of the EOP system and self-rocking takes place with a monotonous tapping practice; the endogen opioid induction that strengthens reattachment experience can also be recognized in the tribal healing rituals (Henry, 1982).

A ritual trance entails several phenomena mediated by EOP.

1. The individual in trance is detached from physical reality and steps out of their everyday life, thus giving themselves to the special experience of trance.
2. The trance is a positive emotional condition with euphoria and ecstasy.
3. The condition does not entail any pain. During the ritual dance, they do not feel tiredness or pain, they can walk on fire without feeling any pain.
4. The trance condition is associated with intensive physical activity, which is generally rhythmic and monotonous.

The trance condition always appears in a social context; the community expects its members to participate in the ritual dance. Henry stresses that besides the ritual leaders, those suffering from illness, loss or disease are most susceptible to trance.

Ritual trance, which entails analgesia, reduced anxiety, euphoria, and amnesia, and the EOP induction can also explain certain miraculous recoveries through immune competence boosted by the EOP system, according to the rationalizing medical anthropology approach. It is important to note that the endogen opioid adaptation mechanism also kicks in when the situation cannot be resolved with a behavioral response. In such cases, the catecholaminergic response modality does not have any adaptive gain, and it is reserving behavior where the endogenous opioids can also have a role, although there is no positive immunology influence at all. With social isolation, the density of the opioid receptors in the brain changes, and the voluntary opioid consumption also increases. Panksepp and Bishop proved that the brain's EOP system had increased activity during social stimulation (game) with an auto-radiography test (Panksepp, Bishop, 1980).

This means that the endogenous opioid system is also a healing factor in the healer-patient social context, which is increased when the patient is in regression and creates a tight therapeutic binding as if recalling the ancient trust-type attachment in the mother–baby relationship.

This requires an almost irrational belief in the healer's magic power, i.e., the beliefs and roles of the given culture also strongly determine the specific psychobiological healing factors. Moerman refers to this cultural structure as symbolic healing, among the universal features of which Dow (1986) stresses that the healer and the patient share the particular cultural and mythological system and defines the references between the patient and the illness as a special component of this mythical world and connects the emotions of the patient with the transactive symbols of that mythical world, until finally the experience and emotions change through the transactional system of symbols. He believes that the social environment has an impact not only on the psyche but also on the bodily processes through symbolic transmission. Béla Buda points out that other interpretations are also possible. Therefore, healing rituals may also be examined with the role theory, symbolic interactionism, and communication theory, allowing for a new description of the organization of experiences for the patient. In this approach, new therapy methods may also be available, such as the correlations resulting from NLP (neuro-linguistic programming) (Buda, 1994). Frecska and Kulcsár (1989) wrote a paper about the relationship between social attachments and ritual healing and the role of endogenous opioids, which contain a lot of assumptions suitable for further consideration.

Thus, in the case of the initiation rituals, the intensive experience (pain, noise, symbolic ritual events) facilitates the cultural-psychobiological coherence of cultural norms and identity as well as the cognitive and endocrine changes that take place simultaneously through the activation of the EOP system and creates an attachment with the community and also strengthens identity. Katz observed in the Kung tribe of the Kalahari Desert that men were dancing on fire, holding ambers in their hands in the state of ritual trance. They spray their strong sweat as visible energy (n/um) on the patient and on other healthy people to be kept away from disease. This simultaneously indicates the healing role of collective cohesion, trance status, ritual synchronicity, and collective attachment to the "mother community" (Katz, 1982). Sensory overload, self-suggestion, and hyperventilation all contribute to this psychological and biological condition. All this can also be interpreted as the use of stress processes for healing purposes, in which the individual can renew the basis of internal and collective harmony by crossing the normal biological boundaries that are broken by the stress processes. This requires vision, an altered state of conscience, and a special energy experience. The trance condition could be the consequence of extreme stimulation or an extreme lack of stimulation, which

happens during meditation. The application of hallucinogenic plants during healing rituals can also contribute to the trance. Such include the ayahuasca wine used by the Peruvian *curanderos*, which alters the experience of space and time, bodily feelings and creates visions. Its role is not healing but is very important in finding the diagnosis and fighting the harmful spirits (de Rios, 1972).

Jilek connects the non-drug induced trance achieved by North American Indian tribes (the Salish tribe in British Columbia and the Plains Indians) with the stress effects in ritual dance (Sun Dance), the heat and acoustic stimulation of the organism provoked by starvation and thirst, sleep deprivation and hyperventilation, which relate to the antinociceptive stimulation of the EOP system (Jilek, 1982). This overexcited trance condition entails bleeding surface wounds created by the Moroccan Hamadsha tribe members, during which the self-induced trance develops (Crapanzano, 1973). The *hadra* ritual is a trance condition (*hal),* which continues until temporary paresthesia and sensory disorders occur, from which the individuals wake up rejuvenated and revitalized.

The social psychophysiology processes of hypnosis provide an opportunity for the special interpretation of reaching the trance state, when the events occurring to the hypnotizer are analogous to the ones occurring to the hypnotized individual. It may be suggested as a hypothesis that even a passive patient can experience a healing trance state in a suggestive and interactive situation and follows the shaman into the trance state.

Beyond the above-mentioned social psychophysiologic framework, one can use a more detailed psychiatric biomedical framework and taxonomies, like Yap (1969) did, based on the phenomenology of the diseases he called "culture-bound reactive syndromes":

Paranoid syndromes
Emotional syndromes
Depersonalization states: *koro*
Fear-induced depressive states: *susto*
Syndromes of disordered consciousness
Impaired consciousness: *latah* reaction
Turbid states: malignant anxiety, *amok, negi-negi*
Dissociated consciousness: certain types of possession syndrome, *hsieh-ping; windigo* psychosis.

Although Yap emphasized that these syndromes are determined by cultural factors in form and frequency, this phenomenology is based on a western allopathic, biomedical taxonomy system. Based on emic understanding, Jilew

does not think that this approach, a "wholesale" translation of these *emic* disease terms into *etic* (Western scientific observer's) categories, is appropriate.

The etic approach has its evidence-based, objectivist worldview, where the category of normality anchored to objective biological measurements creates a difference compared to the local, native cosmological beliefs. Social and cultural anthropology avoids the judgment of normal and abnormal regarding the cultures to be observed. Cultural relativism is suspicious of normality, challenging and multiplying canons. Its existence multiplies acceptable canons for the sake of understanding, inducing anarchy regarding authorities, truths. There is an "emic" empathic drive to understand the observed phenomenon in its terms, and there is another critical one, an etic approach to deconstruct the observed, showing its limitations and culture-boundness.

The universality of disease categories frees disease entities from local social, cultural and individual psychological contexts. The claim for universal biomedical truth is supported by evidence-based, research-derived, statistically reliable, and validated, epidemiologically explorable truth that is universal, independent of place and time. The semiology of the pathological has a parallel vocabulary of symptoms, such as fevers, pains, eruptions etc., and the hermeneutics of disease needs the understanding of the normal at the same time. This double coding needs double sensitivity, one for the standard, the normal, the biological canon, the universal truth, and the other directed toward the disease, the special, deviant, rare, sometimes exotic, but nevertheless universal in its special forms. If biomedicine with its "traditional modern" scientific assumptions excludes these approaches, medical anthropology is invented to deal with them. Medical anthropology based on its cultural relativism has a completely different ethos towards these phenomena. This cultural relativism destroyed the exclusivity of rationalism, and created an off-centering juxtaposition. The hermeneutics of postmodern anthropology rejects totalization and questions the authority of any hermeneutic and refuses any transcendental position.

Browner, Montellano and Rubel (1988) emphasize that an analytic framework combining the emic perspective of ethnomedicine with the etic measures of bioscience can generate valuable new interpretations for cross-cultural, comparative studies of human physiological processes, the ways in which such processes are perceived, and the culture-specific behaviors these perceptions produce. The bio-behavioral expertise and bio-behavioral scientific background establish a firm context, just as Kleinman's double professional identity is reflected in his statement: "We consider the dialectic of nature and culture to be one of the primary theoretical problematics of medical anthropology". Although they also pay attention to the autonomy of the interpretive medical

anthropology approach, when stating: "the biomedical framework has significantly obstructed the wide anthropological and comparative study of disease/illness, health and ethnomedicine, because it has ethnocentrically devalued, if not excluded, the knowledge of other ethnomedicines, including lay beliefs and practice." But the modern reductionist scientific framework is not enough for qualitative interpretation because these methods are reductionistic or incapable of analyzing phenomena within their context.

The emic and etic hermeneutic circularity may constitute a bridge between cultural anthropological (meaning-centered, interpretive and emic) and biomedical (bioscience-based, etic) approach. As Browner points out in the cross-cultural comparative study of folk illnesses, the objective is to understand how specific biological, psychological, and sociocultural processes interact to produce a constellation of signs, symptoms, and behavioral changes that are recognized by the members of a specific cultural group and responded to in a standardized fashion. Ignoring the role of organic factors even when organic signs and symptoms are clearly observable, would be certainly a serious mistake. Identifying the phenomena under investigation in emic terms, then determining the extent to which the described phenomena can be understood in terms of bioscientific concepts and methods help the convergence of cultural anthropological and bioscientific understandings. The aim of this hermeneutic sequence is to place descriptive, emic materials into the standardized, measurable, and verifiable units of bioscience. It is not an easy task because of immanent contradictions listed in the next typology. But the three faces of cultural psychoimmunology is the three dimensions of the tetrahedron model of M-E-O, where objective natural processes, info-social subjectivities and techno-socio-cultural constructions offer multidimensional character and diagnostic-interventive features to the cultural-psychoimmunological phenomena.

Table 11. The three faces of cultural psychoimmunology (after Zsinkó-Szabó and Lázár, 2013)

Neuroimmuno-modulation and immunology as part of Biomedicine	**Psychoimmunology as part of Psychosomatics**	**Social and cultural psychoimmunology as part of Medical anthropology**
bioscientific reductionism	psychosomatic holism	sociocultural holism
analytic	psychoanalytic and narrative synthetic	sociocultural synthetic
upward causation	downward causation	circular causation
linear logic	circular logic	eco-logic
universalistic	personality-based unicity	culture-based unicity
randomized, statistical	case-oriented	culture-oriented

Neuroimmuno-modulation and immu-nology as part of Biomedicine	**Psychoimmunology as part of Psychosomatics**	**Social and cultural psychoimmunology as part of Medical anthropology**
diagnostic, judgmental	acceptive, Rogersian	cultural relativism
semeiologic	semantic	semantic (re)interpretive
truth is out there	truth is in psycho-physiological context	truth is socially constructed
chemical dialogue	encounter	participant observance
animal models	personal-psychological models	socio-cultural models
morphological, organ based	info-logical process-based	(re)interpretive codified context-dependent
codified	context-dependent creative	emic, empathic
re-presenting rationalism	cognitive-emotional approach	meaning centered-interpretive
technocratism	refusal of technocratism	criticism of technocratism
philosophy of instrumental rationality form (committed, conjunctive, closed)	philosophy of communication (disjunctive, open)	philosophy of intercultural communication (uncommitted, open)
voluntary (purpose-driven objectivist)	playful (purpose-driven interdependent)	self-restraining, observant
directive	client-centered, accepting	active –receptive
hierarchy	submissive,	polyarchy
dualism	psychosomatic monism	sociocultural holism
distance	participation	observant participation
synthesis	deconstruction	reorganization
centering	recentering, readjustment	perspectivism construction
social coherence	social difference in personal, narrative context	social difference in socio-cultural context
theory mirrors reality	reality is personal and linguistically mediated	reality is culturally constructed and linguistically mediated
form (committed, conjunctive, closed)	disjunctive, open	uncommitted, pen

In Browner's approach the claim to universality and cross-cultural comparability is brought back by the species-wide universality of human physiological processes. The speech community with biomedical sciences creates a working interface for modern and interpretive postmodern, too. That calls for a stronger "mutualism" between psychobiology, psychosomatics, social medicine and medical anthropology. From this point of view, the debates arguing for the anchoring of medical anthropology among the mainstream disciplines give us support, like Kleinman advises.

Returning to the culture-bound diseases, Jilek shows the cosmological significance of local mythical assumptions, like the traditional Taoist medical philosophy and disturbance of the *yin-yang* equilibrium of the *Koro* (*Suo-Yang,* "shrinking penis") or the Amerindian syncretistic, mythic beliefs of Indio and Mestizo populations in the case of *Susto/Espanto*, as the loss of soul. Jilek gathers several local culture-bound syndromes common in anxiety reaction triggered by specific startle stimuli including echo- and coprolalia, echopraxia, automatic obedience, and aggressive- impulsive behavior. It is called *latah* in Malaysia and Indonesia, *imu* among the Ainu of Hokkaido, *bah-che* in Thailand, *yaun* in Burma, *mali-mali* in the Philippines, *miryachit* in Eastern Siberia, and *Lapp panic* among Samis. In extreme polar, arctic environment a sudden onset of self-aggressive confused behavior occurs, including screaming and trembling, jumping into the icy water; sometimes also directly aggressive acts against self or others ending in stupor-like exhaustion is called *pibloktoq* or *arctic hysteria* among people living in the arctic zone, like Innuits.

A more holistic understanding needs a wider historical and socioeconomic glance on these cultural "reactive syndrome", which connect the culture-bound syndromes to our social neuroscience framework including psychophysiological, psychoimmunological patterns as well. According to Murphy (1973), *amok* and *latah* are not offshoots of Malaysian cultural tradition but the transitional products of modernization and socio-cultural transition. In our *emic versus etic* attitudes regarding these culture-bound syndromes and transitorily altered states of consciousness, it is important to reveal, that etic might be emic, too. A cultural relativist approach must examine whether culture-bound reactions are seen as normal or pathological by the native community, with Ackerknecht's words: auto-normal or auto-pathological. It is important in the case of ritualized possessive states, shamanic states of consciousness.

Placebo

Consequently, we must also interpret the issue of placebo in this context, which has natural neurobiological features, personal cognitive psychological differences, and a determinative cultural context at the same time.

Moerman interprets the placebo effect as psychological and physiological effect expected in relation to the *meaning* in the treatment of the disease. In fact, participation in the healing process itself is also the source of the placebo effect and is, therefore, part of the recovery. It is not an exaggeration to consider the placebo effect as the manifestation of sociocultural effects and social transformation into bodily effects. This is why it may be misleading to consider the placebo effect an aspecific biological phenomenon because meaning and the expected and assigned effects are an important component of it. The symbolic content of the treatment, the conditions activated by it and the evolutionary fixed and mobilized biological patterns make this phenomenon *sensitive to meaning.*

The clinical drug experiments offer the aspecific role of meaninglessness to placebo. The drug investigator does not examine the placebo effect, but excludes it together with other factors that are not related to the treatment. Due to the meaningfulness of the placebo effect, medical anthropologists Scheper-Hughes and Lock consider the placebo and nocebo effect as a non-alienable factor of a disease and healing, a phenomenon (and idea) which reflects the interaction between the body and soul and individual social (social body) and political body (body politic) in its own way (Scheper-Hughes and Lock, 1987). Due to the latter two components, the placebo is often the subject of intercultural psychology and cultural psychoimmunology. Moerman (2004) also suggests the potential intercultural differences of the placebo effect, yet cannot respond to the answer as to how much of the response to a symbolic stimulus is attributable to personal aspects and the history of life and how much is attributable to the given culture. The given healing culture also intervenes in that ideologically; the dominant cosmology of healing has an undoubted effect on the belief factors that control the symbolic layer of healing and which also affects Western technicist medicine. (Let us just think of the so-called TDF model, the 'total drug effect' theory of Claridge, in which the macro and micro context of prescribing and taking drugs are both important, including the industrial interest structures and technical fora, marketing, and all factors from commercial network to the color of the drug as well as the authority and trust aspects of any advice.) So one must include the attributes of the drug taken; the attributes of the ingester (patient); the attributes of the drug provider (doctor/researcher); and finally the setting within which a particular substance is taken. Helman added a fifth factor, the "macro-context". These considerations might be extended to psychosomatics, blurring the scope a bit, where, beyond the chosen psychotherapeutical way – according to Mihály Bálint –, the drug includes the doctor (him/herself), too. These conversation therapies are greatly dependent on professional legitimacy and the clinical setting in which they take place. Psychiatrist and patient must share a common clinical ideology, be it analytical, cognitive-behavioral or neurobiological-

pharmacological framework. This context- and situation-sensitivity points further, and deeper in the medical anthropological "abyss", towards the Dowsian symbolic healing. In this medical anthropological framework of understanding, the therapeutical effect of the symbolic healing depends on the shared cosmology, and the expected-attributed changes dedicated to the ritual symbols, actions and process. While in the psychosomatic concept of the patient with his/her subjective developmental features, personality, life events in personal narrative context, and the doctor–patient communications are dominant, the sociocultural anthropological approach brings the web of meaning in front of the total "drug" effect, as part of each drug factors. The placebo phenomenon plays role in each factor through perceptions, cognitions embodied in personal psychophysiological dynamics.

From critical medical anthropology to clinically applied medical anthropology, various layers may be offered to interpret the placebo phenomenon based on the results of field research. However, there is the personal meaning formation of the patient in the center, which naturally is the target of the above effect factors but is also affected by social psychology factors, such as the physician–patient relationship, its role dynamism, the loyalty or resistance of the patient. We may consider the relationship between the patient and medicinal drug or symbolic elements of the healing practice (drug names, environmental conditions, colors, forms, activity frameworks and modes, rituals) cultural factors. These impressions, impulses, and cognitive events may also affect the patient's mood or trust in a hidden way that is not recognized. The symbolic factors affecting the placebo effect are also unalienable components of the meaning network integrated into the inclusive culture, where both the physician and the patient may be participants accepting it or may be conflict seeking and untrusting critics. These include the ideological attitudes of discourses, beliefs, forms of knowledge, historic and power aspects, commitments, or opposing distance, which all influence the psychological mechanism of expectation-attribution, the placebo effect. Medicine is a practical world full of symbols and the same also applies to pharmacological, psychiatric, surgical or other medical activities. The meaningful and symbolic gestures and rituality of the physician and the healer deeply influence the experience of the disease; this symbolic influence occurring in the medical context leads to physical consequences and is part of the physician-drug effect described by Mihály Bálint.

On the basis of the above, the placebo effect may also be considered a non-alienable cultural psychoimmunology factor. In most diseases under the psycho-vegetative influence, the placebo effect may be increased. In a double-blind experiment comparing the effects of a pain relief drug and placebo (neither the physician, nor the patient is aware whether they use the drug or placebo), 36% of the patients experienced a significant reduction of the pain

as a result of the placebo. Other subjects also experienced the placebo effect in double-blind experiments: 58% in the medical treatment of sleeping disorders, 59% in tricyclic antidepressants, and 62% concerning lithium. A placebo can also have adverse effects as well as psychological addiction. As Schapiro (1970) observed, the green placebo pills were effective for restless, anxious, and phobic patients, while depressive patients responded better to the yellow placebo tablets. Postoperative pain may be suspended with a placebo, and it can be prevented by applying naloxone (Levine 1978). According to Adler and Hammett (1973), even the placebo effect relates to culture, and what works as a placebo in one culture will turn out to be ineffective in another.

The concept of the placebo effect relates to the interpretation framework of symbolic healing (Dow, 1986). The participants take part in a common cognitive system. The placebo effect develops in one-third of the patients. Rapport, mutual trust, and understanding are very important. The confirming presence of the audience, the community and participants may be important for natural people. Culture gives a cognitive framework and meaning to these effects.

Certain authors consider the placebo effect part of the clinical situation. Individuals susceptible to placebo are increasingly anxious, emotionally dependent people with low self-esteem. Placebo provides what is missing, the safety experience of a close mother–child relationship. The placebo provides the necessary conceptual-perceptual framework, which creates order in the surrounding chaos and gives security to the individual's existence. It is especially interesting that analgesia caused by placebo is also naloxone reversible, and therefore the role of endorphins may also be part of the placebo effect. There are also trials doubting that which point out the impossibility to reproduce the endorphin mediated placebo effect (Bánki, 1994). According to cognitive psychological concepts, the effect of a medicinal drug is associated with symbolic elements (syringe, white furniture, etc.) similarly to the shaman's accessories. The behaviorist explanations describe the placebo effect as a conditioned response to the stimuli of the environment or the treatment situation. Zsuzsa Kulcsár points out the importance of the expectance-attribution model in the placebo effect, highlighting the psychogenic mechanism of the expectations for the healing procedures in the context of the given culture and their significant involvement among the aspecific factors of recovery (Kulcsár, 1994).

Finally, immune conditioning, where the conditioning of a substance with a strong unconditional immune biological effect with a conditional stimulus after a while will make the associated otherwise neutral stimulus effective, with an immune suppressive or immune-boosting effect, such as any flavor or scent associated with cyclophosphamide or poly I:C, may also be associated with the placebo effect. Using that technique, Olness and Ader were able to half the application of cyclophosphamide to treat SLE (lupus erythematosus)

with this conditioned, quasi placebo treatment (quotation by Kulcsár, 1994). However, returning to the role of endogen opioids in the placebo effect that cannot be refuted at all, we may raise the question of whether the physicians of our age can sufficiently mobilize endogenous psychobiological self-healing factors. Regardless of whether we talk about the endogenous opioid system responsible for the mediation of social bonds, or the EOP stimulating effect of stress or sensory overexcitement, the pain-relieving role of acupuncture affecting the endorphin media and its immune stimulant role or the placebo effect that can be impeded with naloxone, these healing factors are based on the effect of the manipulation of the antinociceptive, immune stimulant protective factor: the manipulation of the endogenous opioids. This is one of the potential keys to archaic healing rituals. Naturally, the optical delusion of the scientific periods may also be a factor in it, where a new mediator fits as one key fits several locks.

The technical healing tries to influence the fundamental adaptive regulatory processes instrumentally. We must understand that an irrational healing practice does the same using the psychobiological processes developing in the common culture's complicated cognitive system, the symbolic field, expectations, and their attribution.

Consequently, the traditional healing practice is based on the biological adaptation to the stressor and has thousands of forms but deep down they are all related. The sociocultural healing structure deep down is related to a psychobiological, psychoimmunological common denominator.

The great internal anxiety becomes a permanent feature of distorted secondary attachment organizations, primarily the anxious ambivalent type C mother and child relationship. However, the avoidant or anxious response to the disturbed attachment resulting from a mother's negligent conduct can also be the result of a traumatic psychological experience, as a result of which the psychobiological stress regulation is oppressed, and the epigenetic mechanisms lead to the downregulation of GRs. These 'upward' mechanisms also deserve the attention of researchers. They are the immune-mediated psychological consequences of frequent infections and chronic inflammation, described in detail above. Stress effects within families also entail an increased risk of infectious diseases. That is why the history of a child and the factors threatening them must be examined in a number of layers. Chronic and traumatic stress is the consequences of the family's value set and the emotional climate created by the parents (security or insecurity, peaceful or hostile communication), interactions, games, and scripts which in their systematic way may lead to psychosomatic symptoms in the child. All this is in a register-type, coded system of norms with differences in each culture, as Freedman and Gorman showed concerning child education. The composition of the family and the household's sociocultural factors also have a serious effect on the development,

stress sensitivity, and health of the child. The children of divorced parents have a greater emotional burden and experience more stress than children in harmonious families with two parents. During the fieldwork conducted in the village Bwa Mawego, Flinn and England (2003) found higher average cortisol values among children who grew up without any relative support or in single parent families than among children growing under more harmonic circumstances.

The unsecure and unpredictable protecting behavior and unstable moral support were reflected by the variable cortisol levels measured in children; traumatic family events were accompanied by a temporary elevation of cortisol level. Children who lagged in growth for emotional reasons and lacked care and support showed unusually high cortisol levels. The greatest distress risk, elevated cortisol level, and health problems were observed in children growing up in single-parent families where the mother did not have a partner or any relative to assist them. So, the cultural-psychophysiological observations conducted in the field also confirmed its role as a source of stress in the local community of Bwa Mawego.

At the same time, the authors also pointed out exceptions and variety among the individuals, indicating that not each child growing in a problem family showed an elevated cortisol level, and the family structure could not be considered an obvious factor either because are stable single-parent households where the warm and supportive emotional climate has a better impact on the child than in s non-supportive two-parent family full of conflicts. Consequently, there are a number of individual psychological factors that may result in an exceptional situation even despite the above tendencies. The parents' conflict and arguments may burden the entire family, but there may also be an unresolvable bad relationship between one of the parents and the child. The measured cortisol elevation also depends on the person and a durable psychobiological consequence of early trauma, the child's temperament and sensitivity, the actual perception of the situation, and the narrower or wider context. All these are factors that can be observed close only by a field worker. Only emic humility helps understand the local world of meanings in its shaded reality. In that clinical depth measurements conducted with the cultural "meaning-detecting" humility of fieldwork, combining biological objectivity with cultural particularity, the numbers maintain their importance. Flinn and England (1997) measured the 2-20 times elevated cortisol levels reflecting high stress in relation to family conflicts and deep and unexpected family changes.

Punishment, arguments, family conflicts also entail a significant cortisol level elevation, while reassuring and emotional interactions were accompanied with 10%–50% cortisol level reduction. According to the authors, 42.1% of the traumatic family events were accompanied by a significantly elevated cortisol level.

Socioeconomic correlations between protection and vulnerability

At this point, we should also take a look at the human ecology and the evolutionary context. It is the other side of the coin because our immune response to external and internal antigen challenges is strongly influenced by that context, determined in terms of civilization and culture. While in the cases discussed above, the culture had an impact on the immune system with its emotional and cognitive influence through the stress mechanism, in this model, the direction is the opposite because here culture and technology exert an impact on the person's immune learning and consequential response through the microbial, natural environment.

The impulses of the microbial environment exposed to technology and civilization impacts may also have lifelong effects, as described in relation to Strachan's 'hygiene hypothesis'. Perinatal infections themselves may create a durable biological and stress-biology risk based on the epigenetic mechanisms described above. However, the consequences of an allergen-poor environment resulting from the modern hygiene civilization conditions also deserve medical anthropology's attention due to an increase in the risk of allergic autoimmune diseases.

This is an upward system of impacts in which culture and the pathogen immune network impact the attack point and determine the late immune events through life history and development principle-based influence, but here, the learning processes of the immune system played a key role. In the early phase, it is very important in immune learning that the natural environment should be exposed to a number of microbial agents, most of which may be considered our 'old friends' in terms of evolution, according to Rook. A baby comes across these microorganisms, which are part of the commensal flora through the mother and other members of the family, but they also stem from a fitted carpet, the dust in the yard, or domestic pets. The traditional human communities often carry these pathogens with weakened pathogenicity in a subclinical form, but they may even be fatal for other groups that do not have that protection. That is how even child diseases, such as measles, or chickenpox became unintended weapons for the European colonizers against the Indian or Siberian tribal communities.

The organism must tolerate the non-pathogen, often useful microbes of microbiota or the microbial flora of the environment and they also have a co-evolved and regulatory role in the development of the immune system. The regulatory T cells play an important role in the development of the mechanisms restricting the inflammatory, allergic and autoimmune processes.

Those pathogens (smallpox, cholera, etc.) that cause large mass epidemics do not have such an immune-regulatory role because they either kill the

carrier organism or they cannot survive in the given community in a small social group. Western technology civilization and the medical and public health practice also excluded the 'old infections' and 'our old friends' with which we grew up from the child's early immune development. According to Rook, the immune regulatory diseases are becoming more and more frequent, and the healthy development of the immune system is increasingly dependent on the impacts of the natural environment. On the other hand, the exposure to epidemics of city residents and mass societies has remained, as indicated by the influenza and other upper respiratory virus epidemics. Being part of the natural environment for a while is, therefore, an especially important health protection factor for individuals with low SES status.

Human ecological co-evolution can provide many examples. The biodiversity hypothesis is based on Kropotkin's concept of co-existence. The mammal organisms provide several structural biological examples for that. One of the pioneers generating a discourse in this area is biologist Lynn Margulis, who noticed endosymbiosis during the interpretation of the evolution of the cell organizations. The cell components, such as mitochondrion or chloroplast, were all independent microorganisms in a former period of evolution and continued to 'serve' as an associated endosymbiotic cell organ when the eukaryotes developed. However, viruses become part of the organism by integrating into the DNS and occasionally becoming a pathogen threat. The presence of microbiotas which take part in the metabolism of mammals is another field. The commensal microbes play an important role in the processes of the intestines, the immune system, and the brain. Thus, there is also a change in the gene expression of rodents raised in a germ-free environment and the behavioral disorders are also attributed to the germ-free environment. Animals raised in a germ-free environment show a disturbing stress response because the HPA axis activity is also disturbed due to an altered central nervous system gene expression. This may be corrected if the microbiota of the germ-free animals' intestines is restored within the first six weeks.

This rich perinatal microbial environment, which continues during the first few weeks, has a great role in immunology because it takes part in the establishment of the diversified molecular structural network, with its own 'provocative' presence, which builds the memory structure that is also aimed at the fast recognition and elimination of dangerous microbes. Consequently, these microbial signals (peptidoglycans, lipopolysaccharides) are continuous activating factors of the congenital immune system. With continuous background stimuli, these microbial impulses also have an important role in developing the immune regulatory processes, the purpose of which is to stop inadequate immune processes. The Treg cells inhibit or reduce the immune response against the own tissues, otherwise harmless allergens or the huge number of microorganisms in the intestine. What makes this issue a cultural psychoimmunology

problem is that in a technology-dominated hyperhygienic modern civilization, the incidence of such clinical phenomena indicating such Treg inadequacy is constantly rising. The frequency of allergic and autoimmune diseases is increasing, which also applies to multiple sclerosis and IBD. The technocultural conditions, factors, and their potential occurrence and lifestyle features lead to this situation in which the early immune learning weakens. The perinatal conditions and the technocratic birth forms with psychological consequences, raised to a symbolic level by Davies Floyd and discussed above, also entail such a risk. For children born by Caesarean section or other operations, establishing the microbiota of the intestine is delayed and happens irregularly. Children born naturally are definitely in contact with the mother's microbiota. However, in children whose mothers gave birth by Caesarean section, certain autoimmune diseases occur more frequently, such as coeliac disease, type I diabetes mellitus, and asthma, compared to children for whom contact with the mother's microbiota seems to be a protective factor. The unfavorable impact of antibiotics taken during pregnancy and the neonatal period may impact the microbiota and increase the risks of asthma, milk allergy, IBS (irritable bowel syndrome), IBD (inflammatory bowel disease), and obesity.

The comparison of natural people and civilized societies also reflects the same immunological differences. The microbiota of the skin shows greater diversity among those who live in a rural environment than observed among those who live in large cities, where it also occurs with atopic incidence. Similar to the Indians living by the River Amazonas, the biodiversity of the microbiota of the intestine was comparable to that of the individuals living in rural conditions in Malawi, but the lowest biodiversity was observed among those who followed the lifestyle of the United States. The reduction of biodiversity of the intestine meant weaker control of inflammation both in experimental animals and individuals. A natural lifestyle and animal keeping are useful for the diversity of the microbiota. According to certain observations, dogs can protect against allergic diseases.

The Treg cells are responsible for the termination of unnecessary immune activity, and therefore, their disorder may be reflected in persistent background immunity and inflammation. Consequently, the early immune learning processes disturbed by technocultural or environmental changes may also disturb the course of an unnecessary inflammatory reaction, and the symptoms of chronic inflammation and moderately elevated CRP and IL-6 levels persist. What makes them clinically significant is that they are considered significant morbidity markers. Therefore, in relation to cardiovascular and popular health problems of increasing significance in urbanized and Western civilizations, they are also detected in CHD, depression and, in general, reduced stress tolerance.

Other factors may also lead to inflammatory factors and elevated CRP or IL-6 levels because among children who lived in slum-like conditions, in

poverty and amidst crime the CRP was generally higher than 3 mg/l. Where lack of confidence, violent social climate, deprivation, drug use and social uncertainty are dominant factors, the inflammatory indicators are higher.

A pregnancy affected by low socioeconomic status and perinatal stress may also be a factor in the elevated inflammatory markers observed. In adults, perinatal stress may result in elevated inflammatory markers. In adults with an abusive childhood anamnesis, a higher IL-6 level was measured in response to average social stress series (Trier Social Stress Test, TSST). Physically abused children showed higher CRP values during the examination even 20 years later.

We have already described the long-term consequences of the early attachment trauma, which can also be accompanied by chronic inflammation and adds another color to our 'bottom-up' hypothesis stemming from civilization.

Prenatal stress generates long-term changes in the operation of the HPA axis, and the same also applies to the psychosocial stress experienced in early childhood. The same is also strongly present among children of poor socioeconomic status.

However, the maladaptive psycho-immune status caused by psychosocial stressors may interfere with the rich immune stimulant effect coming from the microbiota or, on the contrary, the negative synergy of unfavorable impacts may boost the effects of the psychosocial impulses arriving from the general environment or from the natural and technological environment.

The lack of effective priming from the microbiota may increase the immune regulatory disorder resulting from psychosocial stress. In such cases, the given psychosocial stressors may lead to an even higher inflammatory marker elevation, which may trigger psychiatric symptoms. However, the elements of the commensal flora may reduce the cytokine levels. According to some observations made in the Philippines, when a child grows up in an environment rich in microbes and is surrounded by domestic animals, they can offset even the higher CRP levels likely to occur in adulthood as a result of the trauma of the loss of their mother during their childhood. Such an early trauma leads to long-term stress problems among US citizens.

Life events in a cultural anthropology context

Fate is a set of life events that also involve stress, and it tests the health of an individual based on personality features, individual coping capacity, temperamental and emotional features. It is not an abstract and general psychobiological process but it takes place among the given cultural norms, values, roles, and expectations, in a society regulated by cultural codes. That is why contextual factors need to be examined on the field. Life events are at the center of

attention in cultural psychoimmunology and offer an area where the social psychophysiology recognitions observed in the sociocultural atmosphere of a given world and life provide strategic information for psychosomatics and narrative medicine. The fieldwork in Samoa by McDade offers such research results.

This Polynesian state stretches across a group of small islands in the Pacific Ocean. One hundred sixty thousand people live under partially modernizing conditions, where the capital town Apia is a good example. However, this modernizing world also includes the world of partially rural villages on the coast of Upulu, which also provides agglomeration options. Real and traditional agricultural communities live on the island of Savai'i, where the people cultivate their land. Despite the colonial influence, the population of Samoa has preserved its original Polynesian ethnic and cultural features (O'Meara, 1990). They are proud of their lifestyle, expressed as *fa'a Samoa,* for which the traditional large family, *'aiga,* provides a framework. Western consumer goods and approaches have introduced the inevitable (post)modernization of the islands' urban part. McDade also points out that the changes in the 1970s and 1980s were also accompanied by cultural phenomena and an increase in the number of suicides observed among the young generation. The figure was four times the ratio observed in the same age group in the United States. The research on life events may reveal the correlation between stress caused by social and cultural changes and their health consequences.

The loosening and breaking up the ties within traditional society also leads to weaker social support, which, according to House et al. (1988), increases the risk of early mortality by 2-3 times (House at al., 1988). It is also important in terms of public health because it is an independent risk factor that is as important as smoking, obesity, or the risk of sedentary lifestyle.

McDade's fieldwork may be considered a model example of cultural psychoimmunology because he connected the observation of the social conditions and life events of the youngsters of Samoa with the examination of the immunology functions. Samoa was selected because of the cultural and modernization pressures indicated above and the high suicide ratio that reflected a crisis of values and social distress.

The anthropological perspective of psychoimmunology requires that the fieldworker can identify the specific local Samoan context and meaning of 'social support' and life events. Similarly, the complex meaning of the special psychosocial stressors and social relations must also be clarified for the local and given community. In that, the author was able to rely on Howard's (1986) research, which examined the traditional meaning of life events among the Samoans who migrated to America. The death of a child or partner, a close relative or friend is a strong shock. Important life events include childbirth and abortion, a severe illness, or when a child leaves the family. All this seems

to be intercultural invariance, but the details show the Samoan specificity, the appreciation of social relations against the individual. Thus, e.g., in the ranking order, a severe illness of a relative is in the eighth position, and an own illness is only in the sixteenth position. Interestingly, marriage is a more important life event than divorce because it brings a lot of social obligations into the individual's life.

One of these important traditional obligations is the archaic ritual of gifting, known as *faalavelave*, which deserved anthropologists' attention very early.

Faalavelave is a public, formalized exchange of gifts that takes place during communal ceremonies, such as a wedding, funeral or inauguration of buildings (O'Meara, 1990). The pecuniary food or cloth donations have a high symbolic value, and each is a prestige forming gesture of wealth and generosity. This establishes the position of the donating family in a larger community, and much attention is paid to the nature and amount of the gifts. The *faalavelave* may generate a huge financial debt for families. According to certain respondents, what in the past symbolized considerable emotional and financial support has turned into a businesslike forced gesture with a huge burden and financial risk in the modern world (McDade 2005).

The networks based on traditional extended relatives are turned into stress by the major expectations and obligations (Janes, 1990). However, it is also a source of significant social and emotional support, but its continuation demands permanent presence at family occasions and financial contribution to the family's financial burden, respect for the old, and other inevitable social obligations that are required to maintain the prestige of the family. All this indicates that the experienced social burdens and gains and support are a sensitive target in the changes caused by modernization, and they may entail modifications in the meaning. All this demands attention and humility from the field worker when identifying the real correlation between life events and related psychological consequences.

Consequently, they reveal real cultural and psycho-immunology correlations when they describe the life events in their local and variable in time sociocultural context and complexity. As stressful life events, such as divorce, death or natural disasters, or caring for an incurable Alzheimer patient, trigger serious immune-suppressive effect, and therefore the traumatic life events (bereavement, divorce) may also be associated with the subsequent diseases (Rabkin and Struening, 1976). In the case of the elevated cortisol levels measured in children exposed to chronic stress, more frequent colds and infectious diseases were detected. In the study mentioned previously, the frequency of infectious diseases doubled after stressful life events among the Bwa Mawego children, which may also be accompanied by a sleep disorder, occasional lack of appetite and other ordeals accompanying a social trauma.

Poor and rich, variance and invariance

The particularism of cultural anthropology may be contradictory to the universalism of psychoimmunology, which is based on laboratory observations and experimental methodology, and its basic position generally outlines effective principles, is free of any reductionism. The psychological dimension's subjectivity already seems to ease that contradiction, while despite the deep evolutionary and ethological foundation, the social psychoimmunology approach transfers the reviewed phenomenon into the occasionality of the actual complex social relations.

Whatever the case, the 'input signal' created by life events interpreted in a cultural context and created by a meaningful stress perception and evaluation is comparable with the immune output signals that can also be evaluated well in the field. McDade interprets the level of antibodies against the Epstein-Barr virus (EBV), which may also be considered the cell immunity marker, as such a sign. Considering that 98.8% of the Samoan youngsters are infected by the age of 20 keeping the virus latent depends on the actual immune competence. If it reduces as a result of stress, the EBV reactivates, and the viral antigens getting into circulation provoke a humoral antibody response (Gaser et al., 1991). This is why the higher EBV antibody titer reflects reduced actual immune protection because against the EBV virus the primary protection is the cell-based immune protection. Life events and other social emotions, such as solitude or anxiety, also show a positive correlation with the EBV antibody level, while the stress management exercises or trauma identifying therapy reduce the EBV antibody levels. In terms of EBV, McDade excluded the seronegative subjects from the test sample in a pre-screening exercise and also paid attention to adequate nutrition of the subjects. Higher CRP values were considered disturbing in the test because they obviously could have been the result of intercurrent infection or anything else related to the basic hypothesis.

Consequently, the excluded patients also strengthen the significance of the found data. The researcher used the questionnaire technique to assess the life events and other social factors used in the interviews, such as the death or disease of a relative, the *faalavelave* obligations, satisfaction with the socioeconomic situation, status, social orientation and social relations. The results of the survey conducted among the Samoan teenagers and individuals in their twenties confirmed that life events showed a significant correlation with the EBV antibodies, but SES and social orientation were important factors reducing that correlation. A positive correlation was observed between life events and EBV antibodies primarily in households with a poor SES status, while this correlation was the opposite in households with a good SES status. Otherwise, the individuals demanding social support and sensitive to their social relations showed higher EBV antibody titers to life events than the young people confident about themselves

and not requiring any social support. It is a special Samoan significance and specificity of SES that it reflects the family's ability to respond to *faalavelave* type social challenges that are full of important expectations and obligations. All this reflects the strong social psycho-immune moderating effect of SES, which reflects the financial position. While the prestige of low-income families depends on the success of these 'gift services' that are a financial strain, such a life event is an opportunity for rich families to improve their prestige and status. All this explains the contrary movement of detected EBV antibodies between the low and high SES status families in a sign-changing manner.

Culture, dance and psychoimmunology

Dance as a health support agency, be it preventive, or curative, is a phenomenon of cultural embodiment, a unique cultural-psychophysiological phenomenon. Dance has linguistic content not only between the actors but also between the deeper, unconscious internal layers of one's psychological structure and its conscious rational, self-reflected part of the mind. Gender and identity, habitus, and sociocultural roles are shaped and shared through learning dances (Lázár 2015). This multi-layered expressive function of dance has a profound bodily impact, exerting bi-directional feedback sometimes having regulative effects. Hatch (cites Hanna, 1979) interprets dance itself in the frame of a "behavioral cybernetic approach" of systems concept to understand the relations and interactions between dance performance and psychological, sociocultural, and evolutionary processes. In this human ecological approach, dance is a sociocultural agency used to control and organize social interactions. From the perspective of lifestyle medicine, this organizing function is deeply embodied. It supports healing on somatic, psychic, and social levels at the same time. Dance as part of the "non-naturals" of the medical history is to help the patient cope with his/her troubles, be they casual, or consequential, somatic or psychic, social and cultural. Healing one's life rests upon healing one's lifestyle.

Looking at the aims of lifestyle medicine, not far away from medical anthropological insights, we can soon realize that we meet – at least to a given degree – a renaissance of the old tradition of "Diaetetica." Lifestyle Medicine aims to create the optimal dietary lifestyle, *regular physical activity*, restorative sleep, *stress managemen*t, avoidance of risky substances, and positive social connection as a primary therapeutic modality for prevention, treatment, and reversal of the chronic disease. All of these had more or less influence on psychoneuroimmunological network, as shown in the previous chapters. The medieval books of hygiene and dietetics included motions and dance as remedies for an emotional upset. Dance was mentioned as rather part of an integrated regime that helped to avoid health problems. The medieval medicine

was based on the *Corpus Hippocraticum*, and the balance of the four humors (blood, phlegm, yellow bile, and black bile) was the key to health. Avicenna's *The Canon of Medicine* (al-Qānūn fī al-Ṭibb) also had a great impact. This medical "encyclopedia" emphasized the importance of the so-called "six non-naturals", namely: *air, food and drink, sleep and waking, exercise and rest, evacuation and repletion, and the passions* for health maintenance. Comparing this list with the five health habits (physical training 150 min/week, daily 5x eating fruits and vegetables, BMI under 25, cessation of smoking, daily 1 dl red wine) playing a role in risk reductive lifestyle aims, proves the value of traditional health intuitions. Equilibrium and maintenance of health were offered by the appropriate use of the listed "six non-naturals." The inclusion of dance as part of a health plan had not been unknown in the Middle Ages as one of the *res non-naturals*. According to Roderigo de Fonseca, an Italian physician of Portuguese origin, the dancing of *galliards* was regarded as a form of exercise and as a source of balance. Another influential medieval text was written by Taqwim al-Sihha, the famous *Tacuinum sanitatis*, in which dance is presented together with music (Arcangeli, 2000). The medieval medical tradition saw the happy mood, enjoying the harmony of music and dance as sources of health. Exercise and dance cause "the increase in body heat"; "the limbering up of muscles", "the opening of the pores"; and "improvements in transpiration" and the "expulsion of harmful substances." Girolamo Cardano (1501–1576), in his work *De sanitate tuenda*, argued that physical exercise can benefit health, but it does not prolong life. Arcangeli also cites John Jones, an English physician, who saw only one musical mode, the Doric tonality, stimulating prudence, modesty and sobriety, while other modes excited the passions beyond measure. Similarly, there were medically preferable dances: "*Bargenets, Pavions, Galiardes, Sturgions.*"

Disorders of emotions were thought to be curable by music and dance, too. Another English physician, Robert Burton, in his work *The Anatomy of Melancholy* (1621), offered several genres of treatment for melancholy like hunting, horse riding, walking, playing games, and *dancing,* while Richard Browne even favored natural dance more than horse riding, recommending dancing for several diseases like amenorrhoea, cachexia, and jaundice. The beneficial role of dance as a social activity and physical exercise were also appreciated.

Arcangeli mentions an Italian physician, Giulio Alessandrini, who, living in the 16th century, and serving under the Hapsburgs emperors, met Hungarian dance traditions, and described Hungarians' dances this way:

> If someone sees a Hungarian dancing in the fashion which is customary in their dances; he will perform any sort of bodily movements: now he is laid out still on the ground, then he gets up with his legs at times bent, at times stretched, at times opened wide, he stoops and rises again, and even gathers the whole body in minimal

> space, and then springs by launching his hands here and there, and bursting with shouts.

Alessandrini, in his work *Salubrium sive sanitate tuenda*, quotes an unnamed physician, after the description cited above, saying that this dance as an exercise may strengthen all muscles and tendons in one's hands, arms, chest, back.

István Mátyus, a Hungarian physician, in his book *Old and New Diaetetics*, wrote about dances, too (Mátyus, 1787).

> The powerful dance involves the harms of speedy gait, running and escape, which are raised by the violent twisting of the whole body here and in the flesh. But when it is slow and without any effort, there is no gender that is better than our nature. For it takes away both the hardships of the body and the boredom of the mind.

> The more careful, gentle the dance and quieter than the song, the more beautiful and useful it is. It is ugly, as in other things… the effort over others and the lack of knowledge to moderate itself.

> There are countless examples of blood spitting, pneumonia, hot ailments, cruel main pain, dry disease, and other dangerous whines from the unreasonable dance.

> Those who have the strong passions of the mind have gotten hot. They harmonize it with melodies and chants.

Lifestyle medicine, as written above, has strong efforts in prevention and restoration of consequences of nowadays' stressful and sedentary lifestyle, which includes lack of physical exercise, relative muscular inactivity, metabolic and cardiovascular consequences, obesity and problems caused by coping distortion (alcohol, smoking, chemical comforters, drugs).

Dance as a means of social, spiritual and somatic healing

Anthropology of dance rarely interprets dance as an immanent healing practice, although, from the earliest description of tribal dances, the healing role of the ritual was clear and expressed in many ways. In 1898, Russell, with the finest ethnographer authenticity, depicted the Apache Medicine Dance. A healing dance rite, conducted by Sotli, an old Apache woman. When she arrived to the village, Jicarillas, a medicine lodge and an enclosure were constructed for her and the sick person. The ceremony was ministered by the older men of the tribe chosen to assist in the lodge. The medicine used in the ritual followed the analog, homeopathic principle. As the patient, Kes-no-un-

da was diagnosed with snake and bear disease, so the helpers had to create sand pictures depicting snakes, while the dancer embodied a deity representing a bear. The community side of the healing ceremony offered a chance for other participants also to receive medicine for their disease. The ceremony itself took four days and the last night was the climax of the process.

The women's dance came before the healing ritual, and then they participated in the general dance. The twelve chosen men then took up their position on the south side of the pathway from the gate to the lodge. The clowns ran about among the crowd. The actors created much amusement by their gestures, appearing four times during the night. The dance continued in the darkness until sunrise, when the helpers emptied the lodge and the participants offered cornmeal to the trees, shaking off the last of their ailments. In the morning, the patients were reported to be cured (Russell, 1898). We find a similar description of another Indian healing ritual called "Dark Dance" by Kurath (1964). This is also a women's medicine rite practiced by the Iroquois, which was always performed at night, in complete darkness.

Lorna Marshall (1969) gave a fine-grained description of the Kung Bushman healing rituals as a real group activity known as the "giraffe dance" or "medicine dance". According to Ken Wilson, the archaeological evidence including petroglyphic remnants show that medicine dance is at least thousands of years old. The Bushman healers were thought to cure through their access to *n/um*, a divine force. The medicine dance as a ritual activity helps to activate the *n/um* within the healer. It is different from the shamans' dance-induced trance state, that here, all participants are under the physical strain of the dance. The dance goes on all night, frequently inducing an altered state of consciousness, trance state. Those unable to overcome their fear of losing everyday control of ego functions cannot become healers. A trance state enables the healer to communicate with the spirit world, whose help or support is needed by the sick. The activated n/um is given to the sick to extract illness or sending it away. However, the participation in the shared ecstatic experience is also a source of healing.

What is common in the Apache, Iroquois, and Kung Bushman medicine dance? Probably, it is the enduring physical activity and the altered state of consciousness, both are key elements of the physiological "reprogramming" of the bodily networks. The same is true for the social group bonds, moving together brings bonding together, a shared feeling of strong social attachment. The prolonged physical activity induces physiological changes releasing endogenous opiates, and other above-listed "myo-humoral" mediators and correlated patterns of autonomic nervous system activation might be important healing factor (Frecska, Kulcsár, 1989). The Kung Bushmen take sweat of the exhausted body of dancers and put it on the ill person, which might be exorphin-like medicine in the healing dance. Knowing the multiple "endo-medical"

role of the muscular system with its myokines, humoral factors, active neurological mediators, we might speculate the much wider healing agency of the medical dance.

Although these examples teach us about the ancient medical functions, there are not many reports, and field works about the healing functions of dance in the dance anthropological literature. Its understanding is rather culturalized and not medicalized. Human dance is a cultural behavior reflecting people's values, attitudes and beliefs as well and many cultural forms result from the creative use of human bodies in time and space, and needs interdisciplinary approach, as dance is physical, psychological, cultural, social, and sometimes political at the same time (Kaeppler, 1985).

Comprehending the anthropological understanding and contributions in dance field research, we can screen it from the beginning of anthropology. At the first steps of cultural anthropology, Spencer (1985) had already revealed the psychological importance of dance, which "releases emotional tension", and social and psychological, cultural and religious functions became central themes in cultural anthropology, however, one cannot find the words "health", "healing" in Hanna's comprehending overview of dance anthropological literature. Searching for the word medicine, one might find Marshalls' writing about Kung Bushman medicine dance, and Kurath's report about the above-mentioned Iroquois "Dark Dance". Medical anthropology, as a subfield of cultural anthropology, brought dance anthropology close to the health sciences, dealing with studies of dance in ceremonial healing. Dancing has an impact on health at the personal and social level available to medical anthropological study. The altered states of consciousness, the physiological changes accompanying the vigorous dancing, the psychosomatic phenomena of bodily expressions of emotions, the stress reduction as a consequence of dance create a shared interest between different branches of anthropology.

Human dance has an emotional, transformative content, and its expressive function regarding personal experience contains therapeutic potential due to its psychotherapeutic effects, which may act to release psychic tension. This function of dance, with its cognitive and affective dimensions, is embedded in a social psychological context. Through dance, one can gain control over the body, develop physical fitness, and transform emotions and instincts into linguistically-patterned forms. This skill of expression happens at a deeper level than verbal exploration. This deeper bodily process of 'access and reframe' may gain psychotherapeutic meaning and importance. In a social-psychophysiological context, dance may be a sort of coping mechanism for releasing socially-induced tension and frustration. Keeping in mind that the health consequences of enduring stress as an allostatic load come from evolutionary paradoxes. Our adaptive patterns were developed for a different environment, not for our high-tech, late modern milieu that induce sedentarism and the

jungle of our complicated social environment. The dance incorporates a wide range of evolutionarily-selected skills, such as a sense of rhythm, symbolic capability, innovation and variation, and kinetic ability, which might offer an adaptive outlet for suppressed tensions and unsatisfied bodily (and psychological) needs. This creates room for a slight shift in understanding dance as health protection and restorative cultural agency. As medicalization turns implicit cultural health content into explicit institutional and instrumental forms. Cultural issues with an adaptive function regarding health-related content bring dance into the framework of lifestyle medicine.

The communicative function of dance, which can acquire political significance through the articulation of political attitudes and values, may be able to overcome these obstacles. It may offer a means of control to a submissive member of a minority group, with attendant physical and psychological impacts. It can be more important in cases where the verbalization of personal or social frustration is normally muted. Anthropological analyses of narratives may help with revealing these covert functions of dance.

Healing of dancers and dance of the healers

Mapping the connections between medicine and dance, we find different semantics. Dance medicine as a profession and discourse is not what we were writing above. Dance medicine is an interdisciplinary subfield of medicine, dealing with various dance-related medical issues, including injuries, preventive, surgical, and rehabilitation interventions among professional dancers or those who practice dance as a sport. The research field includes biomechanical, physiological, and neuromotor aspects of dance, nutrition, psychological issues, and the body therapies and somatics area.

The biology of dance is a background discipline. In Hungary, it came to the forfront in the early seventies when the Táncház (Dance House) movement gained wide popularity and the development of folk-dance pedagogy induced public interest. Mihály Nemessuri, a pioneering expert in lifestyle medicine in Hungary, also exerted significant influence on the health support of dancers.

> Motion biology as a discipline deals with the analysis of sports, movements, physical exercises and various sport techniques and just as folk dances, modern gymnastics, ice dance. One of the tasks of biology of human motion in the study of folk dance is to analyze, accurately describe and record the movement phenomenon by means of moderns science and scientific quality. In addition, it also has the task of assisting in the learning of motion and the perfection and optimization of the motion processes. Thus motion biology can serve its own development along the development of folk dance. (Nemessuri, 1974)

In this basic motion research, we can see how science and dance culture are hybridized for mutual development. This is the aim of health medicine, too, which keeps dancers in optimal health for optimal and maximal performance. It is based on the results of scientific analysis of dance technique and its impact on the intensity of teaching, rehearsing, and performing, as well as on the results of clinical studies that examine the mechanisms and course of injury rehabilitation and movement re-education. Professional health protection is crucial, as the dancers' training itself bears imminent risks and physical and emotional strain that may result in temporary or extended disability. Acute and chronic injuries might accompany the overuse of the ligaments, joints, and muscles during a series of performances. The dance medicine is therefore might be seen as a branch of sport medicine, an interdisciplinary agency, where prevention and surgery have equal significance. Dr. Nick Keay, an expert of dance medicine, points to the multilayered tasks of health support including physical, psychical and spiritual layers of helping and healing agency,

> Traditionally, dance medicine has been somewhat the poor relation of sports medicine. Why is this the case? There is no doubt that dancers, of whatever genre, require the physical and psychological attributes of athletes. However, dance involves an additional artistic component where, ultimately, performance on stage is judged not according to a scorecard as in aesthetic sports, rather on the ability of the dancers to forge an emotional connection with the audience. (Keay, 2018)

Dance might have biomedical significance not only as an object of motion biology and biomedical expertise but also as part of mental health during biomedical training. The medical curriculum is a stressful project with high intellectual burden and emotional strain. A medical student has extreme learning strain to incorporate the huge mass of preclinical data, lexical knowledge, the series of serious exams generate prolonged distress with a significant psychophysiological load. Finkelstein (1990) reveals the message of this kind of biomedical enculturation: "study hard and learn a lot; learn to be objective; there is a little place in the practice of medicine for the subjective response".

Burnout is frequent among medical students. A statistical meta-analysis of graduate medical students' burnout included 24 studies of 18,000 students between 2010 and 2017 worldwide, and the emotional exhaustion reached the average 40.8%., cynicism 35.1%, and decrease in efficiency 27.4%. Half of the medical students were affected by some form of burnout.

Teaching art in medical schools might balance these deficits and psychological risks. A medical student summed up her difficulties and experiences and coping the stressors by the dance with these words:

> Medical training is, in many ways, like a disease. There are numerous pathologies in the disease of medical training – sleep deprivation, overburdened interns, error-prone systems, social isolation, debasing hierarchy. Many of these pathologies have begun to be addressed, but I discovered that there was another that had not (yet) been the subject of a blue-ribbon commission or a well-publicized lawsuit – the absence of beauty. Perhaps in the grand scheme of the scourges of residency, this seems like only a minor misery. But for me, it took a palpable toll, one that I wasn't even aware of until the "treatment" started helping me. I look back now and realized that it was the continual infusion of the aesthetics of dance that helped keep me alive throughout those draining years. (Frajerman, 2019)

That is why teaching art in medical schools might have a healing role and a partial solution for handling burnout. At Stanford, about half of all medical students become involved with the arts and humanities through a program titled Medicine and the Muse, which integrates the arts and humanities into medical education. In this program, among several genres, dance proved to be also a powerful source of personal empowerment. Stanford medical student Amrapali Maitra gained her experience of helping homeless, mentally ill women, survivors of domestic violence with dances of several kinds, "folk movement, Bollywood dance, hip-hop, and everyone got so much joy from this. The women started clapping and laughing and dancing around. That opened me up to the worlds of these women." She found professional resources as well.

> Dance is a thread that has always been there. It's a way of seeing and being in the world. I see how it shapes my approaches as a physician. It permits a different kind of expression than oral narrative.

> Certain things you can express through dance – feelings of rage, sadness, protest. In the form of Indian dance I do, we are trained to express mood or emotions with the face and hands and body to show feelings of disgust or peace or anger or love. (White, 2017)

This self-support function of dance might work after completing the medical studies. In our fieldwork, psychiatrist Éva Madarász wrote about similar function of folk dances, she found a source of social support and ways of emotional outlet, at the same time:

> At the Táncház I felt a sort of 'a priori' acceptance. It is hard to explain, but from the very beginning one can feel how one is a member of the community, while there are many levels at which one 'feels' the effect of music and dance: visceral, acoustic and social, personal and collective.

> Folk dances are very disciplined emotionally, and rich, just the opposite of the libertine freedom of disco dances. To live out a destructive force, or cope with aggression can be a preliminary step in building up the personality. Folk dances may help with this, too. I don't know whether the women's dances do it, but the men's dances have an obvious framework for this. Sometimes the shouting of rhymes and spinning around faster and faster may be an outlet for girls, too. (Lázár, 2015)

Thus, wide and evidence-based scientific data verify the efforts to join the dance and other arts to the medical curriculum as a complementary cluster of disciplines, skills and experiences offering mental health. The University of Florida Center for Arts in Medicine offers lecture/discussion, student workshops in dance and other arts and laboratory experiences to explore the links between the creative and the healing arts. Its practical significance is based on the clinical experience in the use of movement to enhance healing in a hospital or community setting. The Undergraduate Certificate in Dance recognizes special competency and achievement in the use of movement to enhance health.

Dance as healing, dance as therapy

Among the Millennial life reform movements of the early Twentieth Century, Eurythmy had anthroposophical roots, as part of Steiner's spiritual heritage. The word "Eurythmy" was proposed by Marie Steiner in 1912. Ita Wegman extended the scope of eurythmy toward healing, as a complementary way of cure, and she saw dance as a kind of panacea with diverse healing potential. This way, eurythmy became an essential part of the system of anthroposophical medicine. In several diseases, Wegman and her followers offered eurythmy as a complementary therapy. The eurythmy is thought to develop imitation skills and the body scheme. In the case of mental disabilities, eurythmy improves body image, facilitates social relationship, motor, and communication skills. Therapeutic eurythmia is recommended in private practices, clinics, sanatoriums, Waldorf schools, and social therapy institutes. It is not an extreme statement, that eurythmy was a historical precursor of the Dance and Motion Therapies.

Creative Arts and Therapy are all-adjunctive therapies utilizing different techniques with shared principles. One of these methods is dance therapy, which is – using Chace's definition – "a specific use of rhythmic bodily action employed as a tool in the rehabilitation of patients…" Marian Chace, as a "Founding Mother", became the first president of the American Dance Therapy Association in 1966. Her method was used in the Psychiatry at St. Elizabeth's Hospital in Washington. Dance therapy was classified as psychotherapy in the 1970s and 1980s, as a result of research into the psychotherapeutic application

of dance and movement. The dance therapists combine verbal and non-verbal communication to enable patients to express their feelings, to participate in human relationships, to develop empathy, to increase personal self-esteem, to develop a more realistic concept of their body image, and through all these to achieve some feeling of relaxation and enjoyment (Chace, 1975).

The American Dance Therapy Association (ADTA) defined dance and movement therapies as "the psychotherapeutic use of movement to promote emotional, social, cognitive, and physical integration of the individual, to improve health and well-being". This definition was extended with the "spiritual integration" content by the European Association Dance Movement (EADM, 2018).

The family of dance and movement therapies is a diverse genre. We might fix the standard "Chacian approach" as the original technique of DMT (Dance/Movement Therapy) invented by Marian Chace, but such restrictions in a creative world of healing by dance is not necessary. Koch et al., in her meta-analysis, refer to this great variability, mentioning dance therapy with ethno-elements, manualized body psychotherapy conducted by dance therapists, and dance therapy with elements of creative movement play. Dance interventions apply various dance styles, mostly traditional folk dance or cultural dance forms (Koch et al, 2019). In her listed dance dialects, "dance languages" one can find Irish set dancing, Greek traditional dance, Flamenco, Poco-Poco dance, Belly dance, Tango (Amador, 2017), and we can add Salsa, Hungarian folk dances, the samples of Dance House revival (Lázár, 2015) or the Cuban *Psicoballet* (Amador, 2017), just as other contemporary dances (jazz, modern, creative dance). The therapeutic aims might also be diverse. Koch (2017) listed five clusters, how DMT and dance might act:

Table 12. Classification of dance agency (after Koch, 2017)

Hedonism	Pleasure and play, non-goal orientation
Aesthetic experience and its authentic expression,	Experiencing beauty, body–mind unity, unity with a partner,
Non-verbal meaning-making	Communication, emotion expression and regulation, social interaction)
Enactive transitional space	Experiencing activity, agency, self-efficacy, constructive resources, test-acting, enactment, rituals, and transformation
Creation	Generativity, productivity

DMT can be a medium of diagnosis, treatment, and intervention that combines creative self-expression and psychological theories, and a medium of

interaction that allows personality to change as a result of the healing processes of dance (Schmais, 1985). Schmais pointed to several effective mechanisms influential in a group setting, such as empowerment, mutual trust, corrective emotional experiences, experiencing cohesion as part of something larger, probing social roles, and active interpersonal learning. It is interesting when the embodied experience is interpreted during dance therapy as a state of flow, including high concentration, absorption, focus on the here-and-now, physical presence, and joy.

Among the above-listed DMT methods, the Cuban Psicoballet dance and art therapy is one of the most widely analyzed dance therapy methods, which gained scientific support based on enormous, massive data sets of analyzed experience, as results of more than 25,000 successfully treated cases. This method combines different expressions of arts like dance and pantomime, theater and ballet, and offered to empower people with disabilities and mental handicaps and improve their quality of life, helping their rehabilitation and their integration into society. Psicoballet of Cuban historical origin had an intercontinental success, spreading over numerous countries of America, Europe, and Asia. This dance therapy was also recognized by the UNESCO. The academic acceptance of the Psicoballet method is proved by its adoption at the University King Juan Carlos, where it was applied as a psycho-geriatric dance therapy method to elder people enhancing their cognitive recovery.

The Hungarian Association for Movement and Dance Therapy was established in 1992 for the training and furthering of dance/movement psychotherapies and body-mind oriented methods in general. In the Association, different approaches of Dance/Movement Therapy and other body-mind oriented methods are also represented, such as Group-analytic Movement and Dance Therapy, Integral Expression and Dance Therapy, Body–Mind Centering, Feldenkrais). These methods help a lot to reintegrate the motion/emotion unity help to reflect on the unconscious process and the psychodynamic abyss.

The Integral Expression and Dance Therapy was developed by Wilfried Gürtler (1950–2003), a psychologist and dance therapist in Munich in the 1980s. Training groups have been established in several locations in Europe in the nineties, and it entered the Hungarian world of psychotherapies. In 1997 this method was introduced in Hungary as well, by the Association of Integral Expression and Dance Therapy) based on self-expression through

drawing, painting, claying, musical instruments, own sound, fairy tales, poetry writing, and therapeutic dance theatre. In this respect, it belongs to the international trend of expressive arts therapy, with a particular emphasis on movement, dance, and physical experiences. The potential for healing resides in the wound and its authentic expression. So, IED-therapists compassionately

come along with the patient's expressive movements, "life dance" as participants of the process themselves. From the IEDT point of view, illness is a path struck by someone in order to keep whole-some (i.e., not separated from themselves) and to integrate a broader concept of health into one's own life.

Izabella Varga sums up the comprehensive therapeutic content of this healing method:

> *Integral* in this case means that dance therapy alloys dance and movement with other therapeutic techniques and theories in a way that the whole is more than the sum total of the parts. Some examples for what our approach draws form: deep psychology, expressive art therapies, prenatal and perinatal therapies, verbal therapy, cognitive behavior therapy, social therapy, hypnotherapy, trance-states, NLP, Gestalt, systemic approaches (such as Hellinger's, etc.). In the late '90s, kinesiology (study of the flow of energy in the body) and trance dances (the cathartic and "trance-formative" effect of altered states of consciousness) were of great impact. (Varga, 2013)

Psychodynamic movement and dance therapy (PMDT) is a kind of "kinetic psychoanalysis". PMDT is based on the unconscious contents brought to the surface by physical sensations, differentiation, correction. It is a real body consciousness work. Our physical feelings are the oldest layer of our own, generated at a predominantly pre-speech age. The "core" of the personality develops in the physical-sensual mood and rhythm upon which the later "layers" are built on. Fractures, anxieties, and desires entrenched in body experiences are sometimes difficult to achieve through words. PMDT makes these elementary body experiences accessible by means of detection and movement. The key to this therapy is that personality is reflected in movement. The larger one's movement repertoire, the more options the individual will have for coping with her own needs and the demands of the environment. By shaping these bodily experiences, the unconscious feelings and relationship patterns associated with them can become conscious and changed.

Individual and relationship work is essential in the PMDT. Simple exercises sensitize our own bodily senses and feelings about others. Solo or group movement improvisation is based on body-conscious work. Due to self-perception, motion improvisation becomes a deeply personal creative work during the group process. In a secure therapeutic relationship, the healer can enhance the patients' self-perception through kinetic, gestural experiences, in a multimodal way. Every 'kinema': bending the body, laying down, standing up, keeping the balance, steps, and jumps, help to reintegrate the connection of the self and the body. It is called 'body-consciousness work', completed by interpersonal 'connection work', integration the perception of the Other's movements in a couple, or by triplet frames. One moves, the other listens, and

vice versa, creating a frame of persistent experience of the connected and related movements of the couple with feedback, establishing kinetic attunements, which develop the essential social skill of empathy. This kinetic dialogue is also about the embodied mutual understanding. The third stage of the therapy includes collective improvisations and kinetic creativity through movements of the pair or triplet. This way, the patients may 're-conquer' their body, and the space and time in a creative process. This leads to enhanced concentration, reality testing, self-trust, and diminishing anxiety. Discussion of movement experiences helps to develop deeper self-awareness. Although not all body sensations can be verbalized, it is essential to connect the bodily and verbal personality parts in the group process.

Table 13. Comparison of IEDT and DMT dance therapies

Integral Expression and Dance Therapy	**Dance and Movement Therapy**
The body system and its sanity.	Reintegration.
The emotional self-awareness.	Enhancement of bodily self-perception.
The personal creativity.	Improvisation.
The kinetic creativity in the Third phase.	The cognitive program of thinking.
The network of relationships.	The kinetic empathy, listening to the Other's movement.
The game of time and space.	Reconquering time and space.
The personal truth and life, structure the emptiness.	Self-perception through the kinetic, gestural experience.

The potential for healing resides in the wound and its authentic expression. So, IDE-therapists compassionately come along with the patient's expressive movements, "life dance" as participants of the process themselves. Every symptom is part of a constructive, and in some way, biographically necessary and understandable coping strategy.

Other more specific therapeutic mechanisms are connected to techniques of DMT, such as mirroring, movement analysis, non-verbal metaphors, imaginative techniques, meditative techniques, introspection, and focusing (Brauninger, 2014).

In a recent meta-analysis of 42 dance therapy research, Koch et al. (2019) verified that DMT decreases depression and anxiety and increases the quality of life and interpersonal and cognitive skills, whereas dance interventions increase psychomotor skills. The meta-analysis regarding the effectiveness of dance movement therapy (DMT) and dance interventions for psychological health outcomes based on results of 41 controlled intervention studies proved the efficiency of the dance therapies. Koch et al. (2019) investigated the results of 21 DMT and 20 dance therapy research, including clusters of quality of life,

interpersonal skills, cognitive skills, and psychomotor skills and clinical outcomes (with sub-analyses of depression and anxiety). The clinical significance of dance therapies is proved by several dance intervention studies Koch et al. have analyzed. These methods conquered clinical terrains like depression, anxiety, schizophrenia, autism, elderly patients, oncology, neurology, chronic heart failure, and cardiovascular disease. Some aspects of the therapeutic success are shared, like improving anxiety levels, quality of life, and body image (Koch et al., 2019). These health gains reflect the "lifestyle medicine" significance of dance.

Dance as a hidden remedy

As lifestyle medicine has a strong focus on stress and adaptation dysbalances, the evidence-based pillars mentioned above show that dance must be integrated into everyday health practice. The dance itself is a proper remedy for the unhealthy consequences of a sedentary lifestyle. Preventive efforts to diminish the risks of Type 2 diabetes, cardiovascular disease, colon cancer, postmenopausal breast cancer, dementia, and depression might urge us to take dance as regular exercise into consideration. In this sense, dance might be a significant "medical" element of lifestyle medicine. Beyond the physiological beneficiaries of the physical exertion, one might be grateful for the cultural, social, behavioral, emotional, and cognitive gifts of dancing as a source of well-being. In an age of alienation, social isolation, and workaholism, this holistic socio-cultural practice might be a mental health panacea. Dance may be a crucial health-promoting agent for the socially isolated, physically, or mentally ill (Houston 2005, Jenkins 2003).

Posttraumatic stress is a common problem. Studies of adverse childhood experiences (ACE) uncovered a silent epidemic of anomic family circumstances causing enduring mental and somatic consequences. Dance-related movement reintegrates traumatized patients with their bodies, the physical exertion through elevated endorphins, irisin, and BDNF might influence their mood, cognitive, emotional, and other psychical functions. As these mental and somatic difficulties are covert, and the victims cannot manage psychotherapy because of institutional and financial reasons, dance integrated in the everyday school practice might be a useful mental health solution.

Refugees, traumatized post-war victims are also offered unsolved challenges for mental health because of their massive number, and the destructive and anomic social milieu, they live in. Uneducated, illiterate youth (as high as 25% in the developing world), itself might be a source of anomy, conflict, migration.

The dance project named *MindLeaps* in Kigali, Rwanda, proves the success of dance as a means of social healing. Researchers and students from Carnegie Mellon University Rwanda and Drexel University guided the standardized

dance program organized among victims of civil war, and their children to develop cognitive skills and social-emotional learning: The results prove that they can succeed in school, enter the workplace and leap forward in life. Their mission statement shows how dance becomes a "social medicine", as the staff, dance instructors, educators, social workers, counselors, and administrators, are dedicated to *building a bridge to education and positive livelihoods through dance*.

They develop the critical cognitive and social-emotional skills of the disabled children, which are necessary for school and work achievements. This agency aims to change the mindset of these "at-risk children" and opening the door to education and employment, which can change their future, who otherwise are left to be abandoned to hopelessness or radicalization.

Migration generates crucial challenges in our age, the complex trauma refugees suffering from generates deep psychological and somatic consequences of traumatic experiences of persecution, flight, and severe, anomic acculturation strain. Dance/movement therapy offers a remedy for the treatment of complex psychological trauma (torture, rape, war experiences). Koch and Weidinger Von Der Recke (2009) report experiences at the treatment center REFUGIO in Munich, Germany, experts of which apply for a multifaceted therapeutic program as an interface of dance and verbal psychotherapy.

Results of applying Psicoballet in the intervention with children and teenagers who have been victims of sexual abuse might be a good sample, too (Cernuda, 2016). The method achieved significant improvements for the 32 children and teenagers suffering from the consequences of sexual abuse. Complaining of anxiety decreased from the pretreatment 77% to the posttreatment 41.3%; the depressive symptoms turned out to have diminished from 83% to 51.03%, and 47% were clinically recovered. As Cernuda summarized the benefits of Psicoballet, it offered a

> way of approaching the memories and painful recollections with dynamics and body techniques that are less challenging for the patient, promoting a therapeutic work embodied, focused on the emotional objection through the corporality that could offer well-being in the current and future life of the patient. (Cernuda, 2016)

Dance is a powerful help not only for those living in an anomic milieu, but is is a source for empowerment and developmental aid for the children having developmental, mental problems, too. Salus and Schanber (1967) deal with dance therapy or with a more exact title, Body movement, and creative expression training of language-handicapped children. As dance itself has a linguistic structure, way of self-expression, this way of helping the development of problematic children proved to be useful.

Dance of the Autists

The therapeutic value of dance for the autistic has been proven. Koch et al. (2014) explored the results of a dance movement therapy intervention based on mirroring movement in a population of 31 young adults with autism spectrum disorder (mainly high-functioning and Asperger's syndrome) to increase body awareness, social skills, self–other distinction, empathy, and well-being.

The authors claimed that autistic participants in the intervention group reported improved well-being, improved body awareness, improved self–other distinction, and increased social skills, and these outcomes seemed to address more of the primary developmental aspects of autism than the presently prevailing theory-of-mind approach. These therapeutic impacts may help to repair deterioration in social functioning and may help to extend social contact as only about 8% of people with autism report having reciprocal friendships (Klinger & Williams 2009). Dance may impact cognition, emotion, and motor functions to improve the social skills of those with autism. The sociability-enhancing effects of dance derived from the communicative function of the dance. The synchrony inbuilt into the collective circle that is formed during a *couple dance* facilitates cooperation and empathy among the interaction partners as motoric mimicry, and synchrony itself develop empathy (Hatfield et al., 1993). We may see that postural and motoric mimicries are part of developing empathy (La France, 1985) and sharing the dispositions of mood is also proper to the dance experience (Neumann & Strack, 2000). The imitation that occurs during the learning of dance may foster better interaction and liking between partners (Bargh & Chartrand, 1999). Dance offers a chance for interpersonal closeness, which facilitates mimicry. Learning and practicing folk dances can be thought of as a form of embodiment. The neural circuits that are activated and are responsible for this imitative, online form of online embodiment promote work as a part of social contagion and induce congruent emotional states in others (Decety & Chaminade, 2003). This is why the experience of 'online embodiment' may be a component of empathy and social cooperation, which is undoubtedly one of the behavioral benefits of collective dance learning and part of its therapeutic value.

Corrective development through dance

Early developmental problem can also be corrected through movement and dance. Hatcher and Mullin, dance therapist and special educator authors deal with the development and implementation of movement in early childhood, as pre-requisite for the mastery of later complex movements (Hatcher & Mullin, 1967). The "hierarchy of movement level" creates a guide for the correction

of "development lags." The development of motion experiences that are weak, under-experienced, or missing in the first two years of existence calls for educators to help the children to re-experience the previously omitted movements. Specific activities are provided to strengthen the development of the total body, with emphasis on on hands and feet, multi-sensory awareness, and body-image concepts.

Aging and dancing

Aging is also a growing epidemiological issue with several health problems. The ever-increasing importance of health psychology in improving the quality of life for older people lends great significance to dance for this age cohort. According to Paulson (2009): "Older dancers positioned the dance as beneficial for their health in terms of physical, psychological and social factors." Recreational folk dance provides social, physical, creative, cultural, and mental benefits for older people, supporting their well-being or helping their rehabilitation (Connor, 2000). Aerobic exercise reverses the loss of hippocampal volume in old age, which improves memory. Physical exertion itself might reduce the risk of Alzheimer's disease by 60% improve cognitive processes, and increase brain-derived neurotrophic factor (BDNF) production. Dance-like exercise can also improve the quality of life of older people if they become more dependent within a nursing home context (Shigematsu et al., 2002).

Some diseases are typically associated with senium, like Alzheimer's and Parkinson's disease.

Social dance, with its lively atmosphere, can be a health-enhancing physical activity among older people without the risk of medicalization. The weekly schedule gives a secure framework, and the regular social dance event recalls a positive reconnection and continuation with one's memory, youth, and history (Roberson & Pelclova, 2013).

In the Dance House Movement, in the last years, Ferenc Sebő and his musician and dancer friends established a Dance House of the Elders ("öregek táncháza") for those participated in creating the "Táncház (Dance House)" movement "once upon a time", and now they are in their seventies, sixties.

Sometimes it is enough to see the dance itself, which might also exert beneficial effects in old age. A folk-dance group from Calgary, the Vadrózsa group, reported their experiences of performing in a hospital setting and several old folks' homes. They had danced in the Alberta Children's Hospitals and and places like that.

> In an old folk home, sometimes this is the only excitement they get. This is sad to say. When we come, they are so happy, the excitement and the joy they can experience. Sometimes someone comes up to us, saying – being Hungarian – he used to dance

these dances when he was young, and he is so happy that we keep the tradition alive. (Lázár, 2015)

Dance and Alzheimer's disease

Aerobic exercise reverses the loss of hippocampal volume in old age, which improves memory. Impaired mobility in older people is associated with an increased risk of Alzheimer's disease, Parkinson's disease, and depression. In a study of 1500 men and women, moderate physical exertion twice a week reduced the risk of Alzheimer's disease by 60%. Irisin induced by physical exertion might also be an essential therapeutic factor, slowing down aging by increasing the length of telomeres and enhancing BDNF production in the brain.

Dance and Parkinson's disease

Parkinson's disease is also a severe neurodegenerative syndrome in which the lack of dopamine and the tremor and rigidity of muscles interfere with the intentional movements and the everyday activities. The emotional expressions are also limited, as gestures and pantomimes are distorted by limited facial expression, slowing of the personal motions. Parkinson's disease frequently leads to social isolation. Although Parkinsonism as a chronic disease might be tempered, it is not curable like the infective diseases. The quality of life of these patients has crucial importance. Results of evidence offered by dance practitioners giving dance hours to patients show that temporary relief of some symptoms is observable, and these patients cope better with everyday actions.

One of the first studies of dance therapy with groups of outpatients with Parkinson's was led by Beth Kaplan Westbrook and Helen McKibben (1989). The healing effect of the Dance Movement Therapy was reflected by diminishing the neurological and emotional symptoms. Tango also proved to be effective in promoting increased functional mobility, balance, and stability in Parkinson's patients.

Similar results are mentioned by Cerruda, who reported Psicoballet as an effective therapeutic instrument in the cure of neurodegenerative disorders (Parkinson's and Alzheimer's), which might reduce the speed of the degeneracy and helps to recover cognitive plots (Amador, 2017).

Overviewing dance therapies with patients suffering from Parkinson's, Hackney and Earhart (2009) have found that dancing the Tango shows the most robust results in fall risk, gait, and balance confidence, and facilitates positive social interaction in comparison to other non-dance exercises. The kinetic world of the Classic ballet language as the Department of Learning of the English National Ballet piloted twelve dance sessions for people with

Parkinson's, based on Nureyev's Romeo and Juliet. Here dance gains new content, as Houston (2011) writes: "Dance is also given a new presence, a new ontological status, one that aligns with conceiving of the form as a therapy, or even as a biomechanical phenomenon, rather than as art or entertainment."

The results of the dance therapy need a multidimensional analysis in a frame of a 'methodologically aware eclecticism', where the quality of life, motivation to continue dancing, and physical and social responses in a dynamic, natural environment of a dance session are also objects of consideration. It needs a complex *behavioral medical* scope of the disease and the healing process. The kinetic reality of the patient is distorted and changing step by step, through various "corporeal shifts of being", often with negative consequences for perceptions of self-identity. Dancing offers a way of reintegration of self and body, by the embodiment of the regained integrity through the movement.

ATTACHMENT, SPIRITUALITY AND HEALTH: PSYCHOIMMUNOLOGY OF FAITH

Dear friends, let us continue to love one another, for love comes from God. Anyone who loves is a child of God and knows God. But anyone who does not love does not know God, for God is love.

(1 John, 4:7)

The meaning of religion itself attaches us to the word attachment as the word comes from the Latin *religat*, a third-person singular present active indicative of *religō* 'he (she, it) binds', *religio, quod religat,* which implies social ties on a spiritual basis that bind members of the society to one another. Mapping the web of meaning "attached to" and "attachment", we may find strong spiritual connotations. Early and adult attachment, relational attachment and disordered attachment are psychological terms that help to elucidate the spiritual and moral conduct of human behavior. Its power may shape the image of deities of the given culture, as Rohner's cross-cultural work dealing with the quality of parenting, the so-called *PARTheory* proved that societies preferring warm and accepting parenting had constructed deities with analogous qualities, whereas societies, where the rejecting parenteral style is the proper feature, had constructed more interfering and distant deities (Rohner, 1986).

Attachment theory offers hermeneutic passages between moral theology and health psychology, helping the translation between spiritual and secular paradigms.

There is a strong need for this translation because the spiritual concept of wholeness and health was substituted by the "secular credo" of biomedicine (Fabrega, 2000) during the Enlightenment. The consecutive disenchantment of the world helped naturalistic rationalism and medicalization to gain wide control over moral and theological aspects and terms of misconduct (Helman, 2007).

The ecological understanding of religion and the world of rituals in terms of Rappaport (1999) helps us to widen the anthropological hermeneutics of attachment, too. Although we cannot find the word "attachment" in the index of his last and comprehensive book, its importance is unquestionable in the Rappaportian framework. The revelation of the evolutionary role of religion in human life, and the adaptive value of different cultural forms and rituals as

regulators in maintaining the relationship with their environment bring his concept close to our inquiry. This also means that rituals, through their expressive and creative function, create a perceptive-cognitive and engaging framework regarding the environmental behavior of the given culture. On the other hand, Rappaport weaves the mutual net of influences between Nature, Infosphere and Society, investigating the relationship between ecology, religion and society. The missing agent is technology, but when Rappaport makes us remember that in modernity science took on the role that religion played in the continuing evolution of life, he covertly gets us to pay attention to the role of the technosphere in closing the tetrahedron-like network of environmental agencies. On the other hand, he urges us to renew the links between religion and science on several levels.

According to Rappaport, rituals are mending the world, which has been analyzed, cut to pieces, and divided into taxonomies and nets by language. The boundaries and barriers created by language are transcended by ritual representations, correspondences, symbolic polysemy and analogies. Rappaport implicitly writes about the "attachment function" of the liturgical and ritual representations: "intrinsic to the chord-like or simultaneous dimension of liturgical representations, at once indexical, iconic and symbolic, to unite or reunite, the psychic, social, natural or cosmic processes which language distinguishes and which the exigencies of life pull apart."

This bonding role – taking part in the regulation of social, political, and ecological relations – is not simple at all, as they bind together disparate entities, processes and phenomenal domains. Rappaport sheds light on the "how" the "bringing together" is peculiar instead of why the elements are to be brought together, with the concept of meta-order. The liturgical representations are orders of orders. In that sense *religat* means – with words of Rappaport (1999) – to "mend ever again worlds forever breaking apart under the blows of daily usage and the slashing distinctions of language."

His famous paradigmatic research regarding the Tsembaga Maring ritual cycle presents such representations: a "sanctified rule-governed sequence of formal acts and utterances during which cosmological oppositions are substantiated in multivocalic representations are transformed from a state of antagonism and fragmentation into one of complementarity and wholeness".

We can reveal similar covert ritual functions in the medical socialization, when symbolic anatomies, alternative realities of subtle field properties, like chakras and the aura of the human body are muted, and the anatomical insight is directed towards the dissected *sarcs*, the reified "soma". The technocratic rite of birth expresses the analytical and detached, technospherically dominated cosmology, as Davis-Floyd (2004) interprets it.

Detachment may be expressed by social attitudes, dismissive and fearful adult attachment, or by the culture of dance as we have shown in a previous

chapter. This ritualism of modernity corresponds with secularization, bureaucratization as well as disembeddedness. As Giddens explains, the rituals of money withdraw social activity from the localized contexts and reorganize social relations across large time-space distances with the help of the symbolic ritualism of exchanging value. The religiosity correlates well with a psychological index, the meaning of life. This covert role of ritual practice helps – as Rappaport writes – "that a single liturgical order may encompass understandings that include the Ultimate Sacred Postulates, cosmological axioms concerning the structure of relations among spirits, qualities, persons, things and processes, rules for transforming these relations and indications of prevailing states of society and nature."

In that sense capability of love and attachment as governing logic may be such a metaorder itself, too. Attachment theory as a hermeneutic framework for psychological developmental aspects of love, faith and fidelity, psychosocial bonds, and disordered behavior like addiction and vice, helps us create a metanarrative driven by conflicting theoretical resources like psychoanalytical frameworks, ethology and Christian theology.

While the psychological *attachment theory* helps in the functional understanding of the therapeutic role of spirituality in distorted attachment, Freud himself interpreted religion in a different way, seeing it "as a universal obsessional neurosis." The way, Marx (1844) paraphrased Novalis' maxima: "Religion acts merely as an opiate", also has hidden significance in our context. He attached the concept of religion to social suffering, and wrote: "Religion is the sigh of the oppressed creature, the heart of a heartless world, and the soul of soulless conditions. It is the opium of the people".

It was an intuitive statement. When we recall the research results of Jak Panksepp, who proved the prominent role of endorphins, endogenous opiates, in attachment and in the bonding experience, we can draw the following web of meaning consisting of religion, bond, opiates and attachment.

Carl Gustav Jung saw religion as a delusion, too. But Jung avoided medicalization in understanding the religious phenomena, realizing "its value in providing assurance and strength, allowing humankind to transcend the instinctive stage of the unconscious into the heights of great moral and cultural achievements" (Wulff, 1997).

Love as a spiritual attachment may be reflected by spiritual detachment from the addictive bonds of the secular world. Harmonic and distorted attachment organizations have serious health psychological significance because of their developmental consequences.

The three kinds or levels of Love must be differentiated; Eros is the physical love, Philia is the brotherly love, when one loves the other because of who he or she is. This may also be conditional because things might change. Agape is the third, the Divine type of love, which is not earned or deserved. This love is freely given

and is unconditional. This is the Love, which frees one from addictions, so harmonic attachment helps overcome disordered attachments. Love may be taken as the chief of all the virtues that enable us to resist the formation of disordered attachments.

Spiritual detachment and the attachment

Spirituality is considered to be human, but humanism itself is not spiritual "by nature". Issues of the material part of the human and even the whole created world can be seen as non-spiritual and non divine – or even counter-divine. Manicheism created a harsh opposition between sinful material created by the Demiurge and the world of light, a dual fight of good and evil, with the final purpose of liberating light from its material prison.

The Christian system of values and beliefs also seem to set the spiritual against the material as in the case of denying the pagan cults of nature or generating feelings of guilt because of sexuality. According to its critics, Judeo-Christian biblical thinking was one of the first candidates to be assigned as being responsible for the western exploitative attitude towards Nature. Max Weber disclosed the nature of "economic asceticism" of the Protestant ethic in the framework of the disenchantment (Entzauberung) of the world. Predestined goodness or proper conduct implies the profit maximizing rationality for a good Christian. The Buddhist concept of Nirvana is also about the detachment from the material world.

Accepting these considerations regarding spiritual detachment, we try to understand the paradox that while spirituality means a form of human detachment from the "real world", spirituality may also serve the reconstruction of another, real world with extended bonding, responsibility, compassion and devotion. The primordial condition of sustainability is the spiritual guarantee of attachment capabilities. We can read on Korten's website: "A balanced and harmonious relationship between human communities and their natural environment is strongly associated with a reverence for the spiritual unity of life and a strong bonding to community and place."

Spirituality depicts a perspective led by covert higher ethical values uncommon in everyday behavior and sensitivity towards signs, symbols and meaning, representing a transcendental system regarding the values of unity, faith, love, compassion, mercy, sacral beauty etc. Spiritual ethics respect all beings, placing us humans within a larger whole. Spirituality challenges economics, searching for humanity, not in material wealth, but in inner wealth, in a creative and responsible being.

Spirituality is associated with spiritual practices like meditation, prayer, divination, listening to the inner voice and visionary and imaginary practices. All of these are common in tuning the Self to the transcendental. According to the

so-called *etic explanatory models,* this transcendental sensitivity may be based on psycho-physiological processes localized in the right hemisphere of the brain.

One thing is obvious; spirituality accepts the authority of a transcendental entity with its universal values. Most religious cultures agree that the core values are love, unity, and compassion; all of them are attached to the personal capability of attachment. Spirituality creates the foundation and context for religious beliefs and traditions. However, formal religious membership in a church does not necessarily mean spirituality in all times as spirituality may be practiced without religious commitment. Finally, spirituality can hardly be imagined without openness and *attachment to the transcendental.*

Spirituality as remedy

One must admit spirituality as a factor that contributes to health in many individuals. Spirituality appears in all cultures and societies. It includes the search for ultimate meaning through participation in religion and/or belief in God, family, naturalism, rationalism, humanism and the arts. All of these factors can affect how patients and health care professionals perceive health and illness and how they interact with one another (MSOP Report III. Association of American Medical Colleges, 1999). Spirituality offers support for needs, giving meaning to life, illness, crises, and death, a sense of security for present and future. It may guide daily habits and provide psychosocial support to a group of like-minded people empowering people when facing life's crises.

As Koenig (1997) proved it in his comprehensive study, spirituality may also be a healing factor. Those, attending church were half as likely to have elevated levels of IL-6. Increased levels of IL-6 are associated with increased incidence of disease. The religious commitment hypothetically may improve stress control by better coping mechanisms, richer social support as well as the strength of personal values and world-view.

Harris, in a longitudinal study among 40 adult heart transplant patients, followed via qualitative and quantitative measures for 12 post surgery months found that participants who consulted God to make critical decisions and felt that their beliefs profoundly influenced their lives were more likely to report a (self-perceived) positive health status. Those who participated in religious activities and said that their beliefs were important, showed better compliance with follow-up treatment, improved physical functioning in the 12-month follow-up, higher levels of self- esteem, less anxiety and fewer health worries (Harris et al., 1995). In a sample of 3148 people from three randomly selected villages, Gupta et al. (1997) found that men engaged in regular prayer had a statistically lower prevalence of CHD.

Kass et al. (1991) found a high spirituality index in his research, which reflected aspects of spirituality with increased life purpose and satisfaction and decreased frequency of medical symptoms. In Koenig's research, those regularly reading the Bible were 42% less likely to have had an alcohol disorder within the past six months than the rest of the sample (Koenig et al, 1994). Levin et al. (1989) found a negative correlation between religious commitment and hypertension based upon epidemiological studies. In their comprehensive overview, Matthews and his colleagues (1998) concluded that religious involvement may be helpful in the prevention of physical and mental illness, in facilitating recovery from illness, and in helping people cope with illness.

They concluded this based on a general overview of research on the relationship between religious commitment and depression, substance abuse, physical illness, mortality, coping with illness, and recovering from illness. It seems so that spirituality may be a salutogenic factor in the case of health problems, which have their roots in the distorted early attachment organizations.

Spiritual attachment

The etymology of the term *religion* refers to the web of meaning of *attachment,* as the Latin root of *religion* comes from *religat* (*um*), past participle of *Religare*, *bind up*. Attachment theory, spirituality and religion are connected by the analogy between child–parent and God–believer relationships. Kirkpatrick showed that many aspects of religious belief and experience reflect the operation of psychological attachment processes, where God or other supernatural entities offer all the criteria of the attachment "proximity maintenance", "safe haven" and "secure base" for those turning to caregivers (Kirkpatrick, 1992).

There is evidence that this spiritual attachment may confer psychological benefits associated with secure interpersonal attachments. Kirkpatrick (1995) also emphasizes that nontheistic religions may also offer spiritual attachment experiences, like in the case of Mahayana Buddhists' devotion to ancestral spirits. Spirituality, perceived relationships with God, meets all the defining criteria of attachment relationships.

That may be one reason why religious experience may heal drug addicts. In the Protestant tradition, closeness to Christ by prayer offers an attachment-like psychological support and security, while in Catholicism it is Holy Mary, who represents the "maternal functions" related to attachment. Religion itself may be seen as a dynamic attachment process. On the other hand, to be far away or separated from God, as in the case of apostasy or deconversion, is a real psychological hell for a believer.

Individual differences in religious beliefs and experiences should parallel the so-called internal working models or mental models of attachment. That

means that distortion of the mother–child relationship may distort the spiritual openness as well, while recovering spirituality with the experience of metanoia may lessen psychological and psychosomatic disturbances caused by the traumas of early socialization. God or other supernatural beings may act so to substitute the role of an attachment figure.

In this healing relationship, God is the "Secure base" and the "Safe Haven", which may relieve the wounds of bereavement and other kinds of loss. Attachment to God may confer emotional benefits associated with secure interpersonal attachments. The secularist, atheist or non-spiritual cultural impact of materialism and consumerism inhibits this healing potential.

On the other hand, it seems obvious that the so-called B type, harmonic attachment organization, is the basis for harmonic personality development, and provides a perfect niche for spirituality representing unity, compassion, and attachment to others and to Nature and to God. This spiritual attachment may have an empowering, substituting function, as one may experience the *Divine significant other* filling the empty place of the missing body/flesh significant other. Two hypotheses may be offered to explain the different frameworks in which spiritual attachment may fulfill its healing essence.

According to the *compensation hypothesis* those individuals with insecure childhood attachment relationships, may be helped by *the compensatory role of spiritual attachment* to adjust to distress. Jesus Christ and the Blessed Virgin Mary may be experienced as surrogate attachment figures. This concept has received support, for example, in findings, showing that distress-driven religious changes and conversions are linked to attachment insecurity. In the case of insecure attachment based internal working models, the person's spirituality reflects stress-provoked distress regulation strategies, in which personal notion of God helps to substitute for the missing Significant Other. Granquist confirmed the compensation hypothesis in the case of adults practicing non-organized forms of spirituality, adopting a New Age orientation (Granqvist & Hagekull, 2001).

The *correspondence hypothesis*, offered by Granqvist (Granqvist & Hagekull, 1999, Granqvist, 2002), constitutes a different model, where early experience of secure childhood attachments establishes the basis of a corresponding relationship with God. (IWM correspondence; see also Kirkpatrick, 1992) The secure attachment organization establishes the basis for better socialization to adopt the attachment figure's religious or nonreligious standards (socialized correspondence – Granqvist & Hagekull, 1999). Granqvist (2002) reported significant correlations between secure attachment characteristics and scores on the socialization-based religiosity scale (Granqvist & Hagekull, 1999).

There is an implication from these findings that apostasy is not necessarily a normative adolescent phenomenon. It is associated more with insecure attachment characteristics and the forming and breaking of other affective

bonds. In addition, attachment studies should be conducted outside of the Western world to examine the cross-cultural validity of the attachment framework as applied to religion and spirituality.

Nonetheless, such studies are entirely relevant to attachment theory insofar as the behavior (e.g., prayer) of individuals in a given religious tradition is directed to some external supernatural figure.

Basic Christian values in the context of human ecodynamics

In the vocabulary of human ecodynamics, *faith* means symbiosis with the divine Other, *hope* is perceived synergy with the future, *love* is about mutualism with the brethren of the human (and non-human) kinds. Faith implies trust, and trust is a central category of economy, social relationships, as Fukuyama assumes in his oeuvre. Faith implies a perception of security, too. Hope is faith and trust in the future. Love is trust and faith in your brethren, and in yourself, as well. Exploring the deep logic of the Christian church, which was thought to be the mystic body of Christ, we find three keywords: *communication, community and communion.* Communication with the Lord, communitas offered to the Lord and via Eucharistic communion with the Lord. Faith is the basic condition under which this can happen with a religious person. Hope feeds the notion that it may happen soon enough. Love is the condition through which, this bond and symbiotic relationship with the Lord and the brethren's acts and deeds.

It is not surprising at all that faith, as a sense of coherence, a sense of meaning of life and hope – including optimism, a positive perspective of the personal future and love as a resource of mutual social support – are health psychological protective factors. Hope and optimism may enhance the psychoimmunological indexes, too. They all have a deep ethological basis as Lionel Tiger proved it in his brilliant work, "Optimism: The Biology of Hope". We will try to prove this based on our behavioral epidemiological data.

Religion: health and bonds in social, mental and bodily context

The etymology of religion expresses the core meaning of its cosmology, behavioral strategy and cognitive framework. The Latin word *religat*, as it was shown earlier, is connected to the web of meaning of 'relation' and 'attachment'. This attachment ring includes the significant Divine Other, the Church as the mystic body of Christ, and the religious community of Christians offering social support and a sense of social embeddedness.

This embeddedness includes social, ideological-cosmological, and transcendental attachment. It is not easy at all to measure and define the depth of the religious status, identity, with its multiple meanings of sociological, psychological or theological contexts. Even the precise determination of religion calls for a multidimensional approach. If we use the tetrahedron model, we reveal the differences of Natural, Social, Technological or cognitive-symbolical, ideological focuses: Roy Rapoport's theory of religions, shaped by the Natural environment, re-presenting adaptive dynamics and representations, or the cultural materialism of Marvin Harris.

Lenski (1961) has identified four dimensions to measure religiosity (participation in the rites, orthodoxy, religious experience, and belonging to religious groups). Glock and Stark (1965) distinguished five dimensions: religious beliefs (ideology), religious practices (ritual dimension), religious experience, religious knowledge and piety practiced.

The health psychological gains of religious attitudes may be evaluated only in the case of a well-mapped spirituality. Spiritual orientation may be measured by Underwood and Teresa's (2002) Daily Spiritual Experience questionnaire, which examines spiritual/religious coping, and social support. The questionnaire "HOPE" (Anandarajah and Hight, 2001) entitled by the acronym deciphering H as 'hope', with O covering issues of organized religion, P standing for a personal spirituality and exercises of personal spirituality and practices, and finally E as effects on care and decision-making.

The "FICA" (Astrow et al, 2001; Post, Puchalski, and Larson, 2000) questionnaire implies the letter F as *faith*, I as the spirituality of personal *importance*, C as the support of the *community connections* (spiritual community of support), and the letter A indicates how people *apply* is as part of their spiritual coping. The "SPIRIT" (Maugans, 1996) questionnaires imply the acronym: S as *a spiritual belief system*, P as *personal spirituality*, I as *integration* into the religious community, R as ritualized practices and barriers, I as medical *implications* and T as planned spiritual plans and interventions in the *terminal (T) status*. Allport and Ross (1967) use two-dimensional simplified tests to explore the religious orientation scale (Religious Orientation Scale ROS) as an intrinsic and extrinsic religiosity.

The protective role of religion in mental health

The protective role of religiosity has been demonstrated in a mental health context by our earlier Hungarostudy studies. Other surveys also consistently proved that a believer with regular religious activity is more protected in the context of health psychology. The regular church-goers report fewer sick days

at work and their quality of life is better because of the spiritual/psychological protection against addictions, smoking and alcoholism. The religious respondents of the Hungarostudy survey proved to be less depressed, less hostile, more cooperative and having better coping methods, they also reported receiving more social support (Kopp, Székely, Skrabski, 2006).

Zonda and Paksi (2006) found significantly lower numbers of drinkers and smokers and higher coherence and refusal to commit suicide among religious respondents. Moreira–Almeida, Neto and Koenig (2006) affirmed that the majority of well-conducted studies agreed that religious practice is positively correlated with psychological well-being indicators (satisfaction, happiness, positive emotional attitudes, and morality). There was also an inverse relationship with depression, suicidal ideation, drug abuse, and alcohol addiction.

The protective role of religious practice against stressors also appears in the case of the elderly, disabled or chronically ill patients. Strawbridge (1997) found a positive correlation between regular religious practice and positive health behavior, physical exercise, smoke-free lifestyle and social support in the case of 2500 people in his 29-year follow-up study. Townsend et al. (2002) verified that religious belief and regular church attendance are beneficial to the immune system, can significantly lower blood pressure, dismiss the risks of coronary heart disease, and suicide. So, it is not surprising that Hummer, Rogers, Nam, and Ellison (1999) found difference in the average life expectancy between believers and skeptics. The difference was 7 years, but it reached 14 years when they compared believer and sceptic Afro-Americans, in their follow-up study involving about 20,000 people (Ellison et al, 2000).

Hungarostudy surveys included only two dimensions of religiosity, religious practice with church group bonding, and spiritual dimensions of religiosity. Simple questions like "do you practice any religion, and if so, how?" helped us to gain deeper insight into a wide cross-sectional population-based study. The possible answers were: non-believer / do not practice their religion / exercise their own way / rarely in the church / regular church attendance and practice: these were the categories reflecting the basic religious habitus.

The questions regarding the meaning of spirituality helped to draw distinctions between the grades and depth of faith to discriminate whether someone's faith pervades their whole life and actions, or if it is just a conventional, formal issue.

Data of Hungarostudy 2013 reflected an ongoing secularization trend; all age groups, even in the oldest age group of sixty-five years of age, the number of those who regularly practice their religion declined compared to data from Hungarostudy 2006, while the number of those, exercising spirituality their own way, has grown.

Alternate spiritualities, distorted attachment and health risks

In the previous Hungarostudy survey, it was striking to see how personal types of spirituality, detached from regular Church praxis were accompanied with worse health psychological features. However, the "compensative versus correspondence" model may help to understand the phenomenon.

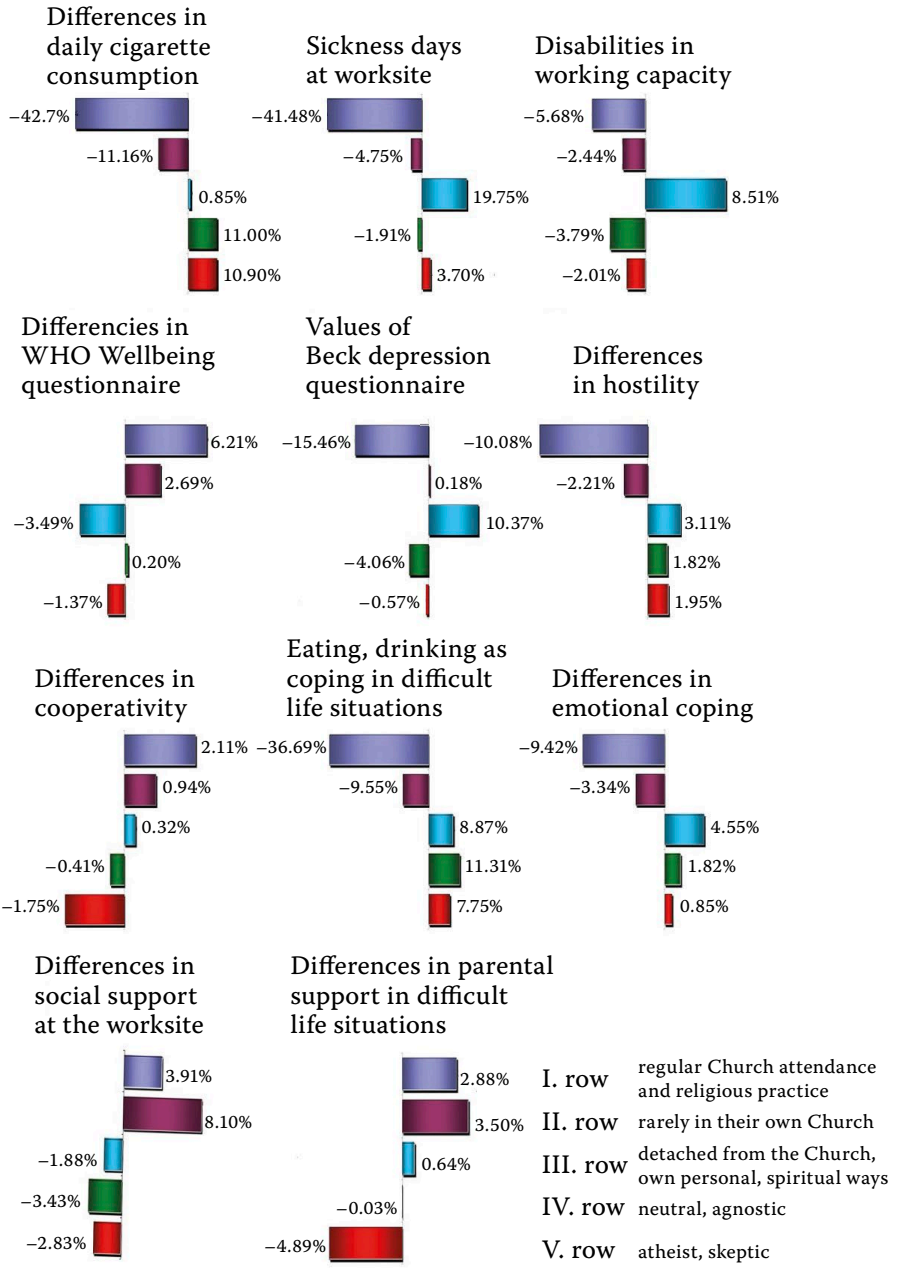
We can also recall anthropological efforts to understand the relationship between personal suffering, psychological handicaps and alternative types of spiritualism. Mullholland (2007) offers such an explanation to connect the New Age Movement, the Bowlbyan attachment and the mentalization framework of Fonagy to explain this hypothesized relationship. His approach differs from the concepts of Kirkpatrick or Granquist, as he has chosen the mentalization framework to explain the complex ways in which "psychological and religious development can be fostered or stymied by variations in and deviations from culturally valorized socialization processes and the historical and class-related socioeconomic forces that shape them."

Mullholland seeks an explanation for the deviant particularism of personal religious cosmologies and strategies and tries to uncover the mechanisms of how the Puritanist, legalistic-orthodox Church practice influenced the relational culture and skills, and what answers were found in the Millennial spiritualism, New Age Movement and New Religious Movements in the case of those who suffered from personal psychosocial burdens, early traumatization, maternal neglect and its developmental psychological consequences.

He applies the mentalization theory as an explanatory model that connects attachment difficulties and the development of narcissistic tendencies with the "own-way" spiritualism of the New Age Movement. We found the traditional, regular Church practice protective, but the harsh health psychological data found among the "own-way" spiritualist supports the approach of Mullholland.

These data prove to be convergent if we see traditional, regular or legalistic orthodox Church practice as a frame of harmonic attachment implying *normative–adaptive attunement* to the given community, family or the wider social system based on an emotionally harmonic and balanced attachment habitus, while the dismissive or fearful-avoidant attachment patterns derived from early traumas such as maternal neglect, may inhibit harmonic social integration, and the person may compensate with "own-way" spiritualism.

Figures of Hungarostudy 2006 on health psychological data in the context of spirituality and religious attitudes. Data recorded in 2002 in a national representative sample of 12,000 informants, research led by Prof. Mária Kopp et al., Semmelweis University, Institute of Behavioral Sciences.



Figures from Hungarostudy 2006 in health psychological data
in context of spirituality and religious attitudes
Data were recorded in 2002 in a national representative sample of 12 000 informants, led by Prof. Maria Kopp et al. Semmelweis University Inst. of Behavioral Sciences

Figure 14. Health psychological effects of religiosity

Religiosity, attachment and health psychology issues

Regarding religious attitudes and adult attachment features, the 2013 Hungarostudy data helps us uncover relationships between sociality, spirituality and the mental health. We found significant differences regarding avoidant, dismissive attachment between the religiously indifferent and those practicing their religion. Examining the importance of religion also proved to show a significant difference in the age group above 35 years in the context of abundant, independent adult attachments between experienced religiosity and superficial religiosity.

This raises the question of affiliation in the pervasive religious experience, which (mostly over the age of 35) corresponds to the compensatory religious affiliation. Data regarding preoccupied adult attachment showed a significant difference in the range of values in the context of religious practice and the difference was significant in the age group under 35 years as well. This may indicate that among those who regularly practice their religion and those having deeper religious experience young people may have significantly higher preoccupied adult attachment tendencies. This may be compensatory in nature, or part of the spiritual-religious "empowerment". However, it cannot be ruled out that the pervasive religious experiences based on the concept of the original sin imply a sense of imperfection and the submissive perspective towards the *Divine significant other*. In this sense, the spiritual attachment may represent another type of correspondent spiritual attachment.

Emile Durkheim introduced the concept of anomie in sociology. The anomie was also measured in the Hungarostudy 2013 Survey to explore the level of purposelessness, social norms, and lack of morality, which are largely responsible for the socially harmful behavior, such as crime, alcoholism, and suicide. An earlier survey, the Hungarostudy 2006, has shown that religious behavior and thinking are associated with lower anomie (Kopp, Székely, Skrabski, 2006). In the current study, we found similar results, although a significant correlation could have only been established among those older than 35 years in age. In the first part of the questionnaire regarding anomie, the offending behavior was separately examined. This question refers to the extent to which the respondent disagrees with the allegation that the rules need to be adhered to – does he or she accept the role of the legal rules, the law. The average value of the offending behavior also showed a significant difference between the different groups of older people regarding the different religious attitudes. Marital or relationship stress index, measured in the case of *spouses/couples relationships*, also correlated with religiosity in all age groups.

Health psychological and quality of life indexes were also measured in the context of religiosity. The coherence index reflects how we find the sense or meaning of life, which was closely related to both religious indices of all age

groups. The WHO Well-Being Index also proved the importance of religion in the elderly group, showing a significant connection. Depression is the most important mediating factor between psychosocial stressors and the physical symptoms (Kopp et al. 2004). It is crucial to realize that religion is a protective factor in this field. In our analysis, we used the Beck Depression Inventory (BDI), a nine-item array in the Hungarostudy 2013; where we found a significant relationship. The highest Beck indexes were found among the non-believers (9.66), those who were religious in their own way showed a moderate (6.08) Beck Index while the best Beck values were found among those practicing regular worship (5.10).

There are many reasons one should look further at the link between religiosity and adult attachment. The 2013 Hungarostudy showed a surprisingly strong trend of dismissive attachment patterns (Csóka, Lázár, 2013). We also had to reveal a strong trend of secularization. Both the attachment styles and the religiosity have importance for psychological health (Székely, Lázár, 2013).

It is, therefore, worth considering what relationships were found between the values of religion and the indices gained from the attachment questionnaire of Bartholomew (1997). The *preoccupied, anxious attachment* pattern showed significance, which may indicate that the correspondence hypothesis is working not only in the case of secure attachment, but also in the case of the preoccupied, anxious attachment, creating an analogous attachment situation with the notion of a secure Other. (One is imperfect – but the perfect Significant Other will provide security, if one meets Him/Her.) This may bear double importance as mental health protective factors of religion may work at the level of disturbed attachments in both compensative and correspondent ways. They can buffer the risks of health deterioration caused by disturbed attachment styles, and internal working models associated with a predisposition to increased morbidity (Lázár, 2001). Behavioral epigenetics proved that early traumatic experiences, such as a disturbed attachment organization, might lead to increased stress sensitivity. The regulatory role of religion in mental and behavioral health care has been confirmed by these data. It is a challenging fact that we found differences between attachment, religiosity and anomie between populations under and over 35 years of age. That may be a result of life course differences, but it may also reflect the socialization differences of the post-industrial, neoliberal cultural and political shift. Another finding, that religiosity, health conditions and WHO well-being score signified gains mostly among those over 35, may be explained by the fact that youth is associated with better health indicators, hence masking the differences under the age of 35. As we revealed in the previous chapter, the contemporary crisis of the marriage institution lends considerable importance to the positive relationship between religiosity and marital stress. The data verified that a complete lack of religion is associated with several problems linked to private life. Our findings are

consistent with the meta-analysis of 1200 studies of the 400 research reports examined by Koenig et al., in which the role of religion proved to be a protective factor in depression and anxiety regarding marriage; the analysis confirmed the protective role of religion (Koenig, 2001).

The respondents under 36 years of age who regularly attend Church and practice their religion showed significantly decreased depression scores compared to those with superficial religiosity or indifference to religion. Religious participants over the age of 35 consistently scored lower on the Beck scale of depression. Religiosity can be of clinical significance among patients with depression, this claim is supported by the data of Dew et al. (2010), who found apostasy of faith leading to a loss of power in young depressed patients, to be a marker of poor prognosis. Religiosity in both age groups was significantly associated with a high coherence index. This corresponds to the previous findings of the 2006 Hungarostudy and offers an explanation for the fact that the higher indices for the meaning of life and faith are protective factors against suicidal intent (Zonda and Paksi, 2006). According to Sica da Rocha et al. (2011), SRPB (spirituality / religion / personal beliefs) in the quality of life showed a positive correlation as an independent variable, and that it is particularly beneficial for people suffering from chronic health problems. Therefore, according to the authors, religiosity can be classified as a life-enhancing factor. Based on the above, the positive relationship between religiosity and health psychological indicators have gained broader multidimensional significance as we could demonstrate its protective role among those who have disturbed attachment style and health risks.

CLINICAL PSYCHOIMMUNOLOGY IN SOCIOSOMATIC CONTEXT

Psycho-oncology

Psycho-oncology assumes a special, aristocratic position in psychoimmunological clinical thinking, and plays a role as a forerunner. It is partly because of the almost two-thousand-year-old opinion of the great Greek physician Claudius Galen (AD 129–217), who lived in Alexandria and who claimed that "melancholic" women developed breast cancer more often than "sanguine" women.

Other historical data of western medicine reflect similar opinions: just like the words of a French physician, Claude Gendron (1701), who tells us that women with "serious depression and high anxiety" are prone to cancer. The next generation of thinkers kept this suspicion alive: as Richard Guy (1759) noted, malignancies occur in women with "hysteric and nervous complaints" and are peculiar to the "dull, heavy, phlegmatic, and melancholic", especially those who have been exposed to "disasters in life, and [on] occasion much trouble and grief". Guy's words carry modern psychosomatic tones and point to the importance of a personal narrative: "women with breast cancer are characterized by a melancholic response to life events accompanied with worries and mourning." LeShan quotes British physician Water Hoyle Walshe, who lived in the 19th century, and according to whom cancerous patients can be described by "the misery of the mind, a sudden turn in fortune, and sadness as a general characteristic", while Paget states that "strong anxiety, deluded hope, and disappointment are so frequently followed by rapid cancer development and growth that it cannot be doubted that mental depression significantly contributes to the impact of other factors favoring cancer development." Paget's naive psychophysiological intuition also describes a prophetic context to 'network medical' understanding of cancer, when he is convinced that the above-mentioned "moral emotions (mental misery, sudden reverses of fortune, habitual gloominess) produce 'defective innervation'… which, in its turn, causes the formation of carcinoma". Another pioneer, Amussat (1854) lends paradigmatic emphasis to losses, bereavement, mourning and grief, as "the influence of grief appears to be… the most common cause of cancer".

According to Willard Parker, a physician in New York, "there is a definite physiological basis that mental depression, especially mourning may lead to

cancerous diseases…". Statistical studies can be found as early as at the end of the 19th century stating that, out of the 250 patients examined, 156 were subject to psychic loads directly before tumor development. In the field of psycho-oncology, LeShan determined the framework of the paradigm, the "crossword puzzle to be filled in" for a long time through his analysis of the personality of tumorous patients, in the scope of which he also considered life history episodes.

The heterogeneity of tumorous diseases, the multifaceted nature of their processes across time, the methodological restrictions, as well as the uncertain retrospective validity of personality tests and life event research have – understandably – made it difficult to reach a unanimous scientific consensus. Reaching a common standpoint was not helped by the fact, either, that the roots of this approach date back to thousands of years. The Chinese concept of the relationship between feelings and diseases was already mentioned in the introduction, and the above-cited early report by Galen and other colleagues proved that psycho-oncology has its historical roots and fundaments in medical thinking.

These statements are not exceptional in that they underline that the history of medicine confirms the relationship between mood, psychic injuries, and tumorous diseases through several observations. As the earlier quoted Hungarian physician and writer László Németh claims, a patient is not like a clothes hanger with an illness put on it: the patients themselves are responsible for the greater part of their illness and this is attributable to the determinants of their life history and to the determinants of the given socio-psychological and societal situation; that is, to the always personal and individual history of the illness.

One of the outstanding paradigm-makers of psycho-oncology is Lawrence LeSahn, who is considered to be a pioneer of the field. As early as the late fifties, his research reports proved connection between the personality features and the oncological status of patients.

In addition to the initially used Rorschach and TAT tests, LeShan mostly applied the 4-page questionnaire of the Worthington Personal History (WPH), which revealed a lot about self-defense mechanisms and everyday lifestyle in addition to major stresses. Taking into account the 2 to 8-hour interview series to supplement the tests, on the basis of the analysis of the 250 patients examined in the course of 14 years, the researcher came to the following conclusions.

A recurrent and fundamental motive repeated was the patient's traumatizing consideration regarding the threatened meaning of their lives, the so-called *raison d'etre*, which was generally related to the split of distinctive human bonds. Both the WPH and all the interviews emphasized the special importance of the interruption of a relationship that was extremely important in fulfilling

earlier creative and social needs. Although such a loss surfaced differently in the special events of individuals' destinies, it was catastrophic for each of them. The seemingly obvious situation of the death of a life companion, the unexpected departure of a beloved child from the parental home, or even the loss of a job could qualify as an internally and decisively important event.

A common characteristic feature of the stories is helplessness: in this situation even increased dating activities remain unproductive, and the person is hopelessly closed up in their solitude despite an accepting environment. Skeptical objection is obvious: why does the majority survive these unavoidable situations? This question serves as a refinement – rather than a hindrance – to the research's formulation of further questions.

LeShan identified another constant motif: the patients examined by him were characterized by an inability to show fury or anger, a sentiment which otherwise would have been perfectly justifiable. In addition, LeShan also witnessed a complete absence of rejection. In fact, psychotherapeutic work carried out with a control group exposed new personality factors and focused on their importance. A decrease in self-confidence and a peculiar antipathy of the patients against themselves were clearly stressed in LeShan's studies.

People in these patients' environments had much better opinions about the patients than the patients had about themselves, which, of course, did not influence the patients' self-image. In spite of their inability to show negative feelings, tumorous patients could fight for the cause of others really intensively and in a combative way. On the other hand, they considered their own desires and grievances to be too minor to display the emotions triggered in themselves. This special incapacity of an isolated person was found by LeShan to be characteristic in the case of 68 out of the 71 tumorous patients treated, while in the control group only three persons were characterized by the same disposition out of 88 patients suffering from other illnesses.

Even in the case of a random patient sample, the author followed the aforementioned key factors. In 24 out of 28 cases (15 tumorous and 13 patients suffering from other diseases), he was able to set up a correct diagnosis by way of relying on psychological characteristics. This worked very differently from making accidental hits.

A third study confirmed the above results. In the examination of 277 patients, 72% of the tumorous patients (n:152) were hit by the loss of a person of major importance, while in the case of patients suffering from other diseases, the occurrence of such loss was only 12% (n:125). The suppression of negative feelings showed a frequency of 47% in tumorous patients, compared to a frequency of 25% in the control group (LeShan, 1977). Of course, the first factor in determining the psychic condition is perhaps the existential state brought about by the disease, and powerless despair may also be a direct result of being made aware of a disease known to be incurable.

Based on LeShan's research, we may also believe that this helplessness is more than just this, and may have other roots. The powerlessness of tumorous patients is not identical with that of depressed ones. In the case of tumorous patients, everyday activities are not hindered by this state and everything goes on in its normal course of events.

On the surface, tumorous patients do not give up, although they have given it up long ago somewhere deep inside: possibly even before the onset of the disease. The inability of "good people" with tumorous diseases to express negative feelings even when they are desperate is an observation that is shared not only by LeShan. According to the surveys by David Kissen (1964), personality traits of low emotional charge or poor emotional outlet were found in half of the patients with lung carcinoma, compared to much lower rates of occurrence detected in controls. Among patients with lung cancer, this rate is comparable to the risk levels associated with smoking and non-smoking.

Nevertheless, more general health psychological features can be identified, and the indices of the tumorous patients examined can be measured against them. In such instances, the focus is on psychoimmunological considerations, which affect the immune biology of the tumor and the general psychosomatic condition of patients suffering from a tumorous disease. It can be presumed, even on the basis of the references and citations above and according to the vast body of psycho-oncological literature, that major psychic factors to aggravate tumor include depression, helplessness, learned helplessness, and loss of control. The psychological situation also demonstrated through experiments by Seligman's model of learned helplessness played a considerable role in psycho-oncological interpretations. Here, mourning can be identified as an example of the type of stress that is experienced as inevitable and irreversible.

Parkes et al. (1969) kept track of the lives of 4448 widows for nearly ten years and found that the highest number of deaths occurred among them in the first six months following the loss of their spouse. Bartrop (1977) was among the first to demonstrate that mourning reduces cell immune responses to mitogens, both in the case of cell lines T and B. According to Irwin et al. (1988), this also applies to NK cell activity. Grossarth-Maticek (1983) verified that the state of renunciation powerlessness, or hopelessness plays a role in developing tumors and in influencing personality. According to Lillberg et al. (2003), the loss of control and a trauma causing helplessness are mostly occasioned by grievous life events that cannot be changed, an irreversible loss, the death of a child or a relative. A meta-analytical examination by Duijts et al. (2003), subject to strict evidence-based criteria, verified that the risk of breast cancer is increased by the death of the spouse, as opposed to changes in family or financial status, which in turn do not increase the same risk. Simultaneously, it calls for caution that no connection was found between stressful life events and relapses in cancerous diseases in large samples. Having regard to the surveillance role of

NK cells, however, it is important to know that – according to Herbert and Cohen (1993) – significant life events of high scores, such as loss and mourning of the loss of one's spouse or taking care of people suffering from incurable diseases, are associated with reduced numbers of NK cells and cell activity. With respect to people suffering from advanced tumors, Lechin et al. (1990) demonstrated that depression was accompanied by higher cortisol levels and reduced NK activity.

The early follow-up survey by Grossarth-Maticek (1984), the so-called *Crvenka study*, affirms this, and verifies the impact of depression in increasing the risk of cancer by 3 to 4 times in the course of a 10-year-long survey involving 1353 persons (aged between 50 and 70) and exhibiting 204 diagnosed tumor patients during the period under scrutiny. McGee et al. (1994) came to a different conclusion after examining the meta-analysis of large follow-up studies extended to include other age groups as well. Yet, the results of Grossarth-Maticek correspond to the findings of LeShan, who was the first to take notice of the fact that the appearance of tumors is frequently preceded by an experience of loss, which triggers helplessness, depression, and renunciation, particularly in patient groups characterized by peculiarly increased sociality, "angelic goodness", and inhibition of aggression.

Psychological studies also seem to justify the assumption that psychological depression may, in addition, lead to the depression of immune defense (immune patrol) aimed to control the tumorous process. In experimental animals, researchers detected immunosuppressive tendencies in the course of stress paradigms triggering renouncement or learned helplessness. Moreover, the concept of learned helplessness directs our attention to life history backgrounds and experiences fixed in personality. In a thoroughly designed prospective study, Penninx et al. (1998) demonstrated that the risk of cancerous diseases increased among elderly adults exhibiting depression and also claimed that the risk lasted for about six years, even with results corrected to include other risk factors.

A follow-up study by Stoll (1986), involving 2000 subjects and using the MMPI personality test results, confirmed that the death rate among people displaying high depression values was twofold 17 years later compared to individuals not showing any depression values. The research following up on 1337 medical students at John Hopkins University was also a longitudinal study: those students who suppressed their emotions, were over-controlled, and did not keep contact with their parents showed significantly more frequent oncological disorders after 20 to 30 years.

Hungarostudy, a Hungarian national health psychology survey conducted in 1995 with 440 tumorous patients identified in the scope of a questionnaire survey involving 12,600 persons, found significant differences in respect of family background, dysfunctional attitudes, affiliation needs and self-esteem.

At the same time, the examined and the control groups did not display any discrepancies in terms of smoking habits, as described by Kaszab, Lázár, Szendi, Szedmák, Lőke, Kopp (1997).

The data gathered in the scope of the research convincingly indicated a pattern that may be associated with the personality exhibiting a type C secondary attachment organization and type C 'cancer-prone personality', as shown by the relevant items of the DAS questionnaire. In contrast with the control group with no tumors, tumor patients had a considerably higher demand for external recognition and for love. The performance expectations and perfectionism did not exhibit any tendency to rise, and there was no difference compared to the tumor patient group in respect of hostility, either, in contrast with the group of cardiovascular patients.

The fact that tumor patients could not count on help from their parents in difficult situations implies family attachment problems. The lack of control and the stability of the social environment also showed a significant difference compared to the non-tumor group. Similarly, isolation and rejection indicate ecosocial disturbances. The avoidance of conflicts, suppression of desires, and search for internal harmony, typical of type C attachments and type C personality, are highly significant.

Increased bodily anxiety, the sensation of being unprotected and fear indicate increased arousal, which is typical of type C personalities. The need for acceptance, dependency, as well as overly social and self-sacrificing attitudes are all characteristics associated with type C personalities, just like rejection as a strategy for defense and for coping, which shows a significant difference compared to the characteristics of the control group. The tumor group is characterized by the lack of cognitive adaptation in difficult life situations.

In a comprehensive prospective study conducted on a large sample of cases, Linkins and Comstock (1990) also demonstrated that, in samples corrected to other risk factors including smoking, depression could be considered an independent tumor risk factor. Following the meta-analysis of 105 samples in 75 prospective studies, Pinquart and Duberstein (2010) verified that the diagnosis of depression and the degree of depressive symptoms correlate with increased mortality. This statement is also valid in the case of depressive symptoms preceding a cancer diagnosis.

Depression is not a fate in itself. It is not exclusively a matter of environmental loads: it is backed up by destiny, the developmental psychology "story" with its peculiar psychobiological "raw material", where disease history is exposed to social relations and life experiences. With respect to cancer patients, Bahnson (1969) found the so-called "centrifugal" family model to be frequent: this is characterized by the emotional distance of family members and children's isolation. Grassi and Molinari (1986) report on similar distances between parents and children. In Pervin's (1990) summary work, five factors are measured:

depression, the state of powerlessness/hopelessness, the suppression of aggression, the disorder of the expression of negative feelings, and, finally, the insufficiency of social support. Based on the above, it can be stated that psychological factors impact the prognosis of tumorous diseases and the duration of survival. Depression, the recurrence of cancer, and survival are mutually interrelated in the form of a *dangerous cycle*. In a meta-analysis, Garssen (2004) verified interrelationships between negative sentiments and worse cancer prognosis in one third of prospective longitudinal studies.

The survival rate of apathetic, depressed, and hopeless oncological patients is significantly lower, while better outcomes are attributable to a competitive, "martial" spirit. Concerning early-stage breast cancer patients with habits reflecting such an ability to cope, Greer et al. (1990) produced evidence for fewer relapses after surgery and better results in terms of 5, 10, and 15-year survival. Similar correlations were shown by Tschuschke et al. (2001) among bone marrow transplanted patients due to leukemia. Therefore, patients' coping strategies seem to be really important: according to several follow-up studies, patients showing their emotions and exposing their inner tension through positive actions will have better prognoses. The "desire to live" is difficult to measure; the reduction of the levels of depression and anxiety, the ability to express emotions, and increased activity will considerably improve both the chances of survival and oncological patients' quality of life. The above unambiguous correlations described in follow-up studies can partly be explained by the fact that more serious psychic symptoms accompany more serious tumorous processes. Based on the experimental results presented earlier, it is reasonable to take care of and support oncological patients psychologically. The central role of endocrine control, the regulation of the immune system by the central nervous system, and the regulation of the hypothalamus have been identified in the process: in these processes environmental stressors and emotional impacts may play a role, primarily in the growth of hormone-sensitive tumors. This is mostly probable between the ages of 40 and 60 as later in life endocrine and immunological activities are weakened and, in the case of childhood tumors, congenital factors are definitive.

Trap of personality

After examining the developmental psychology models in the previous sections, let us return to a stubborn notion of psychosomatics, namely to the issue of personality structure, which provides a predisposition to illness. The notion of personality structure was formulated as a consequence of the presupposition of the 'cancer-prone personality', which was established on the basis of personality typologies and research experience with tumorous patients.

Psychoimmunology focuses on suppressive and repressive emotional tendencies inclined to inhibit/hinder feelings exhibited by permanent personality traits. Regarding much-researched extroversion, neuroticism, hostility and addiction, Chen et al. (1995) did not find any correlation between the above conditions and tumorous diseases. Behavioral characteristics of suppressing feelings, increasingly trying to please others, self-sacrifice, pushing one's own interests to the background, being calm on the outside (and anxious on the inside), and repressing anger are considered as possibly 'cancer-prone' or type C personality by several authors such as Temoshok and Baltrusch. Such attitudes represent a pattern that increases risks. Such a personality pattern is outlined in connection with type I persons and is described by Grossarth-Maticek and Eysenck as being anti-emotional, dejected, helpless, and hindered in the expression of aggression. This latter study is one of the first prospective behavioral epidemiology studies with a large number of participants. The study was started by the researcher in the mid-1960s in Yugoslavia, involved 1353 persons between the ages of 50 and 70 (Crvenka study), and found that the risk of tumors showed a 3 to 4-fold increase as a result of depression over the course of a three-year-long follow-up period.

Numerous other early-stage studies called attention to the suppression of negative feelings. In a 1966 study, LeShan detected the inhibition of the expression of aggression in two-thirds of cancerous patients, while this was characteristic of only one-third of healthy control subjects. In the course of an early-stage study, Dattore et al. (1980) found the psychological indices of emotional repression to be higher in those veteran soldiers who later suffered from cancer as early as two years before setting up the diagnosis. Wattson et al. (1984) detected the suppression of anger and wrath to characterize patients with breast cancer. Although these figures were obtained from patients already aware of their cancer diagnosis, Greer and Morris (1975) confirmed the same by the subsequent analysis of interviews recorded before the diagnosis, that is, within a prospective framework.

Age also seems to be a decisive factor in all this. The connection between the suppression of feelings and cancer could only be detected among patients with breast cancer over the age of fifty, according to Scherg et al. (1981). Low or increased levels of expression of sentiments were also scrutinized as a clinical phenomenon to accompany other tumorous diseases. Indicators correlating with the suppression of feelings included the thickness of melanoma malignum in Temoshok's study (1985), quicker progression of breast cancer in Jensen's study (1987), and worse survival rates of lymphoma in the study by Weihs et al. (2000). The role of repressive coping and the suppression of feelings may also be indicated by the fact that in melanoma patients training programs for mastering active coping strategies led to reduced distress and increased

NK cell activity stimulated by IFN-alpha in the course of a six-month follow-up period. Both 5 and 10-year survival indices proved to be better compared to controls according to Fawzy et al. (2003).

In a psychosomatic approach to cardiovascular diseases, the formulation of the 'cancer-prone' type C personality was undoubtedly assisted by the success of type A personality and behavior. Type A patients leading a stressful life were also measured for tumorous diseases.

A study by Ragland and Fox (1987), covering 17 years and involving the personality testing of 3514 males, indicates that type A males under continuous time pressure and subject to frequent frustrations showed higher frequencies of tumors compared to type B subjects, but this difference can be considered very moderate. Considering epidemiological aspects, smoking habits, and other carcinogens, these findings suggest only nuanced differences can be discerned by the mechanical separation of active and passive life and habits.

In the case of type C patients, melanoma was more invasive, with higher cellularity than in other types of the constitution as established by Temoshok (1985). Greer (1985) also came to a similar conclusion, finding type C features to be more characteristic in breast cancer patients. Temoshok stresses that the manners of adaptation to the environment are organized and developed, in addition to possible genetic bases, through a milieu of early childhood traumas, stress impacts, and other challenges, following the patterns of family interactions.

Simultaneously, the difficulty of discerning this group in epidemiological studies is understandable since a mimicry situation is created by the efforts of such patients to meet social expectations. However, this behavior – neglecting the disease and suppressing temper – may even deteriorate the process of the disease, according to Derogatis.

Dutch researchers Van der Ploeg et al. consider the general overcontrol of emotional life and anti-emotional, one-sided rationality to be parts of this personality pattern. Such repressive protection mechanisms operating through suppression are characterized by the fact that, although instruments verify high physiological arousal and depressed immunity, patients do not notice any repressive protection mechanisms even in themselves: actually, they do not even detect these. It cannot be excluded that this may be socio-culturally programmed. In a review by Cox and Mackay (1982), it is highlighted that carcinoma shows significant incursion – an annual increase of 7% – mainly in the developed countries of North America, Europe and Asia: this development involves radical psychosocial and cultural changes along with the chemical pollution of the natural environment. Each of these developed, civilized, even post-industrial societies are characterized by the disintegration of the extended and nuclear family model, a sense of isolation in large cities, the

rupture of the net of social support, and the flatness of the expression of emotions.

The phase of early childhood socialization and personality development is prominent in terms of the formation of a so-called C-prone personality or TCBP (type C behavioral pattern). On the basis of attachment theory, in a development psychology context – as presented in the previous chapter –, this phase may be determined by the given socio-cultural boundary conditions, such as the issue of the separation of the infant from the mother in the hospital, the role conflict between an emancipated woman's responsibilities and motherhood, or the frequently emotionally injured household of a family without a father. It has already been discussed that the "damage" suffered in this vulnerable phase may also result in direct organic alterations with neuroendocrine intermediation, mainly with the developmental psychological consequences of early traumatization epigenetics and attachment disorders. Different modes of biological – in our case, immunological – response can be damaged by repressive coping styles imprinted at an early age. In their studies, Coe (1985) and Reite (1981) refer to the fact that early separation or the inhibition of the expression of maternal sentiments may result in permanent endocrine, immune and behavioral damage, which was also supported by exploring background epigenetic mechanisms in the 90s.

On the other hand, according to Baltrusch and Thomas' observations, tumor patients tend to describe their parents in their accounts more frequently as having little sensibility, keeping a distance, or being repulsive – compared to a normal population without tumors. Baltrusch detected patients' negative parent image and increased psychosocial and socioeconomic loads in childhood, mainly in patients with gynecological tumors. Low levels of empathy in the family environment and the insufficiency of emotional resonance, as included in the childhood reports of tumorous patients, suggest that patients exposed to increased risks require prevention and family therapy because of the psychosocial ecosystem of the family micro-environment.

Inevitable, inextricable losses and social isolation seem to be particularly perilous for this type of persons. The psychic mode of working of a type C submissive personality, who avoids conflicts, is unable to express negative sentiments, but perhaps perceives these internally, is characterized by avoidance, suppression, and passivity – being paralyzed by anxiety. The social environment rewards this behavior due to its over-social loyalty. However, patients of this kind are not accompanied by social support due to isolation tendencies, despite their compliant behavior. According to Dilman, preservatory neuroendocrine responses associated with passive coping are characterized by increased HPA activation due to prolonged anxiety. The consequence of this condition, which is characterized by permanently increased cortisol levels and hypothalamically decreasing NA content, is a hypothalamically "mistuned"

or dysregulated cortisol feedback threshold, which further increases cortisol levels, thereby contributing to increased lipid metabolism and free fatty acid utilization. This mistuning may arise from a reduction in the number of glucocorticoid receptors, as discussed in connection with the epigenetic explanations already presented.

Life paths, life events

A key to narrative medicine is to explore and bring to attention the interrelationships between personality and life path development. At the same time, psychotherapy is also inconceivable without biographical analysis. Furthermore, trauma diagnostic techniques are reckoned with among psychoimmunological therapy options. In the evaluation of such occurrences, however, the psychosocial medium, the extension and system of social connections, and their dependence on and demand of social support are required to be taken into consideration in addition to personality traits, individual coping abilities, personal efficiency, self-power, and other health physiology features, with all of these having a dramaturgic value in the psychosocial background of diseases. People described by their hardiness, with their increased self-confidence and a definite life plan are more independent in terms of emotional and cognitive approaches. Although they may not need this, they are surrounded by a more extensive social network because of their increased social competencies.

Therefore, the mentality of individuals suffering from a tumorous disease and the life events that occurred to them would merit examination together with their social and psychic context since the number of life-history events is less important than their experience and cognitive, emotional, and behavioral processing.

Which are the decisive events that may be instrumental in the development of tumorous diseases? Early traumatization can be considered the most important factor in this due to perinatal experiences and their epigenetic, stress, physiological, and psychological consequences. The traumatic tear of bondage between mother and child – injury of the so-called attachment – may have consequences that impact adulthood, as shown by statistical surveys. Observations by Baltrusch and Thomas allude to the role of early life events: they showed, with the help of the FAQ (Family Attitude Questionnaire) test, that the early loss of parents or their emotional distancing may also intervene in the development of psychosomatic conditions with likelihood of carcinogenesis.

Early traumas proved to occur more frequently in the case of males suffering from testicular and gastrointestinal cancer. In breast cancer patients, childhood traumas are also associated with higher levels of stress, depression, and fatigue, as claimed by Han et al. (2015). These symptoms are accompanied

by increased CRP levels, interleukin, IL-6, and IL-1 receptor antagonists, just as increased tumor necrosis factor-α (TNF-α) and CRP levels are associated with childhood trauma. It is an important research task to examine the impact of stress on molecular and cellular level information tracks and those related to cancer development the same way that the study by Pant and Ramaswamy (2009) did in the case of epithelial cancer.

According to Palesh et al. (2007), in the case of women who have metastatic breast cancer, stressors of early stages of life are associated with reduced survival. By way of analyzing 48 publications involving 5316 patients, Vainer et al. (2018) found proinflammatory cytokine IL-6 to be a prognostic marker for stomach, biliary duct, gall bladder, pancreatic and colorectal cancer; higher levels of proinflammatory cytokine IL-6 were associated with increased mortality and quicker course of the disease in question.

In the course of the psychosocial examination of patients with breast tumors, Forsen (1990) found a significant connection between life events and carcinogenesis through analyzing – using a modified SRRS (Social Readjustment Rating Scale) – the 6 years preceding the tumor's appearance.

A bridge between epidemiological observations and specific laboratory data was actually created by the measurability of immunosuppressive phenomena experienced in an extreme and typical helplessness state: mourning. Bartrop's (1977) study of fundamental importance demonstrated inhibitions to cellular immune functions in the months following a bereavement. At the same time, however, a 10-year follow-up study of the patients examined did not conclude that the frequency of tumors increased. Bartrop only found differences in the occurrence of atypical skin phenomena (Bartrop et al. 1988, personal communication).

The loss of a life companion is at the top of the life event hierarchy. The motif of loss has a prominent place in the system of thought in dynamic psychiatry and the same significance is attributed to an identical event in psycho-oncology. A study by Scherg (1988) aimed to filter out disorders caused by self-mythicizing remembrances with an impact on associated tests' validity. In this prospective study including the questionnaire-based psychosocial examination of 2789 females attending cancer screening, the loss of the mother in childhood and the loss of a life companion were more frequent in the case of tumorous patients compared to healthy clients. A study by Greene and Miller (1958) indicates that in the case of 33 patients with (myeloid and lymphoid) leukemia, experiences of serious loss in the two years preceding the illness were found in 31 cases. Jacobs and Charles (1980) call attention to the higher frequency of serious life events among children with cancer.

In a study by Rigatos, the death of the spouse or the high importance of forced divorce was verified in a subject sample of 200 patients with cancer and

400 healthy controls in connection with life events examined in line with the SRRS scale. Divorce can be a drama of loss, a drama of the split of social bonds – in-depth comparable with mourning – primarily when one of the parties must endure the break-up of marriage as an undesired solution. In the course of divorce processes, Kiecolt-Glaser et al. detected parameters suggesting significantly reduced T-cell functions. In addition to mourning culminating in powerlessness, the motif of "learned helplessness" and the uncontrollability of the situation may also occur in other social situations. Thus, Mathew et al. (2005) also found higher frequencies of cancer cases in samples of imprisoned subjects.

Based on Greer et al.'s (1979) observations on a large sample, helpless pessimist coping in newly diagnosed breast cancer patients is accompanied by higher frequencies of relapse and worse 5-year survival prognosis. Stress, pessimism, and sleeping disorders have a critical impact on the prognosis of cervical cancer mediated by the HPV virus in HIV-positive patients, according to Jensen et al. (2007).

Hopelessness was associated with worse survival in the case of bone marrow transplant patients in a study by Molassiotis et al. (1997), while, according to Schulz et al. (1996), pessimism was accompanied by a worse prognosis in patients below 60 who went through palliative radiation treatment. Personality factors cannot be separated from social support since the social network of active individuals with positive emotional attitudes is larger, and pessimism also shows a dangerous pattern of a vicious circle as social support decreases. In the case of patients with breast cancer, it was demonstrated that the quality of social support (including the strength of social and emotional support, the number and confidential nature of social bonds, as well as social involvement) positively correlates with longer survival, as attested by a study by Reynolds et al. (2000).

Coping, i.e., the way of stress management, is nothing but the ability to cope with an unpleasant or threatening situation, whereby emotional reactions qualifying and accompanying the situation are resolved, and specific neurohumoral responses are organized.

Some authors make a distinction between the active and passive ways of coping (see Antoni 1987), where active coping is accompanied by increased sympathoadrenal activity, while in the course of passive coping, prolonged activation of the HPA axis needs to be reckoned.

In the course of the meta-analysis of studies examining the ways of coping of cancer patients, it is concluded that the style of active coping – requiring long-term psychic reorganization because of a cancer diagnosis – is more successful, while avoidance strategies work well in the case of less serious, short-term, episodic life events (Suls and Fletcher, 1985). Lower relapse and

lower mortality rates were found by Fawzy et al. (1993) in melanoma patients opting for active coping, while repressive avoidance strategies are associated with worse prospects of survival, according to Brown, Butow, and Culjak (2001). Other hormones generated during stress may also have an important role in some tumors. Thus, cortisol may accelerate tumor growth by increasing tumor metabolism (Romero et al. 1992).

According to Licinio et al. (1995), hormones produced due to the activity of the HPA axis increase the expression of breast tumor oncogenes. As most breast tumors have prolactin receptors, increased secretion of prolactin can also be interpreted as a stress hormone and may also stimulate breast tumor growth. As social support acts as a protective factor, it can also be interesting to observe that oxytocin, frequently interpreted as an affiliation mediator, hinders tumor growth (Cassoni et al., 1996).

All in all, the suppression of negative feelings, hopelessness, pessimism, repression, downplaying the cancerous process, and bad social support can be considered as psychosocial factors most frequently associated with cancer prognosis. Most of these factors – such as the inhibition of aggression, repression, and pessimism, which are frequently associated with anxiety and low self-power, and bad social support as a consequence of these factors – can be classified as debatable type C personality traits. Since anxious and ambivalent attachment organization may be associated with the stress-biology consequences arising from earlier described epigenetic processes which further aggravate psycho-immune inclination to disease. Therefore, cancer risk personality will continue to remain an open issue of psycho-oncology. Cancer patients full of hope, with a social network providing broad emotional support, can be characterized by lower risks of relapse and death. Although the presumption of cancer risk personality involves the ethically inadmissible risk of blaming the patient, if this can be considered a disease aggravating factor, psycho-oncologists and clinical psychologists involved in patient management need to consider it in both personality diagnostics and patient management/supporting psychotherapy, also involving cognitive behavioral therapy components.

For the purpose of comparing psychosocial factors and tumor behavior, the following summary table (based on Fox, 1988) lists the results of the comparison.

Table 14. Connection between personality type / psychosocial factors and the type of tumor to appear later on and survival expectations

Author	Psychosocial factor	Survival	Tumor type
Stavraky	temper, emotional control	longer	mixed cc.
Schonfield	social introversion	shorter	breast cancer
Jensen	suppression of feelings	shorter	melanoma
Temoshok	type C personality	shorter	melanoma
Greer	disposition of hopelessness, stoic acceptance	shorter	breast cancer
Derogatis	arguing, dynamic aggression, controversialist patient	longer	breast cancer
Viitamak	aggression	shorter	mixed cc.
Rogentine	receiving little social support around the surgery period	shorter	melanoma
Visintaner	disease management with problem-solving attitude	longer	melanoma
Ikemi	strong (partly religious) faith	longer	mixed cc.
Reynolds	social isolation	shorter	mixed cc.

Table 15. Connection between depression, personality type, psychosocial factors and tumor to appear later on

Author	Psychosocial factor	Connection	Tumor type
Ragland	type A personality	none	cancer
Ragland	type C personality	exists	cancer
Kaplan	depressive basic position	none	cancer
Sekelle	depressive mood (males)	exists	cancer
Thomas	distance from parents (parents, males) inchildhood	exists	cancer
Hagnell	warm-hearted, extroverted (females)	exists	cancer
Keehn	discharged from the army due to psychoneurosis	none	cancer
Reynolds	social isolation	exists	cancer
Kerr	depression treated in hospital	exists	cancer
Evans	depression treated in hospital	exists	cancer
Wagner	psychotropic drugs in the case of mental patients	none	none

'Cancer-prone personality' in the light of animal experiments

In Riley's (1981) ethologically structured experiment with animals competing for water and food (following 6C3HED lymphosarcoma implantation), 36% of the animals forced to fight perished by the 47th day of inoculation, while by the same date there were no deaths among animals kept in peaceful circumstances. In an experiment by Temoshok (1984), melanoma inoculated into socially interactive hamsters grew smaller and cells were accompanied by an increased lymphocytic reaction. Other authors also share the same opinion: according to their observations, the tumors of viral origin in "angry" mice exhibiting fighting behavior are smaller and less invasive than those of their passive mates. In another study, Temoshok (1987) emphasizes that the interaction of stressors and behavioral differences exert different impacts on tumor growth, therefore, it is insufficient to separate the two groups of animals only on the basis of behavioral discrepancies. Based on data capture through video recordings, it was found that lower tumor mass was detected in calmer (type B) animals, while in the case of more active animals, both Natural Killer cells and tumor size changed in more unfavorable directions. However, when the animals were exposed to stress impacts (shaking), a more active behavior exhibiting rich interactions was accompanied by a better prognosis. In the case of animals exposed to stressors and doomed to incapacity, a decrease in NK cell activity was detected, which was coupled with reduced NK mediated tumor cell elimination. With respect to the assessment of behaviors, it should, of course, be considered whether the detected agitation or passivity is a phenomenon modulated by the tumorous process.

Tumor biology modeling of "psychosocial" stress

Despite ethological limitations and the questionability of expandability, experiments carrying social metaphors give food for thought by conjuring up human psychosocial tumor models in their distant analogies.

The problem of "early trauma" – so important in dynamic psychiatry and interpreted in our bonding-based developmental psychology model, as well as supported epigenetically – inspired an experiment by Ader and Friedmann (1965). They found the carcinosarcoma mortality of prematurely separated juvenile rats to be higher than that of controls. In an experiment to model increased care and tactile contact (handling), Solomon (1980) treated the animals from birth to weaning and found increased primary and secondary

antibody reactions to antigens. Studying another dimension of social stressors, Santisteban and Henry (1971) kept juvenile rats in isolation for 4 to 12 weeks after their birth, and subsequently made them join the other "normal" animals. The following was found: as compared to the control group of "normal" animals, there were frequent occurrences of hypertension, cardiac hypertrophy, and breast tumors as a consequence of social stressors caused by confrontations and competitive situations.

Andervont (1944) examined the stress value and the impact of keeping conditions on rats. Based on congruent results, they reported shortened latency periods of breast tumors. Dechambre (1973) considered overcrowdedness even more unfavorable than isolation in a study of B-l6 melanoma cell growth.

Models of permanent stress and hyperadaptosis

Among theories to explain the unfavorable effects of prolonged physical or social stress, Dilman and Ostroumova's (1984) concept known as the *hyperadaptosis model* is worth considering. There is a reasonable link between hormonal changes accompanying prolonged psychosocial stress and increased tumor growth. The link is the protracted hyperadaptation, with a continued activation of the HPA (hypothalamic-pituitary-adrenal) axis, and permanently increased cortisol levels. The negative feedback regulation of cortisol secretion plays a key role in this model. The negative feedback regulation of cortisol secretion displays similarities to DST test positivity observed in the course of endogenous depression, hypothalamic cortisol resistance, and changes characteristic of the aging process. An appropriate index of feedback signal sensitivity is the proportion of 17-OH-corticosteroid and 17-ketosteroid, which provides information on feedback conditions at the level of the adrenal cortex. Bulbrook and Hayward (1967) deem this index to be a suitable risk indicator in the case of breast cancer. Similar conclusions were drawn by de Waard (1969) in respect of endometrium cancer, and Rao (1970) concerning lung cancer. The dexamethasone test serves as a measure for central regulation, and it was demonstrated that reduced steroid sensitivity was accompanied by higher gastrointestinal mortality, as reported by Ostroumova (1981). The same was observed by Saez in the case of breast cancer patients. Dilman presumes that hypothalamic NA content is instrumental in this reduced cortisol sensitivity. The above is also worthy of attention because the reduced hypothalamic NA and neurohumoral aspects are common in learned helplessness and the passive coping.

Animal experimental modeling and neurohumoral aspects of learned helplessness

According to Shavit et al. (1985), inescapable but not escapable stress against stressors of the same intensity leads to reduced NK cell activity and reduced mitogenic stimulation. The experiment can ensure the possibility of overcoming or the impossibility of resolving the challenge. The following experiment models the substantial difference between these two situations and the state of learned helplessness. A determinant factor in the qualification of the stressor is whether the challenge posed in the experiment has a solution or not. If experimental animals are exposed to simultaneous electric stimulation of an identical number of incidents and duration, provided by the same electric circuit supplying the two compartments, a radically different situation is created by the fact that there is an interruption pedal in one of the compartments but there is no such option available for the other animal. Simultaneous electric shocks are terminated by one of the animals for both, while the other animal cannot do such a thing, which makes the situation uncontrollable for the latter animal. This experiment – unfortunately conjuring up our everyday lives – made it possible for Vogel et al. (1987) to compare the neurochemical responses of the animals concerned.

Compared to the control animal not participating in the experiment, both rats showed increased levels of peripheric A (adrenaline), NA (noradrenaline), and corticosteroid levels. However, in an animal in a defenseless situation these changes proved to be more prolonged and intensive. Hypothalamic NA content was reduced in "copingless" animals, while in animals put into a proper "coping" situation such changes proved negligible. In the hippocampus of properly adapting animals, NA reductions were detected as compared to the powerless group. In mesocortical and mesolimbic areas, dopamine levels showed differences in the group doomed to powerlessness, and serotonin levels in the two groups also shifted in the opposite direction in the septum.

Thus, differentiated neurohumoral responses can be expected in the case of different qualifications of the same stressor or under different external psychosocial circumstances. It manifests not only in respect of cortisol and hypothalamic NA: endorphins are also to be taken into consideration in terms of immune processes showing different changes. In the case of animals capable of controlling the situation, the same amount of electric shocks caused only moderate analgesia, while strong opioid analgesia was observed in animals in a state of "learned helplessness" (Lewis 1980).

Following the removal of the partition wall, the animals immediately turned on each other, fully ignoring electric stimulation. When examining such animals, the biochemical deviations mentioned earlier were not detected.

The problem of unresolvable stress was also verified in an experiment by Visintainer (1982) in the case of Walker 256 sarcoma implanted animals. Based on the authors' experiences, the 50% adhesion rate detected in the control group was coupled with 63% in the case of possibly avoidable stress, while in the case of animals doomed to helplessness, the tumor adhesion rate was 73%. Similarly, by applying an inevitable stressor, the survival of animals implanted with P 815 mastocytoma cells was shortened according to Sklar's study (1979).

As the main mediator of stress, glucocorticoid increases prostate and breast cancer growth, and contributes to the survival of cancer cells of the breast or cancer cells of other origins by reducing the apoptosis of tumor cells, according to Volden and Conzen (2013). And, as a stress hormone, glucocorticoid also reduces the tumor cell killing function of chemotherapy as shown by Zhang et al. (2006). These experiments not only contribute to the clarification of the terms included in our psychoimmunological terminology but also delineate the contours of psychosocial disease generation. At the same time, such experiments offer fate-related narrative elements of the disease by placing the central notions of human observations – such as the experience of desperation and helplessness – in a situational context, and by clarifying neurohumoral consequences.

Psycho-immune gates of tumor formation

In response to spontaneous and continuous tumor formation in the body, increased by viral or chemical or physical provocation impacts, the organism mainly exerts resistance through its natural immunity.

Stress is accountable for the regulation of p53, the gene responsible for tumor suppression, according to Feng et al. (2012), and stress hormones were also shown by Flint et al. (2007) to damage DNA repair mechanisms. Free fatty acids are deemed to play a role in proliferative pool increase (Antoni 1987) and damaging DNA repair mechanisms (Dilman et al. 1981). Due to humoral changes coupled with depression, DNA repair is also reduced, according to Dattore et al. (1980). Research by Kiecolt-Glaser et al. (1985) showed that the DNA repair mechanisms of X-ray radiated lymphocytes of those suffering from serious depression lagged behind those of the control group, even in the case of the regression of benign tumors formed not by malign cells but by ones that lost their mortality. However, there are only assumptions about the mechanism of any possible psycho-biological influence on malignant transformation, such as DNA repair, chromosomal instability, or points of attack offered by transformed but dormant cells. The DNA damaging effect of carcinogens is fended off by several repairing mechanisms, and immune protection also plays an important part in the recognition and destruction of these altered cells. If DNA

repair processes do not operate properly, the survival of abnormal cells will increase.

Glaser et al. (1985) demonstrated in some studies that stress is instrumental in DNA damage and the impairment of DNA repair mechanisms. For example, the frequency of the SCE (sister chromatid exchange) index, detected after floating or electric shocks on the legs, increases in bone marrow cells. The SCE is a sign of genome instability and is related to increased cancer risk. If animals exposed to such stress were pre-treated with sedatives, then the number of chromosome aberrations produced did not differ from controls, as opposed to a significant rise observed in animals enduring immobilization stress. Human observations also indicate the same: Kiecolt-Glaser detected reduced DNA repair capacity in distressed, non-psychotic depressive patients, as opposed to examination findings during the treatment period. In another study, in connection with academic, problem-solving stress challenges, Tomei, Glaser et al. (1990) noticed that when cleaning up cells that are damaged by irradiation, the apoptosis inhibition effect of carcinogen phorbol ester increases due to stress. The depth of depression also correlates with the decrease of DNA repair capacity following irradiation. Animal experiments show that in the case of animals subjected to stress and exposed to carcinogen impact, the level of methyltransferase in the spleen decreases compared to controls; this enzyme also plays a considerable role in DNA repair processes. The data above rightfully suggest that DNA repair mechanisms are affected by stress, which leads to the persistence of a damaged DNA stock and an increased risk of malignant cell degeneration, according to Yang and Glaser (2003).

There may be several other intermediary factors between psychoimmunological mechanisms and tumor progresses, and these are affected by psychosocial and personality factors such as angiogenesis, the activity of the metalloproteinase matrix. This makes it extremely important to scrutinize interactions between neuroimmunomodulation, neuroendocrine factors, angiogenetic cytokines, and inflammation mediators in tumors' micro-environments.

The organism resists to spontaneous and continuous tumor formation in the body – the likelihood of which is increased as a result of viral or chemical or physical provocation – mainly through its natural immunity. This process is termed *immunosurveillance*, in the course of which immune cells spot and eliminate cells affected by tumorous transformation and hinder the growth and development of cells capable of avoiding detection.

NK cells' condition may also play a role in the "pass-through" of transformed cells and in restraining an already growing tumor. Chronic stress reduces both cellular immunity and immunosurveillance and also increases inflammation. Andersen et al. (1998) involved 116 stage II and III breast cancer patients in their research. Individuals experiencing major stress between surgery and chemotherapy displayed lower NK cell cytotoxicity and reduced response to

lambda interferon. Varker et al. (2007) found reduced receptor expression and weakened signalization of NK cells in a group of patients affected by and complaining about high stress. The epigenetic background of the process indicates that in the case of individuals experiencing serious distress, reduced NK cell cytotoxicity accounts for the acetylation and phosphorylation of given histone sections in the background, according to Mathews et al. (2011).

All this in itself does not actually represent an increased cancer risk; however, its role in a multi-factor risk situation cannot be completely neglected. According to Baltrusch (1987), in the case of tumorous diseases of old age, the pathophysiological risk of a tumorous disease can be jointly increased by typical age-related stress impacts (loss of spouse, retirement, solitude, reduced social support, insecurity, and powerlessness), by the reduced immunohormone production activity of the thymus, and by consequential IL-2 level reduction.

Tumorous transformation is not necessarily accompanied by a change in cell phenotype or the development of an immunogenic antigen structure available for lymphoimmuno-recognition. Moreover, even in the establishment of immunogenicity, features to be frequently reckoned with include the inability of recognition, ineffective immune response, or tolerance. The main line of anti-tumor immunity protection is linked to NK (natural killer) and NC (natural cytotoxic) cells. NK cells constitute an independent "third line of defense" between innate immunity and adaptive immunity, with an origin independent of cell lines T and B. At the same time, NC (natural cytotoxic) cells can be classified as macrophages. These cells are key factors in first-line defense against tumors. The protective role of NK cells was demonstrated in the case of several tumor cell lines, as indicated in the research by Whiteside and Herberman (1995). Upon an IL-2 impact, NK cells are converted into LAK (lymphokine-activated killer) cells, which can destroy tumor cells, and the anti-tumor activity of the A-NK cell line is very efficient, as shown in a study by Vujanovic et al. (1995). Tumor cells frequently lose their cell surface MHC markers, which also enhances the anti-tumor effects of natural killer cells. Natural killer cells intervene in the rejection of transplanted tumors (in animal experiments), and delay the formation of metastases. IL-2 and interferon boost their activity, but their role decreases as the tumorous disease progresses. Natural killer cells exert their impact through cell-to-cell contact. Therefore, psychosocial influences reducing NK cell activity increase the organism's disposition to "pass-through" tumors and boost the progression of the disease.

Increased NK cell numbers and activities following acute stress soon sink below normal values in the case of the chronic continuation of the stress impact. Prolonged stress, divorce, separation, nursing an incurable patient, or a protracted examination period may have such consequences. Depression can also have such a gateway impact, as it is associated with lower NK cell numbers, according to Stein et al. (1991).

Evidence is available that in tumor biology processes the T cell groups and the NK cells concerned are negatively affected by depression, solitude, and helplessness in addition to stress, as stated in studies by Irwin (2002) and Zorilla et al. (2001). Levy et al. (1985) found an inverse correlation between distress and NK cell activity among stage I and II breast cancer patients. In 55 newly diagnosed breast cancer patients, Garland et al. (2004) detected lower NK cell activity among those who were earlier impacted by psychiatric illnesses or who were currently experiencing psychiatric illnesses than in the case of those patients who were free from such problems. The situation is similar in the case of other cancerous diseases: in 108 patients with digestive tract cancer, Nan et al. (2004) found an inverse correlation between depression and the number of NK cells (CD56+). Such antineoplastic role of natural killer cells characterized by cytotoxic activity seems to be explainable in the case of certain tumors: utilizing this unaligned natural tumor seeking and tumor destruction ability of NK cells, the organism can also fight against scattered pre-cancerous cells preceding tumors. This role of NK cells is also supported by the fact that they have been demonstrated to have a cytolytic effect against a wide range of in vitro tumor cells (melanoma, carcinoma, leukemia cells). A counter-argument is offered in a study by Hanna (1986), which states that the defects of NK activity are accompanied by increased malignoma susceptibility, particularly in the case of NK cell activity and lymphoma tumor growth, which show an inverse proportionality. Levy et al. (1987) found an inverse proportionality between breast tumor metastasis formation (armpit lymph nodes) and NK cell activity levels. It is difficult to accept the much-proclaimed counter-argument that breast tumors are mute and immunologically unrecognizable. Henderson and Humphrey reported that primary breast cancer triggers an immune reaction, and lymphocyte infiltration can be an appropriate index for prognosis.

This is confirmed by an observation from the opposite perspective, according to which NK activity is lower in melanoma patients than in normal controls; this shows an inverse proportionality with the stage of the disease as well, according to Dilman et al. (1981). A study stating that high family accumulation of melanoma and breast cancer was accompanied by considerably lower NK cell activity calls attention to hereditary and familial motives. These facts can place NK cells – highly exposed to psycho-immune influence and cortisol and opioid impacts – into the focus of the psycho-biology of tumorous diseases.

A number of factors influence connections between stressors and NK cells: Levy et al. (1987) reported that those female patients of stage I and II breast cancer who were highly supported by their spouse or the physician, or in the case of whom the search for social support formed part of active coping, showed significantly higher NK cell activity.

NK cells can restrict both local tumor growth and metastasis formation through their cytotoxic activity and immunostimulant gamma interferon production, which also stimulates adaptive immune responses. Cancer patients are characterized by the functional disorder of NK cells, which can be a consequence of a decrease in the number of NK cells, their reduced cytotoxicity and weaker infiltration. There may be phenotype changes in the background, which are expressed in the reduced representation of activating receptors and in the increased representation of inhibitor receptors.

Macrophages are also deemed to play a role in the anti-tumor activity: these are involved in eliminating tumor cells directly, via cytolytic factors, and as executor cells of the ADCC reaction. This process is stimulated by lymphokines (IL2, interferon), and is affected by several psychoneurohumoral factors. Some polymorphonuclear (PMN) cells also exert an anti-tumor impact as killer cells of the ADCC reaction.

Immunity based on adaptive tumor-associated antigen recognition is also under strong psycho-immune influence, since here as well recognition takes place together with the MHC structure and is stimulated by IL1 and IL2 mediators. Obviously, the condition of the immune system plays a role in the elimination of transformed cells by viruses in certain dysplastic deformations and involve the immune response resulting from the altered antigen and the activity of NK cells.

Antoni et al. (2003) examined gynecological, cervical pre-cancerous conditions in patients infected by HPV 16 and 18 viruses. The researchers found a significant relationship between the conversion of intraepithelial, pre-cancerous neoplasia into invasive tumors and pessimistic, helpless attitudes, evasive coping and increased anxiety. As regards women with seropositive HIV and HPV, overwhelming pessimism in these women was accompanied by lower NK activity and CD3+ CD8+ cell numbers, according to Byrnes et al. (1998).

Tumor "escape" mechanisms outwitting immune protection also merit examination, as their agency is testified by psycho-oncological findings. Such tumor behavior can also be considered an adaptation to the given micro-environment, with genetic alterations in the background. Immunosurveillance is made difficult by two such mechanisms. One of them is to reduce the expression of the MHC I complex and the tumor-associated antigen as attested in a study by Garcia-Lora et al. (2003). The tumor can fend off co-stimulation signals. Thus, T cells will show tolerance towards the tumor without co-stimulation. If tumor cells can increase anti-inflammatory, so-called type 2 cytokine preponderance, such as the IL-10 impact in the micro-environment of the tumor, this will also assist in the "escape" of many tumors, as set out in the studies conducted by Li, Wang et al. (2003). Type TH2 cytokines,

principally IL-10, can suppress anti-cancer processes, for example, NK cell activity. Here again, HPA and LC-noradrenergic activity come into focus, which shift the TH1/TH2 balance in the direction of TH2, as a result of which the effect of IL-10 cytokine is invigorated. Noradrenaline and adrenaline – together with beta-adrenoreceptors – play a role in the regulation of cancer progression. Catecholamines, which mediate the impact of psychological stress can influence proliferation, angiogenesis, and metastasis, thereby providing adjuvant therapeutical value to beta-blockers.

Following the suppression of cytotoxic and NK cell activity, the apoptosis – programmed cell death – of virus-infected or cancer cells is also reduced, according to Khong and Restifo (2002). The above-mentioned TH1/TH2 cytokine shift triggered by stress can play a considerable role in tumor control here as well since this very shift also serves as a mirror of weakened cellular resistance (to tumors) and cellular immunity according to Elenkov, Chrousos, and Wilder (2000). The TH1 cytokine effect weakened by stress is responsible for causing more anti-tumor activity in the surroundings of the tumor, such as increased inflammation and angiogenesis, with the point of attack being tumor growth.

Vascular endothelial cell growth factor (VEGF) can be considered a carcinoma prognostic marker of the ovary, the breast, and the nasopharynx. According to Ohm, Gabrilovich, and Sempowski (2003), VEGF disturbs T cell maturation and the maturation processes of dendritic cells. Lutgendorf et al. (2002) demonstrated a connection between VEGF and psychosocial factors among patients with ovarian cancer. In those who indicated more helplessness and low self-esteem, higher VEGF levels were measured, and anamnestic treated depression or anxiety was also associated with higher VEGF values. According to Lutgendorf et al. (2003), VEGF production in ovarian cell lines is increased by noradrenaline, adrenaline, and isoproterenol (beta-adrenergic agonist); therefore, IL-6 – the cytokine taking part in the stress process and so important in psychoimmunology – also influences angiogenesis and may play a part in cancer progression as well. In vitro, IL-6 increases the proliferation, migration, and invasion of ovarian carcinoma cells and acts as an indirect stimulant of angiogenesis, according to Obata et al. (1997). Constanzo et al. (2005) studied correlations between social support and IL-6 levels, and drew attention to the possibility that psychosocial factors transmit the influence of IL-6 by impacting the inflammatory processes in the tumor's micro-environment.

Basal membrane infiltration and the vascular invasion of tumor cells play a very important role in metastasis formation. Metastasis invasion is increased by the so-called matrix metalloproteinase enzymes, which contribute to the demolition of the cellular matrix surrounding the tumor cell, and ultimately

to the termination of the tumor's isolation. Stress hormones and noradrenaline increase the invasion of cervical or ovarian cancer through these metalloproteinase substances, which can be inhibited by propranolol. As a result of stress, tumor-associated macrophages in a proinflammatory tumor environment lose anti-tumor phagocyte characteristics, and, instead, they produce mediators that increase angiogenesis, tumor invasion, metastasis, and inflammation in addition to cytokines downregulating cellular immune response, as stated by Sica and Mantovani (2012). In patients who have ovarian cancer, serious stress and depression lead to increased MMP-9 secretion by tumor-associated macrophages, which enhances tumor invasivity and is associated with worse prognoses.

Cancer is a symbolic disease, with disorganized tissue not respecting boundaries. In this regard, cancer is a predator, parasite, killer, and finally a victim of the perished parent organism – a symbol of peculiar human ecology and a group of diseases requiring a network-based medicine approach. The harms of civilization – including contamination of the environment with chemical or radiating carcinogens, the disintegration of the social environment, the traumatization of early mother–child relationship, alienation, loneliness without a companion, and a lack of social support – result in weakened immune protection, involving weakened protection against tumorous diseases. Social support, the warmth of living in a family, and the quality of social networks surrounding the individual are related to the human ecological aspect of psychoimmunology. Through the meta-analysis of 87 studies involving data on personality patterns, Pinquart and Duberstein (2010) demonstrated that a higher level of perceived social support, a larger social network, and living in a family/marriage reduce the risk of cancer by 25%, 20%, and 12%, respectively.

The tumorous process from the perspective of PNI

It seems that psychological factors primarily influence tumorous disease prognosis and the duration of survival. The survival rates of apathetic, depressed, and hopeless oncology patients are much shorter. Patients' coping strategies seem to be highly significant: according to several follow-up studies, those patients who can show their feelings and vent out their inner tensions through positive actions have better prognoses. The "determination to survive" is difficult to measure; the survival chances and the life quality of oncology patients are considerably improved by decreased depression and anxiety, the ability to express sentiments, and increased activity. However, based on the experimental results presented earlier, it is absolutely reasonable to provide psychic care and support to oncology patients.

PSYCHOIMMUNOLOGY OF THE "HOLY SEVEN" PSYCHOSOMATIC DISEASES

If Franz Alexander had applied the foundation of his physiological explanatory model to Selye's stress paradigm and its implicit neuroendocrine-immune framework, then the book entitled *Psychosomatic Medicine* would be the first clinical psychoimmunological work. Alexander listed seven diseases from internal medicine: essential hypertension, peptic ulcer, bronchial asthma, rheumatoid arthritis, ulcerative colitis, Graves' Disease, neurodermatitis as diseases with a psychosomatic character, and for generations, these were *the* psychosomatic diseases. Franz Alexander pointed at the critical elements, which now could be listed as parts of the social-psychoimmunological explanatory framework. When speaking about conflict specificity, he framed it in a Cannonian psychophysiological pathology enmeshed with a social context of interactions, conflicts, interpersonal dynamics of early traumatization and romantic attachments, family, and the worksite milieu. Alexander proposed the significant role of antecedent environmental events proximal to the disease onset, which is the basis of life event analysis and narrative medicine and trauma disclosing therapy methods. The Alexanderian concept of the psychosomatic process included the disease precipitating function of stressful environmental events revoking latent, unresolved conflicts from early infantile childhood experience. In the following sections, we are trying to adapt a social-psychoimmunological insight to the Alexanderian "Holy Seven" diseases.

Psychoimmunology of hypertension

Hypertension was thought to be an exception for those who wanted to apply psychoimmunological insights to this disease. However, psychocardiological considerations revealed the importance of inflammation in arteriosclerosis and the role of proinflammatory interleukins in elevation of blood pressure.

According to Singh (2014), the autonomic nervous system's interaction with the immune system also plays a role in the development and progression of hypertension. The volume of the literature on the relationship between hypertension and proinflammatory cytokines is considerable. In animal studies, in the case of mature RAG/- experimental mouse strains with cell deficiency T and B, hypertension does not develop. With T cell replacement, however,

hypertensive phenotype appears, but this is not detected when B lymphocytes are given, according to Guzik et al. (2007). In contrast, the adoption of Treg (CD4+/CD25+) cells prevented the development of angiotensin II (Ang II) and aldosterone-dependent hypertension in the 12-week C57BL/6 mouse strain in Barhoumi et al.'s research (2011).

According to Barhoumi et al. (2011), increased activation of the renin-angiotensin-aldosterone axis causes the aldosterone to generate hypertension and increase vascular inflammatory phenomena. The research group demonstrated the role of macrophage and T helper cells in the development of angiotensin II-induced hypertension and vascular damage, while suppressor T cells were identified to reduce angiotensin's action. Aldosterone increases macrophage infiltration of the aorta and the cortical zones of kidneys. This process is inhibited by Treg cells in the studied mouse strain.

The sympathetic nervous system, which determines the development of hypertension, directly innervates the bone marrow, spleen and peripheral lymphatic system, and thus the immune system cannot be rid of the increased adrenergic activity responsible for hypertension. Cytokines, on the other hand, can influence the circulatory system by increasing the sympathetic nervous system's activity. This immuno-neural circle is enhanced through the sympathetic nervous system agency, which enhances the mobilization of lymphatic cells and promotes migration and infiltration into the affected organs. The TLR response of the native immune system is influenced by the activation of adrenergic, cholinergic and angiotensinergic receptors displayed on the surface of cells, where adrenergic and angiotensinergic receptors enhance a proinflammatory response. In contrast, cholinergic alpha7 receptors have an anti-inflammatory role.

In the development of renal hypertension, inflammatory infiltration of the kidneys and inflammatory cytokines produced by mesangial cells also contribute to kidney damage. But it leads to hypertension in the adventitia layer of blood vessels and to the inflammatory infiltration of the perivascular adipose tissue and to the production of cytokines from macrophages, which also play a role in the tension of peripheral blood vessels determining TPR and the proliferation of vascular smooth muscles. In addition to increased peripheral resistance and an increase in post-load, the influence of resident and migrating immune cells may contribute to myocardial hypertrophy. Toll-like receptors activated by sterile tissue lesions are also capable of activating inflammatory processes. The native immune system connects inflammatory events to the hypertension disease process through Toll-like receptors, as well as adrenergic, cholinergic and angiotensinase receptors (AT1). The application of Treg cells to ward off angiotensin II (Ang II) and aldosterone-dependent hypertension in animal studies indicates that proinflammatory imbalance may play a provocative role in hypertension, which is curbed or preceded by the activity of

suppressor T cells on the cell lines of both native and adaptive immunity. Through pathological positive feedback, "tuned" inflammatory processes in the central nervous system increase sympathetic activity, consequently leading to the mobilization of additional bone marrow core cells, and to the mobilization of spleen monocytes and lymphocytes, which causes inflammatory processes in the target organs and produce additional pro-inflammatory cytokines. The parasympathetic vagus influence reduces the inflammatory process, disturbed in hypertension, and the NFkappaB activity is weakened. The decrease in the expression of the α7-nACh receptor in the animal model of hypertension might reduce parasympathetic influence.

It is worth mentioning here that angiotensin convertase enzyme inhibitors and blockers reduce CRP and IL-6 secretions increased by angiotensin-II activity, according to Sano et al. (2001) and Zhao et al. (2013).

Atherosclerosis as an inflammatory process

On the other hand, the target range of risk factors, atherosclerosis itself, can be considered a local inflammatory process, the cellular and cytokine factors of which are affected by neurohumoral influence under the conditions of depression, as well as chronic and acute stress. In terms of health, characteristic risk traits such as hostility and anger are associated with increased catecholamine secretion and increased autonomous nervous system activity. Psychological stressors influence the endothelial function, adhesion processes and local chemotaxis, as well as NK cell activity and white blood cell count. Acute and chronic stressors increase the risk of platelet aggregation by increasing the level of hemostatic factors and acute phase proteins, according to Ho et al. (2010).

Several studies have shown elevated CRP levels in patients with coronary artery disease associated with depression, as observed in 68 IHD patients by Taylor (2010). In addition, Surtees et al. (2008) found that higher CRP was associated with a doubled risk of a myocardial event.

Depression, anxiety, and chronic stress are considered independent risk factors in ischaemic heart disease. It is noteworthy that this association is true even with mild depressive symptoms. A follow-up study by Barefoot et al. (1996), extending to a period of 27 years, showed that ischaemic heart disease developed 65% more frequently among people with depression. The public health importance of this phenomenon is underlined by the fact that while depression ranked fourth among the most common diseases responsible for mortality and loss of ability, and cerebrovascular pathologies ranked sixth, according to forecasts, ischaemic heart disease and depression are expected to be in the top two places soon, and cerebrovascular pathologies will occupy

the fourth place. Atherosclerosis is an inflammatory-fibroproliferative process according to Ross (1999). For us, this is especially important, because immunological and inflammatory processes during atherosclerosis bring ischaemic heart disease even closer to the field of psychoneuroimmunology. A common feature of ischaemic heart disease and cerebrovascular pathologies is local damage of the vascular wall. Infectious factors can trigger subendothelial deposition of atherogenic lipoproteins, in addition to smoking, hypercholesterinemia, and hypertension. Also, maladaptive immune processes play a role in chronic inflammatory processes, according to Polyzos and Ketelhuth (2015).

Even in the earliest stages of disease ("fatty streaks"), sticky monocytes, T cells and lipid-filled macrophages play a crucial role. An important element in the advanced process remains to be the accumulation of macrophages and T cells, along which the proliferation of smooth muscle cells and connective tissue cells can be observed. Inflammatory mediators reflect immune events that play a role in the disease process, and inflammation accelerates the progression of the disease. Animal studies have also recorded an increase in inflammatory markers in the circulation of animals exposed to immobilization or isolation stress. Human observations confirm this because in healthy adults elevated cellular adhesion molecules due to acute stressors were detected by Mills and Dimsdale (1996).

Suarez et al. (1996) found cytokines of peripheral monocyte origin to be high in subjects with high hostility in recalled angry states of mind, as opposed to subjects exposed to such tests but not exhibiting hostility. Thus, in addition to anxiety, depression, and chronic stress, hostility and anger can also be considered independent risk factors in the development of ischaemic heart disease and acute cardiac events. Anger and hostility are different concepts because while anger is an emotional state, hostility is a personality characteristic, including a cynical, distrustful attitude that attributes hostility to others, which can form part of an angry, aggressive attitude. Hostility can be considered a multilayered characteristic with cognitive, affective, and behavioral elements. Therefore, its treatment also requires a cognitive-behavioral therapy effort, as the Williams Life Skills training exemplifies, which incorporates enhancement of emotional reflexivity and homeostasis, correcting cognitive style, impulse control, empathy and communication skills.

Nikkheslat et al. (2015) consider inflammatory processes as a common contributor to depression and ischaemic heart disease, as the inflammatory processes link unpredictable chronic stressors, depression, and cardiovascular disorders. Such mediating variables are acute phase proteins observed during depression by Maes et al. (2011), an increase in circulating complement levels, inflammatory cytokines, IL-1β, IL-2, IL-6, IL-8, IL-12, TNF-α, and interferon-γ (INF-γ). Depressive symptoms are proportional to IL-1 alpha, IL-1 beta, IL-8, monocyte chemotactic protein, and TNF alpha cytokines. Marsland et al.

(2007) found a link between IL-8 levels from peripheral monocytes and the severity of depression in a relatively large community screening study, which is also interesting because macrophages isolated from plaques produce IL-8 to an increased extent. This does not preclude a substantially different assumption that inflammation itself is the primary phenomenon that triggers both depression and the atherosclerotic process. As part of the treatment, IFN-alpha and interleukin-2 are used to develop mood and behavioral changes similar to depressive symptoms, according to Capuron and Miller (2004). However, higher CRP levels, IL-6, and VEGF (vascular endothelial growth factor) may be observed in depressed patients suffering from ischaemic heart disease compared to non-depressive patients (Nikkheslat et al., 2015). The activity of the HPA axis varies along with glucocorticoid receptor (GR) resistance. Although the degree of depression was correlated with CRP and IL-6 levels, the multi-variable analysis suggested that, in addition to classical cardiovascular risk factors, depression and inflammation were both independent variables, as attested by Kop et al. (2010).

Risk personality

Thus, concerning the dynamics of emotional and health psychological factors, as well as vascular pathologies, there are various interactions in the early, intermediate, and advanced stages of the disease. Such interactions often take effect in the tissues of the immune processes that vary through the transmission of the depressive state.

Internal medicine was open to psychological factors and the dynamics behind ischaemic heart disease and to the therapeutic modification of the so-called type A personality elements in the prevention of re-infarction. The "precursor" of the so-called type A competitive, hostility-prone personality pattern experiencing frustrations and a constant feeling of being under time pressure was already mentioned. The American founder of psychosomatic medicine, Flanders Dunbar (1947) wrote about a pattern of a personality prone to heart disease and heart attack, calling the pattern a disease of "top dogs" and "would-be-top-dogs". Although the concept of type A risk personality has been narrowed nowadays, the role of hostility has been retained as a cardiovascular risk element. In the so-called type D personality, emotional disturbances of adaptation to the social environment also play a role. Denollet (1996) draws attention to negative feelings, pessimism, and social inhibitions in this type of personality. People with type D personality traits tend to have higher levels of anxiety, restlessness and depression in almost all life situations, but these feelings are not shared with anyone for fear of rejection. In heart patients with type D personality, cardiovascular problems such as peripheral vascular

disease, the need for angioplasty or bypass surgery, heart failure, heart transplantation, heart attacks and the chance of death are three times higher, and the personality type (type D) is considered an independent risk factor based on the meta-analysis of 49 studies.

According to Suarez (2012), anger and hostility are independently linked to inflammation and depression, and hostility and anger together have a much more intense association with inflammatory symptoms than either of these conditions alone.

Hostility with depression is a good predictor of an increase in IL-6 levels. Stewart et al. (2009) correlate hostility and IL-6 only among subjects with depressive symptoms. Janicki-Deverts et al. (2010) studied relationships between hostility (measured by a 20-item CMHO scale) and TH1 cytokines (IL-2, TNF-alpha, INF-gamma) and TH2 cytokines (IL-4, IL-5 and IL-10) in healthy subjects. Both TNF alpha and IFN-gamma are correlated with hostility indicators according to Suarez et al. (2004), but for subscales, TH1 cytokines were correlated with cynical disposition and did not correlate with the aggressive response. Mommersteeg et al. (2008) found a positive correlation between hostility and cytokines TH1 and TH2. According to Sjögren et al. (2006), IL-6 positively correlates with cynicism, hostility, hopelessness, depressive moods, vital exhaustion, poor coping and low self-esteem.

The psychoimmunological interpretation of the relationship between chronic stress and cardiovascular pathologies is supported by the fact that chronic psychological stressors exert influence on endothelial functions and chemotaxis (Ho et al. 2010). Cytokine, white blood cell and antibody variables detected in episodic risk situations are often associated with an increased risk of acute coronary syndrome or heart failure in a given situation. With a high risk of myocardial infarction, low-intensity inflammatory processes can destabilize atherosclerotic plaques, increase the risk of plaque rupture, especially in increased psychological risk situations.

Factors of links between depression, acute and chronic stress and ischaemic heart disease, adrenergic and cortisol hyperactivity, inflammatory cytokines and autonomous nervous phenomena all form a common socio-psychophysiological, behavioral, psychosomatic framework for the dynamics of ischaemic heart disease and cerebrovascular pathologies, which is integrated even deeper into the PNI framework by inflammatory processes and the effects of acute-phase proteins.

These vegetative neurological effects include changes in heart rate variability and increased catecholaminergic effects including changes in plasma K ion levels and an increased risk of platelet aggregation, arrhythmogenicity and catecholaminergic influence of blood fat levels. This information network integrates neural, autonomic, hormonal, and immune networks that organize affective phenomena.

Heart rate variability (HRV) is related to various neuroses, posttraumatic stress syndrome, generalized anxiety, and a state of social anxiety. In Metabolic Syndrome, higher depression, higher CRP values, and lower HRV values can be considered independent and additive risk factors. Anxiety neurosis is associated with a decreased value of HRV, where the anxiety state coupled with depression triggers a more significant decrease in HRV, which is also associated with a 2-3-fold increase in cardiovascular morbidity. HRV disorders may also trigger an increase in proinflammatory cytokines, which affect the HPA axis, and reduce HRV through increased sympathetic and parasympathetic activity. This can be considered negative feedback because sympathetic nervous system activation protects against the adverse effects of proinflammatory cytokines. Aronson et al. (2001) found a link between HRV and IL-6, TBF alpha in decompensated heart failure. An increase in TNF α was a strong predictor of decreased HRV. HRV deviations and increased sympathetic tone also affect immune processes. The relationship between increased IL-6 levels and decreased HRV values can also be attributed to the increased sympathetic tone observed during decompensation.

According to Taylor et al. (2010), some frontotemporal cortical areas are informationally related to the processes responsible for maintaining stress response and homeostasis, and the functioning of this network is also reflected in the Heart Rate Variability (HRV) indicator. It is valid for the different stages of ischaemic heart disease that the immune system can play a role in both the formation of atherosclerotic plaque, and the thrombotic consequences and the processes of consequential myocardial damage. According to Kop et al. (2011), immune processes might play a role in myocardial hypertrophy, too. Psychological health indicators, relevant for PNI, such as quality of life, self-esteem, or vital exhaustion, are related to IL-6 levels or CRP levels (Marteinsdottir et al. 2016). Depression, often observed in people with heart failure, also correlates with IL-6 levels, according to Moughrabi et al. (2014). It is important to note that, as a result of the psychoimmunological aspects of sleep, sleep disorders are also associated with increased cardiovascular mortality, the transmission of which is associated with inflammatory factors and the cytokine network. Among the TH1 cytokines involved in the coronary artery atherosclerosis process, IL-12 plays a role, alongside gamma interferon and IL-18, according to Ranjbaran et al. (2007). T cells in the artery wall are considered to be the source of gamma interferon released under the influence of IL-12 and IL-18. In this process, the degradation products of angiotensin, such as AngIV, which also contributes to the profile of endothelial cells and vascular smooth muscle cells in the inflammatory processes of the vascular wall, may also increase the formation of thrombosis (Ruiz-Ortega et al., 2007).

With regard to the cytokine network, AngIV may also contribute to an increase in IL-6 and TNF-alpha production by activating the NFkappaB sign

pathway. Factors of innate immunity also play a role in the modeling of coronary processes and atherosclerosis, since the information processes of Toll-like receptors are important in the inflammatory response to tissue damage. Mediators of related signals, LBP, CD14, MD-2, TLR4, MyD88, and NF-kappaB all deserve attention. Innate immunity and endotoxin/TLR4 stalk pathways can also offer a preventive and therapeutic target in arteriosclerosis and, according to Stoll et al. (2006), innate immunity might be an intervention target during myocardial infarction.

Atherosclerosis and myocardial hypertrophy in the context of inflammatory processes

If cellular processes of vascular atherosclerosis are interpreted in a network framework, the cardiological and immunological approaches become inalienable. Immune factors for coronary artery atherosclerosis include macrophages, T and B cell lymphocytes, NK cells, the cytokines such factors produce, acute phase reactants (e.g., CRP), factors involved in thrombosis, factor VII, fibrinogen, and adhesion molecules. In the case of the so-called early atherosclerosis (fatty streaks), endothelial damage is due to risk factors, altered flow dynamics due to hypertension, hypercholesterolemia, and chemical irritants. The most important of these are chemical irritants that enter the body through smoking. Lipids, macrophages, and T lymphocytes play prominent roles in the pathophysiological processes of the vascular wall during this early life period, which can still be considered reversible. In the next phase of plaque formation, growth factors produced by platelets, endothelial cells, and macrophages already play a significant role, which results in increased growth of smooth muscle cells and additional cell migration processes. Endothelial dysfunction and muscle cell proliferation also affect deeper layers of the vascular wall. T cells, macrophages, and mast cells also play a significant role in the advanced atherosclerotic process due to their activated state, their cytokine-producing role, in the scope of which fibrin deposits and lipid-containing phagocytes accumulate in the intima layer. During this period, the lumen does not narrow due to competent vasodilation, but the lesion breaks into the deeper layers, and above it collagen and smooth muscle form a thin, chasm "fibrin cap", the injury of which easily develops thrombus and vascular lesions. In advanced atherosclerosis, endothelium, intima and lamina elastica are damaged, and the rupture of plaques leads to the complete blockage of the vascular wall. This signifies immune changes, with nonspecific markers reflecting inflammatory processes like the increase in CRP, which is associated with cardiovascular events – as described by Danesh et al. (2004) on the basis of longitudinal epidemiological studies. CRP, an indicator of a chronic inflammatory process of

low intensity, has an activating effect on endothelial cells and accumulates in plaques. However, as indicated earlier, IL-6 and TNF alpha may be considered predictors of the arteriosclerotic process. Inflammation, which initially has an adaptive value and removes the harmful factor, is closed into a perilous circle of chronic inflammation, lipid modulation, oxidation and vascular wall damage. The emergency also worsens amid cytokine communication, as ischaemia also releases cytokines from myocardial cells, which increase plaque instability and thrombotic blockage of the coronary artery.

However, pathogens entering the blood might be seen as risk factors, with which some of the vascular macrophages may also come into contact through congenital immune reactions. Macrophages, called fat-containing "foam" cells, are built into the vascular wall from circulating monocytes, where scavenger and Toll-like receptors appear on the cells, and activate the congenital immune response, increase lipid uptake, oxidative cell response, and macrophage metabolic activity.

Lipid-eating macrophages mobilize growth factors and produce cytokines, which attract additional inflammatory cells to endothelial injury. Lymphocytes can play a passive and active role in the construction of atherosclerotic plaque, but the role of activated T cells is important.

Plaques contain mainly TH1 and, to a lesser extent, TH2 cells. Cytokine production due to T cell activation explains the elevated level of IL-6, which can be considered a risk factor. IL-1 and TNF alpha stimulate the binding of monocytes, platelets, and macrophages to vascular endothelium. Cytokines and metalloproteases produced by activated macrophages and T cells can contribute to the rupture of adult plaques leading to hearth attack and stroke.

Among the inflammatory aspects of ischaemic heart disease, we can examine pathogens' role, as this also has a psychoimmunological context. Chlamydia pneumoniae and cytomegalovirus (CMV) double the risk of acute coronary syndrome, as described by Danesh et al. (1997).

Pathogens do not need to trigger acute infection: they can have an indirect effect on the disease processes of ischaemic heart disease, but against the background of such epidemiological associations there are other causal factors, such as age, low SES indicators, and the existence of chronic psychological distress.

Immunological aspects of myocardial hypertrophy and heart failure

Numerous studies, including Pasic et al. (2003), have indicated that CRP and inflammatory cytokines (IL-6 and TNF alpha) are predictors of mortality in heart failure patients. Myocardial infarction and hemodynamic overload as well as heart failure activate inflammatory cytokines. Kapadia (1999) attributes

this role to certain factors of the immune system in the processes of vascular remodeling, hypertrophy, apoptosis of myocardial cells and altered gene expression. Fibrosis of the myocardium leads to worsening pump performance by enhancing the "stiffness" of the heart muscle, which is affected by inflammatory processes. Inflammatory factors play an essential role in the processes of circulatory atrophy in the form of cardiac cachexia in end-stage heart failure. Myocardial muscles react with IL-6 and TNF-alpha secretion to the condition of heart failure, and – against the background of increased cytokine production in heart failure – increased sympathetic nervous system activity also plays a role as described by Parthenakis et al. (2003). Thus, the multi-directional neuroimmune-cardiac network plays an important role in heart failure and is of interest to prognostication in addition to important in treatment.

The above factors indicate the organism-level relationship between cardiac and immune processes. These factors can be weighed individually, and the involvement of the immune system is difficult to dispute.

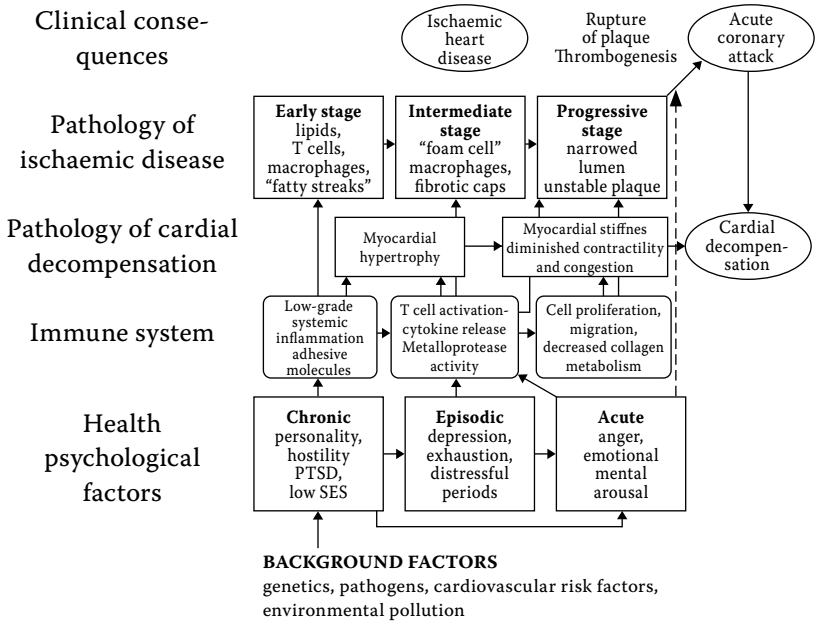


Figure 15. Coronary artery disease in the light of stress and psychoimmunological consequences

If depression is seen as a mediator between psychological variables and cardiac consequences, the question is how immunological factors changing in the process play a role in this. Depression is predictive of both first and second heart attacks and sudden cardiac death. Depression can result from emotional distress, distress and helplessness caused by the underlying disease, a

narrowing quality of life, or the social and economic effects of this situation, but it may also be the effect of inflammatory phenomena associated with atherosclerosis in the central nervous system. The depression that accompanies circulatory disease is mainly due to energy loss, fatigue, irritability, while micromania misconceptions, guilt, low self-esteem are uncommon, according to Kop (1999). Fatigue and vital exhaustion often precipitate the occurrence of myocardial infarction, due to chronic stress and persistent inertia. The so-called "somatic depressive syndrome" associated with sleep disorders, fatigue, loss of appetite, and psychomotor changes, is a more accurate predictor of postmyocardial mortality than the "cognitive-affective" depressive syndrome characterized by loss of interest, anhedonia, self-esteem disorders and suicidal urge. Collecting its data from several cardiac centers around the world, the INTERHEART study found nearly 12,000 samples of myocardial infarction: the study identified significantly higher perceived stress rates compared to similarly large disease-free samples. Furthermore, the research demonstrated a low locus of control and higher depressive indicators compared to the control population. General distress at home and at work increased the risk of myocardial infarction, which was more pronounced in the case of periodical distress (Kivimäki and Steptoe 2018).

Psychoimmunology of peptic ulcer

The psychoimmunological aspects of peptic ulcers are affected by the fact that frequent childhood abuse was associated with a significantly increased risk of stomach ulcers with a 4.2 chance ratio. According to a large cross-sectional population-based study (U.S. National Comorbidity Survey), the odds ratio in the context of ulcer disease and generalized anxiety disorder was 2.8 after the results were corrected for sociodemographic characteristics, comorbid mental disorders and physical morbidity. Another broad population-based study found a slight association between stomach ulcers and trait neuroticism.

Numerous reports indicate the relationship between the action and relapses of peptic ulcer and life events. Inhibiting the attainment of personal goals can also contribute to peptic ulcer complaints, especially for ambitious type A personalities. In a study conducted in Denmark, anxiety also appeared among host factors, where the risk surplus was thus divided: in addition to H. pylori (4.3 odds ratio) and smoking (3.8 odds ratio), anxiety sedatives (minor tranquilizers 3.0 odds ratio) also showed high levels. Both smoking and anxiety require psychotherapeutic support. Levenstein (1997) in the Alameda County study found a link between depression and the incidence of anomia and peptic ulcer (1.7 odds), after correcting the sample for smoking, drinking, messy eating, sleep deprivation and liver disease. In a follow-up study of 4,511

American adults by Anda et al. (1992), the number of incidences of peptic ulcer in the case of those who considered themselves stressed over the next 13 years was found to be two times higher. In this sample, the frequency difference was found to be 3 times higher in the case of those who were under severe stress.

Psychotherapy and hypnotherapy in the treatment of gastric ulcers produce moderate results, and do not achieve the success of Helicobacter eradication. Also, the "specific" therapeutic gains of psychotherapy do not reach the value of psychotherapy among people with IBS. In the case of chronic diseases, psychoeducation and therapeutic patient management can help to improve poor compliance, adherence and ineffective treatment. Helicobacter positivity is not always associated with ulceration, so many elements among the "host factors" – such as stress, smoking and alcohol consumption, which also increase ulcer risk, as well as correcting unjustified non-steroidal inflammatory medications – may require a behavioral medicine approach.

Asthma

Personality traits and asthma

Oftentimes controversial study results certainly cannot be simplified in this area, either. Using test surveys (TAT, Rorschach, Wolff PP), Fine (1963) found that asthmatic children are more irascible, introverted and dependent than children in the control group. At the same time, he noticed characteristic differences between genders as well. Some researchers perceived asthmatic patients as lacking in self-confidence as well as being immature, restless, and tense, while according to others, such as Block (1964), asthmatic children are characterized by polite sociality and broad imaginative powers as well as by aggressiveness and irritability. Doubts may arise as regards the relevance of these personality features, but hidden uniformities (e.g., intensive emotional arousal) may also be found behind these controversial characteristics. Neuhaus (1958) compared asthmatic children with a group of children suffering from chronic cardiac disease, but he did not find any substantial differences and simply accounted for anxiety and dependence for the chronic disease concerned.

Genetic and environmental backgrounds

Based on family accumulation and twin studies, Schwartz (1952) deems it confirmed that hereditary factors moderately prevail in the background of exogenous asthma. According to Marshall (2004), the suspicion of genetic risk

seems to be properly grounded in the case of many allergic diseases, including bronchial asthma. It can be reflected in the family anamnesis of asthmatic patients, which can be predictive in allergy and asthma. According to Mojtabai (2005), the psychopathological load of parental background, parents' depression, or panic disorder will also increase the frequency of atopic illnesses in childhood if the parent is also atopic. Regarding genetic involvement, it can be interesting to note that 70% concordance was shown in twin studies of monozygotic twins in respect of higher IgE levels; however, in the case of asthma, this concordance was only 30-40%.

According to Blumenthal (2005), the genetic chromosome locations most probably responsible for atopy are 5, 6, 11, 12, 13, 16, and 20. These include IL-13 responsible for the TH2 immune signal path (chromosome 5), IL-4R for synthesis (chromosome 16), and STAT-6 (chromosome 12), but the metalloprotease coded on chromosome 20 also plays a role in this.

Simultaneously, by way of genetic mechanisms it is difficult to explain the dramatic increase of the frequency of allergic diseases observable in western societies, as pointed out by Beasley et al. (2000). The environmental *hygiene hypothesis* assesses the civilized, western-style way of life and environmental changes. According to the theory, reduced exposure to pathogens breathed in and consumed deteriorates immune tolerance established by T regulatory cells, which leads to a loss of TH1/TH2 balance and the generation of allergic symptoms, while in deprived environments or among people living under third-world circumstances the incidence of allergic conditions is lower.

In the light of these, allergic diseases can be considered increased, complex, multifactorial immune responses to environmental stimuli, glycoproteins, and antigens, with the interference and interaction of genetic susceptibility and environmental impacts. The flexibility of gene vs. environment interactions is expressed in the polymorphism of genes responsible for receptors sensitive to bacterial components, and the disorder expressed in atopic diseases can also be rooted herein. Thus, for instance, the polymorphism of gene sections TLR4 and CD14, responsible for recognizing bacterial endotoxins, can also intervene in increased atopy/asthma risk, according to Williams (2009).

Social issues in psychoimmunology

It has been mentioned that bronchial asthma is included in the psychosomatic disease list of Franz Alexander. Alexander also stresses the multiplicity of causes: in addition to heredity, causes include birth traumas, organic diseases in childhood, increases in the vulnerability of certain organs or organ systems, nursing and caring for the child (early socialization), infantile or childhood physical traumas, traumatic emotional experiences in infanthood

or childhood, the emotional climate of the family, the specific personality traits of parents and siblings, subsequent physical traumas, late emotional experiences related to personal or work relationships.

On the contrary, and partly in support of Alexander's approach, studies of psychological factors over the years have permitted to state four definite principles:

1. There is no exclusive personality formula predisposing to asthma.
2. Asthmatic patients – especially children – reveal a strong unconscious inclination for dependence. This desire makes them vulnerable to imaginary or actual loss experiences.
3. This inclination can probably be traced back to the conservatory role of parental attitudes.
4. Hindrances to desires or conflicts arising from such desires can trigger an asthma attack.

In the psychosocial mapping of asthma, personality surveys focused on revealing the patient's transactional coordinates and peculiar conflict areas. Early traumas and parental stress impacts are evidenced to play a role in the background of early asthma attacks in the first year after birth. TH1-TH2 cell shift and TH2 predominance – triggered by the stress hormones already mentioned – surface here as well.

The availability of asthmatic adolescents (the most frequently examined age group) and recovery associated with an increased demand for independence in the teenage period could also serve as a basis for analyzing dependence conflicts in the Alexandrian sense. The family environment's pathogenicity seems to have been verified by experience based on a wide range of data: the removal of asthmatic children from their family environment leads to a remission of complaints. It also appears to be verified that if a child removed from the family environment is exposed to certain antigens that always provoke attacks in their home, the child will not respond with an attack when being distant from their parents. This is also supported by the ineffectiveness of house dust allergen provocation repeated in a hospital environment. Regarding the background of all this, Long et al. (1958) emphasize the pathogenicity of the conflict field and the therapeutic option of environmental change to guarantee "protection".

Of course, all this plays a role only in a small fraction of asthmatic patients, but in these cases there is no reason to doubt the role of emotional and vegetative mechanisms shaped in this particular conflict framework. In a study of 25 patients, Purcell (1962) detected the above tendency in 13 cases, while emotional factors seemed to be neutral in the rest of the cases. Excessive fear of separation or the attack-provoking role of being confined and threatened is

deeply based on the inability to cope with such threatening situations. So in a given scope of the disease, evolution is determined by the "dramaturgic" conditions affecting the patient. McDermott and Cobb (1939) managed to demonstrate the role of these situational and interpersonal factors in 40% of the first attack circumstances, while in 60% of later attacks. In a study of the pathodynamics of 209 asthmatic patients, Ago et al. (1982) noticed that significant psychosocial stressors were detected in 91.8% of the patients during the year preceding the onset of the medical condition. During childhood, this mainly involved the separation of parent and child; in the case of young patients, the principal causes included interpersonal conflicts in the family and at the workplace; and widowhood in the elderly. The correlation between personal coping and disease is indicated by the fact that in another study involving 74 patients four factors were compared with the perceived dynamics of asthma, including life events preceding the disease, the role of psychosocial stressors, behavioral features, and the burden of early life events. In the case of adult patients, correlations with the degree of severity of asthma were shown in terms of the size of workloads, a fussy, choleric personality, and a lack of interest in social support, while positive, problem-solving behaviors contributed to the remission of symptoms. Asthmatic relapse may occur even after symptoms subsided in the long term for years. Nagata et al. (1999) found that the relapse of the disease after several years of complete remission could be traced back to a much higher frequency of stressful life events than in controls. Moreover, a study by Araujo (1973) demonstrated that asthmatic patients display higher life event indicators, but their ability to cope with stress and social adaptation is low, and these patients were administered higher doses of steroids to treat asthma attacks. 83% of the patients studied by Knapp (1960) suffered from periodic depression. Remorse and a sense of shame occurred in 63% of the patients studied, and 78% displayed marked food and medication abuse.

The possible connection between the sudden death of asthma patients and depression is known. Strunk et al. (1985) found depression, a lack of disease consciousness and self-care, as well as repression regarding asthmatic symptoms, and interpersonal conflicts to be frequent. According to Miller (2009), depression intensifies cholinergic imbalance and parasympathetic activity, which increase the risk of sudden death. According to McFadden et al. (1969), intravenously administered atropine inhibits bronchospasms triggered by hypnotic suggestion. Neild and Cameron (1985) loosened bronchoconstriction by inhaled ipratropium bromide; however, it must be borne in mind that agents to block parasympathetic activity have a bronchodilator effect themselves.

The conflict field of asthmatic patients is overlapped by conflict experiences triggering the disease and resulting from the disease. Perhaps not even the strictest exploratory work of the patient's life history can reliably separate their intertwined dynamics in a chronic disease occurrence. Through mediation by

several psychosocial factors, asthma morbidity and mortality can be connected to family structure features as well. The rejection or the actual or threatening loss of the beloved other can all be triggering components if coping mechanisms are depleted. Resolution of remorse by confession and divulgation – or even the self-defensive act of crying – can act as archaic and chronic substitutes for asthma attacks. This communicative notion of "organ talk" is supported by another series of observations. In the case of children hindered in expressing strong emotions, an attack is triggered by the situation, while if the flow of emotions is not situationally impeded, no attack occurs.

On the other hand, breathing work altered in the course of laughing and crying may provoke an attack, according to Knapp et al. (1960). The researchers analyzed the "circumstances" of 406 attacks in 9 asthmatic patients in terms of emotions and atmosphere: attacks were preceded by anger, irritability, restlessness, and arousal in 34%; patient-reported erotic arousal and increased motor activity in 10%, and 5% were characterized by depression preceding the attack. During the attack, 40–60% experienced depression, defenselessness, and hopelessness. Their majority was characterized by the inducement and the inability to cry, and only 5% were able to cry. It is an absolutely peculiar conflict when the patient "learns" to elicit asthma attacks for the benefit of diseased behavior as a means of escape from reality.

Summarizing the above, the triggering factor can be the loss of a prominent other person in nearly half of the patients. In addition, however, an entire series of cumbersome or positive situations eliciting strong emotions can be provocative, with intensive arousal in the background, which can be expressed only partly by way of crying or through any other affective activity, and the rest of the emotional charge is diverted to the channel of "organ talk".

Obviously, it needs to be emphasized in this respect that in the context of obstructive pulmonary diseases, environmental factors should all be considered separately, including respiratory tract irritation by prolonged cigarette smoke or other air pollution, as well as chronic asthmatic pathological processes following certain viral and other respiratory infections. Also, the correlations presented are more justified in the case of bronchial asthma starting in childhood, which proved to be extrinsic.

In the light of the psychoimmunological approach, those data are also important according to which psychosis occurring in asthmatic patients makes the patient exempt from attacks. Although there are observations to the contrary, Sabbath et al. (1952) detected a definite exemption from attacks during the psychosis of 32 patients characterized by asthmatic anamnesis. In such asthmatic patients, there was a change in the bronchospastic response to provocative respiratory drugs, histamine, and methacholine during psychosis.

Studies of the psychophysiological background of the observations and assumptions above verified the connection between psychic condition

changes and alterations in pulmonary function values through the hypnotic suggestion and conditioning techniques applied. According to Luparello et al. (1968), hypnotic suggestions eliciting experiences of exposure to danger can trigger bronchoconstriction, while suggestions eliciting pleasant experiences can trigger bronchodilatation. Studies by McFadden (1969) demonstrated that suggestions of presence of an allergen could trigger bronchospasms. 40 adult asthmatic patients acted as subjects in a research where they breathed in inhalants described as allergens of various concentrations but otherwise neutral. These patients were compared with controls consisting of healthy people and patients with bronchitis and sarcoidosis. Appreciable increases in respiratory resistance were observed only in the asthmatic group (19 out of 40 reacted this way to suggestion); while some of these participants (12 persons) complained about definite breathing difficulties. The applied placebo eliminated complaints. This observation is also supported by Luparello (1970), according to whom, the inhalation of provocator carbachol as a bronchodilator causes a reduced rate of bronchoconstriction. The fact that these changes are influenced or suspended by atropine renders probable the parasympathetic mediation of the central nervous system's impacts. The fact that the observations made on patients suffering from the disease at a relatively low degree could not be repeated by Weiss et al. (1989) on seriously ill asthmatic patients can also be evaluated in such a way that these factors prevail variably in different cases of the pathological process.

During the 6 months following the hypnosis treatment of 27 adult asthmatic patients in ten sessions, Maher-Loughnan (1962) detected a definite reduction in attack frequency and reported larger subjective improvement than in patients subject to bronchodilator treatment.

According to a case study by Mason and Black (1958), in the course of a two-and-a-half-month hypnosis treatment, skin tests repeated on a weekly basis showed a decreasing tendency following posthypnotic suggestions to decrease the symptoms of extrinsic asthma and rhinitis. However, sensitivity could be transferred to other patients as demonstrated by the Prausnitz-Küstner reaction. In 6 asthmatic cases, Edwards noticed that the value of FEV1 improved after hypnotherapy, 4 patients out of the 6 showed further improvement even after the closure of the therapy. In a prospective, randomized, single-blind control study, Ewer and Stewart (1986) demonstrated in the case of patients suffering from moderate and medium-stage asthma that a 6-week hypnotherapy results in a 79% improvement of methacholine test response in patients with strong hypnotic susceptibility, and as regards home symptoms, test subjects report on a 41% improvement, reducing bronchodilator use by 26.2%.

Although the methodological value of the studies' above calls for caution for reason of the small sample size and the indefiniteness of the subpopulations

examined, the role of psychoneurohumoral mediators between psychosocial factors and the experienced bronchospasm can be indicated.

Numerous studies have suggested the possibility of conditioning asthma attacks where even the image of the object provoking such an attack in nature can trigger the attack itself. These studies are closely analogous to the immune conditioning experiments by Speransky, Metalnikov or Chorin or later by Ader, meaning that learning mechanisms also play a highly significant role – in addition to biological impact factors – in triggering asthma attacks.

A well-known example of this is a patient of McKenzie, where a paper rose could elicit an asthma attack usually triggered by a real rose. It was demonstrated by a series of tests that inhalations – otherwise not containing allergens – can trigger an attack if the patient was told that the allergen is present. Ikemi and Nakagawa (1962) triggered eczema through oversensitivity conditioned with methylene blue. Histamine reaction (egg-white – sulfurous smell) can be conditioned, and a special allergic response can be generalized based on learned associations. According to Gauci et al. (1994), the response to allergens of the nasal mucous membrane – and, at the same time, nasal tryptase release – can be conditioned in patients with perennial rhinitis. Asthma attacks appear as conditioned and learned responses in many cases, and this phenomenon can also be used in the treatment of bronchial asthma by eliminating the learned connection and by applying cognitive behavioral therapy methods.

The social psychophysiology of asthma

A key component in this process is the nature of the relationship between parent and child. In asthmatic children, projective tests showed greater dependence on the mother, closer relationships, and increased sensitivity to separation. In general, families of asthmatic children are rigid, inhibited, overprotective, and with conflict management problems, therefore, in the course of family therapy, they might increase realistic expectations from each other and the ability to express suppressed emotions. The importance of a therapeutical approach to the family as a system is highlighted by the fact that when analyzing asthmatic children's psychiatric symptoms, 70% of them appear closely connected to family problems such as marriage problems, behavioral disorders or diseases of the parents. Therefore, the so-called family asthma programs are most effective in the treatment and prevention of childhood asthma. These programs essentially mean that parents and siblings learn, together with the sick child, the basics of preventing asthma attacks and a healthy lifestyle, including relaxation and breath-control exercises, therapeutical gymnastics, and knowledge of the disease. Thus, both asthmatic children and their families master skills to prevent attacks, and no self-destructive

cycles – leading to the aggravation of attacks – arise from the anxiety of the patients and their families.

Based on a number of studies, asthmatic patients are characterized by disorders of self-esteem, symptoms of depression, anxiety, and interpersonal conflicts to a higher degree. According to Mathé and Knapp's (1969) findings, asthmatic patients do not react to stress effects by increased adrenaline secretion, and they report significantly less on the sentiments of anger and annoyance. This phenomenon corresponds to Alexander's observations, according to which in an emergency situation, asthmatic patients react by calling for assistance and self-surrender rather than by exhibiting increased activity. A physiological projection of this response mode is parasympathetic predomination. As this condition corresponds to anxiety – by way of the person involved giving up the situation psychophysiologically –, it is important to develop effective methods for active coping within the scope of treatment. Such opportunities can be provided by swimming and therapeutical gymnastics as fundamental components in preventing asthma attacks.

The stress preceding an asthma attack is frequently an experience of loss or disappointment, living through an important person's real or imaginary loss. From the point of view of the disease's outcome, the probability of mortality, both high and low anxiety, and panic conditions are pathological. The first group is highly vulnerable because of increased medication – primarily due the increased administration of steroids – while the second group is vulnerable because of the negation of symptoms and the early interruption of taking drugs. The suicide rate of asthmatic patients is higher than the average, regardless of age or gender.

Pursuant to the social and psychophysiological approach, the course of the disease depends on biomolecular features and broader environmental and socioeconomic factors, individual psychological backgrounds, and conflict-solving skills (coping mechanisms), as well as on the quality of family and other social support. The unfavorable impacts of psychological stressors on asthma are abundantly recorded, as reflected in paper of Wright, Cohen and Cohen (2005).

A broader social and psycho-physiology dimension is indicated by the fact that Adler et al. (1994) demonstrated a correlation between bad socioeconomic conditions, a stressful lifestyle, subjugated minority existence, poverty, circumstances in urban slums, and the incidence of asthma.

Taylor et al. (1997) examined the patterns of chronic stressors arising on account of low socioeconomic status (threat of poverty, socially subjugated minority existence, violence, and crime; mobility impairment, insufficient traffic conditions, unavailability of healthcare services) in respect of the environmental stressors of the living environment, the workplace, and the family. Based on such data, a correlation can be observed between the frequency of

the asthmatic complaints of children living in affected urban areas and bronchodilators' prescriptions.

Burdening life events and experienced distress show an inverse correlation with socioeconomic status. On the other hand, perceived control and social support correlate with the socioeconomic situation. Unfortunately, studies of psychosocial factors as environmental factors associated with asthma are not so abundant.

According to Kiecolt-Glaser et al. (1994), the richness of social support and social relationships is a protective factor, with several psychoimmunological consequences as evidenced by our study. Social support reduces distress, assists in perceiving challenges differently, offers appropriate coping frameworks and expands resources. A broader social network is associated with less anxiety and depression and with reduced non-specific distress. Simultaneously, social support can aggravate symptoms in the form of over-protective and over-anxious parent behavior or in the form of over-dependence on medical assistance in the case of asthmatic patients, according to McNichol et al. (1973), and Liebman et al. (1976). On the other hand, social isolation considerably deteriorates asthmatic patients' situation, i.e., morbidity. Fisher et al. (1993) detected more attacks, more frequent duty service referrals, and insufficient treatment in the case of children of socially isolated parents.

Autoimmune clinical pictures in a psychosocial and personality psychology context

Several autoimmune diseases such as multiple sclerosis (MS) and systematic lupus erythematosus (SLE) affect cognitive and affective conditions and behavior. In the case of tumor patients, affective changes and behavioral features can be affected by immune mediators such as TNF and IL-6. On the other hand, permanent functional disorders of the HPA axis can reduce the organism's resistance. The affective personality traits characteristic of autoimmune clinical pictures can partly overlap in patterns observed in tumor patients and allergic patients, respectively. Dupond et al. (1990) found that overwhelming kindness and hyperconformity – to be classified as type C personality traits – are characteristic of patients suffering from lupus erythematosus, polymyositis, and Sjögren syndrome. In SLE patients, helplessness is an important mediatory link between pain and distress experienced by patients, the anxiety symptoms reported, depression, and other stress symptoms. Gholizadeh et al. (2018) demonstrated the role of helplessness by the five-item Arthritis Helplessness Index scale.

The onset of autoimmune diseases is also frequently preceded by a life event with a high score in patient reports, but literature features only a few controlled

studies about this. Koehler (1985) provides an account of stress experiences and the imbalance of protection processes before the onset of rheumatoid arthritis. Sensitivity to losses is indicated by the interconnection between disease dynamics and mourning. McClary et al. (1955) classify irresolvable pain and loss experience because of the loss of prominent human relationships – already detailed in the characterization of tumorous patients – as factors provoking the onset of the characteristic immuno-pathological clinical picture of SLE. Although these patients were characterized by compulsivity, activity, and a desire for independence, other socio- and psycho-immunological factors may also intervene, such as an excessive desire to comply, an anxious feeling of dependence on judgments by others, the anticipated threat of shame.

Observations by Otto and MacKay (1967) indicate that in the case of female SLE patients, emotional desolation in childhood and stress loads in the period preceding the disease were of a higher degree than in the case of the patient group selected as controls with experience of bleeding during pregnancy. In this sample of 28 patients, relationship conflict disorders played a prominent role, along with emotional deprivation, in family anamneses. By reason of such data, personality tests are worthy of attention in the case of SLE patients. In view of family psychology anamnestic data and disturbed HPA feedback, the type C personality concept seems reasonable here, as indicated by studies by Rigó (2001), who also confirmed this by demonstrating the presence of type C personality traits in SLE patients. According to Dupond et al. (1990) and Boyle (1990), none of the excessive conformity behaviors, including the so-called pathological kindness, low self-esteem, the inhibition of aggression and the inability to express disagreement, can be restricted to the character disposition mentioned in psycho-oncological clinical pictures, and this also applies to TH2 type autoimmune clinical pictures, such as SLE.

Studies regarding coping styles can also verify the validity of the pattern above, since according to Iverson et al. (1995), SLE patients are also characterized by passive avoidance strategies. Self-blame and avoidance are accompanied by more physical and social incompetence and depression.

In the case of chronic purpura, Agle et al. (1969) consider masochistic and hysteroid features to be characteristic of female patients suffering from the painful ecchymoses of the condition explained by autoerythrocyte sensitization.

Rheumatoid arthritis

Rheumatoid arthritis – the clinical picture of the widespread disease in terms of gravity, and requiring a separate system of medical institutions – can also be a good example of the clinical diversity of immuno-pathological diseases.

Dinarello and Moldawer (2001) emphasize that several autoimmune procedures, including rheumatoid arthritis, are characterized by the prolonged activation of the native immune system. Besides consequential metabolic deviations, the inflammation is accompanied by tissue deterioration and remodeling in a chronic and uncontrolled pathological process.

In this disease, even animal experiment results suggest a "psycho-immune" influence prevailing in the development of the disease. Still, experiments of psychosomatic pretensions in this field showed only moderate success in clarifying correlations between character, personality and the disease. According to some authors, the formation of this clinical picture – affecting about 2-4% of the population – can be influenced by any of the following: the inhibition of the suppressor cell line T, TH1 or TH17 dependent immune mechanisms, the insufficiency of Treg activity, reduced functioning of the HPA axis, and weakened glucocorticoid dependent anti-inflammatory functions. The autoimmune model of rheumatoid arthritis is also affected by hereditary factors (HLA 9, HLA B 27). By nature, the arthritis syndrome is a collective term for several pathological forms appearing in different clinical pictures (arthritis psoriatic, Behcet syndrome, Felty syndrome, etc.). Correlations between life events, stress, and the autoimmune process can be elucidated by the already presented observations of Jorgensen (1994), according to which reduced hypothalamic CRH production in response to cortisol, in the form of increased prolactin secretion with a pro-immune effect, is perceptible in a rheumatoid arthritis process.

Based on Moos' (1964) summary, the personality prone to such clinical picture(s) is expressed quite early, with personality features including excessive control, masochistic, self-sacrificing tendencies, workaholism, perfectionism, and rigidity. Other authors delineate a dependent personality compensating through aggression in the background of such a personality. In his conflict-specificity-based model, Alexander (1950) presumes the following logic in the course of occurrences related to rheumatoid arthritis. Childhood is characterized by the suppression of revolt against dominant, restrictive, and overprotective parental behavior and by the concurrent evolution of dependence on parents. In adulthood, the target of aggressive and impulsive behavior due to inhibited rebellion will be the life companion in a dominant position, which explains the disorder of female roles perceivable many times in women with rheumatoid arthritis. Simultaneously, the pathogenic consequences of impulsivity hardly controllable this way include increased muscle tone, which may lead to the deterioration of joint surfaces.

With respect to pathomechanism, Solomon (1974) holds the psycho-immune influence responsible for the protracted circulatory presence and the deposition of immune complexes. The importance of stress-provoking agencies is indicated by the fact that the disease's onset is frequently preceded by stressful life

events, such as the loss of a spouse, divorce, loss of a job, or depressive mood disorders. The course of the disease has better prospects for the individuals with a positive frame of mind, displaying more cooperation, higher consciousness, and strong morality than for persons characterized by apathy, depression, dependence, solitude, and emotional insecurity. Suffering from the same disease, Norman Cousins wrote about the healing power and self-curing example of humor, optimism, and a positive frame of mind in his book.

Low levels of DHEA have a psychoimmunological significance here as well. Rheumatoid arthritis is associated with low DHEA, low cortisol levels, and high proinflammatory IL-6 levels, according to Cutolo et al. (1999). Low DHEA levels and cortisol/DHEA dissociation precede the onset of rheumatoid arthritis in young women of premenopausal age, as stated in a study by Masi et al. (1999).

Pathological processes on rheumatic joint surfaces are characterized by the overgrowth of the synovial cells of joint surfaces, and the overproduction of enzymes to dissolve connective tissue following chondrocytes and synovial cells, as well as by Ca resorption by surrounding bones. Lymphocyte invasion, consequential cytokine and inflammatory mediator production, and the P substance production of nociceptive C fibers surrounding the joint surface are also important components of this pathological process. Synovial C fibers increase the levels of SP, neurokinin A, and CGRP in the joint, and their impact is enhanced by the sympathetic nervous system's activity. In the presence of SP and bradykinin, fibroblasts show proliferation and increased DNA synthesis. Histamine induces chondrocytes to produce collagenase, while synovial fibroblasts respond to an SP effect by prostaglandin and collagenase production coupled with a proliferation response. Background triggers of these responses can include macrophages, synovial cells, as well as IL-1 and IL-6 produced by the endothelium, and TNF produced by macrophages acting as contributing factors.

The TNF-producing role of synoviocytes was also demonstrated in rheumatoid arthritis. These factors can be shown in high concentration in the joint fluid and can also be made accountable for the organism's response (fever, acute phase reaction). The positive feedback regulation cycle of mediators can maintain a chronic process. Autoimmune joint event processes in a neurohumoral micro-environment are potentiated through catecholamine effects by the sympathetic nervous system.

Some authors interpret these neurohumoral processes as neurogenic inflammation. In experimental circumstances, the inflammation provoked is reduced in animals pre-treated with capsaicin to reduce T fibers, and the gold treatment included in classic therapy also damages C fibers without a myelin sheath.

It can be assumed that neuroimmunomodulator influence – mediating stress impacts and psychophysiological processes – predominates in the medium of provoked HLA-DL expression developed in the environment of synovial cells and IL-1, and SM mediator effects.

Psychosocial rheumatology

Animal experiments seem to provide evidence for the influence of social factors. In rat experiments, the frequency of polyarthritis (provoked via subcutaneous administration of mycobacterium butiricon) increases with litter number and the elevated proportion of males competing for females. In the case of arthritis provoked by collagen, it was found that acute stress provided moderate protection regarding the course of the disease, while chronic stress increased arthritis incidence by 40%, according to Rogers (1980).

The onset of the disease and relapses are associated with the psychic states of depression, mourning, and sorrow with surprising frequency. At the end of the past century, Sir William Osler wrote the following about rheumatoid arthritis: "the disease is frequently associated with concussion, sorrow, and pain".

Most frequently indicated life events include the loss of a close person, life companion or relative, or the fear thereof: mourning, divorce, infidelity, and loss of employment as well. Ludwig (1952) published a peculiar observation revealing the symbolic "recurrence" of life events: a patient "attached" relapses of arthritis to the anniversary of the loss of the beloved person.

Graham et al. believe that patients with arthritis can be characterized by an attitude of being strained in constraints, intending to break free. As regards life events, the author highlights the motif that a change is required to derail the individual from the track of customary psychological adaptation. Also, Alexander (1950) and Rimon (1969) highlight the importance of the subjective qualification, the personal "semantics" of events. In relapsing female patients who lived to see the crisis of their marriage and disregard, both the rejection of male society and the experience of revolt got strengthened. However, the new role can be eventually refused, and many times this refusal ends up in hopelessness and resignation. This dramatic line is almost a symbolic replica of the experience process of tumorous patients. The authors witnessed wrath followed by depression, a peculiar temporal organization of sentiments seen around the disease's relapses. According to early observations, depressive mood disorders precede the appearance of physical symptoms by weeks or months in the case of a third of patients. Of course, this can also correspond to a symptom accompanying the prodromal phase of a systemic disease, where depression is a consequence of an already onset chronic inflammation.

Depression and rheumatoid arthritis

According to a controlled study by Ganz (1972), 47% of patients are characterized by depressive symptom generation. Based on the frequency of conditions to be described by disorders of self-blame and self-esteem, Ludwig (1952) considers the degree of depression to be serious. Other authors describe inhibitions in the expression of intense emotions and anger. Kutemeyer (1963) reports on a phenomenon reminiscent of psychosomatic symptom changes: depression can be relieved in the appearance of joint-related symptoms. More than 50% of rheumatoid arthritis patients suffer or have suffered from depression, according to Marques-Deak et al. (2005). The background mechanism interlinks depression with rheumatoid arthritis: both clinical pictures include regulation disorders of the HPA axis and hypothalamic CRH as a common feature. Zautra et al. (2004) measured higher IL-6 levels in peripheral mononuclear cells in depressive rheumatoid arthritis patients suffering from stress. Here, IL-6 connects depression and rheumatoid arthritis. At the same time, the phenomenon can be interpreted conversely as well. Depression in patients receiving IL-6 therapy because of cancer or bone marrow suppression also raises the possibility that depression observed in rheumatoid arthritis patients is secondary and is a consequence of increased cytokine production.

Moos and Solomon (1964) distinguish between two groups of patients regarding the course of the disease and the psychological components. Better prognoses are generally associated with better compliance, higher awareness, a sense of social responsibility, role motivation, and strong morality. Worse disease outcomes accompanied the emotional lability, dependence, irritability, apathy, depression, and loneliness of patients characterized by poor adaptation and coping. It is difficult to answer the key question – which came first: the chicken or the egg? – in the relationship between depression and the disease. Although, according to Hart (1970), all chronic, painful, and recurring diseases lead to depression, a contrary experience is the absence of depression in rheumatic patients, where the disease is very serious, extremely prolonged, and exists for decades. Ganz (1972) did not find a correlation between psychiatric symptoms, illness duration, and medications applied.

Similarly, thought-provoking observations are presented by Krammer (1961), who detected the efficiency of MAO inhibitor antidepressants in the improvement of the physical condition of rheumatic patients. By administering imipramine, Scott (1969) reduced joint rigidity and pain and reported improving motor functions. In spite of heterogeneous data, it is indubitable that a considerable part of clinicians are concerned with the psychosocial impacts of rheumatic diseases.

According to Geenen et al. (2006), stressors increase inflammation in patients suffering from rheumatoid arthritis. Mental and physical efforts often

cause reduced responsiveness in the sympathetic nervous system. This defect preceding the disease depends on various factors: inflammation indicators can all be influenced by earlier and current stress impacts, early life events, or post-traumatic stress conditions. Major life events can positively or negatively influence the course of rheumatoid arthritis depending on the duration and severity of the stressor and the degree of the accompanying stress response. Based on personality characteristics, the effect of the stressor on the disease varies individually.

Personality traits and rheumatoid arthritis

Investigations of the personality, the psychic "interface" between environmental impacts and triggered or triggering emotional disorders "can generate" heterogeneous results. Studies by Moos et al. (1964) and Mueller (1961) agree in that most cases of arthritis are characterized by compulsivity, accompanied by rigidity, perfectionism, strong control, workaholism and masochistic self-sacrificing tendencies. Ludwig's (1952) investigations did not find the set of causes to be uniform at all. He mostly met with low tolerance of frustration instead of the "long-suffering" nature deemed to be characteristic. Studies by both Alexander (1950) and Johnson (1947) delineate a type that is dependent on interpersonal relationships, displaying overcompensating attitudes through aggression, sacrificing. At the same time, the person controls their environment through their martyrdom. Mueller (1961) considers a self-uncertain personality increasingly sensitive to others' impulses – mainly rejection – to be characteristic, which coincides with Moos and Solomon's (1964) opinion. Of course, this ramifying typification does not invalidate Alexander's presumption that conflicts can play a role in the development of the disease.

In adulthood, such a person will exhibit aggressive and impulsive behavior in dominant positions due to their inhibited rebellion. This explains the disturbances of female roles many times perceivable in women with rheumatoid arthritis. Simultaneously, increased muscle tone can also play a role in the pathogenetic mechanism of impulsivity – this way hardly controllable. Self-sacrificing, compensating moralist tendencies can provide opportunities for resolving remorse caused by impulsiveness. Although Alexander described this conflict pattern primarily in connection with female patients, psychoanalysts in controlled studies – in the course of "blind diagnostics", where the diagnosis of the disease of rheumatic patients mixed with various types of psychosomatic patients was attempted – found the same conflict pattern relevant also for male patients. It was demonstrated in 80% of male and 53% of female patients. Other authors doubt the specific nature of conflicts. According to Rimon (1969), some of the rheumatoid arthritis patients display genetic determination

more intensively, but these patients are not free from their psychodynamic influences, either. Based on personality and conflict analyses, the general impression can occur that at least in a part of the cases – not yet specifically determined today – patients go through the stages of submission, rebellion and aggressive behaviors, as well as finally the stage of attempting to dominate as part of their personality development and life path. As adults, such patients evolve into personalities impeded by sentiments striving for truth, and also tend to be moralizing, controlling, tyrannical, conscious, and guided by remorse, particularly in manifestations of aggressiveness. The majority of them is characterized by long-suffering and masochist tendencies. Meyerowitz (1968) did not find substantial differences in the conflicts of twins that were discordant with respect of arthritis, which indicates the limitation of Alexander's presumption.

Alexander himself also offered a psychophysiological explanation to the way of integrating the organic basis and the psychosocial pattern shared by a considerable part of patients into a single framework, according to which suppressed aggressive attitudes and impulses appear in the increased muscle tone of patients, which intensifies pressure on joint surfaces by the collective tone increase of the muscles to move such joints and can eventually lead to joint surface damage. In his psychophysiological studies, Gottschalk et al. (1950) examined hypertensive patients and patients suffering from rheumatoid arthritis through EMG tests, and did not find any discrepancies in the course of performing neutral tasks and at rest. However, RA patients showed increased muscle tone in response to challenges of personal concern and content.

Many causes in a common channel – a system anomaly

Solomon (1964) was the first to attach importance to psycho-immune correlations in the mediation of psychosocial elements. In his supposition, reduced resistance and decreased or disturbed immune response triggered by stress effects can be caused by the difference in the quantity and the prolonged circulation time of antigen-antibody complexes. This explanation can be verified through the development of streptococcal glomerulonephritis, and oligoarthritis – detected as a part of rheumatic fever. However, such pathogenesis of rheumatoid arthritis has not yet been verified. Among several assumptions, the hypothesis of Hamerman and Sandson (1970) deserves attention, according to which the polysaccharide proteins of the basal membrane, collagen, and the cartilage have antigen properties that cross-react with potential exogenous virus antigens. Alternatively, virus antigens can also appear on the surface of connective tissue elements. Besides, Short (1957) found that more than half of

the patients associated the root cause of the disease with a certain occurrence in the following ratios:

Table 16. Anticipatory events before the onset of rheumatoid arthritis

mental or physical burdens	27%
infection	16.7%
cold effect	10.6%
surgical intervention	5.5%
trauma	5.1%
pregnancy	2.1%

The presence of the rheumatoid factor in healthy subjects indicates that these anti-gamma-globulin antibodies do not play an absolute and exclusive pathogenetic role: they only act as markers of altered immunoreactivity. In addition, they can also have an anti-idiotypic function. The group of seronegative arthritis shows that characteristic joint damage can also occur in the case of potentially dissimilar genetic disposition (HLB 27). Our knowledge about the pathogenetic role of immune complex deposition causing vascular lesions can serve as a basis for determining the possible points of attack of psycho-immune influence since a disturbed immune response to antigens can easily lead to vasculitis and genetically programmed potential immuno-pathological "derailing" through the perplexing dynamics of immune complexes and the disorders of elimination processes.

An intermediary role can equally be ascribed to the following: neuroendocrine factors of stress, the sympathetic nervous system, muscle tone, and the immune system commanded by the extrapyramidal system between the psychosocial and emotional "upside" and the joint surface inflammatory "downside".

Role of the sympathetic nervous system

Tonic sympathetic activity also plays a role in the progression of arthritis. The increased tonic sympathetic activity of spontaneous hypertensive animals (SHR/NCrlBR strain) leads to more severe arthritis than in normotensive Wistar-Kyoto animals. This can be explained by the fact that sympathetic efferents enhance the sensitivity of sensory fibers. At the same time, nociceptive excitation increases local sympathetic excitation at the spinal marrow level as well. And all sympathetic efferents act as factors to stimulate tissue mediators, including prostaglandins.

The nervous system's role is also highlighted by the fact that moderate inflammatory phenomena appeared on the paretic leg of RA patients after paralysis, which also applies to the appearance of erosions and rheumatic Heberden nodes. Increased sympathetic tone induced by stress can lead to RA flares, according to Baker (1982). As shown by twin studies, increasing stress can provoke the onset of arthritis. The favorable effect of guanethidine on rheumatoid arthritis was verified not only in animal experiments: the intensity of the pain decreased in patients, and morning rigidity also loosened by the second week of treatment. However, the influence of the sympathetic nervous system only partly explains the phenomenon.

In rheumatoid arthritis patients, peripheral sympathetic nervous system alterations also deserve attention. Alterations include the reduced density of beta2 adrenoceptors on mononuclear blood cells, which indicates increased adrenergic loads, according to van der Voort et al. (2000), but neuropeptide Y released from sympathetic fibers is also a good indicator of this disorder. Increased NPY levels in the serum display correlations with the severity of complaints by patients suffering from rheumatoid arthritis. Higher NPY levels are associated with a shorter duration of pain, according to Holmlund et al. (1991). If the system of neural connections is outlined in respect of joint surfaces, one needs to know that the afferent information of local nociceptive fibers not only mediates pain but also stimulates the release of inflammatory mediators. Neuropeptides released from the peripheral nervous system play a role in the pathological process of rheumatoid arthritis. Such neuropeptides include the already mentioned NPY and VIP, SP, and CGRP (calcitonin gene-related peptide).

Tachykinins' role was demonstrated in immune processes associated with the bronchial mucosa, Substance P plays such an immune-role, too. It can be explained by the chemotactic role of Substance P that PMN leukocytes are already present in the earliest synovial lesions of rheumatoid arthritis. Simultaneously, capsaicin pretreatment to deplete both SP and damaging peripheral afferent fibers without a myelin sheath significantly reduces inflammatory responses triggered by electric stimulation or through the injection of damaging substances, as described in a study by Gamse (1981).

SP is released from peripheral sensory nerves and its inflammatory role is well-known with respect to NK1 receptors. SP is present at increased levels in the joint fluid of patients. Its role in arthritis was also demonstrated in animal experiments by Keeble and Brain (2004). CGRP, also released from sensory neurons, can offset the inflammatory effect of SP. VIP has a similar anti-inflammatory effect and it can also be detected in the synovial cells of patients suffering from either rheumatoid arthritis, or inhibiting inflammatory cytokines, or chemokines, or matrix metalloproteinases, according to Juarranz et al. (2004).

It is also thought-provoking that the arthritis of joints more fully supplied with nociceptive nerves is also more severe. As demonstrated by X-ray images, the neonatal capsaicin treatment of rats with arthritis decreases the severity of arthritic deformations. If SP is administered into animal joints of lower risk of arthritis and with fewer SP fibers, the severity of arthritis will increase. Systemic gold treatment – otherwise forming part of classic RA treatment strategies – reduces the number of C fibers/nerves with an SP content by 23%, while myelinated fibers remained unchanged as shown in a study by Levine et al. (1986). The role of local afferent C fibers seems to be verified based on the above. The same as elsewhere, Substance P is one of the dominant local connections between sensory nervous occurrences and immune events in this case as well.

On the other hand, these data confirm the involvement of increased muscle tone – treated as a psycho-motor component of the onset of the disease – and local proprioceptive and nociceptive neural processes in the pathological process. According to Alexander's suggestion, suppressed aggression, i.e., the inhibition of venting out hostility through dominance, results in increased muscle tone.

There must be a local "ecosystemic" balance between the joint's sensory and motoric innervation, as reflex loss results in proprioception disorders, and because damage to local sensory fibers can also result in neuropathic joint damage. However, this will not invalidate the fact – also supported by experimental data – that losses of neural activity of hemiplegic or poliomyelitic origin reduce the local progression of rheumatoid arthritis.

This also coincides with the fact that the rheumatic deformations of joints controlled by the dominant hemisphere and thus induced to more intensive motion are more severe.

Inflammatory Bowel Diseases

Impact of psychosocial stressors on intestines: mediators and consequences

In patients with colitis and colostomy, intestinal contractions are more intensive and prolonged and are intensified by the environment's disturbed psychosocial stimuli. Contractions are also enhanced by notions of the experience of loss, depression, and the discontinuation of social support. In animal experiment conditions, colitis deformations – increased lymphocyte infiltration of the mucosa and the submucosa – can be triggered through stimulation to provoke conditioned evasive behavior.

In normal circumstances, VIP and SP nerve fibers innervate intestinal glands, capillary vessels, and immunocytes' surroundings in the lamina propria. Their numbers decrease under inflammatory conditions of active ulcerative

colitis, particularly expressed in abscessed crypts. These nerve fibers can be found in increased numbers in the hypervascularized area of active or settling mucous membranes. The inflammation process also destroys tissue areas characterized by mineralocorticoid receptors. Some authors, such as Nagura (1996), consider the abnormal distribution of neuropeptide and mineralocorticoid receptors in the background of immunological and physiological damage to the intestinal mucosa and the chronicity of the clinical picture to be a pathogenic factor. Others achieved remission through the topical inner surface lidocaine treatment of the inflammatory process: this can draw attention to sensory neurons' role in sustaining the disease. It is worthwhile to note here that lidocaine reduces SP release.

Acute psychological stress creates another psychoneural condition for IBD patients by reducing abdominal pain threshold, giving rise to inconvenient distress, and ending up in a dangerous cycle. A salient feature can be derived from animal experiment data, namely the permeability of the intestinal epithelium, which is decisive in terms of the disease's onset and recurrence. This determines the extent and seriousness of occurrences between the microbiota's bacterial challenge and the intestinal mucosa barrier. The permeability of the intestinal mucosa increases upon applying experimental stressors, which provokes changes in the interaction between host and bacteria.

In the case of rats, immobilization increases both jejunal and colonic permeability for marker molecules and antigen type proteins. Simultaneously, this permeability also means the opening of gaps between epithelial cells, as evidenced by electron microscopic images. Chronic stress also aggravates the impact of acute stress: thus, for example, separation from the mother increases the permeability-increasing effect of immobilization stress. Cholinergic neural effects also contribute to the expansion of permeability induced by the stressor, and mast cells also play a role in this. In experimental animals, the histamine content of the colon's mucosa is increased by stress, depending on both the central CRH level and IL-1 level. Experimental stress affects the interaction between the host and pathogens in the intestinal lumen. Admission and entry of bacteria into the mucosa of the intestine are enhanced by catecholamines. As dopamine and noradrenaline increase during stress, consequently the presence of E.coli in the mucosa of the caecum of mice gets higher. Similarly, after the catecholamine pretreatment of Peyer's patches, researchers detected increased Salmonella cholerae-suis and E.coli admission to the mucosa.

What has been established by research in respect of the skin-brain-CHR-mast cell circle in dermatological psychoimmunology can also be important in the case of peripheral CRH. This means that CRH and SP released from enteral neurons in response to a stress impulse increase bacterial adhesion as well as the mobilization of mast cells. This impulse is a "starter pistol" type event since T cells activated as a consequence, as well as IFN-γ and TNF-α

produced by them can further intensify the inflammation and the increase of permeability.

Another aspect of the impact of stress on the intestines is increased motility and increased liquid secretion. In animal experiments, immobilization, noise impact, unavoidable electric shocks on the leg all increase large intestine motility by CRH mediation in test animals. Simultaneously, saliva secretion is also enhanced by immobilization stress.

The peripheral administration of CRH antagonists fends off the impacts of immobilization stress, and reduces stomach motility. The central nervous system and peripheral activities of CRH in stress both play a part in the increase of gastrointestinal permeability. On the other hand, CRH acts as a peripheral inflammatory cytokine. It stimulates IL-1, IL-2, and IL-6 secretion; IL-2 receptor expression on peripheral lymphocytes, in turn, increases T and B lymphocyte proliferation, and augments NK cell cytotoxicity. However, it has an ambivalent effect on the cytokine production of endothelial cells. CRH-1 receptors mediate an anti-inflammatory effect, while CRH 2 is proinflammatory. CRH is important for us because the CRH level of lamina propria immune cells was found to be increased in active ulcerative colitis.

In animal experiment conditions, colitis deformations – increased lymphocyte infiltration of the mucosa and the submucosa – can be triggered by stimulation to provoke conditioned evasive behavior. In a monkey experiment, the animal's mourning reaction is accompanied by ulcerative colitis, and similar phenomena occur when the monkey is placed into a hostile or deprived environment.

Immuno-psychology of inflammatory bowel diseases

The psychosomatic context of IBD (colitis ulcerosa and Crohn's disease) can also be discussed in terms of the psychological interrelations and human social relations in the background of stressors. Psychosomatic factors play an important role in the dynamics of the disease. Also, in patients suffering from chronic intestinal disease, early disorders of the mother and child relationship and injured secondary attachment organization constitute important psychological factors.

In reports by ulcerative colitis patients, the picture of the mother is delineated as controlling, dominant, rigid, poor in emotions, and punitive according to Finch and Hess (1962), and Wijsenbeek et al. (1968). In addition, Crohn's disease patients also paint a picture of a cold, controlling mother poor in emotions as reported by Cohn et al. (1970). Some mention is made of the symbolic disorder of detachment from the mother. The verbal expression of feelings is many times disturbed. The socialization of the experience of pleasure can also be considered as disturbed. Indeed – according to our own

hypnotherapeutic experience –, joyful experiences of ulcerative colitis patients are difficult to mobilize in the course of their age regression in hypnosis.

Children with colitis were mainly characterized by a passive self-image, suffering as a basic experience, loneliness, and resignation. Frequent maternal behavioral features include hostility, rejection, or compensating, overprotective attitudes triggering dependence; the role of martyred self can also be typical, according to Mohr et al. (1958). Fathers appeared to be passive persons in general, staying away from childcare. Patients described their behavior as self-submissive. Direct observations confirmed the phenomenon in addition to mothers' reports. Family patterns are characterized by tension, a negativistic climate, with inhibitions of the expression of sentiments, disputes, and conflict evasion, and frequently occurring rejection of humorous manifestations, according to Engström (1991) and Grossarth-Maticek (1983). Engström's results indicate attachment disorders: the social support sensation of the 20 children examined, who all suffered from IBD, is lower, and the parents are repulsive and negative about deeper personal relationships, which may concurrently indicate an early attachment disorder.

The protective role of social support is indicated by the fact that Crohn's disease patients living in a supportive relationship can be characterized by lower disease activity indicators (Best-index) than fellow patients living alone or devoid of social support, and the former also show a more favorable picture in respect of anxiety, emotional lability, and depression.

The breakup of the relationship with the important other constitutes a factor in deteriorating prognoses, very similarly to tumorous diseases or AIDS. Based on the analysis of 30 relapses, Engel (1955) found actual or threatening separation in the background of the renewal of the illness in 24 cases. Lindemann (1950) detected the provocative role of mourning in 75 cases out of 87 patients.

All this confirms our assumption about the mother–child relationship detected in the early type C ambivalent secondary bonding system, which is characterized by anxiety. Accordingly, the personality development subject to the deterministic effect of early traumatized mother and child relationship and its psychophysiological consequences can contribute to the emergence of the disease in the case of existing susceptibility. It indicates, at the same time, that the social and psycho-immune pathology logic needs to be reckoned with in other immune pathology clinical pictures as well, in addition to tumorous diseases.

Character formulas similar to type C personality are described in personality surveys. Children with colitis are typically lonely, resigned, and hindered in verbalizing feelings. The experience of pleasure is also disturbed. Adults are characterized by perfectionism, moralizing tendencies, compulsivity, anger, and the inhibition of refusal. Feireis (1986) detected the absence of premorbid psychic properties only in 29% of patients, while Wietersheim (1994) found

features of dependence and inhibited aggression, indicating an increased disposition for relapse, in the case of stress events in 22 cases, as well as independent, aggressive and dissimulating behavior in 11 cases in the course of examining 52 patients. The latter cases can also be associated with compensating for independent attachment in response to the mother's conduct.

Adults also seem to be mainly characterized by perfectionism, conformism, peculiar alertness, moralizing tendencies, proneness to worry and anger, and an inclination to repress refusal. Life is subject to rationality rather than to sentiments. On the basis of the experiment, these issues can be summarized to delineate a typical personality picture. Regarding patients, compulsive personality traits were found to be characteristic in 23 cases out of 40 by Wittkower (1938).

Intrapsychic conflicts as triggering or predisposing factors are also considered. Based on Murray's studies (2019), marriage, leaving the parental home, separation from the mother played the main role in males, while in the case of females, frequent conflicts included issues around marriage, pregnancy and miscarriage. Of course, the disease can be considered frequent in this age group, so perhaps investigations need to be refined to determine specificity precisely. However, it is indubitable that – mainly based on Engel's (1995) work – the attention of research shifted from intrapsychic conflicts to interpersonal interrelations and conditions. Research highlights here include the absence of separation from parents, the preponderance of receptivity in exchanging feelings, and excessive jealousy. Due to their inability for carefree wholeheartedness, such patients' personality appears to be immature, giving an impression of narcissism. At the same time, this also ties them to the person providing the most important social support – in general, to the life companion / spouse replacing the parent's personality –, and this dependence is not only a source of frustration but also a framework of their sensibility.

Consequently, threats appearing as existential crises in patients' consciousness, which are converted into somatic immune occurrences, need to be highlighted concerning this area as well. In such somatic immune occurrences, the inner vulnerability and powerlessness of the patients prove to be decisive motives.

Life events, stressors

If disease dynamics are considered, we can see that gastro-intestinal discomfort frequently sets in after some hours or several days following circumstances constituting distress. The peaks of distress accumulating in the gradual appearance of symptoms proved to have a provoking impact. At the same time, in a report by Engel (1955), the gradual development of symptoms also followed challenges of life events requiring the individual to act in variable

manners including showing increased responsibility and fulfilling augmented expectations of the environment. In 26 out of 30 patients, symptoms were preceded by a life event or changes in the environment.

Life events preceding the occurrence of the disease can be divided into two main groups. In one of the categories, patients went through the disruption of a relationship important for them or the disruption of a dependence relationship (mourning, separation). In the other group of events, patients fear pressures from requirements, the possibility of failure weighs on their mind, and they may even deem average expectations to be impossible to comply with.

Mourning, disappointment in love, serious conflicts with parents, or divorce / forced separation all elicit ulcerative colitis symptoms in patients and can directly precede the onset of the disease. Lindemann (1950) attributed a provocative role to mourning in 75 cases out of 87 patients. In most cases, mourning proved to be irresolvable by McKegney (1970) in the case of an early loss of parents in childhood patient history.

If the challenge a priori exceeded the reserves possible to be mobilized by the patient, or if the patient could not count on sufficient social support and assistance, then the probability of the outbreak of ulcerative colitis also appeared to be increased as shown by Mohr's research (1958). Similarly, the threat of humiliation, which poses a danger of reduced self-esteem for the patient, also seemed to be provocative, according to Marder (1967).

Although the turn to evidence-based medicine predominated correlations outlined through the casuistry of early psychoanalytic theories, stress, physiology, and psychoimmunological factors offered a new framework of interpretation for anecdotic reports of low case numbers.

Table 17. Psychosocial stressors and IBD (after Mawdsley and Rampton 2005)

Variable *Burdening life events*	**Patients**	**Result**	**Reference**
Life events before the appearance of the disease retrospective analysis	60 ulcerative colitis patients	Positive correlation	Fava GA, Pavan L.: Large bowel disorders. I. Illness configuration and life events, *Psychother Psychosom*, 1976, 27:93–99.
Retrospective analysis of the life events of the two years preceding the relapse of the disease	70 Crohn patients, 44 ulcerative colitis patients	Positive correlation in the case of Crohn's disease no connection in the case of ulcerative colitis	Paar GH, Bezzenberger U, Lorenz-Meyer H.: The correlation between psychosocial stress and disease activity in patients with Crohn's disease and ulcerative colitis, *Z Gastroenterol*, 1988, 26, 648–657.

Variable *Burdening life events*	Patients	Result	Reference
Investigation of life events preceding recrudescence	30 ulcerative colitis patients	Positive correlation	Bach O, Wild HJ.: Life stress events preceding illness episodes in multiple sclerosis and ulcerative colitis – a comparison, *Z Gesamte Hyg*, 1990, 36, 442–443.
6-month prospective tracking of life events in the function of relapses	124 IBD patients	Immediate positive correlation	Duffy, L. C. et al.: Relevance of major stress events as an indicator of disease activity prevalence in inflammatory bowel disease, *Behav Med*, 1991, 17, 101–110.
2-year follow-up study regarding relapses	32 IBD patients	No connection with life events	North C.S. et al.: Do life events or depression exacerbate inflammatory bowel disease? A prospective study, *Ann Intern Med*, 1991, 114, 381–386.
1-year follow-up study of life events and relapses	108 IBD patients	No connection	von Wietersheim J, Kohler T, Feiereis H.: Relapse-precipitating life events and feelings in patients with inflammatory bowel disease, *Psychother Psychosom*, 1992, 58, 103–112.
A comparative retrospective 12-month study of ulcerative colitis patients and healthy subjects	122 ulcerative colitis patients	Higher life event incidence in colitis patients	Tocchi A. et al.: Familial and psychological risk factors of ulcerative colitis, *Ital J Gastroenterol Hepatol*, 1997, 29, 395–398.
Connection between a 1-year prospective analysis of life events and the recrudescence of the disease	60 ulcerative colitis patients	Positive connection between life events and relapse	Bitton, A. et al.: Psychosocial determinants of relapse in ulcerative colitis: a longitudinal study, *Am J Gastroenterol*, 2003, 98, 2203–2208.
16-year retrospective analysis of parents who lost a child	21 062 parents who lost their child	No increased IBD incidence	Li, J. et al.: Psychological stress and inflammatory bowel disease: a follow-up study in parents who lost a child in Denmark, *Am J Gastroenterol*, 2004, 99, 1129–1133.

Variable	Patients	Result	Reference
Burdening life events			
Prospective 2-year analysis of the connection between depression, life events, and recrudescence of the disease	18 Crohn patients	Positive correlation between life events and relapses (simultaneously or within 8 to 12 weeks)	Mardini HE, Kip KE, Wilson JW.: Crohn's disease: a two-year prospective study of the association between psychological distress and disease activity, *Dig Dis Sci*, 2004, 49, 492–497.
Chronic stress			
Prospective 2-year analysis	62 ulcerative colitis patients	Higher PSQ scores are accompanied with higher risks of recrudescence	Levenstein, S. et al.: Stress and exacerbation in ulcerative colitis: a prospective study of patients enrolled in remission, *Am J Gastroenterol*, 2000, 95, 1213–1220.
Connection between endoscopic findings and PSQ	46 ulcerative colitis patients without symptoms	Connection between PSQ values and mucosa deformations	Levenstein, S. et al.: Psychological stress and disease activity in ulcerative colitis: a multidimensional cross-sectional study, *Am J Gastroenterol*, 1994, 89, 1219–1225.
Daily stressors			
28-day follow-up studies, connection between stress and personal health condition estimates	10 Crohn patients	Positive connection in some patients	Garrett, V. D. et al.: The relation between daily stress and Crohn's disease, *J Behav Med*, 1991, 14, 87–96.
1-year-long follow-up study regarding the correlation between stress and disease exacerbation	11 IBD patients	Positive correlation	Greene BR, Blanchard EB, Wan CK.: Long-term monitoring of psychosocial stress and symptomatology in inflammatory bowel disease, *Behav Res Ther*, 1994, 32, 217–226.

Table 17 above (after Mawdsley and Rampton 2005) indicates a connection between psychosocial factors and IBD. However, demonstration of such a connection requires demanding and thorough research, since contradictory data may raise doubts. A stressor in itself – even a most severe one, such as the loss of one's own child – does not increase incidence and prevalence. The series of data above also show that retrospective studies mainly verify these correlations. It is probably important for patients to find connections in their narrative between the disease and life events / personal history. Although this has a distorting effect, numbersome data indicate that connections can be found between endoscopic findings and stress even in a dormant state not yet causing symptoms.

The PSQ index of the questionnaire to survey personal stress experience offers a noticeably more precise and calculable indicator regarding life events. The personal meaning of life events is overly variable, which applies to depression as well. This correlation was verified in the case of Crohn's disease patients as well – even if in a low number of subjects – in the framework of a two-year-long follow-up study. Also, it was demonstrated by Mittermaier et al. (2004) that, in the case of inactive IBD, higher depression indicators were associated with a higher risk of recurrence in the course of an 18-month-long observation period.

The importance of life events is indicated by Kegney's study (1970) of 40 patients, who found severe life events important in the case of 86% of ulcerative colitis patients in the period preceding the emergence of the disease, more precisely half a year earlier. This rate among Crohn's disease patients was 68%. This life event was the parents' loss in 43% of the cases regarding ulcerative colitis patients. In general, the adaptive capacity of ulcerative colitis patients is considered to be reduced: their adaptive capacity is subject to strong dependency, they endure failure and refusal with suppressed anger and with a sense of powerlessness because of their inability to cope with the situation. This condition then burdens both the disease experience and its environment, further complicating symptoms and environmental reactions.

The assessment of a situation is a function of the personality stemming from the interplay of character and experiences. What conflicts and personality traits can be distinguished in patients who have ulcerative colitis? Children with colitis are perfectionists, poor in emotions, have rigid characters, and give the impression of "young adults". In general, disorders in mother–child relationships are typical, primarily formed by the mother's disciplinary actions, outbursts of anger, and ambivalence, which prompts the child to suppress negative feelings quite early. For female children, such a mother appears as a punitive, controlling, "omnipotent", inexorable, cold, and egocentric person. This induces the child to resort to the roundabout manipulation of parents at an early stage. As opposed to the above, male children's loyalty increases.

Results based on studying the mother generally describe a peculiar joylessness, a pessimistic and unhappy attitude. Studies reported behaviors manifesting worries about the child, perfectionism, and ambitious attitudes. There was a conspicuous disorder composed of natural sentiments, love, and caring concern. Ulcerative colitis generates a peculiar symbiosis between mother and child thereby establishing a legitimate situation for dependency demand, a camouflage for both parties. However, some can accuse this interpretation of being based on idiopathic clinical malice towards families of such unfortunate persons due to the generalization and value judgments implied. However, if study results are accepted as facts, perhaps such descriptions promise the possibility of involving family therapeutic tools. Typically, the role of the father is relegated in such families for whatever reason. In a video-recordings-based family dynamics description, Jackson (1966) paints a peculiar picture. Common features identified in the eight families involved in the study included quiet talk, the inhibition of showing emotions, and attitudes to avoid disputes or conflicts. In addition, the refusal of humorous manifestations, and the rarity of showing tenderness were typical. Expressions of originality were not rewarded. The examined families were characterized by isolation and reservedness: a minimum number of friendships surrounded such families' social life. The catastrophic significance of the interruption of such a relationship appears to be unambiguous.

Although generalization seems unjust in respect of the vulnerable patients, therapists may not be exempt from personal psychology analyses, to avoid blaming the victim: if an opportunity exists, psychotherapy is provided. Especially if such facts involve aspects relevant to the relationship between the physician and the patient. Such patients transfer the need of dependence to the physician, thus imposing increased responsibility thereon. Therapy interruption is accompanied many times by the perilous recrudescence of the complaints and the clinical picture.

Deformations of the organization of the personality and cumbersome challenges of the environment can only be converted into a clinical picture by the fate of the patient if the patterns above are mediated by psycho-vegetative/psycho-immune channels possible to be explored up to the digestive tract.

The primary symptom generator of continued intestinal inflammation is the complex protective alertness mentioned earlier, which concurrently organize motility, mucus production, and immune protection. In fact, this also constitutes the subject matter of the first line of psychophysiological studies. Wolff (1966) examined colostomy patients for membrane mucus production, and the contractility of the bowel section studied, together with the lysozyme content of the stool. An investigation of the intestine's basic tension indicated that contractions are more prolonged and more intensive in colitis.

The intensity and duration of contractions were increased, along with lysozyme secretion as a result of disturbing psychosocial type stimuli from the environment. Increased bowel activity in response to stimuli triggering anger, refusal, and excitement gave rise to petechia type lesions on the mucosa. Prolonged and intensive contractions characterize the bowel section with colitis. Simultaneously, some authors reported decreased colon tone and motility in conditions of insufficiency, powerlessness, and hopelessness (Almy, 1961). Other authors detected a contrary effect on patients: increased spasticity. Karush (1968) detected, also in the case of colostomy patients, intensification in segmental contractions. In the case of a major loss, the homeostasis disintegrates, leading to tissue destruction by the activated local immune system, including the inflammatory necrosis of the mucous membrane of the mouth, the so-called "trench mouth disease". However, alterations can probably be triggered by other forms of extreme stress, by unbalancing the local homeostasis and the continued and increased activation of GALT, induced by food allergies, damage to the intestine's epithelial cells. We have every reason to suppose that these local processes are fundamentally influenced by the specific vegetative stimulus patterns arising in response to psychosocial stressors.

Graves' disease

In analyzing this disease classified into classic psychosomatic clinical pictures, the psychosomatic approach, the indubitable immuno-pathological character of the disease, and familiarization with the neuroendocrine regulation of the thyroid cover the entire scope of interest of psychoimmunology.

Autoimmune hyperthyroidism is explained by the fact that the thyroid escapes from hypothalamo-pituitary control, and autoantibodies (LATS, HTS) are produced against thyroid cells, consequent upon which T3 and T4 synthesis increases and TSH production by the pituitary gland decreases.

The role of infective factors can also be associated with the onset of the disease. A virus or bacterium component can induce the production of an antibody, which cross-reacts with a human TSH receptor in the framework of a so-called antigen mimicry effect. For instance, *Yersinia enterocolitica* possesses a structural similarity that can elicit the presumed cross-reaction with human thyrotropin receptors.

The consequences of the clinical picture in terms of circulation (tachycardia, cardiomyopathy) and metabolism (hypercatabolism, weight loss) are due to the potentiation of the catecholamine effect and the stimulation of oxidative processes. An idiopathic immuno-endocrine-immune loop becomes complete as increased thyroxine production increases the cellularity, mass, and function of the thymus, thereby enhancing thymus hormone production.

The thyroid ensures its functional stability through multi-level feedback regulation. TSH, the pituitary trophormone determining the thyroid's hormone secretion, is controlled by the self-regulatory negative feedback impact of T3, the active thyroid hormone, and by TRH, the tripeptide produced by the hypothalamus. Therefore, central impacts mediated by the hypothalamus can also be enforced besides such a negative feedback mechanism. The TRH-TSH-T4,T3 chain would comfortably accommodate the simplifying linear cascade model, which partly characterizes the psychosomatic approach, and which would squeeze disease development into the framework of the stress paradigm by way of examining the life events provoking hyperthyroidism. But this is no way the case: the essence of the disease is indeed hyperfunction escaping from the impact of TSH. Moreover, based on early studies by Bram (1927), the role of environmental and psychological factors in triggering the disease seems to be indubitable. When interviewing 3343 adult patients, psychosocial circumstances were broken down as follows with respect to the onset of the disease:

Table 18. Anticipatory events before the onset of Graves' Disease

Sorrow, mourning, sense of inefficiency	61%
Experience of personal threat/danger, traffic accident, injury	13%
Minor surgery	7%
No particular cause specified	6%
Infections	5%
Childbirth	4%
Iodine abuse	39%
Thyroxin administered	1%

Even taking the error rate of self-mythicizing retrospective subjectivity into consideration, these data do not appear to be groundless if compared with other researchers' observations. Based on the studies of Alexander (1950) and Bennett and Cambor (1961), the factors and events precipitating hyperthyroidism can be grouped into three large groups:

1. situations where the individual's compliance is insufficient or hindered;
2. acute or threatening emergencies exceeding the individual's reserves to decrease and resolve fear;
3. situations where the individual is prevented from taking care of others.

Lidz (1949) considers actual or imagined separation, mourning, or the violent or threatening breakup of emotionally important relationships to be triggering factors in predisposed individuals. The majority of endocrinologists

avert the disease's psychosocial interpretation, although Astwood sees a nearly 50% correlation between the onset of the disease and a prominent life event. According to Mandelbrote, in case of a sudden emergence of symptoms, the danger is more frequent in patients' experiences; and divorce and separation are mostly associated with slower development. The assessment of psychosocial pathological factors also raises a reversed logic: according to this, these coping disorders have underlying metabolic changes and neural impacts of the latent disease already operating deeply underneath. This supposition seems to be contradicted by a mass of data collected by others, who refer to the emergence of the disease, which manifests in relapse dynamics. In a longitudinal study by Ferguson-Rayport (1956), recrudescence was perceived in the case of those who could not cope with the emotional and adaptive challenge of mourning, separation, emigration, or the loss of financial security. On the other hand, Gibson's hypothesis is supported by the fact that an increase in T3 can precede the emergence of symptoms by weeks or months, and as increased T3 can be accompanied by nervousness, this can be quite a burden in coping with everyday events.

Studies to assess the role of neuroendocrine mediation between the environment and altered thyroid function did not verify Alexander's presupposition that increased TSH production during stress would elicit hyperthyroidism. It is impossible to identify the very onset of the disease. Therefore, the appropriate testing of the presupposition could not be performed. On the other hand, TSH levels are already unchanged or reduced in the course of the development of the disease; subsequently, researchers' attention was directed to relapses.

Voth et al. (1970) in their 12-year follow-up study, 239 patients were followed by scintigraphy tests, and regular psychological control tests were performed in the case of 63 participants. Emotional loads and increased local and diffuse iodine intake were measured and compared to the data of the control group. In the positive group above, the activity of nodules did not change in periods without loads. On the basis thereof, the authors concluded that there is a positive correlation between changes in environmental and emotional loads, hot nodules, and diffusely increased thyroid activity. Unfortunately, the authors could not measure TSH levels during their research, so the intermediary mechanism could not be clarified.

In the scope of this study, the experimental investigation of the connection between stress and thyroid functions was carried out with the help of interviews, hypnotic or other suggestive procedures, and burdensome life situations (examination situation). In healthy veterans, the hypnotic recall of war experiences increased serum iodine levels by 32%–200%. In medical students, a 4-hour PBI increase was detected in examination situations by Tingley et al. (1958). Similarly, after watching a horror movie, definite PBI increases were detected in patients with untreated hyperthyroidism, lasting for 1 hour after

the movie's end and PBI settled only 24 hours afterward. Such a change was more prominent compared to changes detected in euthyroid and treated patients. In their case increased values settled after 24 hours. In untreated hyperthyroid patients, intensive electrodermal changes and robust heart frequency growth could be observed. The fact that hyperthyroid patients were more sensitive to threatening experiences and that the activity drop evidenced by scintigraphy showed intensive hormone mobilization suggests a connection between the processing of stimuli and experiences, on the one hand, and the functional disorders of the thyroid, on the other hand. A study by Dongier (1956) indicates that this deviation was not identified by the comparative examination of neurotic/excited vs. calm persons, so the above feature is peculiar only to hyperthyroid patients.

Nevertheless, an indubitable deficiency of these investigations is that the PBI does not provide information about T3 levels, and TSH levels were not measured. Zuckermann et al. (1966) managed to trigger a 21% TSH increase in 10 out of 11 subjects with 8-hour sensory deprivation, which correlated with emerging excitement and depression. The stress effect can be properly followed up to the pituitary gland. The neuron networks in charge with the control of the hypothalamic areas responsible for TRH production are suitable for forwarding stress stimuli. The anterior and ventral areas of the hypothalamus receive appropriate information from the hippocampus, the amygdala, and the mesencephalon as well. In a dog experiment, the stimulation of the hippocampus resulted in an increased secretion of thyroxine. Based on studies of injury and stimulation, it seems that limbic and habenular neural network connections are involved in the control of hypothalamic functions that control TSH release.

In Basedow's disease, the pathological induction role of TSH cannot be verified, but its role in maintaining the disease can be excluded. On the basis thereof, researchers rejected Alexander's interpretation of the role of TSH as a stress hormone. This was confirmed by the following: in the case of hypophysectomy, in the presence of LATS, the integration of J 131 is seamless in the course of T3-T4 generation. From the endocrine point of view, the picture is made more complex because other stress hormones, such as vasopressin, also increase the integration of the iodine indicated and likewise increase PBI levels in the case of pituitary insufficiency. Of course, the intertwining of endocrine functions is rather natural than surprising. The ACTH mobilization effect of T4 is known, and as corticoids reduce TSH secretion, a feedback effect can be established between the two main metabolic organizer hormones through the creation of hypophyseo-thyreo-hypophyseo-adreno-cortical-hypophyseo-thyroid and adrenortico-thyroid regulatory loops. Eventually, corticoids elicit PBI level reduction and decreased iodine metabolism at the level of the thyroid. Hyperthyroidism itself is also accompanied by increased ACTH levels. Today a considerable role is attributed to increased catecholamine sensitivity in the scope

of the interpretation of hormonal changes characteristic of Basedow's disease. Such hormonal changes are to be interpreted as a consequence of metabolic roles and hormonal effects. At this point, psychosomatic analysis needs to be converted into a somatopsychic assessment since irritability, motoric restlessness, sleeping disorders, and emotional lability can be a consequence of catecholamine-dependent cerebral processes altered in a condition of hyperthyroidism. On the other hand, these symptoms are also characteristic of agitated depressive conditions. All this serves as evidence for the neuroendocrine system's two-way communication and explains the difficulties of the causal relationship of reciprocity between diverse psychic neuroendocrine occurrences.

If the environment's role cannot be identified along this line, let us examine potential environmental effects prevailing along immunopathogenesis. High T4 and T3 levels in Basedow's disease are ensured by antibodies with a hormonal effect, including HTS (human thyroid stimulator), LATS (long-acting thyroid stimulator), and LATS protector, which – even in terms of their immuno-endocrine significance –trigger endocrine effects, which result in reduced pituitary TSH production due to increases in T3 levels induced by them.

LATS is a specific IgG, which achieves increased iodine admission, integration of iodine into thyroglobulin, and consequentially increased glucose oxidation by raising intracellular cAMP levels in accordance with the THS effect. The structure of LATS and TSH are different. LATS is presumably an antibody produced against an antigen corresponding to the thyroid's microsomal cell generation structure.

LATS is bound by thyroid homogenate. Other authors consider it an antibody against thyroglobulin, and according to Mori et al. (1971), it is the surfacing of so far hidden antigens that can activate the immune process.

According to other researchers' – including Adams et al.'s (1971) – presuppositions, the LATS protector IgG (inhibiting LATS decomposition) is more important in the provocation of hyperthyroidism. Interestingly, the lymphocytes of patients with Basedow do not contain LATS globulin: LATS secretion can only be detected in a small group of cells in the course of mitogen provocation through phytohaemagglutinin, as stated in a study by McKenzie et al. (1961). The fact that no LATS production provoking antigen can be found is highly thought-provoking in respect of the antibody role of LATS. Even so, it may as well be that LATS is a derivative of LATS protector, that is, another antibody. However, the autoimmune process is indubitable since the lymphocyte infiltration of a Basedow thyroid indicates inflammation.

As evidenced by extended immunology studies, the occurrence of microsome, thyroglobulin, and thyroid anti-colloid antibodies is increased among the relatives of Basedow patients. This, in itself, does not indicate a disease of course: it indicates perhaps disposition only, which is explained by the absence of symptoms and positivity in respect of healthy relatives. However, the role

of the hereditary factor affecting immunity appears to be undeniable. This is certainly not restricted to Basedow's disease, as, in fact, twin studies indicated more frequent occurrences of Hashimoto's thyroiditis in identical twins. Hashimoto's thyroiditis shows the highest titer of antibodies. The kinship of the two diseases is also indicated by the fact that Basedow's disease is also more frequent among the relatives of patients with Hashimoto's thyroiditis. Many researchers question the pathogenic role of autoantibodies in triggering the disease. However, not only IgG but IgM antibodies also occur in the course of the disease. It may also be the case that it is not the endocrine target that is affected by psychosocial burdens and difficulties of coping with experiences stemming from the personality: it may well be the case that genetically programmed immune affection is decompensated. In this respect, an appropriate explanatory model is offered by the impact of intensifying the TH1/TH2 shift through increased HPA and LC/NAergic activity. Another hypothesis follows the same logic: accordingly, the possible neuroendocrine targets of stressors include the suppressor cell line of clones producing antibodies, the defective functioning and insufficiency of Treg cells, which – if repelled – result in increased thyroid stimulant antibody production. An animal experiment observation reflects a contrasting mechanism: in the chicken strain called Obese Strain (OS) Austrian researchers identified spontaneous autoimmune thyroiditis. IL-1 increases glucocorticoid production in the body through a negative feedback cycle. This fails to occur in OS chickens. The situation worsens because levels of corticoid binding globulin (CBG) are higher in these animals, so active free glucocorticoid levels are even lower. As a consequence, of all this, the self-restraining negative feedback of autoimmune processes is disturbed. Background interactions may include the escape of autoimmune clones and glucocorticoid IL-2 suppression to contain inflammatory processes. Upregulating of VIP receptors by glycocorticoids is eliminated, thereby the "falloff" role of the VIP effect is hindered.

Immune balance shifts towards the TH2 cell line, which produces autoantibodies through increased HPA and stress-induced catecholaminergic effects. The flare of the process can also be alternatively explained by the – stress induced – psycho-neuromodulator suppression of the T suppressor line to suppress autoaggressive cell population B.

Personality factors and multiple sclerosis

The psychoimmunological importance of the disease is justified by factors mediating psychosocial factors affecting the course of the disease. Thus, the patient's course of life can depend on a number of factors sensitive to stress mediating factors. Schreiber et al. (2015) list the following factors as

increasing premorbid vulnerability: repressive coping patterns, attitudes of avoidance, inhibition, irritability, reduced extraversion, neuroticism, confused responses to rewards, and proneness to somatization. Following from this, in a study by Goretti et al. (2009), patients who have multiple sclerosis chose to cope by avoidance rather than active problem-solving. Communication disorders between the central nervous system and the immune system can act as disease factors at several points. An important disorder is the cross-talk phenomenon, which prevails in the mimicry phenomenon between the microbial antigen and the myelin base protein. Disorders can be caused by a hypo- and hyper-responsive immune system, and mistuned HPA axis response disorder can be a similar kind of problem. This latter can also manifest in insufficient HPA responses elicited by actual stress, and low cortisol levels as well. This situation is similar to blunted HPA responses observable in rheumatoid arthritis and atopic dermatitis, which are accompanied by reduced TNF-alpha activity as evidenced by Goretti et al. (2009).

Fatigue in multiple sclerosis positively correlates with the levels of proinflammatory cytokines: IL-1, IL-6, TNF-alpha, and IL-12. The development of multiple sclerosis is affected by suppressor T cells, HLA-DR expression, and cytokine patterns. The degree of inflammation is increased if the activity of the CRH–ACTH axis is disturbed, or if there is another functional disorder in the hypothalamo-pituitary-adrenal axis, and therefore no negative feedback effect prevails.

Although in EAE animal experiments, HPA activity of reduced sensitivity shows an obvious correlation with the disease's progression, human observations verified increased glucocorticoid base levels, and adrenal gland hypertrophy is frequent among MS (Multiple Sclerosis) patients. The post-mortem examination of MS patients showed increased CRH fiber density in hypothalamic areas. In the course of the relapse of patients who have multiple sclerosis, reduced DST rates are yielded, which means that no HPA suppression is detected upon the administration of dexamethasone. Van Winsen et al. (2005) demonstrated reduced glucocorticoid sensitivity in multiple sclerosis patients showing a relapse, and identified correlations between clinical impairment and the reduced sensitivity of glucocorticoid receptors.

The influence of psychosocial stressors was confirmed by many articles. Charcot – one of the first to define the clinical picture – remarked that the trauma of mourning could play a role in the development of the disease. In respect of the onset of the disease in MS patients, Grant et al. (1989) detected important encumbering life events in 77% in the preceding 5-6 weeks to 2 months, compared to 35% detected in controls. Twelve out of the relapsing MS patients indicated a temporal relationship between psychological stressors and relapse.

In a study of 36 patients, Mohr (2000) found a correlation between GD positive lesions and the conflicts perceived, and a meta-analysis extending to about 14 studies verified the connection between disease progression and a stressed lifestyle. Burns et al. (2014) also clearly demonstrated that the risk of permanent T2 lesions – evidenced by MRI and rendering a worse outcome potential – is increased by stressful life events.

Nisipeanu and Korczyn (1993) conducted a study among MS patients in areas endangered during the Gulf War. Among the 32 patients exposed to protracted life-threatening stress, the number of relapses was lower than earlier. This suggests that a major trauma may even have a protective effect.

In the background of relapses, virus infections are accumulated, as verified in 68% of cases in a study by Panitch (1992). It would be worthwhile to study whether the virus infection of the respiratory tract plays a provocative role in such a case, or if the virus infection acts only as a parallel indicator of the impaired or disturbed immune competence of the host.

Multiple studies demonstrated correlations between stressful life events and the relapses of multiple sclerosis. In a meta-analysis conducted by Mohr et al. (2004), 14 out of 20 studies complied with evidence-based criteria, and the meta-analysis clearly demonstrated the connection between stress impacts and sclerosis relapses, although no stressor-specific connection could be verified. The risk of recrudescence doubles already in the month following the stress impact, while infections entail a triple risk of relapse. In another prospective study, Buljevac et al. (2003) demonstrated a connection between stressors and the relapse of the disease, which proved to be independent of intercurrent infections.

Stressful life events can include conflicts with a close relative, workplace stress, problems with property, the loss of a relative, friend, or even a pet, financial problems, and relationship crises. According to Brown's research (2006), the accumulation of acute stressors is a critical component. Mitsonis et al. (2008) also found the stressor's content to be critical, while they did not find any correlation in respect of the nature and severity of the stressor involved. The same team found perceived anxiety and stress to be dominant. In a prospective study by Beck et al. (1988), there were increases in gamma-interferon and TNG levels detected two weeks prior to relapse, which settled following the relapse.

According to a meta-analysis carried out by Briones-Buixassa et al. (2015), the most important stressor influencing factors include the duration, severity, and frequency of the stressor, and the factors that reflect stressor impacts include cardiovascular reactivity and heart frequency.

These data are not at all free of contradictions, and there is no conclusive evidence for the psycho-immune working of the pathological process, either.

The beta2AR on TH1 cells influences cell migration to the central nervous system's affected areas, to the brain, and to the spinal cord, thereby enhancing the development of multiple sclerosis, which is an inflammatory response, as stated by Elenkov et al. (2000) and Kohm and Sanders (2001). On the other hand, Fassbender (1998) was able to verify the regulatory disorder of HPA feedback in MS patients. As opposed to control subjects, in the case of the 23 MS patients, DST test positivity was demonstrated. Cortisol reduction failed to occur after dexamethasone was administered.

The degree of feedback disorder is correlated with the degree of depression and/or anxiety. On the other hand, correlations were verified between depression, anxiety disturbed HPA regulation, and liquor leucocyte numbers, as well as demyelination nodules evidenced by imaging devices. Regarding psychoimmune factors, multiple sclerosis combines many burdens:

– Patients are frequently hindered in their motility.
– Its unforeseeable and changing symptoms represent a threat.
– Uncontrollability and incalculability are features of the clinical picture.

Simultaneously, physical constraints are accompanied by variable neural symptoms, affecting sensory and mental functions as well. The course of the disease is also affected by the patient's coping skills: problem-focused coping is accompanied by less depressive symptoms and disabilities, while passive coping centered on emotions is accompanied by mood disorders, depressive symptoms, and higher stress; furthermore, patients less typically adopt an active coping style, including problem-solving and reliance on social support. Patients very often do not feel they have control over the disease. On the other hand, a sense of control is associated with higher self-esteem, less distress, and less depression. An optimistic attitude and personal efficiency enhance self-care and self-assured behavior, and social support is also important.

Depression is much higher in patients who have multiple sclerosis than in the average population, and can reach as high as 50%. In addition, depression is also exacerbated by low socioeconomic status and emotion-centered coping; and the role of proinflammatory cytokines in depression is also an issue.

Patten et al. (2017) estimate depression in 50% of multiple sclerosis patients, while there is about 10% co-morbidity with other psychiatric clinical pictures. The authors consider depression in multiple sclerosis to be reactive in nature and associated with restricted motility functions and other neurological losses. The depression of patients who have multiple sclerosis is effectively improved by psychological support, psychotherapy, and antidepressant medication. Besides the mitigation of symptoms, the improvement of life quality and subjective existence constitute a major result. At the same time, psychotherapy has been identified to contribute to reduced INF alpha levels.

Psychoimmunology in Dermatology

Based on clinical and experimental observations, it seems well-founded that the brain can influence and block skin processes. According to Locala (2009), a close relationship was shown between stressful life events and the onset of skin disease with immune pathological dynamics. Lugović-Mihić et al. (2013) found close correlations between emotional stressors, psychiatric diseases and skin diseases such as acne, alopecia, atopic dermatitis, herpes simplex, psoriasis, urticaria, viral warts, and vitiligo. Filaković and colleagues (2009) found a comorbidity of nearly 30% among dermatological patients regarding depression.

The neuroimmuno-cutaneous system

The outer covering, the skin is of ectodermal origin, so we can hardly be surprised by the rich network of nervous, endocrine and immune components of this organ, which can be easily verified by light and electron microscopy. This system of relationships, which makes the skin a neuroimmuno-cutaneous system is also manifested in the anatomical, physiological and pathological characteristics manifested in diseases. The "external covering" of the internal body surface of the airways and the intestinal tract can be compared to this system, so in this sense we can also speak of a neuroimmune-enteric or neuroimmune-bronchial system. The allergic symptoms in all three systems follow a similar pathology, in which, in addition to dendritic and other APC cells, TH1, TH2 and TH17 and Treg cells, tachykinins and Substance P play a prominent role, but somatostatin and VIP also play an important role in influencing mast cells, lymphocytes, secretory and muscle cells. Among the neurotransmitters and neurohormones of the skin, in addition to substance P, VIP, somatostatin, neuropeptide Y, neurotensin, CGRP (calcitonin gene-related peptide), and neurokinins all play a role. The prolactin, MSH and ACTH hormones present in the skin, as well as the catecholamines, enkephalin, endorphin and acetylcholine, can play an immunomodulatory role.

As a sensory organ and primary defense line, the skin has a rich sensory innervation, but it is also rich in post-ganglionic adrenergic and cholinergic fibers. The sources of the already mentioned substance P, VIP and CRGP can be the sensory and vegetative nervous systems, but these mediators can also be released from the cells of the epidermis and other dermal cells. The targets of neuropeptides are the antigen-presenting dendritic cells and the migratory Langerhans cells, but the neuropeptides also affect the endothelial cells, and we have already mentioned the key cell under the influence of CRH, which is strongly influenced by stress mechanisms, the mast cell, which thus completes

a special "brain–skin" circle. So, it means a reciprocal, immune-neural connection, where Merkel cells and Langerhans cells, keratinocytes and melanocytes also play a role in the production of neurotransmitters in the skin. Merkel cells are located near nerve endings, and Langerhans cells also have dendrite-axon connections. Similarly, direct contact between mast cells and nerve fibers can be observed.

Mast cells are responsible for the symptoms of atopic dermatitis, which cause hives and local allergic edema. Thus, the increased IgE production, the dysfunctional TH1/TH2 shift, and eosinophilia all have a symptom-maintaining and aggravating role through the mast cell, and stress effects play a major role in this, according to Elenkov and Chrousos (2000). The TH1/TH2 shift increased as a result of stress, creating a cytokine milieu favorable to the atopic response through increased IL-4, IL-10 and IL-6 levels and reduced IFN-alpha production due to stress, which increases skin symptoms. In atopic dermatitis, the role of the IL-23-TH17 axis can also be raised, similar to those already involved in asthma.

A direct sensory nerve stimulus, axon reflex, which releases neuropeptides from the peripheral nerve endings, can lead to the activation of mast cells. In addition to the mobilizing effect of antigen and IgE, cytokines, hormones, and neuropeptides such as somatostatin, neurotensin, CGRP, and especially substance P are capable of activating mast cells. NGF can also be considered a mast cell growth factor and can also trigger mast cell degranulation. Other growth factors, such as SCF (stem cell factor), affect mast cell physiology and sensitize mast cells to PACAP (pituitary adenylate cyclase activating polypeptide), which is considered important in the post-traumatic physiological response and has a similar effect to VIP.

The skin may be involved in the immuno-neural interactions observed during stress. This is indicated by an increase in the number of activated perifollicular macrophage cell groups and degranulated mast cells and a decrease in intraepithelial T cells as a result of stress.

Baldness and the inhibition of hair growth caused by stress are attributed to Substance P and NGF-dependent macrophage and mast cell activation. Mast cells also play a major role in immunosuppression caused by UVB radiation and sunburn. This phenomenon is indicated by the common frame for "neurocytokine" connection, because the immunosuppressive effect of mast cell-derived TNF triggers, among other things, the activation of the latent herpes virus after sunburn. TNF secretion by mast cells is facilitated by CGRP released from damaged nerve endings caused by UVB burns.

Psoriasis and atopic dermatitis are exacerbated by stress. All of this is a good example of the cross-talk phenomenon between mast cells, neurons, and keratinocytes, in which the increased production of CRH as a result of stress and the increased expression of the CRH receptor play a role. Mast cells themselves

are capable of synthesizing and producing CRH in response to IgE, and also have a CRH receptor. Rita Levi-Montecalcini recognized precisely this "neuroimmune" role of the mast cell. In addition to the neural activation of mast cells, mast cells are also an "interface" connecting station for mediators of peripheral nerves and local inflammation. The environment of the surrounding nerves is rich in mast cells, and the manipulation of sensory fibers affects the local density of mast cells. It is important to see how key elements of the local immune-neural network, including the histamine, serotonin and cytokines produced by it, all modulate NANC neurotransmission.

NANC fibers display both histamine (H1, H3) and serotonin (5-HT2a) receptors. These receptors are increased in inflammatory conditions, and the released TNF lowers the stimulus threshold of afferent C fibers and directly increases the secretion of Substance P, neurokinin A, and CGRP. As part of the stress response, neurotransmitters secreted by sensory fibers also influence barrier functions by inducing inflammatory processes. According to Raap and Kapp (2005), a higher level of neuropeptides and a greater density of neuropeptide-positive nerve fibers are characteristic of lesions with atopic dermatitis.

In addition to mast cells, the central elements of psychodermatological phenomena are dendritic cells, the so-called Langerhans cells, which are also influenced by Substance P, CGRP. Although Substance P is one of the key factors in inflammatory processes, in certain situations Substance P and CGRP can inhibit antigen presentation. Since Langerhans cells are located near CGRP-containing fibers and CGRP is able to inhibit Ag-presenting cells (Langerhans cells, macrophages), local administration of CGRP may not result in a prolonged hypersensitivity reaction, which can be attributed to the inhibitory effects between the surrounding nervous system and the immune system.

Psychodermatological symptoms

Neuromediators play a role in a range of dermatoses exposed to psychological influence, such as vitiligo, prurigo, psoriasis and atopic dermatitis. Both the development and recurrence of psoriasis can be caused by psychological stress. Mazetti et al. (1994) estimate stress before the first symptoms of psoriasis to be between 32% and 90%. In two-thirds of cases, the stress takes place within two weeks before the onset of symptoms. Psoriasis patients are more sensitive to stress than the control group, and the beneficial effect of psychotherapy on psoriasis is also known. Psychiatric distress can be detected in two thirds of patients, often without external stress. Following surgical or traumatic denervation, psoriatic lesions regress, according to Pincelli et al. (1994). During psoriasis, the density of intraepidermal nerve fibers containing Substance P increases. In the nodular lesions of prurigo, the density of nerve fibers and SP,

VIP, and CGRP increased, which cannot be considered a secondary lesion due to scratching, according to Abadia-Molina et al. (1992). Cooper (1994) also observed neurocutaneous changes in atopic dermatitis. The number of Substance P and CGRP-containing fibers increases and adrenergic innervation decreases, while somatostatin-containing fibers disappear according to Pincelli et al. (1990). All this refers to the weakening of the factors that inhibit the local inflammatory process.

Psychoimmunology of psoriasis

The onset of psoriasis is often preceded by a psychological stressor and a serious life event, which can also play a role in flare-ups of psoriasis symptoms. Richards et al. (2005) found lower baseline cortisol levels and low cortisol response in patients with stress-related psoriasis flares similar to those found in atopic dermatitis. All this points to disturbed or exhausted hypothalamic HPA regulation, which may be a consequence of chronic stressors. At the same time, the catecholamine level was elevated (Buske-Kirschbaum et al., 2002) and following the stressor, the circulating CD4+ and monocyte count increased and the CD3+/CD25+ T cell count decreased in psoriasis patients. Locally produced neuropeptides can also contribute to the maintenance of the disease. In the psoriatic plaques themselves, the density of nerve fibers increases, and local levels of calcitonin gene-related peptide (CGRP), Substance P (SP), vasoactive intestinal peptide (VIP), and NGF (Nerve Growth Factor) all increase. T cell and keratinocyte proliferation following NGF effect, mast cell migration, degranulation, and the chemotaxis of memory cells are also enhanced.

Psoriasis is the result of immunological events based on a complex genetic basis. For a long time, the histological characteristics of psoriasis were leukocyte infiltration of the epidermis and its deep layer, keratinocyte proliferation, and an autoimmune process mainly based on TH1, mediated by TH1 cytokines (gamma interferon and TNF alpha). But the TH17 cytokine network also plays an equally important, central role in the development of lesions. TGF beta and IL-6 produced by Treg cells and keratinocytes also play a role in this process and help the transformation of naïve T cells into TH17 cells. IL-23 produced by dendritic cells, Langerhans cells and keratinocytes induces further TH17 expansion, and due to IL-22 produced by the increased number of TH17 cells, the number of keratinocytes increases. IL-22 stimulates the keratinocytes of the skin and activates the STAT3 pathway, and acanthosis occurs in addition to the proliferation of keratinocytes. IL-17 and IL-22 increase the infiltration of the skin, closing the psoriatic vicious circle. IL-36, produced by keratinocytes, further deepens this, because it activates resident dendritic cells and

increases the pathogenicity of TH17 cells through the release of IL-23. But IL-17 produced by activated TH17 cells also attracts neutrophil granulocytes to the affected tissue area. The levels of gamma IFN and TNF-α of TH1 and TH17 origin were also increased in these tissues.

Psoriasis is a real psychosocial immune disease, since the skin changes aggravate the patient's state, who is also under stress for other reasons and has serious psychological problems. The quality of life deteriorates, social stigmatization, difficulties at work can all lead to increased stress and even depression. 40% of patients report serious emotional and mood disorders, and depression and anxiety symptoms may also be present in more than half of patients.

The psychoneuroimmune nature of psoriasis is confirmed by the fact that therapeutic stress reduction has a good effect on the effectiveness of the treatment. But other psychotherapeutic methods have also proven to be effective, such as hypnosis. Cognitive behavioral therapy resulted in a reduction in the frequency and intensity of symptoms even six months after the treatment, and stress reduction and imagination techniques also had a good effect on the development of psoriasis.

Atopic dermatitis

Atopic dermatitis (AD) is a chronic, recurring, highly itchy skin disease provoked by allergens and infections, which can otherwise be considered a national disease in developed countries. Chronic inflammatory phenomena, damaged barrier function of the skin, and disruption of skin regeneration processes are characteristic of the disease. The early stage of atopic dermatitis is characterized by dryness of the skin, loss of water and a reduced protective role against environmental pathogens. In the early phase, Th17-related cytokines: IL-6, IL-17A and IL-23 play a role. Months later, TH2 cytokines, IL-4 and IL-13 predominate, with an unchanged gamma IFN level. TH2 cytokines, IL4, IL5 and IL13, produced by T cells attracted to the given area, have been detected in AD. IL-4 and IL-13 are responsible for the production of IgE by B cells, which is the result of increased activity of intracellular STAT-6. IL-5 is responsible for the development, activation and survival of eosinophils, in atopic dermatitis both the IgE level and peripheral eosinophilia can be observed, according to Leung (2000). IL-4, IL-5, IL-10 and IL-13 produced by allergen-specific T helper cells taken from the symptomatic skin area mainly reflect a TH2 cytokine profile, according to Brandt and Sivaprasad (2011). The disease can be characterized by both TH1 activity and a temporary predominance of TH2 activity. According to Thepen et al. (1996), their dominance varies, and this appears in the context of the sequential cell activation of TH2 and TH1, whose dynamics depend on the chronicity of atopic dermatitis. The exhausted, hyporeactive HPA axis and hyperactive LC adrenergic activity may play a role

in this, which, in turn, may create an increased TH2 milieu for allergic hypersensitivity and the phenomenon of atopic dermatitis.

Due to the development of TH2 dominance, we have to take into account the role of stress inducing a TH1/TH2 shift, also the role of the pro-TH2 cytokines TSLP, IL-25, IL-33, which are able to polarize dendritic cells and contribute to the enhancement of the TH2 response, is also worth mentioning. TH2 cytokines (IL-4, IL-5, IL-13, IL-31, and IL-10) all play a role in the symptoms of atopic dermatitis. TH2 cytokines also play a major role in the maintenance and chronicization of atopic dermatitis, the synthesis of IL-4, IL-5, IL-6, IL-10 and IL-13 increases, as a result of which the IgE level rises, while circulating CD4 and IFN-gamma produced by CD8 lymphocytes decrease. This TH2 predominance is characteristic of the acute phase, which later shifts towards TH1 as the disease progresses. Changes in several immunological parameters have been described in atopic dermatitis, such as a decrease in the number of circulating T cells, reduced responsiveness to mitogens, reduced cytotoxic potential of monocytes and NK cells, reduced response to chemotactic mediators, and peripheral eosinophilia. In patients genetically sensitive to irritating environmental antigens, increased IgE production and increased histamine release from mast cells occur even without stress. But the skin, as a protective wall, can also become permeable to provocative antigens, which can lead to allergies.

IL-4 and IL-13 stimulate IgE synthesis and shift the B cell response from other Ig isotypes to IgE. But their effect increases the expression of the adhesive molecule VCAM-1, which collects eosinophils at the site of inflammation. IL-4 and IL-10 are triggers of mast cell proliferation, and IL-5 has a role in further recruitment and stimulation of eosinophils. During the stimulation, cytotoxic proteins are released, such as the eosinophil cationic protein (ECP), which helps to extend the lifespan of the eosinophils and causes mast cell degranulation.

Antigen-presenting cells (Langerhans cells, macrophages) both have a surface IgE receptor. Chronic clinical consequences, chronic lichenification, and hyperkeratosis are associated with the proliferation of mast cells and eosinophils, and in atopic lesions, increased IL-12 expression and IFN alpha activity can be detected, which also indicates the involvement of TH1 processes. So, after the acute allergic response induced by IL-4 and IL-5, in the consolidation phase, IFN-alpha secretion is the determining factor in atopic dermatitis. IL-12 produced by activated eosinophils and macrophages causes this shift from TH2 to TH1 dominance, according to Boguniewicz (2004).

TNF produced by macrophages, antigen-stimulated T cells, and mast cells all play an important role in the maintenance of chronic eczema. Various food allergens (cow's milk, eggs, peanuts, sea crabs, fish) are capable of provoking

atopic skin reactions and flaring up existing atopic dermatitis through IgE mediation.

Chronic eczematous skin diseases of non-allergenic origin form another subgroup. Questions arise regarding the reduced HPA activity observed in patients with atopic dermatitis, the background of which is the effect of persistent proinflammatory cytokines following chronic inflammatory processes of the skin, and the consequent reduction of HPA axis activity may also play a role, according to Turnbull and Rivier (1999). In addition to the persistent activity of proinflammatory cytokines, the negative feedback effect of persistently elevated cortisol levels can also lead to a decrease in the activity of the HPA axis. Tausk suggests a hereditary factor behind the reduced HPA activity observed in people with atopic dermatitis, but draws attention to the fact that the compensatory element expressed in the increased number and increased sensitivity of the glucocorticoid receptors of the peripheral immune cells results in a response leading to an increased TH1/TH2 shift even to a minor rise in cortisol levels to stress.

Chronic stress or inappropriate, abusive or negligent, maternal behavior also leads to disturbed responsiveness of the HPA axis. The catecholamine influence (noradrenergic, adrenergic innervation) shifts the TH1/TH2 shift in the latter direction, suppressing the IL-12 activity responsible for TH1 induction, while catecholamines promote the TH2 response by increasing IL-10 secretion. Ionescu and Kiehl (1988) measured higher noradrenergic levels in adult patients with atopic dermatitis even at rest, which indicates internal anxiety. Among adults with atopic dermatitis, Buske-Kirschbaum et al. (2002) measured elevated basal levels of norepinephrine and adrenaline, and the activity of the LC-sympathetic IR-adrenal axis showed increased activity in response to stress. Endogenous cortisol also promotes the apoptosis of eosinophils and basophils, so stress mediators can act as a brake by increasing the apoptosis of eosinophils and basophils, however, with the depletion of the HPA axis, the chronic allergic response can also intensify, according to Meagher et al. (1996).

The range of therapeutic interventions that act as a general stressor buffer or reduce the psychoimmunological response is wide, and many points of the involved networks offer opportunities for intervention. At the social-behavioral level, structural patient education programs, habit modification methods, and dermatological education programs can be applied. Cognitive-behavioral therapy, intensive short term dynamic psychotherapy (ISTDP) are aimed at psychological-cognitive processes, while autogenic training can influence the patients' autonomous nervous system, and moderate the heightened activity. These therapeutic interventions can all affect the severity of eczema, itching and scratching, i.e. the course of atopic dermatitis.

Personality, emotionality, and psycho-immune dermatology

Alexander and French (1948) suggested, as early as in the 1940s, that the inhibition of the expression of anger and hostility causes increased stress in children suffering from atopic dermatitis. In Alexander's classification, atopic dermatitis – under the name *neurodermatitis* – was one of the seven psychosomatic clinical pictures. In the model, the authors attributed specific roles to different emotional conflicts in the elicitation and maintenance of the given medical condition. According to Alexander, the suppression of anger due to rejection by the mother plays a role in increased emotional stress, early mother–child relationships and developmental psychology. In addition, personality problems caused by the distorted early relationships in the background of the conflict-specific pattern presumed by him can also explain psychoimmunological clinical features, which are deeply affected by stress-biology processes.

This inhibition can also be matched with the "shyness" characteristic of allergic patients and conjures up the problems of the suppression of aggression, so important in psycho-oncology. The issue of early mother–child relationship is cited by numerous related personality studies as well. According to Kagan (1991), children suffering from allergic illnesses are characterized by shyness, withdrawal, and inhibition in addition to hypertonicity, higher levels of catecholamine derivatives in the urine, and higher cortisol levels in saliva. According to Jasnoski et al. (1994), multi-directional links were detected between shyness, immediate oversensitivity and anxiety traits. Hay fever, eczema, asthma, and urticaria are proportionate to excessive kindness, introversion and fatigue, as described by Bell's (1990) study. Immature, uncertain, anxious, dependent, rejecting, overprotective and unconsciously aggressive mothers do not ensure skin contact to provide security. Due to a lack of caressing, tenderness, and warmth, a contradiction between the desire for symbiosis and the simultaneous fear of that can be typical. In atopic patients, situations causing infantile uncertainty are pathogenic. 60% of "eczema" mothers do not calm down their baby, while this behavior occurs in 16% of the control group members.

According to epidemiological data, childhood atopic eczema increases the risk of ADHD – that is, attention deficit hyperactivity disorder – in later stages of life, as Buske-Kirschbaum et al. (2013) stated. Inflammatory cytokines accompanied by higher psychic stress and allergic inflammatory processes can have an adverse impact on the development processes of the prefrontal cortex, and altered neurotransmitter activity can develop an ADHD clinical picture. On the other hand, higher stress levels detected in AHDH patients can deteriorate atopic eczema because of psychoimmunological background factors. Genetic factors and prenatal stress increase the morbidity of these diseases as common risk factors.

Divorce, mourning, and family conflicts are frequent before the recurrence of the illness. In 55%–86% of atopic dermatitis patients, emotional stress was among the triggering factors, according to Picardi and Abeni (2001). Kodama et al. (1999) examined disaster stress after the Hanshin earthquake, involving 1457 patients diagnosed with atopic dermatitis. In seriously affected areas, the frequency of the recurrence and aggravation of the illness were considerably higher one month after the disaster. Picardi and Abeni also emphasize that emotional stress associated with life events of great weight is accompanied by the recurrence/aggravation of atopic dermatitis. According to Scheich (1993), increased everyday stress effects intensify atopic dermatitis symptoms, leading to deteriorating symptoms and increased pruritus. Consequential psychic difficulties, social stigmas and cosmetic problems lead to further depression, social stress, and a vicious psychosocial circle, further complicated by inadequate coping characteristics.

Hashiro and Okumura (1998) found patients suffering from atopic dermatitis to be more depressed and anxious than control subjects. NK cell activity was also significantly lower in patients with atopic dermatitis. In their research, anxiety measured by STAI (State- Trait Anxiety Inventory) affected NK cell activity.

According to Kaneko and Takaishi (1963), urticaria can be triggered and aggravated by emotional factors. In their study of 27 patients receiving hypnotherapy, the authors found that symptoms had subsided in five cases, symptoms had nearly resolved in 9 cases, and considerable improvement occurred in 8 cases through hypnosis; the treatment proved to be ineffective only in 5 cases. In the course of the 7-month follow-up, there were only a few cases of relapse. The longer the illness prevailed, the less effective hypnosis was. Results showed similar correlations with hypnotic susceptibility. The results of relaxation suggestions lagged behind the results achieved in hypnosis targeted to eliminate symptoms.

In another study, the authors were able to trigger urticaria by the hypnotic suggestion of the conflict situation and the suggestion of hotness in patients, in these cases urticaria was experienced to be triggered by physical warmth and emotional conflicts. In examining 53 patients suffering from urticaria, IgE values were high in several cases, even in the absence of the provoking antigen.

Mason (1952) endeavored to treat ichthyotic erythroderma – known as incurable – by hypnosis, and achieved a selective reduction of symptoms by selective hypnotic suggestion (first directed to the left hand), and variable improvement of 50 to 95% by extending suggestion to the entire body. No relapse was experienced during a period of one-year patient follow-up. The remission of ichthyotic erythroderma was proportional to hypnotic susceptibility.

Teshima (1991) explained the etiology of alopecia universalis by psychoimmune factors, and combined small doses of immunosuppressive medication with relaxation and stress relief, and five out of the six patients showed considerable improvement. It was only the control group treated with corticosteroids that did not show improvement. Background processes are indicated by the fact that in the case of patients involved in both autogenic training and imagery treatment, T helper/processor proportions significantly decreased, and the relative proportion of NK cells increased.

The psychoimmunological character of alopecia is supported by the fact that the clinical picture explained by autoimmune origin is frequently preceded in adults by states of subject loss and mourning, as shown by Misery et al. (2001). Colón et al. (1991) also found depression and anxiety to be more frequent. Liakopoulou et al. (1997) observed social inhibition and disorders of social relationships in children.

Shenefelt (2003) found stress management techniques and relaxation treatment to be effective in treating atopic dermatitis. Ehlers et al. (1995) found autogenic training, cognitive behavioral therapy, and a combination thereof to be effective in the improvement of symptoms, in the reduction of itching, and in the reduction of steroid medication. Ikemi and Nagakawa (1962) had favorable therapeutic experiences using the combined treatment in the cases of allergic dermatitis and food allergy. According to Stangier et al. (2004), the intensity of symptoms (strong itching) before treatment, low IgE, and coping development played a verified role in the effectiveness of psychological treatment. Stewart and Thomas (1995) found hypnotherapy to be beneficial in atopic children and adults.

IN PLACE OF A SUMMARY

Behavioral network medicine and psychoimmunology

Based on our review of the behavioral, pathophysiological and clinical aspects of psychoimmunology, we can see the legitimacy of the systemic bio-psycho-social approach for relevant pathologies of high public health importance. In the event of a change in attitudes, the extensive network of psychoimmunological specialists will be able to accommodate and integrate the diagnostic and therapeutic tools of psychosomatics, clinical psychology and lifestyle medicine agency, in addition to biomedical care (Lázár, 2018). The bio-psycho-social approach itself offers a network theory framework to understand the complex "communication" between our neuroendocrine, immune, musculoskeletal and adipose tissues in the "network of networks" of social psychoimmunology. In this redefinition, inter-organ communication networks, neuroendocrine adaptive and maladaptive interaction nets, neurocognitive networks organizing perception and behavior, and the interacting social networks and patterns of socioeconomic and cultural factors all require a networked interpretation as the basis of intervention.

The broader and narrower social networks, the narrative web of the individual's personal, old and current life-history events, the perception and evaluation patterns immersed in the enduring traits of personality (hemisphere differences, type A or type C personality patterns), all affect the physiological functioning of the hub-like HPA axis during stress.

Endocrine-immune connections have many central nodes, but among them CRH and cortisol have a prominent hub-like role. Among cytokines, IL-1 cytokine can be evaluated as such a hub that exerts influence on many organ systems, such as the central nervous system, immune response processes, or influence on osteoclasts in the skeletal system. At the cellular level, the monocytes, Lagerhans, or Kuppfer cells, mesangial or glial cells producing IL-1 and IL-6 in the connection of networks. NK cells and the TH1, TH2, TH3, TH9 or the lymphocyte group TH17 cells play also hub-like central role generating different immune sequences. Similarly, Treg cells also play a distinguished physiological-clinical role in the communication network of immune processes. Topological networks of the studied neuroendocrine-immune phenomena can be examined at different levels, at an inter-organ level, at intracellular and genetic-transcriptomal levels. Network scaling should also be used at a

population level to study psychoimmunological phenomena in the context of behavioral epidemiology. On a narrower somatic level, such networks are created by the comorbidity patterns revealed by large-scale data.

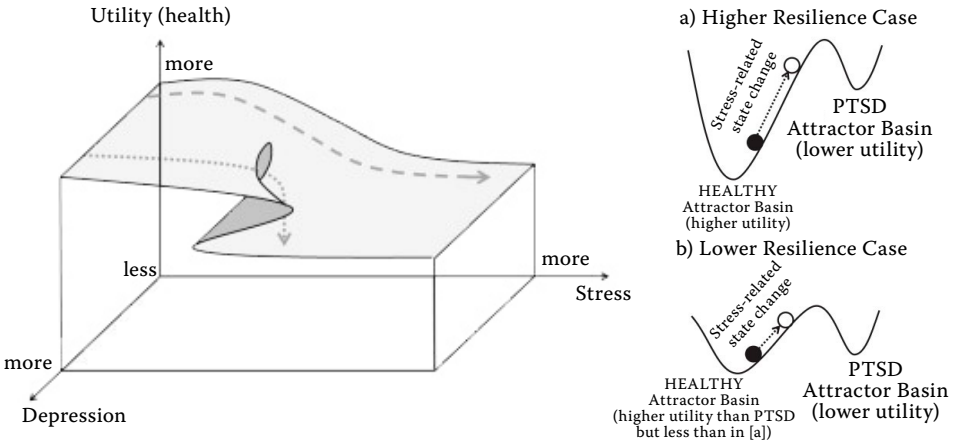
As "motif", we can identify local regulatory loops as well as pre- and postsynaptic regulatory circuits, but we can also identify such complex loops in the action tissues of different cytokine groups. Interaction graphs show a more intense picture within a given impact community than outside the community concept. This is true for most immunomediators, even if many of them have cytokine effects on distant, neural and other tissues, and may even be produced out of the immune system – such as adipokines and myokines of fat or muscle tissue, or glial cells of the central nervous system, as we have seen regarding IL-1 and IL-6.

For us, the most important thing in bio-psycho-social modeling is the interconnected, hierarchical multilayered network of these networks. Nevertheless, sometimes these network patterns occur only temporarily, which can, however, play a symptom-creating or pathological role. Examples of this can be seen in the social transduction theory of depression, or in the consequences of early traumatization, which can result in the change of alleles or in effects of epigenetic influence.

In an attempt to make a dynamic model of these networks, we can identify different patterns of quasi-evolutionary but regulated systemic network processes in our model, including acute, adaptive, chronic, and maladaptive processes. In an adaptive case, the system flexibly returns to its original homeostatic dynamic equilibrium state, when the stressor challenge is over. Alternatively, the endurance of the allostatic situation can lead to another contorted disturbed allostasis, in which, for example, central sensitivity to cortisol (negative feedback) decreases, and the same happens in the periphery, leading to diminished sensitivity toward cortisol and elevated risk of chronic inflammation.

Thus, from the point of view of systems biology, the stressor transfers the dynamic biopsychosocial system which is organized as a network of networks, from one attractor basin to another with a lower adaptation value and usefulness. The *attractor basin* as a phase space constitutes the state of dynamic systems: in this case a complete biopsychosocial network ensemble, any element of which changes to the specific attractor. This can be called the basin of attraction, where the stressor moves the system to a different attractive "field", which causes the system to be placed in a boundary position, or the stressor slows the return to the optimal attractor basin. In this case, an attractor – borrowed by analogy from mathematics – is a specific subgroup of the phase space of the dynamic biopsychosocial (BPS) system, a specific event and it limits the interval range of processes that ensure the functioning of the system in a homeostatic dynamic equilibrium or, allostatically to meet the increased

challenges, while ensuring basic conditions. The dynamic system, which operates as a "network of networks", depends not only on environmental perturbations, which can be called stressors, but also on the person's perceptions, body type, memories, coping patterns, state of life and genetic characteristics. Allostasis is reflected in allele change, gene transcription level change, epigenetic consequences, metabolic activity differences, receptor desensitization or other changes in receptor sensitivity, as well as in changes of telomere length. Biopsychosocial resilience is denoted by the distance of the condition as an attractive pool from each other's narrowed, damaged, maladaptive or preclinical "pool". But resilience is also characterized by the strength of the vector field in the given attractiveness basin, which helps to return quickly to the specific attractiveness, i.e. homeostatic physiological equilibrium, laboratory normal values and ratios.



Figures 16-17. Stress resilience and the attractor basins (after Oken, Chamine and Wakeland 2015)

This can also be measured as an allostatic score, which is made up of changes in physiological indicators that reflect stress and loss of balance. The original list of these variables had ten items: systolic and diastolic blood pressure, hip-to-waist ratio, total cholesterol and HDL cholesterol, glycated Hgb, night collected urine cortisol, epinephrine and norepinephrine, and DHEA-S. The allostatic score shows a link between childhood poverty and workplace fatigue. It is an immanent indicator of biopsychosocial system states and represents different attractive pools. Social psychoimmunology has expanded the allostatic score, including CRP, IL1, and IL/ TNF alpha, or fibrinogen.

For the understanding of neuroendocrine-immune events, it is essential to map intracellular pathways, which are in fact part of the following: the exploration of the network of proteins, intracellular signal pathways, trans-cryptic factor-DNA interactions, and the cell interactomic and secretomic network.

Such special attention is given to NFkappaB activity, and in addition we could also list important network elements that can be taken into account at proteomic, transcriptomic levels.

We can also extend temporary network alignments in a multilayered network system to the connection pattern of different information patterns. This can be called *forward or reverse "edgetics"*, variations for genotype phenotype relationships, and for forward or back-to-back run-off paths in the context of different factors. Regulatory changes due to chronic stress (GR receptor down-regulation, negative feedback, TH1/TH2 shift, elevation of proinflammatory cytokines, peripherial glucocorticoid insensitivity) are associated with psycho-developmental anomalies, psychosocial ecosystem disorders, childhood abuse, and other abuses with epidemiologically proven increased disease risk. In the depths of this relationship, we also find the social transduction theory of depression, which follows psychosocial influence on transcription changes in the depths of the cell. The symbolic or specific threats and relationships of the social environment are translated into networked physical experience by many neural networks and centers such as the mentalization network, the neural structures responsible for detecting social rankings and the system of centers involved in the regulation of social behavior, which we have linked to the HPA activity and the immune system. The networked approach provides an opportunity to make Cannon, Selye and Alexander's paradigmatic insights a common cornerstone of psychoimmunology and networked pathophysiology and the clinical practice. Alexander's inalienable merit is that he revealed the psychosomatic features of internal medical diseases, involving the immune system. Selye has found a networked connection between the stressed target organ, neuroendocrine system and the immune system, while Cannon connects adaptive (network) patterns of the sympathetic and parasympathetic system with the challenges of the environment in the *"fight-or-flight versus tend-or-mend"* framework. The systemic approach to behavioral medicine can integrate the above bio-psycho-social network approach and the vision of evidence-based biomedicine through network medicine.

Neuroimmunomodulation, the wired connections of innervation, and the multi-directional network of information created by receptors also give strategic importance to the network approach to psychoimmunology. In fact, these network images are mostly patterns entrenched in their evolutionary history, captured by adaptive advantages over time, and new environmental situations can make them maladaptive. Social networking images of social relationships, dominance versus submission, social support versus exclusion, loneliness, success and recognition versus loss of rank and ostracism – they all point to these existential extremes. Post-traumatic syndromes, derived from human conflicts and abuse, can also be sources of pre-disease and risk situations. These psychosocial networks and mapped life history patterns can all be

understood as psychoimmunological risk factors. There are multi-network situations. Such is the pattern of personality development influenced by the early mother–child relationship, which leads to social psychological and even cultural consequences affecting social networks. Such alterations may affect, through epigenetic consequences, the later functioning of the stress axis. But these may be the impact of severe losses on the neurophysiological networks, which organize behavior, the regulatory circuits of the HPA axis or those processes which immediately manifests in transcriptomic changes.

Exams are also multi-network situations involving several layers of social psychosomatic patterns, in which we find the involvement of neural structures related to the social hierarchy, as well as neurophysiological and stress physiology-related phenomena connected to control. Dominance and submissiveness, inhibited power motivations, the perception of social-evaluative threat are all dynamizing multilayered networks, where "hubs" are the "interfaces" entrenched in the archaic depths of evolution.

Psychoimmune risk groups

When trying to identify psychoimmune risk groups in the healthy population, we link the approahes of preventive medicine and lifestyle medicine with the knowledge of (social)psychoimmunology. Immunosuppression due to chronic distress carries the greatest risk among people with already impaired immune systems (elderly, alcoholics, drug users). Life events that cause a threatening negative (and sometimes intense positive) emotional ordeal and the immunological effects of recurrent stress periods can range from days to months. The psychoimmune risk situation can also be maintained by a sustained cognitive and experiential pattern that maintains the experience of crisis even at cognitive-emotional and visceral depths, as we see with PTSD or when diagnosing an incurable disease. This may require thoughtful psychological support in certain vulnerable, risk population or chronic patient groups, so the healer has to perform psychotherapeutic tasks.

Social and socioeconomic networks

The expected average life expectancy of the cumulatively disadvantaged social strata (African-American population in the USA, Roma population in Hungary) is lower, and can total a difference of up to 10 years. In this prognostic disadvantage, the economic and sociocultural situation of the disadvantaged strata accumulates and includes the following: lack of education, patterns of behavior resulting from and maintaining anomic circumstances, and the frequency of childhood abuse. On the other hand, other disadvantages arising

from low socioeconomic status, poverty, socially submissive minority existence, threats of violence, crime, disability, insufficient transport conditions, and the unavailability of health services can have pathological consequences of chronic stressors. Low socioeconomic status in childhood is associated with higher IL-6 and CRP levels in the adult population studied.

But in other social strata we might also find consequences of social-psychoimmunological background. This can come from a job that disrupts regular, healthy sleep patterns, or from other ongoing and chronic distressing work. Examples include higher cancer mortality in the middle-aged group of physicians as compared to values of the peer group, and the high incidence of cancer morbidity and mortality among the majority of retired chief medical practitioners.

Behavioral epidemiological studies of society's macro-networks, such as Grossarth-Maticek's Crvenka-Heidelberg research or the series of Hungarostudy research led by Mária Kopp, may offer a wealth of data that reveal network connections important for psychoimmunology. Thus, the mediatory role of depression between socioeconomic factors and somatic consequences was demonstrated by statistical route analysis. Traumatic experiences in childhood, or hostile marital conflicts result in elevated proinflammatory cytokine levels, as explained by the inflammatory theory of depression. The perception of hierarchy, the psychoimmunological influence of dominance and submissiveness are also important from an ethological perspective.

Narrative life history network

The characteristics of diverse stages of life, early childhood events, life events, stressful life stages, life events with loss of control and status, bereavement, divorce and unemployment can all be important in the course of a medical history or for psychoimmunological purposes. The practice of narrative medicine or the practice of trauma disclosure can help in the treatment of the patient.

Childhood and old age make a person psychoimmunologically vulnerable due to immaturity, or due to the immune system's degeneration, the so-called *immune-aging* with loss of function. These possible impairments include traumatic conditions experienced during an early mother–child relationship and adverse childhood experiences (ACE). Studies show that a range of traumas experienced in childhood and in the adolescent stage, as well as during aging cause a significant decrease in the hormone-producing function of the thymus. Severe life events are more common 1-2 years prior to the onset of certain diseases. In the case of Adverse Childhood Experiences (ACE), the more points are affected, the higher is the chance of the following: proinflammatory

cytokines and elevated CRP, persistent cortisol increase, and chronic (autoimmune) inflammation of a wide variety of organs. According to a study by Dube et al. of 372 autoimmune patients discharged from hospitals, 85% had one and 15% had more ACE points. The results show that each ACE point increases the likelihood of being hospitalized with the affected autoimmune disease by 20% between the ages of 19 and 64. This rate is reduced to 10% per point over the age of 65 (Dube et al. 2009).

In view of the developmental psychological weight of early traumatization and childhood abuse, stressful psychosocial experiences, the situational/evaluational characteristics of personality patterns and the patterns of behaviors serving as feedback for social situations, as well as associated psychoneuroimmunological processes, the whole patient, with his life story, personality and specific emotional world, is at the heart of networked medicine.

Risk networks assigned to life stages

Some stages of life can also be risk-provoking due to the different nature of the developmental stages of the immune system. In the case of genetic predisposition to asthma, Mrazek (1986) connected the onset of the disease to family disorders and childhood psychosocial exertion. The psychological burden of going to kindergarten and starting school can affect certain lymphocyte subgroups. Also, psychosocial deprivation in children in orphanages is accompanied by different immune characteristics. Among these children, higher secretive IgA levels of saliva and more frequent eruptions of herpes simplex were observed. These critical periods are often associated with stressful psychosocial changes. Autoimmune processes such as ulcerative colitis begin in late adolescence, while cancers are more common in early old age.

Old age also constitutes a specific risk group, because, in addition to the loss of status, which is characteristic of old age, the narrowing of social roles, the narrowing of social support, and the appearance of loneliness and socioeconomic disadvantages, the immune system also ages and the receptor composition of the cells changes. The effectiveness of vaccination in elderly persons also weakens. Thus, the elderly partner caring for an Alzheimer's patient has a decreased cellular immune response and a weakened response to influenza vaccination, and the wound healing of the elderly is also more protracted. Also, in autoimmune and allergic pathologies, changes are considered to be a disorder of immunological self-regulation, and the flexible dynamic system shows a regulatory vulnerability that is more exposed to stress. The TH1/TH2 balance shifted in the direction of TH1 can be described by the word "immunaging/inflammaging", which means a serious change in the neuroimmune network and impacts transcriptomic, cellular and neuroendocrine immune networks as a whole.

Personality patterns, character maps with psychoimmune consequences

Among the (measurable) personality traits affecting the psychoimmunological risk situation, we can mention learned self-efficacy as opposed to learned helplessness, optimism versus pessimistic orientation, internal or external control, fatalism, stoic attitudes versus combative adjustment, the different ability to express emotions, the mobilization of social support as opposed to alexithymia, and the situation of social inhibition. Several attempts have been made to outline personality traits susceptible to psychoimmunological diseases. Among the first, LeShan (1956) outlined a repressive, oversocial personality pattern with inhibited aggression among cancer patients. Moos and Solomon (1965) described the existence of a specific personality pattern among autoimmune patients, especially among rheumatoid arthritis patients.

Such specific personality patterns include a 'cancer-prone personality', as identified by Temoshok and Dreher (1992). According to CTBP (C type behavior pattern), this type of person is extremely kind, loving with suppressed anger, and high internal tension. Eysenck and Grossarth-Maticek (1994) describe their so-called Type I personality as a person who is too cooperative, avoidant of conflicts, rigid, self-sacrifice-prone and predisposing to hopelessness and depression. This image is similar to the characteristics previously formulated by Kneier and Temoshok (1984), where persons following repressive styles of coping strategy that avert anxiety-provoking ideations, suppress emotions and provide an avoidant response. Repressive coping reactions were operationally defined as the discrepancy between reported anxiety and that shown physiologically (electrodermal activity) in response to anxiety-provoking statements in an experimental procedure. In these individuals cancer has worse prognosis. Greer and Watson (1987) make a similar claim when they write that "suppression of emotions, especially anger, is central to this pattern of behavior". Similarly, Bleiker (1995) says that "anti-emotionality has a predictor role in cancer." The disturbance of expression of emotions also appears in people with allergic skin diseases. This is reflected in the personality characteristic of atopic dermatitis and eczema patients who exhibit "shyness", which is also a form of social inhibition. Behavioral inhibition and the predominance of right hemisphere activity might also be associated with psychoimmunological consequences. For all these reasons, the concept of Solomon's 'immunosuppression prone' personality pattern can also be a common denominator for the above personality types. In these typologies, including the LeShan model, there is a disturbance in the perception and expression of emotions.

There are unfavorable psychoimmunological consequences of shame that roots in the dynamics of social-evaluative threat, and a lack of social acceptance. Further risk can be mentioned in the case of the so-called *Inhibited Power*

Motive Syndrome outlined by McClelland (1982), which consists of external inhibition rather than internal inhibition, and creates a sense of loss of control and helplessness.

Table 19. Personality patterns and psychoimmunological risks

	Personality patterns with	
Increased psychoimmunological risk		**Reduced psycho-immunological risk**
Anti-aggression, renouncing, helpful, oversocial, external control, "angelic" affiliative personality (LeShan 1956)		Heightened commitment, internal control, "hardiness" (Kobasha 1979)
Type C personality, inhibition of aggression, inhibition of awareness of emotions, increased anxiety (Temoshok 1992)		High SOC (sense of coherence), increased sociality
Shyness (allergy) (Jasnoski et al. 1994) CTPB (C type pattern of behavior)		Hard, tough setup
Inhibited Power Motivation (IPM) (McClelland 1982)		
Right Hemisphere Prefrontal EEG Dominance Behavioral Inhibition System (BIS)		Left Hemisphere Prefrontal EEG Dominance, Behavioral Activation System (BAS)
Shame, self-submission, pessimism		Success, Dominance Optimism, laughter

On the basis of the above, it can be seen that the relationship between multilevel networks is indicated by cohesive trends. Personality traits are partly life-historical consequences, often strengthened in the fabric of harsh socioeconomic disadvantages and such traits become a source of additional obstacles and difficulties in the form of a vicious circle.

If we look at the immunobiological consequences of sleep deprivation, we can see that neutrophil granulocytes show a decrease in phagocytosis (Staphylococcus aureus) after 48 hours of sleep withdrawal, and lymphocyte DNA synthesis is increased, which is induced by a decrease in PHA. Palmblad (1979) draws attention to the immunological risks of disrupting normal sleep patterns induced by occupations common in medical and military roles. On the other hand, immune-boosting hormone effects detected during deep sleep can contribute to the healing processes. Two immune stimulant hormones, growth hormone and the maximum secretion of melatonin are conditional on deep sleep.

Regarding the immune risk situation of otherwise healthy persons, we should mention bereavement first. Chronic, insurmountable stress can pose a psychoimmunological risk. The traumatic experience of severe loss, inertia, and helplessness also depends, to some extent, on the quality of spiritual social support. A person who is abandoned in traumatic circumstances or who loses their much-loved job or important social role may also experience a serious loss. In such a case, spiritual and social support often becomes insufficient, and the person feels alone.

Psychological strains such as the examination period may be a temporary immune risk factor, especially for persons without adequate self-strength and without social support. In order to locate these persons, the institution's life coaching service, psychological specialization or medical services offer assistance.

Overwhelming work stressors, impending or elongated unemployment, imbalance of effort and reward and the lack of control over requirements at work, conflicts in the workplace, and situations triggering frustration, aggression, submissiveness, harassment and ostracism can be sources of PNI risk. The processes leading to burnout and the psychosomatic consequences of burnout are all of importance, as we saw in previous chapters. The conflict between the family and the workplace, as well as a symptomatic, marital conflict-laden family background can exacerbate this situation in the way already discussed.

The stage of retirement poses a risk not only as a result of the loss of the usual environment, but also for the loss of relatives, spouses and friends during this period, which is exacerbated by a decrease in the production of thymus hormones at this age, as well as by the deterioration of immune functions. This may also require the organization of self-help groups with preventive and social support in the age group concerned.

Somatic disease network: comorbidity on psychoimmunological scales

In view of the incriminated psychosocial effects (see relevant results of ACE studies), proinflammatory cytokines and inflammatory factors (IL1, IL6, TNF alpha, CRP) are considered serious markers of morbidity and, due to their chronic inflammatory effects, they are associated with the development of cardiovascular diseases and, based on the inflammatory theory of depression, they are considered a source of mental disorders. PNI screening can be used for the early detection and prevention of many somatic pathologies. This may also be confirmed by identified links between reduced HRV values and proinflammatory cytokines.

Increased HPA axis activity is also characteristic of the following conditions: chronic stress, anorexia nervosa, malnutrition, compulsive (obsessive-compulsive) neuroses, panic disorder, physical exhaustion, chronic active alcoholism, withdrawal conditions, diabetes mellitus, childhood sexual abuse, functional gastrointestinal disorders, the last trimester of pregnancy, hyperthyroidism, and Cushing syndrome (Chrousos, 1998).

From a psychoimmunological point of view, pathologies characterized by insufficient production of CRH or loss of sensitivity due to an underactive HPA axis, and decreased responsiveness to inflammatory stimuli are also important. In this case, the inadequacy of endogenous immunosuppressive feedback may increase the risk of autoimmune or chronic inflammatory diseases. Such disorders with reduced HPA activity include fibromyalgia, atypic seasonal depression, chronic fatigue syndrome, adrenal insufficiency, rheumatoid arthritis. All this should be borne in mind when conducting psychoimmunological screening or examination.

Immunological pathologies, infection or cancer, allergic, autoimmune and weakened immunity deserve inclusion of psychoimmunological anamneses. The patient's examinations and therapy need to be extended in the direction of PNI due to the fact that relapses may be related to psychosocial factors, and the chronic nature of diseases also requires a bio-psycho-social approach.

The other range of patients to be screened consists mainly of persons requiring psychotherapeutic treatment of psychological problems hidden under the surface of somatic diseases, in whom the symptoms of recurrent colds, respiratory infections and prolonged infections may attract our attention and in whose case we may suspect depression.

Recurrent herpes labial or varicella relapse in old age may indicate the role of immunosuppressive endogenous and external influences in the form of herpes zoster. The literature indicates that imaginative training in psychoimmunological care, combined with relaxation, has also been found to be effective in treating otherwise therapy-resistant disorders such as recurrent aphthous stomatitis.

A separate group of psychoimmunological patients is people with allergic diseases. The psychotherapeutic and hypnosis-based treatment of allergic phenomena (bronchial asthma, etc.) opens up a wide scope for behavioral medicine. On this basis, atopic dermatitis, chronic urticaria, urticaria gigantea and other allergic skin diseases can also be included in treatments with psychoimmunological care. A psychoimmunological approach can also be found in dermatological care and allergist care.

The psychoimmunological approach to rheumatoid arthritis is also justified in both theoretical and practical treatment. In the scope of such work, however, extensive teamwork is required between rheumatologists, psychotherapists,

physiotherapists and psychoimmunologists. We see promising initiatives with self-help groups for people with rheumatism.

A separate area of psychoimmunology is psycho-oncological care. In addition to the psychological care of cancer patients, there is also space for specific psychoneuroimmunological intervention. Psychoimmunological treatment focuses on stress management, the facilitation of the experience of controlling the situation, the elimination of helplessness, the relaxation of internal anxiety and tension, as well as on the exploration and resolution of the traumatic experiences of the personality.

Conditioning the immune response – a neuroimmune network phenomenon

Conditioning the immune response has a paramount importance in the history of psychoimmunology, a phenomenon which, thanks to the Pavlov disciples Speransky, Chorin and Metalnikov, was predicted as early as in the 1920s and 1930s. These researchers suggested that neural and immune processes were interconnected and even part of a cognitive system, because they could be conditioned and taught. This legacy was revived by Robert Ader under the name of psychoimmunology, when saccharin, as conditioned stimulus, was associated with the cyclophosphamide effect as as an unconditioned stimulus, and it was discovered that after a while of conditioning, the antigen response to the sheep red blood cells was weakened by saccharin, which was otherwise immunologically ineffective. The conditional stimulus associated with cyclophosphamide may also have a suppressive effect on NK cell activity. Klosterhalfen and colleagues also found the cyclosporine effect to be conditionable in rat strains with arthritis. But it was not just arthritis progression that researchers were able to slow down by conditioning cyclophosphamide immunosuppression. A similar result was achieved in the New Zealand mouse strain with SLE (lupus erythematosus) using saccharin as a conditioned stimulus.

Histamine secretion, which plays a key role in allergic processes, can also be conditioned in this way, and this can be considered as indirect evidence of psychoallergology. Ader (1981) proved the immune-conditioning of the type IV hypersensitivity reaction.

Of course, not only immunosuppressive, but also immune-enhancing effects can be conditioned. Herbert Spector (1996) overviewed the immune-enhancing effects of conditioning the immune response. Ghanta et al. (1985) conditioned camphor with poly I:C to enhance the effective immune response against myeloma cells injected from the outside. If the activity-enhancing effect of adrenaline NK is associated with a sweet liquid called sherbet, an effect that enhances NK cell activity can be detected as early as on the fifth day, as opposed

to the neutral effect of the sherbet associated with physiological saline or irregular adrenaline. The conditionability of the antigen-specific immunotherapy effect is evidenced by the fact that this phenomenon also applies to antigen cross-sensitivity. Spleen cells DBA/2 represent an alloantigen common to the YCB lymphoma tumor antigen. In the BALB/c mouse strain, the growth of lymphoma was inhibited by camphor as a conditioned stimulus associated with the immunization of the DBA/2 spleen cell with antigen, as opposed to those animals that were not associated with immunization, where rapid and unhindered tumor growth was observed.

Thus, it is not only the immune activity in general that might be conditioned, but the antigen-specific immune response is also conditionable. All this not only shows the cognitive nature of immune processes, but can also point towards potential therapeutic options in practical immunology in the future.

Narrative network of memories and experience processing

Disruption of experience processing is a problem at the crossroads of psychological and physical processes. The practice of daily spiritual self-defense shows how important it is to talk. The most important player in the social network providing spiritual support is the confidant with whom deep secrets can be shared. Purification rituals were used to relieve the inner spiritual load, an important part of which is conscientious introspection for internal analysis. In introspection, an internal verbal analysis of the contents of consciousness – or even confession – takes place, where the verbal burden is dissolved by absolution. Verbalization is an important element of alleviating of the traumatic content of experience.

Dynamic psychiatry assumes that the mechanism of repression is one of the causes of the development of diseases. The pattern of experience and information that has been transformed from the conscious to the unconscious, framed by a common neural structure, can already appear in a physical shape as a symptom, as a specific organ language. More and more neural network centers are identified along the information path between the social environment and stress response, they convey status threats, social assessment threats (SET) and social submissiveness to the immune network. This is the lateral prefrontal cortex (LPFC) that is responsible for assessing the social context, which is responsible for adaptive behavior management in a network connected to the intraparietal sulcus, hippocampus and VMPFC areas, and as part of the "aversive strengthening network", LPFC affects stress pathways through the amygdala, hypothalamus and periaqueductal gray matter.

But it is also important to bring to the surface repressed, unconscious traumatic content, and the psychoimmunological significance of this lies in the

exploration and communication of traumatizing life events trapped in the unconscious and in the sharing of the associated feelings and experiences.

The sharing of traumas in a written form, called expressive writing, can have a positive effect on both immune processes and disease symptoms (e.g. rheumatoid arthritis) as well as can result in a higher antibody response, as demonstrated by Petrie et al. (1995) following hepatitis B vaccination in medical students. The lack of awareness or disclosure of traumas, and the awareness of emotions are a complex phenomenon. Rejection, repression, dissociation, alexithymia, and the isolation of feelings are not equal in weight or significance: some are state-like, others are trait-like organizations of cognizance, emotions and behaviors. Pennebaker's experimental paradigm is based on the trauma disclosure deals with re-publication of deep thoughts and feelings about traumatic experiences. This kind of direct exposure to traumatic experiences has health benefits, but not in all patient groups.

Individuals with repressor adjustments are characterized by low levels of expression of negative emotions, while increased negative expression of negative sensations is characterized by neuroticism, and therefore the therapeutic effect is weakened. Similarly, not much therapeutic advantage comes from talking to post-traumatic stress patients, according to Gidron et al. (1996).

Pennebaker et al. (1988) conducted an experiment to examine the subsequent immunological and health consequences of the written recall of traumatic life events in undergraduate students. Prior to the 4-day study, immediately after and 6 weeks later, proliferative T cell responses to PHA and ConA mitogens were studied. Students who experienced traumatic events, as expressed in their written work, showed a greater change in the proliferation of T cells for mitogen than those who wrote about a neutral event. Those students who had done trauma disclosure work contacted their doctors less often later with issues related to having caught a cold. In people who had previously refused to process traumatic events verbally but were effective in writing, the change was quite significant.

Christensen et al. (1996) studied the effect of oral trauma disclosure on NK cells. The research confirmed their hypothesis that the stress accompanying the oral processing of traumas causes a significantly higher NK increase among those found to be hostile-minded on the Cook-Medley Hostility Scale compared to the non-hostile control group. In addition to an increase in short-term NK cell activity, the role of an increase in the sympathetic nervous system's adrenal activity and the effect of acute standby are likely. This phenomenon can therefore be explained by the immune-stimulant role of short-term stress, but it can also be explained by physiological changes resulting from the cessation of the suppression of stressful thoughts. At the same time, trauma detection can also involve risks. Geck et al. (1997) researched the immunological effect of exploratory psychotherapy in HIV positive patients suffering from depression due to the loss of a close relative. In patients undergoing suggestive

therapy, mood impairment followed a half-hour conversation, and this also triggered a decrease in CD4 cells, while people who reported a traumatic experience reported positive mood swings in addition to a higher number of CD cells. In the longer term, however, the group receiving the suggestive therapy also showed an increase in mood, but trauma detection among depressed HIV patients may reduce immune processes, according to Geck's (1997) study.

Interpretative person in the grip of internal and external networks

Psychosocial stressors and the demanding challenges of the environment become a sharpened threat through the mechanisms of perception and evaluation. This hazard-in-the-art interpretive work is carried out by cognitive neural networks and cognitive network structures. We know more about the responsible centers, we know which centers show a change in post-traumatic stress syndrome and which centers are responsible for mentalization processes, which neural structures detect humiliating signs of power coming from the social rankings and dominance that create painful submissiveness. We understand the neurophysiological contrast between control and loss of control, the role of learned helplessness and depression in somatic consequences. We are familiar with the networking of social behavior (SBN) organizing neural centers, the connections between the neural networks organizing aversive behavior and the stress mechanism of the HPA axis.

One of the targets, the central "node" or "hub" of these networks can be the transformation, reframing or overwriting of cognitive evaluation processes. That is why we see that a significant number of PNI therapies used for the most serious diseases, e.g., cancers, are cognitive and behavioral in nature, and we also see the use of this treatment in allergic diseases and in the treatment of asthma. This can be considered a central element of stress management.

Rational cognitive therapy is also of great importance. One of the key elements of the patients' anxiety is the awareness of the disease, the deterioration of their situation, and the burden of the notion of intractableness. These cognitive-emotional burdens might be alleviated by the motives of the reassessment of the situation, the reevaluation pathological cognitions associated with the situation, and the reconsiderations of automatic thoughts reflecting extremes. The psychophysiological gains of this have already been indicated in the context of the reassessment of distress and its evaluation as a survival facilitating challenge.

During cognitive therapy, the risk situation that has been evaluated as threatening becomes analyzable and manageable. This is already an in-depth therapeutic achievement, as the situation assigned to the inertia experience

and depressive psychoimmunological influence, to the depletion of the hypothalamic NA, the prolonged cortisol secretion enhancement, and to the immune-depressive effects mediated by central opioid noradrenergic can be reduced.

According to Antoni and colleagues (2002), the blending of cognitive behavioral therapy and relaxation/stress management resulted in an increase in naïve CD4+ T cells among HIV-positive subjects. Psychoimmunological risk states are connected with developmental patterns, early maladaptive schemas, which are self-defeating emotional and cognitive patterns established from childhood and repeated throughout life. The distorted attachment and adverse childhood experiences lead to emotional memories of past hurt, tragedy, fear, abuse, neglect, unmet safety needs, abandonment generating such pathological schemas. Early maladaptive schemas can also include bodily sensations associated with such emotional memories. Maladaptive schemas are typologized by metaphoric names, like in the case of games of transaction analysis. Such types of schemas are the *Vulnerable Child, the Angry Child, the Impulsive Child, the Detached Protector, the Punitive Parent, the Healthy Adult.* The theoretical connections with psychoanalysis, attachment theory, and psychoanalytic object relations theory are based on the integrative feature of this psychotherapy, including combination of cognitive behavioral therapy, transpersonal therapy, and Gestalt therapy, too. If we list the maladaptive schemas based on Young, Klosko & Weishaar (2003), we can divide them into five groups:

Table 20. Psychoimmunologically relevant dimensions of schema therapy

Disconnection/ Rejection	**Impaired Autonomy and/ or Performance**	**Impaired Limits**	**Other-Directedness**	**Over-vigilance/ Inhibition**
Abandonment/ Instability	*Dependence/ Incompetence*	*Entitlement/ Grandiosity*	*Subjugation*	*Negativity/ Pessimism*
Mistrust/ Abuse	*Vulnerability to Harm or Illness*	*Insufficient Self-Control*	*Self-Sacrifice*	*Emotional Inhibition*
Social isolation/ Alienation	*Enmeshment/ Undeveloped Self*	*Insufficient Self-Discipline*	*Approval-Seeking/ Recognition-Seeking*	*Unrelenting Standards/ Hypercriticalness*
Defectiveness/ Shame	*Failure*			*Punitiveness*

The bold items show that the maladaptive schemas might overlap with psychoimmunological risk personality patterns, states and dispositions. Schema therapy aims to influence these patterns using "limited reparenting" through the use of the therapeutic relationship and follows the change of schemas via

the *schema diary* recording the patient's progress in relation to all the theoretical concepts in schema therapy.

The advantage of humor coping is that humor wards off the immunosuppressive effects of daily stressors on saliva IgA levels, according to Martin and Dobbin (1988). Laughter increases spontaneous lymphocyte blastogenesis and the activity of NK cells, which is explained by decreased cortisol, adrenaline, and dopamine catabolites (DOPAC) levels and the ensuing decreased immunosuppressive effects, according to Berk (1989). Berk et al. (2001) found even wider positive outcome of mirthful laughter on such immune-parameteres, as elonged elevation immunoglobulins, activation of uncommitted, helper and cytotoxic cells, B cells, elevation of helper/suppressor ratio, and gamma-interferon level.

Serenity and laughter not only lead to a decrease in cortisol levels, but also increase beta-endorphin levels and have a beneficial effect on NK cell activity. Because humorous videos and laughing shows have a stress-relieving effect and increase NK activity, the authors consider laughter a useful cognitive-behavioral therapy technique. At the same time, depression and hostility reduce the immune activity-enhancing effects of laughter according to Takahashi et al. (2001). Bennett (1997, 2003) found higher NK cell activity in people who often laughed.

A very important cognitive therapeutic element of psycho-oncological treatment is that the patient should not see cancer as an insurmountable, incurable disease, the treatment of which further impairs one's quality of life, but should see it as a disease that is possible to overcome and in which, in addition to therapy, the main ally is the natural immune protection of the body that can once again be effective.

We need to look at the benefits of this patient condition. This interprets the disease from the psychosocial ecological point of view discussed earlier. In this way, there is a chance to remove the obstacles arising from that very personality disposition which paves the way for the return of the pattern of experience leading to the previous disease and which can be a hindrance to healing at the beginning. This, of course, also functions as a mirror of repressed needs, so such practices also yield existential and self-knowledge related gains.

At the same time, Rogers' therapeutic condition must be met. The warm atmosphere of unconditional acceptance and the empathy-based communication help the patient to find safety in the doctor–patient relationship. The safety experience of "clinging or attachment" creates a unique "neurohumoral climate" for therapeutic change. The psychobiological turn of hope, the creation of a positive setting, the regaining of the experience of control over the disease can be considered a key event of psychoimmunological treatment.

Relaxation methods, biofeedback, imaginative methods

Relaxation and biofeedback are both classic networking therapies that connect and reframe networks generating psychosomatic symptom through motor instructions and sensory detection. As cognitively qualifying, emotional and hard-to-access unconscious patterns become available "from the bottom up" in this treatment, psychosocial networks and neuroendocrine immune networks also become available.

Peavey et al. (1985) normalized low phagocytosis with 10-12 sessions of biofeedback/relaxation treatment in a group with increased stress and low phagocytosis. Kiecolt-Glaser et al. (1985) significantly increased NK cell activity during a 12-session relaxation treatment in 45 elderly people. Jasnoski and Kugler (1987) raised the IgA level of saliva of 30 undergraduate students by way of making them relaxed and imaginative. Gruber et al. (1988) used a six-month relaxation/imagining technique to increase the proliferation response to mitogen, NK cell activity, and IL-2 levels. Hall and Kvarnes (1991) were able to increase the number of circulating lymphocytes and metastasize thymosin levels in prostate cancer patients through relaxation and controlled imagining.

The effectiveness of relaxation can be shown even in the elderly, as studied in Kiecolt-Glaser et al. (1985) as relaxation treatment significantly reduced distress and increased the T cell response to PHA mitogen.

Relaxation itself has a beneficial effect. By optimizing the vegetative tone, reducing arousal and reducing stress, relaxation achieves a more favorable homeostatic balance, with the mediator creating optimal conditions for immune cell function. Jacobson's progressive relaxation, or autogenous training is recommended. This training can be continued by the patient at home with the help of a tape recorder. Simonton's practice of guided imagining in an altered state of consciousness can be added to the available toolbox.

The methods used and analyzed by Hall, Simonton or Rossi are understood to provide an interventional interface at the level of the internal body-image organized in the right hemisphere. A guided body representational image experience, known in hypnosis practice as inner visceral vision, is an interventional option created in the detour of a changed state of consciousness, where patients also experience being in control of their bodies.

The traumatizing event, which also functions as the trigger for a hidden learning process on the basis of a sense of helplessness, also requires this learning process be reversed.

Donaldson (2000) for example, treated patients suffering cancer, AIDS, and infectious diseases with mental imagery and achieved an enduring increase of white blood cell counts after a short, transient decrease. Visualization and guided imagery over approximately 90 days led to a significant increase in white blood cell count. Kiecolt-Glaser et al. (2001) combined hypnosis and

relaxation, and among the stress-exposed groups, hypnotherapy prevented stress-related CD3+, CD4+ proliferation reduction in study subjects and compensated for IL-1 secretion decreases in white blood cells.

Rossi, who combined psychobiological research and Milton H. Erickson's hypnosis theory and practice, sees the solution to the problem as a pattern of psychobiological behavior encoded in state-dependent memory and patients' reorganization of pathological processes.

Meditation, progressive relaxation, hypnosis, and guided imagining techniques are capable of producing anti-inflammatory effects. These methods significantly reduce TNF-alpha, IL-2 and gamma interferon levels. Similarly, through these methods the inflammatory response to a number of allergens, antigens as well as the inflammatory response to histamine and capsaicin are reduced.

Meditation practice also has an acute and chronic effect on the autonomic nervous system, resulting in reduced activation, increased skin resistance and a decreased heart rate. A meta-analysis of nearly 31 TM (transcendental meditation) exercises demonstrated a decrease in vegetative response skills, activation, faster habituation, as well as lower systolic and diastolic blood pressure. Since the influence of chronic stress is partly mediated by prolonged activation of the sympathetic nervous system, meditation and relaxation exercises can have a beneficial PNI effect even through reducing sympathetic tone and accelerating habituation.

Hypnotherapy

Since Rossi (1986) believes that the disease is essentially a state-dependent pattern of information or behavior, it is assumed to be possible to mobilize the patient's own potential for change by reconfiguring his/her emotional dynamics. This happens through the state-dependent information pattern, which can affect both the hormonal and immune systems, and can reorganize, break the block, bring it to the surface, and verbalize it. All these reverberation circuits, neural network patterns have both psychosocial and neuroimmunological network consequences. Hypnosis in this sense is the conversion of inaccessible, isolated networks into accessible networks, the multi-directional gain of which is a change in emotional tone and mood position that affects the symptom and heuristic reassessment of the patient's situation.

Erickson's view is that the symptom is a signal from the unconscious signaling that the natural growth of part of the personality is hindered and that a creative solution is needed. Developed by Erickson and Rossi, indirect hypnosis therapy allows the patient to reorganize state-dependent memory and psychosomatic patterns of behavior with the help of the therapist.

The task of the exploratory work of psychotherapy may be to bring to the surface a traumatizing event embedded in the right hemisphere, and formations of experience information. Such dissociated, repressed memory islands can be detected in hypnosis using a regressive technique. Early traumas – despite their apparent isolation as a result of state-dependent learning – can even be triggered by a seemingly innocent call sign, which may trigger pathological psychophysiological reactions, which may also play a role in hidden psychoimmunological learning processes.

In an altered state of consciousness, all this can be made available to the patient in a reorganized way. In this case, the therapist can use the symptom as a calling key to recall the state-dependent memory in order to get to the abnormally entrenched pattern and behavior and to allow the patient to reorganize the traumatic pattern. The sense of control over healing is in the patient, the healer might stimulate this. This therapy also bridges the barrier expressed by the alexithymia, the hypothetical communication gap between the two hemispheres. At the same time, we must face the risks of this method of intervention, because we can either deepen or trigger the process. Unfortunately, there is little data in literature to rely on to speak about the unfavorable experiences the risks of hypnotic intervention might have produced. Caution with regard to this experimental treatment is therefore necessary.

Kiecolt-Glaser et al. (2011) studied the role of hypnosis and relaxation treatment in immunosuppression in stress-free periods and when under acute stress caused by severe exam loads among 33 medical students. The researchers found that hypnosis reduced the suppressive effect on the T cell proliferation response to mitogen, of CD3+ and CD4+ T cells and IL-1 production levels of randomly selected medical students. There was an increase in the proportion of CD3+ and CD4+ cells proportional to the number of relaxation treatments. Trakhtenberg (2008) weighed the effects of directed imagery (GI) and revealed its stress-relieving role in the immune system, with cell-specific imagining affecting white blood cells and lymphocytes. In the initial period, a decrease in white cell count is observed, and the sticking of white blood cells also occurs earlier. Another psychoimmunological effect of hypnosis has been shown by Hall et al. (1981), who increased T and B cell immunity with hypnosis.

Gruzelier (2002) summarized the effects of relaxation, self-hypnosis and guided imagination on basic immune indicators. Hypnosis is able to cushion the negative effect of exams on the immune system, and studies on guided imagining have also demonstrated hypnosis' specific effect on a particular immune cell. In the imagining group, an increased immune response was observed and fewer viral infections were observed during the study period. In a third study, Gruzelier and his research team of HSV2 carrier subjects experienced 50% reduction in herpes recurrence, decreased anxiety and depression,

improved mood, and increased antiviral NK cell activity following six weeks of hypnosis treatment.

Rossi (1986) links the mode of action of therapeutic hypnosis to the neuropeptide system and thus evaluates the neuropeptide system as a common element of hypnotherapy and psychoimmunological processes. The flexibility provided by the neuropeptide network can be the basis for the development of psychosomatic phenomena organized through patterns of traumatic experiences encoded as state-dependent memory traces. Neuropeptide effects are also indicated by a persistent, smeared hypnotic effect other than the prompt effect of neurotransmitters. We know the role of endorphins in situations of learned helplessness and in unavoidable and uncontrollable stress. Therefore, if neuropeptides play an important role in situational rating, and if behavior and psychosomatic adaptation and their effects are decisive in modulation of immune processes, then hypnosis can help to organize situations through the modification of pathological neuropeptide patterns, just as using cognitive therapy (development of coping skills, restoration of individual control, treatment of threatening distress as a challenge, etc.). This way, complex therapy might reorganize the pathologically entrenched psychophysiological patterns.

Lifestyle medicine and behavioral therapy

In addition to cognitive and emotional psychoimmunological risk factors, behavioral and lifestyle factors also play a role in the immunological consequences of stress situations. Insufficient amounts of exercise, disturbed sleep patterns, obesity, smoking and drug-taking behavior can all contribute to changes in immune status, to the increased production of proinflammatory cytokines, and the ensuing depression also leads to an unfavorable psychoimmunological pattern.

In the therapeutic solution of distorted coping methods, it is very important to review addictions such as smoking, alcoholism, narcomania in the given lifestyle framework. In this case, a complex psychotherapeutic behavioral therapy treatment of addictions is recommended.

Lifestyle medicine is a typical and long-term interdisciplinary field of networked medical approach and practice. It is networked because it relies on evidence-based research on bio-psycho-social networks, and the examined levels offer attack points for intervention on several levels.

The links between different biomedical phenomena and lifestyle, quality of life, personality patterns and behavioral data often clarify circular and networked relationships on the basis of new research data on public health and behavioral science. The (already mentioned) "five commandments" of lifestyle medicine are the following: no smoking, up to one ounce of red wine per day,

fruit and vegetable consumption five times a day, 150 minutes of dynamic exercise per week, sports and a BMI under 25. After all, obesity and cardiovascular inflammation, depression and its immunological consequences are associated with the endocrine functions of adipose tissue in the PNI network, and this is also the case with the active musculoskeletal system that produces myokines and also affects nervous system functions. Lifestyle interventions limiting the use of chemical comforters as distorted coping also affect optimal immune function. Eating vegetables and fruit five times a day also helps to ensure optimal immune function through trace elements. Since mere information does not change entrenched behaviors and as in certain cases health propaganda can make people indifferent and, as the undoubted failure of health promotion in the USA shows, personal pathways to behavioral change must be taken. Two health sociological studies compared health behavior data from 1988–1994 to 2001–2006: King and et al. (2009) found that obesity increased from 28% to 36% (over 30), physical activity decreased from 53% to 43%, five times daily fruit and vegetable consumption decreased from 42% to 26%, and follow-up behavior to five health practices decreased from 15.8% to 8.2%. These data make one wonder why, despite strong anti-smoking measures and propaganda, smoking rates have not changed significantly (from 26.9% only to 26.1%), and why moderate alcohol consumption has increased from 40% to 51%. All this indicates that simple health education is not enough in itself. Psychosocial processes, characteristics and behavioral modification tools related to lifestyle medicine and health behavior make patient education, patient management and lifestyle advice important and also make the use of behavioral therapy elements understandable. Influencing coping skills, coping characteristics, therapeutically affecting patients' mood and improving the quality of social support are all important therapeutic tools. These efforts have now become part of the standard of care provision for chronic immune-pathology and cancer patients. A particular shift in emphasis is shown by the appearance of movement therapy and the fact that lifestyle medicine has taken to the fore.

Exercise is also one of the effective stress-relieving options. This effect can be measured even in terms of applying medication. For example, in depression, exercise and physical exercises have a similar effect to Zoloft. Exercise regulates the inflammatory system. This effect itself initially occurs as a physical stressor and raises the alpha levels of IL-6 and TNF, and the increase in IL-6 has a non-proinflammatory effect. On the contrary, high levels of cytokines mobilize anti-inflammatory mechanisms. Prolonged exercise reduces inflammation in people with otherwise persistently high levels of inflammatory cytokines. This is also true for the so-called *inflammaging*, a mild inflammatory disease in the elderly caused by the presence of higher cytokines.

Starkweather (2007) conducted a 10-week study with subjects between the ages of 60 and 90, which included 30-minute walks five days a week up to 60%

of the maximum cardio load of the subjects. The results were compared to those of the 10 older adults who were not engaging in regular physical activity. Individuals exposed to physical activity reported significantly lower stress, a better mood and a better quality of life. Their physical performance and mental freshness also proved to be better, the most important thing in psychoimmunological terms was that they showed a significant decrease in IL-6 levels.

Kohut et al. (2006) used an 80% cardio load three times a week for 10 months in a group of 83 people aged between 64 and 87. The health effects of exercise were clearly positive: depression decreased, optimism increased, flexibility and coherence improved. Cardio exercises reduced CRP, IL-6, IL-18 levels and improved alpha levels of TNF. All this was independent of depression, optimism and a sense of coherence. This also had a positive effect on wound healing. Hamer and Steptoe (2007) studied the effects of mental stress on 207 people. Those who were out of training (physically unfit) showed higher systolic blood pressure and lower fitness, and higher systolic blood pressure was associated with higher IL-6 levels and an alpha TNF response to stress.

The TNFalfa response induced by stress was five times higher among the untrained persons compared to the physically fit individuals, who produced a lower inflammatory response to stress. Gradation was important in the training program, training with a high heart rate increase can even cause post-traumatic stress, and gradation helps to adapt both physically and psychologically. However, these therapies are often part of a common, complex therapeutic regime, so the clinical experience gained with them and the results of analyses of their use are reported separately.

The relationship between stress and respiratory infections is known in a number of summary reports: Miller and Cohen (2001) performed a meta-analysis of 9 psychological, immune-effect therapeutic interventions. The evaluated studies were made up of observations in adult subjects and included observations of infections in chronic patients, upper respiratory tract infections, exam stress, high levels of hypnotic suggestiveness, and hypnosis therapeutic experience. Psychotherapeutic interventions included stress management (16%), relaxation (26%), trauma detection (10%), hypnosis with immunosuggestions (31%), hypnosis with immunosuggestions versus sheer relaxation (7%), and conditioning (10%). Surprisingly, improvements were most likely to be seen in relaxation and hypnosis, and mainly in sIgA levels. In the case of trauma detection, an increase in the EBV titre was mentioned, while in the conventional trials the NKCC indicator was mentioned as a significant effect.

Since stress, emotional state, and many health psychological characteristics also affect the dynamics of cancer development and progression, cognitive-behavior therapy and stress management also play a major role in psycho-oncological treatment. In addition to the role of cognitive-behavioral therapy at the cancer biology level, cognitive-behavioral therapy can also have an effect on

the role of improving the doctor–patient relationship, treating stress, depression and social support. Improved immune response, slowing down the metastasis process, angiogenesis, tumor cell migration and tumor invasion may also be affected by the immune factors that vary from psychotherapy as stated by Lutgendorf et al. (2010).

Spiegel and his colleagues (1992) observed an 18-month survival in patients who did not receive psychotherapy as opposed to the 36-month survival of the expressive-suggestive group therapy used during the research. An increase in lymphocyte proliferation was observed in breast cancer patients as part of a monthly intensive intervention program according to Andersen et al. (2004). In the same follow-up study, Andersen et al. (2004) examined a group of tumor patients who were first given weekly training and then the training was accompanied by monthly therapy. The training included developing positive coping and problem-solving skills, the provision of social support, the improvement of health and learning relaxation techniques, and also paying attention to compliance-enhancing patient training. According to the 11-year follow-up study, in which 114 out of 227 breast tumor subjects were treated, the first intermediate results indicated that there had been a positive difference to control in terms of both mortality and tumor recurrence. This may be due to neuroendocrine immune factors already known.

Psychosocial intervention regularly includes relaxation therapy, which was also carried out among cancer patients as described by Schedlowski et al. (1994) and Larson et al. (2000). Such comprehensive intervention contributed to a decrease in anxiety, an improvement in mood, and a decrease in cortisol levels, an increase in lymphocyte proliferation, and a shift in TH1 cytokine production (IL-2, IFN-gamma) according to Carlson et al. (2007), McGregor et al. (2004), and Antoni et al. (2009). This is important because TH1 cytokines are immune mediators that enhance cellular immunity against tumors. As part of cognitive-behavioral stress management training (CBSM), Antoni et al. (2009) examined 300 women with breast cancer over the course of a year. Even the first post-intervention measurements showed reduced cortisol levels in female breast cancer patients. Phillips et al. (2008) observed the highest cortisol level change among the most intense psychological change indicators and therapies in those with the greatest commitment to relaxation. This is important because higher cortisol values measured among confirmed breast cancer patients correlate with poorer survival, according to Sephton et al. (2000).

Due to the serious and chronically distressing nature of the disease, the behavioral oncology approach to cancer has now gained civil rights in biomedicine due to the evidence-based psychoimmunological data already presented. Between 2001 and 2012, 24 malignant cancer treatments were examined by Subnis et al. (2014). Most of the studies looked at patients with early breast cancer and included two main therapeutic directions: cognitive-behavioral

therapy and complementary medicine. From the point of view of the indicators of PNI (cytokines, etc.), cognitive behavioral therapy appears to be the most effective in cancer patients, but in other psychoimmunologically understood pathologies, many forms of psychosocial interventions may be relevant.

In fact, for PNI, the studies that examine the relevant neuroimmunological processes in an evidence-based way can be understood. Only 26 out of 291 studies during the study period met the strictest evidence-based criteria in Subnis' meta-analysis. 75% of the studies involved breast cancer, the majority of which involved patients with early cancer and almost a quarter of patients with Stage 3 advanced cancer. Prostate cancer patients were also included in the studies, most of which also involved early-stage patients; only one study dealt with late-stage "surviving" prostate cancer patients. In addition, only 8% of the studies dealt with other tumors (cervical cancer, lungs, colorectal). Nearly two-thirds of the therapies studied referred to cognitive-behavioral therapy, while a third were related to complementary medicine. Complementary therapy includes yoga, meditation, Chi-Kung exercises, wellness-based stress reduction and massage. In the research, yoga included breathing exercises (hatha yoga elements), asanas, meditation and imagery exercises. Complementary therapies included massage and slow-motion exercises, and Chi Kung gymnastics with its specific postures, visualization and meditation elements. Although not mentioned in the study, Tai Chi is also such a movement therapy element, which can impact PNI parameters in a favorable way.

Massage therapy is often completed with reflex therapy acupressure treatment. The alternative treatment with a spiritual approach to the body–soul–spirit balance was added to the spiritual practice of forgiveness in addition to yoga and meditation. Half of the therapies studied by Subnis were carried out by clinical psychologists, 3 therapies were led by nurses, 2 therapies were led by physicians; suggestive therapy was carried out by group therapists, social workers, art therapists and imaginative therapy specialists. Leaders of massage therapists, yoga and Chi-Kung exercises with experience in alternative therapy took part. The duration of the therapeutic processes took an average of 10 hours, but there were some therapies that were limited to one-and-a-half hours of trauma-finding and expressive writing. In addition, the authors also analyzed cognitive behavioral therapy practice consisting of 18 sessions, each lasting 30 minutes.

A third of the studies looked at psychological, neuroendocrine and immune indicators together, but at least one marker was tracked for each. Depression, negative mood, distress and anxiety, as well as quality of life, coping modes, and specific psychosocial skills were all subjects of measurements. In a third of the studies, the effect of therapy affected the cytotoxicity of NK cells, with two-thirds of the studies dealing with cytokine levels. More than half of the cognitive-behavioral therapy studies showed appreciable and significant

neuroendocrine-immune changes, such as an increase in gamma interferon levels or a T lymphocyte proliferation response to anti CD3. The authors pointed out that, although it is not possible to draw a consistent conclusion on the effectiveness of therapy based on the data examined, even a three-hour psychotherapeutic encounter (first conversation) could trigger a significant change in immune indicators. In 10 randomized clinical trials, i.e., more than a third of the cases, significant immunological differences (e.g. an increase in NK cell activity) were demonstrated by the authors, but only two studies showed significant changes in cell count. McGregor and Antoni (2009) came to a similar conclusion concerning cognitive-behavioral therapy interventions, emphasizing their effect on neuroendocrine immune indicators.

If we want to summarize the possibilities of psychoimmunological intervention, the interventions can be divided into the following groups:

a) cognitive-behavioral therapy stress management methods,
b) relaxation methods, biofeedback, imagery methods,
c) hypnosis,
d) supportive, expressive and trauma-finding methods,
e) massage and exercise,
f) immune conditioning.

Stress-relieving cognitive-behavioral therapy in psychoimmunology is a form of psychotherapeutic treatment that results in improved immune competence. This may be remediation of immunodepressive conditions (depression, learned helplessness) and, in the longer term, treatment to modify the risk personality (type C), repressive coping mode, therapy to restore personal efficacy and control. Behavioral therapy support helps to cope with the disease, to manage the new existential situation and disease awareness, and to improve quality of life. But psychotherapeutic support can be important to achieve proper compliance/adherence in relation to the treatment staff, doctors, nurses, physiotherapists, etc. and even to the often impersonal healing institution itself. This important help involves a number of gains in chronic diseases, which might also manifest in the decrease of symptoms, the slowing down of the progression of the disease and increased survival time. Psychoimmunological gains are also multi-layered, affecting the dynamics of stress processes, reorganizing the system of social support and change the transactive dynamics influencing it. Psychoimmunological interventions might modify risk personality traits and behaviors, transforming negative emotional factors, low self-esteem, shame, repressive coping, feeling helpless, pessimism, etc. into a positive emotional state, reinforcing a favorable pattern of serenity, hope, active coping, learned personal efficiency, coherence.

Eliminating the feeling of insufficiency and involving the patient in treatment can already be an effective help. The spirit of coping with the disease and the feeling of internal control also increase immune protection and the survival of cancer patients treated with guided imagery. The cognitive and cathartic techniques of psychotherapy might enhance active coping, the control experience, but instead of real control, even perceived control can be a protective factor according to Sieber et al. (1992). Increasing personal efficiency, changing negative thoughts, and reducing stress sensitivity can have a beneficial PNI effect. Studies in HIV patients have shown that positive immune changes continued even after 6-12 months as a result of cognitive behavioral stress therapy, according to Antoni (2000).

Of course, social support in a therapeutic baseline can also be an intermediary factor, because the sense of social support reduces the level of stress hormones (cortisol, catecholamines) according to Seeman et al. (1994). Positive expectations and hope might be also important factors. Positive exposure can be the main element of therapy, because in guided imagery or other forms of hypnosis the patients' expectations are also influenced. One can ventilate feelings of stress or imagine the processes of a more effective immune system under hypnotic suggestions. But cancer patients' ideas mightalso be modified in cognitive-behavioral therapy, when the therapist focuses on the possibility of effectively coping with the life-threatening disease by cognitively reorganizing negative perceptions and by building positive perceptions.

In the treatment of HIV/AIDS patients, cognitive/behavioral therapy, cognitive reassessment of stress from disease, of life situation and of stigmatization, building a new coping strategy, psychotherapeutic patient management and training, treatment of distress and depressive symptoms have a proven effect on slowing down the progression of HIV disease. Psychological changes are closely followed by neuroendocrine and immune changes, as indicated by immune and viral biomarkers reflecting disease progression, as shown in the research by Carrico and Antoni (2008). In HIV/AIDS patients, cognitive behavioral therapy and stress management reduce anxiety and improve depressive mood disorder, enhance acceptance and increase perceived social support. Similarly, by reducing distress, a decrease in NA and cortisol secretion can clearly be tracked by way of measuring urine remnants. As a result of effective therapy, even a period of 10 weeks of therapy improves the immune system of HIV/AIDs patients and increases the number of cytotoxic T cells. This is also manifested in the growth and control of the antibody titer against herpes virus (HPV). This effect persists even after 12 months as shown in Antoni's (2012) study. The treatment also reduces the HIV viral load and slows down disease progression as a result of declining depression. According to Antoni (2012), there is a correlation between lab and clinical outcomes as well as the degree, intensity and length of the therapy applied.

Network medicine's contribution to PNI

Research into genetic polymorphisms, exploring the relationship between genetic and phenotypic patterns through transcriptomal data, i.e., through the so-called "edgetics" analysis, the network analysis of genomic, proteomic, metabolomic, secretomic and microbiome data as well as the contextualization of the encompassing "network of networks", requires a further turn in research. Such an integrative interpretation is offered by the "social transduction" theory of depression and the preserved transcription response to looming environmental challenges (CTRA), in which even the presumption of unresolved stressors triggers a proinflammatory transcriptive deviation.

The networked structure of the pattern indicates that the threat of changes in social networks (loss of status, ostracization, humiliating exam situation) causes a molecular pattern change detected at the pre-transcription genetic level. Such results are seen in the bio-psycho social context of allele shifts permitted by genetic polymorphisms, and social epigenomics also provides such a layered network for interpretations.

Network medicine of sickness behavior

The principle of "medicus curat, natura sanat" is in fact a key idea in the contact between medical wisdom and freedom of action. The freedom of treatment can be understood from actions interpreted in the Hegelian sense, when laws determine the range of freedom based on the presumption of integrity of the bio-psycho-social networks concerned.

Even the basic situation is contradictory, since the layman calls the disease itself fever, somnolence, depressed mood, even though it is already part of the networked self-medication of the body, in which transcriptomic shifting, the start of cytokine production and immuno-neural changes jointly act.

As a result of peripheral infection, cells of innate immunity are activated, and through IL-1alfa, IL-6, TNF alpha cytokines, our brain learns everything, because cytokines from the bloodstream reach the target genomes, passing through the circumventricular organ of the brain. They directly reach the microglia and astrocyte cells, which play a large role because peripheral cytokines are short-lived and have difficulty getting into the cerebral parenchyma anyway. Proinflammatory cytokines of the immune system reaching the target regions of the brain produce a coordinated physiological and behavioral response, and symptoms of disease behavior, which includes fever, slow-wave sleep, social retraction, decreased appetite, reduced levels of accessible plasma iron, and increased levels of acute phase proteins. In fact, this is nothing less

than the occasional strategic shift of the individual, the reorganization of priorities. It is, in fact, a change of scale. The opponent is no longer time, it is not the task, it is not the competitor, and it is not the predator: the opponent is microscopic, yet it is a more threatening and primordial opponent against which a cell-to-cell manner of fight is required. But it is the body's physiological strategy that determines success. Like cytokines, this molecular-scale signal reaches the brain, then microglia, astrocytes, and perivascular macrophages transmit and "turn on" the evolutionarily entrenched physiological syndrome and behavioral response called disease behavior. Molecular, cellular and organ and organizational text layers form what is happening. This is the co-functioning of network layers, where the struggle of cells is more ancient than our (main) mammalian behavior and the technological drug-using forms of our adaptation and the various institutional roles (often masking what our physiological heritage requires).

The evolutionary meaning of disease symptoms is obvious, but because of their inconvenience, we try to avert them. Even moderate fever (below 38 degrees Celsius) or iron deficiency in the lab can trigger drug-prescribing reflexes, the elimination of fever, and iron supplementation. Yet, these organizational reactions inhibit the reproduction of the pathogen and mobilize the body's resources for combat (glucocorticoids, acute phase proteins). Glucocorticoids are also considered suspicious, as they curb the immune response at so many attack points. But in an acute situation, they are often used to brake the body's overreaction and heightened energy consumption, which also offers negative feedback and dampens the further release and exaggerated mobilization of the innate immune system. The organization's networks have the structural wisdom of hundreds of millions of people of evolution: they have specific vital "tacit knowledge". Behavioral elements seem to indicate performance limitations, even though the process is embodied in this heroic performance in this other microscopic dimension called healing. Behavior takes the form of energy-boosting, withdrawn activity, inhibited motivation, anhedonia and even prolonged deep sleep, but this is not passivity, but a turn towards another field of combat including taking out paid sick leave, social welfare and enjoying care in a specific social-psychoimmunological "tradeoff" situation.

Looking further afield, disease self-control is hardly different from depression, and even in the inflammatory theory of depression, the chronic struggle with the pathogen itself is the picture of a mood disorder. What ruins a patient's life in the long run could be helpful in the short term.

But here personal energy loss is actually the redirection of energy to the cellular battlefield, which at the metabolic level is very energy-intensive. There is also a network benefit of a decrease in social interest, appetite, and libido: all this helps to avoid the spread of the pathogen, further infection, spread of

the disease in social networks. If all this is disrupted, it will finally be at the expense of both the individual and the community. All this is an evolutionarily evolved and preserved way of functioning, which responds to the bacterial challenge through its transient patterns. But if the activating effect of cytokines is prolonged, this internal struggle becomes a lost war, and then maladaptive disease behavior develops, accompanied by protracted lethargy, sleep disturbances, depression-like behaviors and experiences, cognitive disorders, according to Godbout and Johnson (2009).

Network approach and options for psychoimmunological treatment

The pathological core of psychoimmunology is neuroimmunological and/or immunoneural stress processes and tuned regulatory disorders in chronic or extreme or vulnerable situations. The shifting of the HPA axis might be a consequence of stress experiences resulting from early distress or perinatal infection, is entrenched by epigenetic mechanisms, or is the result of reduced glucocorticoid response or glucocorticoid insensitivity due to persistent stress loads. The consequence of this might be an overturning of homeostasis, pathogenic breakdown of coordinated processes, immune processes of inadequate intensity and/or direction and decreased response or chronic inflammation.

Concerning the network approach and the system approach, we need to understand that some physiological and genetic markers are associated with improved stress resilience, and we need to see that we have therapeutic or developmental tools to enhance resilience and immunity to stress. These may include systemic desensitization, which reduces panic, sensitivity to phobia-inducing effects, or hypersensitive response to allergens. Biofeedback, relaxation, schema therapy and other cognitive-behavioral therapy techniques help integrate emotionally overloaded and memory-filled internal associations. In this case, therapy helps the psychoimmune system to return to the positive attractor basin. For example, mindfulness training can help to sort allostatic parameters, which is reflected in elongated telomeres, the settling of immune functions, improvements in catecholamine or HRV indicators and the resolution of cortisol levels.

Sociosomatics of the Man-Environment-Organism (M-E-O) in a network theory framework

In the biopsychosocial disease model framework, evidence-based research confirms the importance of a multi-looped system of information pathways

and networks ranging from the dynamics of social existence through psychoneural networks to genomic processes. These new models have reshaped the pathological models of several widespread diseases (depression, cancer, and cardiovascular diseases). Such new network models are expressed by the *conserved transcriptional response to adversity* or the *social signal transduction* theory of depression. The influence of increased proinflammatory cytokines following stress processes induced by symbolic social emergencies also contributes to the development of mood disorders.

The physiological stress responsiveness also depends on developmental psychological processes and exhibits sociosomatic logic embodied in the psychobiological and epigenetic consequences of traumatic early mother–child relationship disorders and impaired secondary attachment systems. Central and peripheral attenuation of the hypothalamic-pituitary axis can cause cardiovascular, inflammatory gastrointestinal disorders and can also trigger psychoallergic and psycho-oncological processes. The sociosomatic network processes of M-E-O contain pathways of action in different directions. For example, the effects of acute and/or chronic disease burden, impaired performance and disability on working capacity, socioeconomic status, family life, and recreation are biosocial phenomena. All of this can present sociosomatic tasks to be solved by lifestyle medicine.

Poor patient management, psychiatric stigmatization, or an unfounded diagnosis of a fatal or incurable disease can worsen patients' socioeconomic status through impacting infosocial and infosomatic effects. The sociosomatic pathways of the network include health risks from deteriorating socioeconomic conditions (SES), workloads, impending unemployment, or long-term unemployment. Even impending unemployment can be a severe sociosomatic stressor, can cause an increase in blood pressure, and the decrease in NK cell activity it induces may reflect a place in the workplace status hierarchy. In the case of psychosocial pathways, the condition of burnout or phobic anxiety complaints can make one incapable of work and can increase social isolation. Along the sociopsychological trajectories, socioeconomic status, education, occupation, income have a combined effect on mental health and, due to consequences, they are associated with sociosomatic consequences and a lower average life expectancy. Low socioeconomic status and anomy are associated with an increased risk of depression and anxiety. Maternal stress, the loss of a parent, and low socioeconomic status increase the risk of developing post-traumatic stress disorder. The fate of migration is associated with an increased risk of psychological stress, an increased risk of suicide, and the development of psychotic disorders. The social dynamics of our daily lives, the unfavorable experiences of child abuse (ACE), attacks on our place in the social hierarchy, losses, situations of dominance, morbid family system dynamics, stress, hostility, lack of support for group dynamics in the workplace, threatening

unemployment saturate the sociosomatic relationships of the M-E-O system through profound physiological network events. In the following, we assess the world of sociosomatic phenomena from this point of view.

After a stressor effect, a given sociosomatic system may return flexibly to its original homeostatic dynamic equilibrium state, or the prolongation of the allostatic position may lead to another regulated, disordered "second" homeostasis, which may manifest in pre-traumatic stress disorder and post-traumatic stress disorder. Thus, from the point of view of systems biology, a given sociosomatic stressor shifts a dynamic, biopsychosocial system organized as a network of networks from one *phase space* to another, with the latter phase exhibiting a lower adaptive value and utility state. Phase space is a state of dynamic systems: a complete set of biopsychosocial networks, any element of which changes towards a given attractor. This can be called the "basin of attraction", where the stressor moves the system into a different, borderline attractor "field", or, alternatively, the stressor slows return to the optimal attractor. The dynamic system operating as a "network of networks" depends not only on the environmental perturbations that can be called stressors but also on the stress subject's sociocultural characteristics, personality, memories, coping patterns, physiological condition, and genetics.

Abnormalities observed following chronic stress (glucocorticoid receptor downregulation, decreased negative feedback, TH1/TH2 shift, elevated levels of proinflammatory cytokines, peripheral glucocorticoid abnormalities, loss of empathy, developmental psychological anomalies, burnout, and unemployment) present an increased risk of disease. In the depths of this relationship of impacts, we also find the social signal transduction theory of depression, which follows the psychosocial influence up to transcriptional changes in the cellular depth.

Social-psychoimmune networks offer a multi-directional point of development of health services. Psychoimmunological diagnostics can be integrated into occupational health services, the everyday job of GPs, while in hospitals clinical psychologists, physicians with a degree in psychotherapy can cooperate with other specialists. Although the education of psychoimmunology has been present in the training of undergraduate doctors and psychologists as an elective course for a long time, there are no specialized professional health service for PNI patients. This would require the introduction of vocational training with an exam licensing for this service, which, at the same time, would result in the expansion of the psychosomatic approach (Lázár, 2018). For the population at psychoimmunological risk, the occupational physician system can provide the widest and earliest access by integrating clinical psychological competencies (test psychology, psychophysiological screening practice, lifestyle counseling, cognitive-behavioral therapy, relaxation therapy). Social

psychoneuroimmunology also offers additional therapeutic tools for outpatient clinical practice, and the treatment of chronic stress, inflammatory processes and frequent comorbid depression also requires psychotherapeutic skills. For example, stress induces an increased proinflammatory cytokine load among those with autoimmune disease, which is partly due to downregulation of the peripheral glucocorticoid receptor in leukocytes and consequent attenuation of inhibitory effects, according to Miller et al. (2002). Thus, by preventing stress and reducing stress sensitivity through cognitive behavioral therapy, the upregulation of the cortisol receptor in leukocytes may be promoted, which offers more effective treatment. In addition, stress management interventions provide help to those with persistent psychological stress effects, as demonstrated by studies by Antoni et al. (1991), Goodkin (1998), and Lutgendorf (1997). Therefore, psychoimmunological therapy seeks to restore the homeostasis and allostatic optimum of neuroimmune processes and attempts to do so on several levels by offering a "network of networks" therapy.

An overview of the behavioral, pathophysiological and clinical aspects of sociosomatics confirms the legitimacy of a systems-based biopsychosocial approach for several diseases of great public health significance. Psychosocial networks and mappable life history patterns can be interpreted as sociosomatic risk factors. There are situations in which the networks come into contact: both in time and impact. Such a pattern of early mother–child relationship leads to personality development, as well as to social psychological, and even cultural consequences with respect to social networks, which may affect the later functioning of the stress axis, and may have epigenetic consequences. The broader and narrower social networks, the narrative web of the individual's unique, previous and current life history events, the perception and evaluation schemas related to the permanent features of the personality (hemispheric differences, type A or C personality pattern) – all affect the HPA axis and the physiological functioning related to stress. Severe losses also impact personal life by the neurophysiological networks that organize behavior and the regulatory circuits of the HPA axis. One such sociosomatic phenomenon may be the anticipation of an uncontrollable stressor effect that immediately manifests in changes at the transcriptomic level. However, "social signal transduction" pathways interpreted in this way may be activated by symbolic, anticipated, and imagined threats. These sensitive pathways may persist as a self-sustaining mechanism for months even after traumatic or perceived threats.

Social network images of social relationships, dominance versus submission, social support versus exclusion, loneliness, recognition of success versus being ignored refer to these existential extremes. In addition, post-traumatic syndromes, which feed on human conflicts and abuse, can also become specific disease-preceding conditions and risk situations. Thus, the social context can,

again and again, have a profound effect on the processes of neuroendocrine and immunological networks that are entrenched in the archaic depths of evolution, and their vulnerability and strength might be understood as our evolutionary heritage.

The *networked sociosomatic approach* is a new field of science with a wide range of interpretations that actually serves personalized medicine, as its focal point is always the special and unique patient understood in his or her particular environment.

ADDENDUM

Cultural Psychophysiology

Satellite symposium of the 5th International Congress of Psychophysiology (Szirák, Hungary, 1990)

General Secretary and Program Committee: P. Molnár, Zs. Kulcsár, I. Lázár

Abstracts

G. Bethlenfalvy, Zs. Kulcsár
Hungary
Eötvös Loránd University, Hungarian Academy of Sciences, Budapest

Buddhist meditation and the third unconscious

Both in the early and later Buddhist practice, described in the paper, meditation starts with the inhibition of the conscious brain. As a result, deeper insight and visionary experience appear. We propose that these experiences originate from a third layer of the unconscious, which, compared with the personal unconscious of Freud or the collective unconscious of Jung, is a much more complex psychic system. In developmental terms, it represents pre-human, animal capacities, in a psychophysiological context; it can be related to the archaic brain mechanism and at the human level to the right hemisphere.

G. Claridge
Great Britain
The University of Oxford, Department of Experimental Psychology

Literal creativity and psychosis in authors

Whether or not it is merely folklore belief that there is a universal connection between psychosis and creativity, there are undoubtedly many fields of art and science where famously creative people suffered from mental illness. It is argued

that examining the lives and works of such individuals can inform us about the nature of psychosis and at least some forms of creativity. To illustrate this theme, there will be presented the result of a recently completed, detailed study on ten authors living in the historical period from the Middle Ages to the 20th century, all of whom suffered from psychotic illness, evidence for which is documented in their writings.

O. Eisler
Hungary
National Institute for Nervous and Mental Diseases, Budapest

Self-esteem and vitality – toward an energetic model of the dysthymic disorders

Our extended depression model deals with somatic and mental fatigue, dysthymic disorders and aging as the more or less reversible decrease of the adaptive energic level, and sees affectivity as a vital energetical regulation system. The known biochemical, electrophysiological, neurological, chronobiological, and psycho-social "types" of depression describe the different levels of this regulation. Some data suggest the possibility of psychosomatic origin in brain diseases, particularly between cerebrovascular problems, epilepsies and dementias. In our opinion, in all – somatic and mental – disorders, it is obligatory to increase the level of vital energy. The intervention is possible at any level of regulation. In the human vital energetical regulation, self-esteem has a particular control function.

L. Földényi
Hungary
Eötvös Loránd University

The early death of romantic authors

If we go back to the turn of the 18th-19th century, it is surprising how many writers, poets and painters died at a relatively early age. If one tries to find out the cause of this, the first thing to reexamine is the meaning of Romanticism. It could not be considered as a purely artistic movement if so many representatives died of it. I believe that Romanticism tried to shake the very grounds of European civilization and was the first sign of the universal crisis we are now living in. Art is like the peak of an ice-mountain: the depth is surround-

ed not by artistic questions, but by existential ones. The Christian culture was not able to protect people against the fear of death anymore, i.e., against the idea of the purposelessness of life (long before Nietzsche, Hegel announced *the Death of God* as early as 1798). The nihilism that spread around Europe in the age of Romanticism was the sign of a cultural earthquake. The teleological interpretation of Being lost its meaning, and there seemed to be no possibility for the Oriental way of thinking either, according to which life's purpose is life itself. A vacuum came into being, and most of the Romantics who perished at an early age died of this. Any kind of medical treatment proved to be ineffectual; so extraordinarily desperate and hopeless people like the Romantics could be healed, thoroughly new thinking and a new view of life had to arise within that cultural vacuum that makes its power felt even in our days.

G. P. Ginsburg
USA
University of Nevada, Reno

Social psychophysiological mechanisms of empathy in the conduct of close personal relationships

"Caring" has been argued to be a central component of personal relationships. However, its mechanisms of operation are unclear. Cari Backman and I propose that effective mimetic displays, especially facial displays, are a major mechanism of caring and help to establish mutuality. We propose that caring is revealed through the communicative function of facial displays. The affective display of a partner is the occasion for a mimetic response by the subject. The mimetic response is a display which matches the partner's affective display but has no tie to any intrapersonal affective state of the subject. Nevertheless, it does serve as a basis for a potential empathic interaction sequence, and it can guide the affective quality of subsequent interchanges since it carries implications for actions. For example, a mimetic pain display following a display of pain by the partner implies a forthcoming sympathy sequence, which in turn implies providing help to the partner and subsequent relief of the partner. These mimetic phenomena facilitate shared affective states and coordinated joint action. Currently, we are investigating mimetic facial responses of people to videotapes of emotional facial displays of others, either intimate partners (e.g., spouses) or strangers. Mimetic facial reactions of the subjects are recorded electromyographically and on video, along with autonomic reactions. The results of this baseline study will be reported.

M. S. Kopp
Hungary
Semmelweis University, Budapest

Anxiety, freedom, and democracy

The links between science, clinical practice and politics are not always evident to us. Recent changes in Hungary have affected all areas of life and serve as a reminder that such links between apparently separate areas do exist. Arousing anxiety is one of the most important instruments of tyranny, not only of dictatorial societies but also of the dictators of the family, school, workplace, or organizations. The essence of anxiety is the inability to actively control situations perceived as threatening – the experience of this lack of control and the inability to avert the impending threat. The person or group possessing crucial information can withdraw the possibility of control or portion it out as a reward; in this way, anxiety is aroused in those affected. Avoiding anxiety is a vital driving force. If the rules of punishment are predictable and are proportional to the errors committed, anxiety may play an adaptive role in society. If the rules are impossible to follow or do not exist, the helplessness, the exposure to inevitable punishment that cannot be avoided by activity becomes a weapon in the hands of those who can deprive other persons of the possibility of control over their situation. The essence of democracy lies in the fact that, within the limits of the circumstances and possibilities, we have the right to know the essential information applying to our situation. The individual can feel free if he or she can obtain important information determining his or her situation and can actively intervene and take action to avoid dangers and choose among possibilities.

I. Kosza
Hungary
Analysis of the fate of the Hungarian nation

Studying the Hungarian history, the psychiatric literature and the self-psychological processes, the author says that the Hungarian nation is very frustrated. Thinking in Jungian model, these frustrations accumulated in the collective unconscious of the nation. These frustrations used psychological energy. According to the author, this psychological energy has its sources. These are the stable national identity feeling, the stable social background, the good family background, and the faith. In the past 40 years [i.e. ca. 1945–1990], the political system tried to destroy these sources. As a consequence of this process, the persons' ability to tolerate the frustrations is minimized in the

cognitive level. The author's opinion is that the greatest frustration of the Hungarian people was the decrease/diminishment of the country's territory and the defeated revolution in 1956. After the revolution, the Hungarian nation gave up. The statistics show a collective dying process of the nation, and the author thinks that it is integrated from the collective unconscious. This time is the great period of Hungarian history because the political changes can turn back this process, although this turn needs at least decades. The knowledge of this theory gives tasks for the experts and even for the Hungarian nation.

Zs. Kulcsár
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Eötvös Loránd University, Department of Personality and Clinical Psychology, Budapest

Right hemisphere and physiognomic perception: combination of internal and external experience

An interface function is suggested to characterize the right hemisphere (RH), which is supposed to connect internal and external experience. The interface hypothesis, supported by neuroanatomical, neurophysiological, neurological and psychological evidence, seems to provide a comprehensive theoretical frame, within which several kinds of personal functions, found to be mediated mainly by the RH, namely loosening of the "ego boundaries" in "altered states of consciousness", hypnotic susceptibility, identification, introjection, physiognomic perception, and related phenomena, like transcendental mediation, etc. might be interpreted. The danger – in addition to the advantage – of the RH function is pointed out, and alexithymia is considered a defense device against the possible harmful right-hemispheric effects. The question of psychosomatic symptoms vs. psychotic states is discussed in this connection.

Zs. Kulcsár, G. Bethlenfalvy
Hungary
Eötvös Loránd University, Hungarian Academy of Sciences

Peaceful ways of coping with stress and frustration: toward the psychophysiology of reconciliation

Alternative ways of coping with uncontrollability, unpredictability and frustrative non-rewarding, i.e., different kinds of stress and loss, traditionally considered to be pathogenic conditions both in psychopathology and in

psychosomatic research will be discussed, and the biological mechanisms underlying an all-accepting attitude, providing a basis for successful coping will be outlined. Based on common physiological and psychological aspects, namely endogenous opioid activation and accepting uncontrollability, respectively, an analogy of stressful events, play and exploration, will be suggested. Turning to the question of detachment and renunciation, the role of specific functions, as interpreted by E. Grastyán, together with right hemisphere cognition, will be connected to the psychological problem of reconciliation. Religious, mainly Buddhist teachings, will be cited to exemplify peaceful ways of coping, also touching upon the question of altered states of consciousness.

I. Lázár
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Tétényi Teaching Hospital, Budapest

The way to the other side of the mind

We regard the broad spectrum of therapeutic techniques inducing the altered state of consciousness as homogeneous and not as a collection of separate methods. The Leuner KB, the autogenic training, some means of hypnosis seem to be in close relationship with each other in the case of induction. In our examinations, we focused on the accompanying phenomena of the ASC induction using thermography, GSR and verbal self-report. Under the induction of hypnosis or Leuner method, as well as pure autogenic training, one can observe lowering of the skin conductance, warming up of the hands, while in the parallel EEG brain mapping reflects an alpha wave predominance in the dominant hemisphere, mainly in the occipital region in all forms of ASC induction. Presuming the predominant role of the right hemisphere in processing the interoceptive (nociceptive, proprioceptive) information, the interoception during the relaxation helps the patient to carry himself to a transient right-hemispheric dominance during the ASC. It is attempting to think of the right hemisphere as an open field to the unconscious, or as the real locus of it. As one can realize an alpha wave shift to right, there is a shift to the so-called *Primary Process thinking*, and to the perceptive ego state as well during ASC. As the ASC opens the creative and therapeutic horizons by this shifting for the archaic, holistic and metaphorical thinking processes with deeper emotional content, we can consider this state a special "psychological" topos, where the psychoanalysis of Jung, or the symboldrama of Leuner, and the archaic personal symbol-generation of poetry, or folk-songs and fairy tales can be connected in the sense of emotional adaptation, and self-cure. A topos, where the way of the pure physiological interoception leads.

N. T. Malan
South Africa
Potchefstroom University, Potchefstroom

Acculturation stress amongst a population of African Vendas

Acculturation, as a result of increasing, is an ongoing process amongst various cultural groups in South Africa. Accompanying this process there is an increase in psychological stress, and the development of so-called western type diseases like hypertension, coronary-heart disease and diabetes mellitus. This study aimed to investigate the physiology of acute stress in three groups of subjects with unacculturated Vendas (UV), living in a traditional rural setup, acculturated Vendas (AV) living and working in western economy and a group of whites (W). These groups were subjected to a passive coping stressor (cold pressor) and an active coping stressor (Crawford Dextary Test) while blood samples were taken after each stressor and blood pressure was continuously monitored by a non-invasive method. The AV group showed significantly higher reactivity for prolactin, cortisol and GH values perhaps indicating a higher baseline stress level as a result of the modulating effect of acculturation. A new method will be discussed for the expression of cardiovascular reactivity in the form of indexes, where both the rate of change and amount of change is taken into account, which gives results correlating more closely with clinical findings for the occurrence of hypertension amongst acculturated black populations.

E. Moussong-Kovács
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Postgraduate Medical University, Budapest

Hope – a characteristic coping style

It is an accepted view that stress mechanisms and psychoimmunological processes mediate the striking effects of adverse life events on psychological and somatic health. But, remarkably, the same stresses did not affect all exposed individuals in the same way. The ability to cope with a stressor is the most critical determinant of the organism's response. We know authentic self-reports upon the general strategies of survival, e.g., "a Tragic Optimism" as Viktor Frankl defined his own behavior. This kind of positive expectations about the future – namely the hope – has been studied mainly in its emotional, cognitive, and cross-cultural context (J. R. Averill). Our approach to this state of mind is based upon previous experiences with the pictorial expression of contrasting

emotions – depression, anxiety, hopelessness. These painful feelings of distress and despair have often been represented as abyss or impasse from wheresoever one could not escape by one's proper means. Contrariwise, the signs of perseverating efforts, ascending trends of movement characterized the drawings if we asked for an expression of the sentiment of hope.

M. Naboulsi
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Centre d'Etudes Psyshiques, Tripoli

Psychosomatique de la guerre

Les événements traumatisants de la guerre libanaise forment des catastrophes des menaces directes de la vie et ont le caractère de la gravité de leurs effets. La situation de catastrophe peut être à l'origine des nombreuses manifestations et maladies psychosomatiques. Dans un échantillon de 100 personnes, collecté par parmi ceux qui ont vécu ces circonstances désastreuses depuis au moins six mois et qui étaient auparavant exempts de toute maladie, nous avons: Les somatisations hystériques en 18 cas, des troubles cardio-vasculaires chez 20, des crises angineuses chez 4 personnes. Des poussées hypertensives en 6 cas. Un sujet est décedé par AICV une semaine après l'explosion. Des troubles digestifs fonctionnels chez 9 personnes; des crampes musculaires chez 13; des troubles sexuels chez 10 sujets. Ces catastrophes aboutissent au déclenchement et à l'activation du fantasme de la mort. Tous nos sujets vivaient l'état d'alerte permanente et manifestaient aussi différents aspects du comportement d'évitement.

The traumatic events of the Lebanese war form disasters of direct threats of/to life and have the character of the severity/gravity of their effects. The disaster situation can be at the origin/root of many psychosomatic manifestations and illnesses. In a sample of 100 people, collected from those who have experienced/lived through these disastrous circumstances for at least six months and who were previously free of any disease, we have: Hysterical somatizations in 18 cases, cardiovascular disorders in 20, anginal attacks in 4 people. Hypertensive flare-ups in 6 cases. A subject is killed by AISV a week after the explosion. Functional digestive disorders in 9 people; muscle cramps in 13; sexual disorders in 10 subjects. These disasters result in the triggering and activation of the fantasy of death. All our subjects were on constant alert and also exhibited different aspects of avoidance behavior.

Y. Oomura, K. Sasaki
Japan
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Newly identified brain glucosensor and neuroendocrinological function

A phasic increase in acidic (a) and basic (b) fibroblast growth factor (FGF) was found in cerebrospinal fluid after feeding. Food intake was suppressed dose-dependently by application of aFGF or bFGF antibody in the lateral hypothalamic area (LHA), feeding center. The suppressive activity of aFGF was twice as potent as that of bFGF, and minimal dose of aFGF for the food intake suppression was p mol order. The active region of aFGF was the N-terminal amino acid sequence (1–15), and the C-terminal one (114–140) had no effect. The aFGF suppression of food intake was caused by protein kinase C activation of glucose-sensitive neurons in the LHA. In situ cDNA hybridization study, aFGF-antibody staining indicates aFGF production in ependymal cells, and its transfer to neurons in the LHA, amygdala etc. after feeding. Cerebroventricular glucose, but not mannitol application, caused aFGF to increase in the cerebrospinal fluid to a peak two hours, and it then returned during the next three hours to the basic level. Thus, the glucosensor on the ependymal cells reacted to the glucose increase in the cerebrospinal fluid after feeding and released aFGF. The mechanism may be the same as that for insulin release from pancreatic B cells. Passive avoidance by animals was significantly more accurate when tested two hours after glucose application than when tested at other times, or after saline control application. This corresponded to the peak of aFGF in the brain. The effectiveness of aFGF seems to be partly due to its effectiveness in a region commonly related to memory. Clamping gerbil carotid arteries produced ischaemia, which damaged hippocampal CA1 neurons. Pretreatment with aFGF or bFGF prevented this damage. The FGF may be the most potent feeding suppressor and has various important physiological function.

M. Peseschkian
F. R. Germany

Women and society under the transcultural aspect of positive psychotherapy by the year 2000

Introduction and Contents:
(a) Positive Psychotherapy and Transcultural Aspect; (b) Transcultural Aspects: East–West Concepts; (c) Examples; (d) Social changes and the image of the

man; (e) The application of Positive Psychotherapy for everyday life; (f) Man and wife – misunderstanding; (g) The five stages of Positive Psychotherapy: 1. Observation/detachment, 2. Inventorying: unity and equality in the family, 3. Situational encouragement, 4. Verbalization: contribution of women to peace, 5. Goal expansion: an equal voice by the year 2000; (h) Concluding remarks; (i) Seven lights of unity.

N. Peseschkian
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Academy of the Medical Association of Hessen

The three pillars of positive psychotherapy

Since 1968, I have been working on a new concept of self-help and psychotherapy, which I call Positive Psychotherapy. The principles and techniques of this method are explained in detail in my book *Positive Psychotherapie: Theorie und Praxis einer Neuen Methode*. Now I would like to discuss how this concept can be applied within the framework of Cultural Psychophysiology.

1. The Positive Starting Point: This starting point presupposes an answer to the two questions: What do all people have in common? In what ways are they different? We try to describe general concepts of medicine, psychotherapy, and psychiatry in terms of Positive Psychotherapy, to make new ways of thinking accessible to the patient, and to provide stimulus for a new orientation within therapy and self-help.

2. The Process With Regard to Contents: It is generally the case that functional and dynamic connections are given careful attention in psychotherapeutic, psychological, and pedagogical literature. We, however, made it our task to critically and systematically examine the contents of education (upbringing), of inner conflicts, and conflicts between people. This process of looking at the game rules thus enables us to accomplish two things. We can identify the family's existing capacity for self-help and, at the same time, work through the conflicts in the family.

3. The Five-Stage Positive Psychotherapy: An additional motivation for our work was the need for a conflict-centered therapy that is as efficient and effective as possible. This strategy is divided into: observation/distancing, inventory, situational encouragement, verbalization, and broadening of goals. The "five stages" is a model that shows how psychotherapeutic directions – even ones that differ significantly – can work together. All of them can be described as Positive Psychotherapy and explained as follows: work with the individual patient / work with partner groups – work with the nuclear family / work with

the extended family – the ecosystem / ecotherapy – psychoses / therapy without the partner / positive group psychotherapy / positive self-help groups.

K. Pribram
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Radford University, Radford, VA

The place of brain in the ecology of mind

For a number of years, I was puzzled by how processes mediated by frontolimbic forebrain connected with those of the posterior cerebral convexity. As an example: How do the pragmatics (rhetoric) of language operate on referential semantics? In one essay, I proposed that perhaps the connection is made external to the organism by way of culture. More recently, I realized that there is, in fact, a part of the brain that mediates this connection: the central part of the brain consisting of the somatosensory motor systems. These provide the syntax by which perceptions (processed mainly by the posterior cerebral convexity) and feelings (processed mainly by the frontolimbic systems) come in contact with and operate on the environment. Evidence and ramifications will be discussed.

T. Rudisch, P. Molnár
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Rehabilitation and Work Therapy Center, Nagyfa,
Szent-Györgyi Albert Medical University, Szeged

Adult consequences of infantile bonding dysfunctions (on the genesis of psychopathic conditions)

In the process of healthy personality development, the presence of significant others, is one of the basic conditions of Ego development. Meltzoff and Moore recently recognized the biological basis of this function by describing the phenomenon of human imprinting. This function, being necessarily connected with the notion of critical period, suggests the possibility of early, later difficult to be corrected, damages and/or malfunctions. Given that memories of neglecting or even hostile mother are present well over chance level in life histories of individuals with psychopathic, sociopathic or borderline personality disorders, here is a high possibility that the early imprinting period with bonding dysfunctions is behind some of the above-mentioned psychopathologies. Psychological physiology studies of E. Grastyán, as his associates (including

one of us), revealed the aversive nature of inhibited approach tendencies, therefore the conjecture of a mechanism characterized by learned inhibition of inborn bonding tendencies behind the above conditions became feasible for experimental testing also in humans. Our experimental data with alcoholic psychopaths support the notion of the frustration of inborn bonding tendencies as factors of sociopathic conditions.

M. Schleidt
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Research Group of Human Ethology in the Max Planck Society

Moving in the beat of seconds: analysis of time structure in human and chimpanzee actions

Experimental evidence suggests that successive sensory associations are integrated into temporal segments of a few seconds. Furthermore, it has been found that motor activity is segmented in a similar time domain: this is true both for the organization of speech and for movement patterns. The preferred temporal segments in all these cases are approximately 2 to 3 seconds. It seems that this kind of segmentation of action patterns transcends that of the human species. Hand–body contact (one of the action patterns studied in man) was analyzed in chimpanzees, and it revealed that the preferred intervals are similar in both species. These findings suggest somewhat similar mechanisms in temporal processing in apes and man.

H. Sexton
USA

The treatment effect of contrasting activity-based groups on neurotic inpatients

A study of the therapeutic effect of two activity-based groups is presented. 80 hospitalized neurotic patients were given two contrasting group forms in a pseudoexperimental design. One group was interactive, using exercises requiring cooperation and designed to evoke a reflection over the participants' style and personal problems. The other group engaged in non-demanding, pleasant, and individually oriented hobby-like activities. Talk about problems was discouraged. Both groups took place in a positive social atmosphere. All patients continued to receive the other treatment modalities on the ward, which is oriented to a multi-modal, primarily group-based approach, both activities were videotaped throughout the project, which were scored by independent raters

to make sure that the groups functioned as described. All patients were independently evaluated pre- and post-therapy, and also at a 6-month follow-up, on a standard test battery, which measured social function and symptoms. DSM-III diagnoses and demographics were recorded, Ego strength was also measured. The findings are presented and discussed both as to treatment implications and as to the effects of a positive social climate on symptomatic individuals.

H. Sugano
Japan
University of Occupational and Environmental Health, Kitakyushu

Psychophysiological studies of fragrances

Psychophysiological effects of fragrances were studied using EEG, Single Photon Emission Computed Tomography (SPECT) and microvibration (MV). It was found that some fragrances such as lavender, jasmine, musk and alpha-pinene, the main constituent of fragrances in the forest, act on the mind. Inhalation of Alpha-pinene produced an increase in cerebral circulation, which is dominant in the right hemisphere. Almost all fragrances decreased cerebral circulation except musk. In CNV and MV studies, muscle and mental relaxation were seen in the case of lavender and Alpha-pinene. Present studies disclose that the use of fragrances is an effective remedy for release from stress.

I. Varga, M. Dorner, A. Szvatkó
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Eötvös Loránd University, Pedagogical Counseling Centre, Budapest

Sensory integrative therapy: some Cultural Anthropological analogies and new aspects of the biological development

We have applied Sensory Integrative Therapy (Ayres, 1972) with hyperactive, learning disabled and emotionally disturbed children. Methods and devices will be presented on videotape. We have realized that in these children, who, because of their attentional problems, were not easily acceptable for educational programs and analytically oriented play therapy, the activation of the vestibular system restores many "archetypical" experiences, which could help in the reorganization of their pathological sensorimotor and autonomous functions. Recent results on the organization of behavior in fetal life will be discussed, and converging data supporting that the vestibular system plays an essential role in the process of patterning sensorimotor and autonomous functions.

T. Virág
Hungary

Specific traits in the psychic structure of descendants of Hungarian Holocaust survivors

In the described cases, the psychodynamic picture characteristic of children and grandchildren of survivors unfolded gradually. It was possible to observe the unconscious identification with the persecuted and destroyed members of the family. This identification is the more striking as usually these parents never mentioned their background to their children. In these cases, the extremely strong aggressive drive against the mother or father was characteristic. Therefore, I have considered it particularly important to work through the wrath felt by my patients against their parents and to objectivate it into hatred of inhuman circumstances. in the selection of therapy it is extremely important to recognize that our patients belong to families which are survivors of the persecution. In the spirit of Ferenczi's ideas in the analysis of Holocaust survivors, I have put great emphasis on spontaneous auto-therapeutical tendencies. From among the effects emerging through the analysis I attempted to reinforce those in which the spontaneous endeavor to work through the trauma was discernible. The attitude to seek recovery was evident in the case of B's father, who possessed the capacity of auto-therapy: he remarried and became a father again. Another patient's parents were searching for remedy when choosing a spouse with a different religion. However, they did not succeed in auto-therapy. Nevertheless, even anxiety-dreams are attempts to deal with traumatic experiences. The classic Freudian analytical technique uses the uncovering and working through of unconscious fantasies. In the above cases, it was reality that was the pathogenic factor. One could follow that in the acting-out system of survivors there emerged the continuity of the family's life but this continuity was transmitted by a distorted system of information. This was so because parents tried to interrupt their fate's continuation by remaining silent about their secret. We witness the failure of attempts to suppress collective traumas: in spite of trying to forget deliberately, they never forget and thereby make others remember as well. They try to conceal the secret by not speaking about it, but they nevertheless transmit it through their behavior, voice, gestures. As a result of condensation, it is not the entire past that is reconstructed but only a cogent part which, like the finds of the archeologist, provide its total image. The goal of therapy is an attempt to terminate the symptom-formation induced by the parents. A precondition for this is the ability for survivors' descendants to work through their grief. If – as a result of this – grief is becoming conscious, the road is open for the verbal remembrance of lost relatives and one can hope to assist in stopping the mute compulsion for repetition.

Psychoneuroimmunology

Satellite symposium of the 5th International Congress of Psychophysiology
(Martonvásár, Hungary, 1990)

Honorary President: B.D. Jankovic, H. J. Baltrusch, E. S. Vizi,
General Sercetary and Program Comittee: J. Szelényi, I. Lázár,
A. Guseo

Abstracts

H-J. F. Baltrusch, J. Andrés, W. Stangel
F. R. Germany
Blood bank, Division of Immune Hematology & Transfusion Medicine, Medizinische Hochschule Hannover

Psychosocial stress; coping and blood platelet functions

Recent research on platelet functions is reviewed. Blood platelets are now generally accepted as a model for various aspects of the synaptic apparatus and the neuronal system. The role of platelets in immunity is discussed. Platelets are involved in interactions with leukocytes, in phagocytosis, acute inflammation, harmful immunity, anaphylaxis, and allergy as well as in tumoral processes, including metastasis. The role of stress and psychological factors in blood clotting, fibrinolysis, platelet adhesion, and aggregation and in platelet count and other functions is outlined. Emphasis is given to own studies and to mean platelet volume (MPV) as a possible marker of different coping mechanisms with stress. Own findings are reported, which demonstrate significant psychological differences in healthy persons with increased and decreased MPV. Another marker of stress appears to be platelet monoamine-oxidase activity (MAO); changes have been noted regarding different psychological conditions, psychiatric, as well as somatic disease in which psychosocial conditions play a prominent role. It is concluded that platelet functions, in particular MPV and platelet MAO activity would be worthwhile subjects of future psychoneuroimmunologic research.

H-J. F. Baltrusch, E. Gehde, I. Titze
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Early childhood and youth of cancer patients, and its possible neuroimmunomodulatory effects

Animal studies indicate a relation between early experience and altered immune functions in later life, especially tumorous processes. Depending on the specific stress paradigm and coping ability, different immune parameters could be either enhanced or depressed, thus indicating that the interaction of psychosocial growth with neural and neuroendocrine development may be a pivotal factor of adult immunocompetence. Semi-prospective, as well as retrospective studies in cancer patients show a typical pattern, which includes parenteral understimulation and a lack of emotional closeness to parents during early childhood and youth. Contrary to their controls, 'cancer-prone' persons and cancer patients describe their parents as more neglecting, emotionally distant, less loving, less protective and rewarding and more rigid and stereotypical. Our own ongoing European study in more than 1,100 cancer patients and 1,500 cancer-free controls, using the Family Attitudes Questionnaire (FAQ) appears to support this notion. A report given on the spontaneous associations in the FAQ of cancer patients at different sites yielded statistical differences in regard to closeness to parents and the total number of losses and bereavements during childhood and youth. Despite the methodological difficulties and fallacies of this type of approach, our data appear to be in line with similar studies. The possible psychoneuroimmunologic consequences of early childhood understimulation are outlined and discussed, and further research implications are presented. In order to prove a relationship between early experience and immunological changes, study design is presented, which includes standardized stimulus sets and recording of physiologic data

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Definition of a biopsychosocial risk profile in cancer

Today there is sufficient evidence that psychosocial factors, as well as certain coping strategies may play a prominent role in the onset and progression of

malignant disease. In recent research, a pattern has emerged that – in analogy to coronary prone behavior pattern (Type A) – has been labeled Type C or biopsychosocial cancer risk profile, encompassing suppression of anger, hostility, anxiety and other negative effects, as well as high social conformity, lack of self-assertiveness, rationality, and anti-emotionally and self-sacrificing behavior. Infrahuman and human studies suggest that specific coping styles under stress may be associated with specific biological responses, including neuroendocrine, immunological and possibly also other physiological functions. The importance of this biopsychosocial cancer risk pattern will be elaborated in regard to its clinical significance, screening of persons being at high risk for cancer, to therapy, rehabilitation, as well as to future research in biobehavioral oncology.

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Individual psychosocial differences and the effects of experimental stress on human immunity

The few experimental studies on stress and immunity with human subjects seem to contaminate the psychological and physical aspects of stressors. We were able to show some effects of mild 'purely' psychological stress in the laboratory on several parameters of human immunity. Moreover, the results suggested that stress induced changes in distributions of T-cell subsets and Natural Killer cells appeared to be dependent on personality characteristics, e.g. locus of control and neurotics, and emotion during the stressful situation. Results of a second experiment, using a larger sample, and a broader range of immunological parameters, will be shown and discussed. The role of "perceived control" will be emphasized.

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Classical conditioning of Natural Killer cell activity (NKCA) in humans – replication and extension of previous results

Behavioral conditioning techniques are frequently employed to demonstrate the involvement of the central nervous system in physiological processes. Recent data suggest that the activity of the immune system in animals can also be influenced by classical conditioning. However, so far results are available concerning the modulation of the immune system by conditioning in man. Recent results from our laboratory now suggest the modifiability of the human immune activity by a behavioral conditioning protocol. The present study was designed to replicate and extend our previous findings with additional controls. Healthy subjects (n = 24) were randomly distributed into four experimental groups. Conditioned subjects (n = 6) received a sherbet sweet (conditioned stimulus, CS) immediately followed by a subcutaneous injection of 0.2 mg adrenalin (unconditioned stimulus, US) on four consecutive days. After 15 min. adrenalin administration results in a significant increase of natural killer cell activity (NKCA; unconditioned response, UR). Two control groups were exposed to the sherbet sweet (a) in a combination with a saline injection (saline control; n = 6) or (b) followed by adrenalin injection but in a non-paired manner (nonpaired control; n = 6). In order to control the effect of a daily regimen including adrenalin administration and possible residual effect, a third control group (n = 6) received the sherbet sweet followed by adrenalin injection on all five days. On conditioning day 5, all experimental groups were provided with the sweet and injection of saline. Conditioned subjects re-exposed to the CS showed a significant increase of NKCA. Despite the same treatment, no enhancement of NKCA (saline control) or only a small increase of NKCA (nonpaired control) was observed. These results suggest a modulation of the NKCA by associative learning and provide further support of conditioned immunologic reactivity in man.

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Release of noradrenaline from sympathetic innervation of the spleen. Are immune cells the targets?

The release of NA from rat spleen was investigated. Spleen strips loaded with 3HNA were superfused with Krebs solution and stimulated electrically at different frequencies (2-8-32 Hz) with the same number of pulses. It was found that stimulation-evoked release was frequency dependent: the higher the stimulation rate was, the higher outputs was observed. CH-38083, a highly selective alpha-2 antagonist was able to remove the presynaptic negative

feedback control and increased significantly the stimulation-evoked release. L-phenylephrine, a selective alpha-l agonist evoked a prompt increase of intracellular calcium, measured in isolated polymorphonuclear cells using Quin-21. It is suggested that in lymphoid tissue (e.g., spleen), the immune cells are also targets of NA, released from sympathetic noradrenergic axon terminals and that there is an alpha-1 adrenoreceptor mediated interaction between noradrenergic innervation and the immune cells. (Cf. N. Fabris: *A neuroendocrine–immune theory of aging*.) Among the systemic theories of aging, the "immunological theory" received in the past some attention due to the apparently intrinsic derangement that occurs in the immune system with advancing age and the impact that such a derangement has for various body functions. In fact, some age-associated alterations in the neuroendocrine and in the immune system are mutually interdependent, as revelated by the fact that experimental manipulation on one of the two systems modifies and sometimes restores the function of the other one. Experimental and clinical evidences will be illustrated in support of the view that the age-associated failure of the thymus or of neuroendocrine centers is not an intrinsic phenomenon, but rather depends on the modification occurring in the functionally-linked partner and that a "neuroendocrine-immune" more than a pure "immunologic" theory may offer a better approach to understand the aging mechanisms.

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Metastasis and neuroendocrine system in stressed mice

Considerable experimental evidence is available that indicates that psychological stressors affect tumor incidence and progression in laboratory animals. The aim of the present work has been to determine the effects of the application of defined paradigms of psychological stress on primary tumor growth and spontaneous metastasis in syngeneic mice kept in a low-stress environment and implanted with Lewis lung carcinoma. The stressors examined are the anticipatory anxiety caused by the periodic application of spatial disorientation (SD), early maternal deprivation, behavioral despair, physical restraint, and avoidable vs. unavoidable foot-shock in conditioned animals. The most notable results are obtained with SD, which reproducibly causes a significant and parked increase in metastasis weight independent of primary tumor growth: marginal and scarcely reproducible results have been obtained with the other experimental paradigms used. The nature of the mediators operative in the

effects of SD has been examined by direct assay or administration of specific neuroendocrine effectors. In these conditions, the participation of plasmatic glucocorticoids appears to be insignificant, that of beta-endorphin is significant, whereas the adrenergic system appears principally involved. An increase in the urinary excretion of melatonin is observed upon the application of SD, which accompanies the observed increase in lung metastasis weight. These findings indicate that psychological stressors may influence tumor metastasis by host's antitumor resistance factors through neuroendocrine mechanisms, which have been presently preliminary identified and which are currently under further investigation. These factors appear specifically relevant for tumor spread and curability by antitumor agents, with implications of interest for experimental and clinical situations.

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Interaction of psychological factors and immune parameters in cancer patients

The immune system can be regarded as a central mediator in the course of many illnesses. The basic requirements for an interaction between the psychological and the immune systems are neuronal and/or humoral influences. The central axiom is the interdependency of the three subsystems. Fifty cancer patients were investigated longitudinally in a feasibility study within 18 months. Especially, the suppressor cells and beta-endorphin were correlated with the psychological state and the helper and suppressor cells with the trait parameters. It is supposed that different personality characteristics are able to modulate the neuroimmunological response.

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Personality, emotion and immune function in cancer patients

Influences of cognitive factors on immune function could be mediated by the CNS and the immune system via neuroendocrine and other neurotransmitters. As dispositional factors linked to an elevated risk for developing malignant

diseases, a 'cancer-prone behavior' pattern (Type C) has been postulated. Key concept is the suppression and denial of negative emotions and/or the inability to express emotions. Fifty cancer patients were investigated longitudinally. Significant correlations between psychological and immune variables were found. Anger control and rationality correlated with beta-endorphin. Our results suggest that emotions and ways of coping can modulate the immunological response.

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Conditioned immune-pharmacologic effects and adjuvant arthritis in rats

In four experiments we demonstrated conditioned stimulus (CS)-elicited depression of the development of adjuvant arthritis (AA) following a taste (CS)-cyclophosphamide (CY) pairing. In a further study, AA was enhanced by re-exposing rats to a taste CS previously paired with a low dose of CY. Because conditioned CY effects are confounded with conditioned taste aversion (CTA), we searched for a drug that would not induce CTA. AA could be inhibited by re-exposing rats to the taste previously repeatedly paired with cyclosporine (CS+) as compared to animals with the same history but re-exposed to the taste previously not paired with cyclosporine (CS-). Animals did not avoid CS+ consumption. Therefore, we interpret our data as reflecting an associative learning process that affected the development of an autoimmune disease.

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Artificial maternal behavior and immune response in male and female rats

Exposure to foster pups elicits chain-like behavioral events in non-pregnant, non-lactating female and in male rats. The very first occasion of pup-exposure educes aversive reactions and avoidance of the young rats. During continuous exposure lasting for several days complete maternal behavior develops, that is: retrieving of pups, nursing and crouching, a characteristic posture to expose the nipple for the pups. The aversive reaction activates stress mechanisms, and the later developing maternal behavior is associated with moderate prolactin (PRL) release. Our experiments reveal that the mechanism underlying the

activity changes of dipeptidyl peptidase IV (DP IV, EC.3.4.14.5), an enzyme present in T helper cells, is rapidly responding both to catecholamines released during the avoidance phase of pup-exposure and to PRL released during ongoing artificial maternal behavior. This highly sensitive model is recommended for the study of relationships between neuroendocrine functions and immune mechanisms. The presentation will be illustrated by a video-movie (11 min): Korányi, L. – Yamauouchi, K. – Arai, Y.: *Episodes of Artificially Induced Maternal Behavior in the Rat.*

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The effect of oral contraceptives of different content on the hemopoiesis in neuro-immuno-endocrinological context

During screening the white blood cell count of healthy young women, taking contraceptives with estrogen content we found a tendency of decreased leukocyte number while RBC was unchanged. The significant differences among the groups of women using pills with different estrogen content were indicating the effect of the contraceptives on producing white blood cells. In animal experiments with estrogenic steroids, strict leukopenia was reported, which was accounted for by immediate inhibition of maturation of the WBCs and direct effect on the microenvironment of hemopoiesis. Depressed cellular immunity has been reported in women taking contraceptives (Barnes et al., 1974). Estrogens are reported to decrease splenic T helper cells (Kalland, 1980) and inhibit the production of IL-2 (Henriksen and Frey, 1982), suggesting a modulation of T cell maturation process. Otherwise, women taking oral contraceptive exhibit enhanced humoral immunity (Ball et al., 1969), which may be due to the diminished T suppression function (Paavonen, 1981). In our present survey the qualitative spectra of WBCs of women taking "mini pills" (of varied estrogen content), Ovidon (0.05 mg etinilestradiol) and Rigevidon (0.03 mg etilinestradiol) were compared with each other and with those abstaining from contraceptives but having the same characteristics. Our findings indicate that low estrogen content contraceptives exercise an impact in the same direction but to varied extent on the granulocytes and lymphocytes in circulating blood. This explains the relative lymphocytosis experienced with a minimum drop of lymphocytes in women taking estrogen. The values of women in the test groups were in the normal range, but the differences proved to be statistically significant. In evaluating our findings, a review of the neuroendocrinological role of estrogen will be made.

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Association between functional brain asymmetry and immune responsiveness

An association between functional brain asymmetry and immune responsiveness has been first suggested in humans where a higher incidence of immune disorders was observed in left-handers. However, these observations remain controversial. The discrepancies in the different human studies probably result from differences between patient populations. Furthermore, in these studies, only the clinical signs of immune disorders were taken into account. The immune status of the patients was not investigated. In order to overcome the difficulties encountered in human studies, we developed an experimental approach where we demonstrated an association between asymmetrical brain functions and immune reactivity in mice of several strains. Mice were selected for right- or left-handedness using a paw-preference test and tested for their immune responsiveness. In female C3H/He mice, mitogen-induced proliferation of T-lymphocytes was higher in left-handers but B-lymphocyte mitogenesis and natural killer cell activity (NKCA) were not correlated with paw-preference. In contrast, in males of the C3H/OuJ strain, mitogenesis was not correlated with paw-preference, but NKCA was higher in right-handers. In NZB mice which spontaneously develop autoimmune disease including lupus like glomerulonephritis and hemolytic anemia both anti-erythrocyte and anti-DNA antibodies earlier in left-handed animals. These results demonstrate that functional brain asymmetry, as assessed by paw-preference, is associated with immune reactivity in mice. This association shows that some immunological parameters have a genetic basis and involves sex hormones.

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Cognitive defensive strategies mediating between stress and health

Defensive operations are believed to be of significant importance to maintain psychological well-being under stress. In this investigation, the purpose was to examine how psychological defense mediates the effects of chronic and acute stress on psychological and physiological indicators of health and well-being.

Our study involved 70 (stressed) teachers who filled out questionnaires on stress situations, coping styles, stress reactions, and general health. The defense was measured by two questionnaires and by Kragh's tachistoscopic Defense Mechanism Test. In our laboratory we submitted the teachers to a mild psychological stressor and collected cardiovascular and immunological data. The results indicate that psychological defense does relate to several important psychological and physiological parameters, in particular to subsets of T-cells and Natural Killer cells in peripheral blood. The relationships of psychological defense to both physiological parameters as well as to self-reported stress symptoms and subjective general health will be reported.

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Women after breast cancer operation

Diseases are caused by a combination of biological, psychic and social factors. Their course depends on these factors as well. After a breast cancer operation, all women suffer from severe disturbances of their self-esteem. Physical disturbances and irregularities in interpersonal relations ensue. The author developed a psycho-oncological program of care that focuses on a theme-centered group therapy, according to R. Cohn. It aims at supporting women with surgically treated breast cancer to control their disease and to reintegrate themselves socially. For evaluation, we used questionnaires about symptoms and behavior, according to Hock and Hess. After therapy, the physical and psychic ratings of 75% of the women thus treated had returned to normal.

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Age and dementia-related changes of cholinergic structures of lymphocytes

The cholinergic structures of peripheral blood lymphocytes (PBLs) were studied in healthy young and old individuals and in people with different types of dementia. The acetylcholinesterase (AChE) enzyme activity had the same value; the number of muscarinic acetylcholine receptor (mAChR) and nicotinic acetylcholine receptor (nAChR) increased with age. The activity, the nAChR binding sites decreased and the mAChR binding capacity was increased

in the lymphocytes of AD/SDAT patients as compared to the values of the healthy, old controls. Our results show that the changes of cholinergic structures observed on neurons can also be found on PBLs. Our experiments confirmed the supposed similarity of cells in the central nervous and immune system.

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Age-related changes in humoral immune response

During senescence, the immune system undergoes profound alterations associated with both a progressive decline of immune responsiveness to exogenous antigens and an increasing incidence of autoimmune phenomena. The immunologic alterations seem to play a major role in the biological processes of aging. To analyze the age-dependent changes of the B cell functions, we followed the antibody response against different antigens in old mice and tetanus toxoid in elderly people. A delayed primary immune response, a prolonged IgM response and a definite IgA response have appeared as characteristics of the immune response in old age. The results showed a delay of IgM-IgG switch and a slower maturation of B cells during immune response process in old age. It seems to appear a special T helper dependent switch-mechanism from IgM to IgA in specific immune response in the process of aging. Administering different "anti-aging" drugs, we have tried to moderate these age-related changes.

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Reduced cellular immune function during depression and mania

The authors investigated the cellular immunity (ADCC) in 22 consecutively admitted, physically healthy, nonalcoholic inpatients with DSM-III diagnoses of primary major depression (n = 11) and mania (n = 11), aged between 20 and 60 years (mean: 44.05 yrs). All patients received low or medium dose of psychotropics. The mean ADCC activity of depressed (36.3 + 24.1) and manic (46.l – f 28.1) patients was significantly lower than the same value of the 20 healthy,

drug- and alcohol-free controls of similar age ($p < 0.001$ and $p < 2$ cm in 47% and $< 2 < 4$ cm in 47%), status for axillary nodes was negative in 49% and hormonal receptors were negative in 43% of the patients. In this sample, 60% of the patients experienced at least one stressful life event in the six months before the appearance of the first symptom of the disease, mostly in the area of health (37.2%) and bereavement (14%), and in the event category of undesirability (87%): the scores for stress according to Holmes positively correlate with tumor volume and number of positive lymph nodes.

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Altered signal transduction and cholinergic modulation of lymphocytes in healthy aging

In our previous work, we showed alteration of the cholinergic system on lymphocytes (PBLs) – due to healthy aging and in Alzheimer disease. The expression of these structures could be increased on PBLs of the control young group due to mitogenic or cholinergic stimulation, while the response of PBLs from the aged and demented groups was significantly lower, according to their known decreased immune functions. Stimulation with phorbol ester via proteinkinase C pathway resulted in an increase of AChE, while the expression of mAChR was completely abolished. Using suboptimal doses of PKC inhibitors (117 and retinal), the decreased proliferative response of PBLs from the aged group was partially restored, which suggested an underlying constitutively higher PKC activity. This was further proved by measuring PKC activity, which revealed not only significantly higher total PKC activity in the aged group but also a higher proportion bound to the membrane in the resting state of PBLs. Since PKC phosphorylates various proteins – among them Ti-CD3 complex and mAChR –, our results suggest that the age-related decrease of immune function and mAChR of PBLs is related to a higher rate of phosphorylation of certain proteins by PKC. Considering the known similarities of immune and central nervous systems (CNS), the altered signal transduction via the PKC pathway demonstrated here might explain the decreased cholinergic response characteristic of CNC of the aged.

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Psychological interventions, immune functions and cancer

Taking a multifactorial model of illness as a starting point, the possible role of biopsychosocial factors in diseases in which the immune system plays a pivotal part, like cancer and AIDS, is discussed. At present, there are only few studies in which the nexus between psychological stress and psychological coping and immune variables have been scrutinized during the clinical course of the disease by means of quasi-prospective investigations. A future task of biobehavioral and psychoneuroimmunologic research is to deal with the question of whether immune competence can be influenced by psychological interventions and which forms of psychological interventions may exert an influence on certain immune parameters. The few studies carried out thus far in this connection may show the way.

ABOUT THE AUTHOR

Imre Lázár graduated as a medical doctor, specialized in internal medicine and occupational medicine. He has a Master's Degree in Medical Anthropology from the Brunel University and a Ph.D. in Behavioral Sciences from the Hungarian Academy of Sciences. Between 2004 and 2013, Imre Lázár was leading the Medical Anthropology Department of the Institute of Behavioural Sciences, and since 2015 he has been the head of the Medical Humanities Research Group at Semmelweis University, Budapest. He is a full professor at the Institute of Social and Communication Sciences, Károli Gáspár University of the Reformed Church, Budapest. He has authored a number of monographs (e.g.: *"Attached files"*, Cambridge Scholars Publishing, 2015; *Dance of the Avatar: Embodying Gender and Culture through Dance,* Nova Science Publishers, 2015) and co-edited (with H. Johannessen) *Multiple Medical Realities,* Berghahn Books, 2005; and (with A. Lūse) *Cosmologies of Suffering,* Cambridge Scholars Publishing, 2015.

In writing this book, I partly relied on my previous works listed as follows:

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