



Chronic stress and Person-Centered Medicine

VELJKO ĐORĐEVIĆ

Centre for Palliative Medicine
Medical Ethics and Communication Skills (CEPAMET)
University of Zagreb School of Medicine, Croatia
E-mail: veljko.djordjevic1@zg.t-com.hr

We are witnessing the unprecedented development of medical science and the evolution of the medical profession, which promise to revolutionize healthcare and significantly improve patient health outcomes. Personalized medicine is the latest life-science innovation that is informed by each person's unique clinical, genetic, genomic and environmental data. One of the very important topic to consider when referring to personalized medicine is stress. Stress is an adaptive trait which evolved to help humans react to difficult and possibly dangerous situations. The perception of stress is influenced by one's individual experiences, genetics, and behavior. Stress can be acute as well as chronic. The acute stress response was essential to survival in a time when human beings faced many physical threats. The stresses of modern life, however, are more likely to be chronic and often psychological and interpersonal. Despite this, the body reacts to today's stresses as though it were still facing a real physical threat. Exposure to various forms of stress is a common daily occurrence in the lives of most individuals, with both positive and negative effects on brain and body function. The impact of stress is strongly influenced by the type and duration of the stressor. Stress can affect people of all ages, genders, and living circumstances and can lead to both physical and psychological health issues. In its acute form, stress causes only transient changes within the body. Different factors may prolong these „fight, flight or freeze“ reactions in the body. Chronic stress is a response to emotional pressure for a prolonged period over which an individual perceives he or she has no control. Chronic stress can occur in response to everyday stressors that are ignored or poorly managed, as well as to exposure to traumatic events. When the brain perceives stress, physiological and behavioural responses are initiated which lead to allostasis and adaptation. Over time, allostatic load can accumulate and the overexposure to different stress mediators can have adverse effects on various organ systems, leading to disease. In humans various factors influence the response of the hypothalamic-pituitary adrenal axis (implicated in many theories which relate chronic stress with health morbidities) including the type of stressor, the duration of the stressor, and personal characteristics (1, 2). Hans Selye experimented with animals putting them under different physical and mental adverse conditions and noted that under these conditions the body consistently adapted in order to heal and recover. Selye describes three stages of the General Adaptation Syndrome, including a brief initial alarm reaction, followed by a prolonged period of resistance, and a terminal stage of exhaustion and death. Selye defined stress as the non-specific response of the body to any demand placed on it. The body's principal physiological responses to stressful stimuli are mediated by the sympathoadrenal system and the hypothalamic pituitary adrenocortical (HPA) axis, which are, in turn, mediated by the hippocampus. The

physiological response to stress consists of both a rapid component and a slower one, acting in a coordinated temporal manner to reestablish homeostasis (3). The rapid response involves the activation of the sympathetic nervous system, which increases the levels of circulating norepinephrine and epinephrine and elevates the levels of norepinephrine in the brain. This is referred to as the „sympathetic-adrenomedullary system.” The slower, longer-lasting response requires the activation of the HPA axis, and begins with the release of CRF into the circulation from the paraventricular nucleus of the hypothalamus, which then stimulates the pituitary gland to release ACTH into the bloodstream. The released ACTH accelerates the discharge of glucocorticoids from the adrenal cortex. In addition to glucocorticoids, other mechanisms are associated with the detrimental effects of stress on the hippocampus, including the excessive release of glutamate and the repeated activation of glutamate. Psychological stress is a major risk factor for the development and progression of a variety of diseases. Chronic exposure to stress diminishes health and increases susceptibility to mental disorders. Severe and/or prolonged stress can have health consequences and adversely affect the immune, cardiovascular, neuroendocrine, and central nervous systems. Psychoneuroimmunology (PNI) is the study of the interaction between psychological processes and the nervous and immune systems of the human body (4). Modern advances in psychiatry, immunology, neurology, and other integrated disciplines of medicine have fostered enormous growth for PNI and chronic stress is among the important issues in PNI. The immune system and the brain communicate through signalling pathways. As with the stress response, the inflammatory reaction is crucial for survival. There is now sufficient data to conclude that immune modulation by psychosocial stressors and/or interventions can lead to actual health changes; indeed, stressors can produce profound health consequences. In one epidemiological study, all-cause mortality increased in the month following a severe stressor – the death of a spouse (5). Theorists propose that stressful events trigger cognitive and affective responses which, in turn, induce sympathetic nervous system and endocrine changes, and these ultimately impair immune function (6). Stress is thought to affect immune function through emotional and/or behavioural manifestations such as anxiety, fear, tension, anger, and sadness and physiological changes such as heart rate, blood pressure, and sweating. Researchers have suggested that these changes are beneficial if they are of limited duration, but when stress is chronic the system is unable to maintain equilibrium or homeostasis. More recently, there has been increasing interest in the links between interpersonal stressors and immune function. Chronic stress is often considered a negative modulator of cognitive functions, including learning and memory processes. Mental stress, which may range in intensity from mild to severe posttraumatic stress disorder (PTSD), has been reported to impair memory, possibly

by elevating excitatory amino acid and glucocorticoid levels, which in turn induce excitotoxicity and hippocampal atrophy (3). Chronic stress influences the onset and/or severity of cognitive decline in various disorders, including Cushing’s syndrome, posttraumatic stress disorder, hypothyroidism, Alzheimer’s disease, and depression. The hippocampal formation, an important brain structure in learning and memory, is particularly vulnerable to stress hormones due to its high density of glucocorticoid receptors, in spite of its remarkable plasticity. Stress mediates a variety of effects on neuronal excitability, neurochemistry, and the structural plasticity of the hippocampus (7). Chronic stress leads to structural changes in the brain. Changes occur in neurons and their synapses in the hippocampus and medial prefrontal cortex. These produce impairments in working memory and spatial memory, as well as increased aggression (8). Posttraumatic stress disorder (PTSD) is an extreme response to a traumatic event characterized with a persistent re-experiencing of trauma through recurrent and intrusive recollections or dreams, persistent avoidance of stimuli associated with the trauma, numbing of general responsiveness, and persistent symptoms of increased arousal. The net result of all these changes includes a wide range of dysfunctions and personal maladjustments, as well as a reduction in the overall quality of life. PTSD most frequently occurs among combat veterans who experienced wartime-related psychological trauma. However, it seems that simple exposure to a stressful event is not crucial for disease development, although the amount of stress is proportional to the chances of developing the disease. Despite numerous treatment approaches and schemes, PTSD is now considered to be a chronic disease with a lifelong course. When speaking about stress, trauma and its consequences, we must include an examination of the situation in Croatia. During and in the aftermath of the Homeland War (1991-1995) a significant number of people were exposed to long-term and intense traumatic experiences: participation in military action, proximity to danger for military personnel and civilians alike, confinement in concentration camps, rape, hundreds of thousands of refugees, a long-lasting occupation of almost one-third of Croatia’s territory, challenges to peaceful re-integration, a difficult post-war transition period, and myriad economic problems. Tens of thousands of Croatian veterans are undergoing treatment for chronic post-war PTSD, and a significant percentage of them satisfy the diagnostic criteria for long-term personality changes (after catastrophising events and PTSD). A large number of Croatian war veterans and civilian war victims have significant psychological problems, and at the same time refuse or delay psychiatric treatment. Along with individual personality features and the specific type of traumatic experience, the post-trauma social support network has a significant effect on the clinical picture of PTSD. As scientists, physicians, and humanists, we must ask ourselves how much we have done to improve social support for these people. Do war

veterans and other victims of the Homeland War feel accepted in society, and proud of their contributions to the Homeland War, or do we often witness just the opposite occurring? We are familiar with the Werther effect, and at the same time we often witness the media mentioning sufferers of PTSD in a negative context. How much have we, as a society, really invested in their psychosocial and physical rehabilitation? Rather than forcing our war veterans into early retirement, would it not have been more useful to invest our resources into developing their skill set and enabling them to perform jobs for which they are suited despite their disabilities (9)? Will rape victim testimony (with the goal of financial reparations) after more than twenty years bring about a greater re-traumatization, and how will we provide psychological support in these cases? How prepared are we for transgenerational trauma and what have we done to mitigate or prevent its effects? Do we have well-developed palliative care for PTSD-suffering war veterans and their family members? Do we have quality rehabilitation centres? We do not have veterans hospitals, and we are lacking a clear and concrete program that deals with their physical health. Despite all of our knowledge regarding the link between chronic stress, PTSD, and physical health, we do not have clear epidemiological data regarding the physical health of war veterans and their family members as well as other victims of the Homeland War, nor do we have concrete programs related to their physical rehabilitation. There is a lack of education of healthcare professionals regarding the specifics of communication with sufferers of PTSD as well as the link between PTSD and physical health. We are lacking domestic scientific research into the link between somatic illness and PTSD, and there is a lack in the general involvement of the academic community in this region. Why? Those suffering from PTSD are an important part of our community, and the worst approach would be to ignore them, as if this is something happening somewhere else, to someone else. Within this context, we invite you all to think about your potential contribution to professional and research projects related to the interconnectedness of chronic stress, PTSD, and somatic well-being as well as therapeutic programs for this vulnerable population in order to prevent even worse consequences. We must act now to support the survivors.

We are witnessing the unimagined development of medical science and the clinical profession, but what is left and what will always stand is a relationship between the healthcare professional and his/her patient: a relationship that opens the door to a successful diagnosis, treatment and healing (10). Thanks to recent advances in neuroscience, we are now able to describe and discuss the biological mechanisms that underlie the doctor-patient relationship. We now know that different physiological and biochemical mechanisms take part in complex functions, like trust, hope, empathy, and compassion, which are all very important elements in the doctor-patient re-

lationship. The main advantage to approaching the doctor-patient relationship from a neuroscientific perspective is that doctors, psychologists, and healthcare professionals can better understand what kind of changes they can induce in their patients' brains, further boosting the professional's empathic and compassionate behaviour (11). Does becoming a doctor really require being torn out of the milieu, culture, and social context in which one grows up and lives? Can one grow and make progress outside the context and culture in the first place; does life or health exist only as a postulate of biology or health is something much larger? Can only a healthy man be satisfied and happy, or can even a sick man relax and be happy? Is happiness only a moment or a state, an event or a process? Is medicine strictly a science or it is both a science and an art? If it is also an art, what is the artistic in *ars medica*? In medicine no two patients are alike, nor are there two identical responses to an agent or a stressor. If we treat two patients in the same way, we could be treat one of them inadequately. Since medicine requires creativity, the physician is a creator. He/she creates a new process in an encounter with each patient. Person-centered medicine is always a new and unrepeatably creation.

Therefore, together with the development of personalized medicine, there has been a parallel development of person centred medicine, which is extremely important for patients with chronic PTSD (12). Treatment outcome often depends on the art of communicating with patients suffering from chronic PTSD, and proper communication with the patient's family and within and among the medical team(s), and with different stakeholders as well as others is extremely important. It is especially necessary to develop educational programs dedicated to challenging situations in communication and the use of the person-centered medical interview (13, 14). The promotion of person-centered medicine and people-centered healthcare has been occurring in Croatia for decades. Professor Andrija Štampar, considered by many as the father of public health, pioneered various public health projects in Croatia and abroad. Recently, a group of enthusiasts gathered here to undertake the creation of a variety of projects related to the development of person-centered medicine. Good health is the product of both the individual and the community; health is not a given, it is something that must be fought for, worked toward, and invested in. Good health represents the ultimate material, spiritual, and cultural resource of a society. In order for this to be successful, we must overcome numerous obstacles in our path, obstacles which dehumanize, so that we can find ourselves on a path that leads to the humanization of man, who has no earthly predator but himself, and the civilization to which he belongs. In order for us to be successful in this humanization of mankind, and in this progression from a culture of illness to a culture of well-being, we must stop living for illness and start fighting for health. It is imperative, as individuals and families, as citizens and com-

munities, and as healthcare professionals that we view each person as a unique individual, whatever their biopsychosocial needs may be, and not merely as a diagnosis or the sum of their symptoms. To be reflected in the other in person-centered medicine is also a common civilizational path, paved by the rational and emotional mind, and a real artistic endeavour on the journey to the culture of health, and from the culture of health to the culture of the good, the good as a blessing of the civilization in which we live and create today. Everything is in the human relationship. Homo homini remedium.

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