New aspects in the pathomechanism of diseases of civilization, particularly psychosomatic disorders. Part 2. Chronic hypocapnia and hypercapnia in the medical practice

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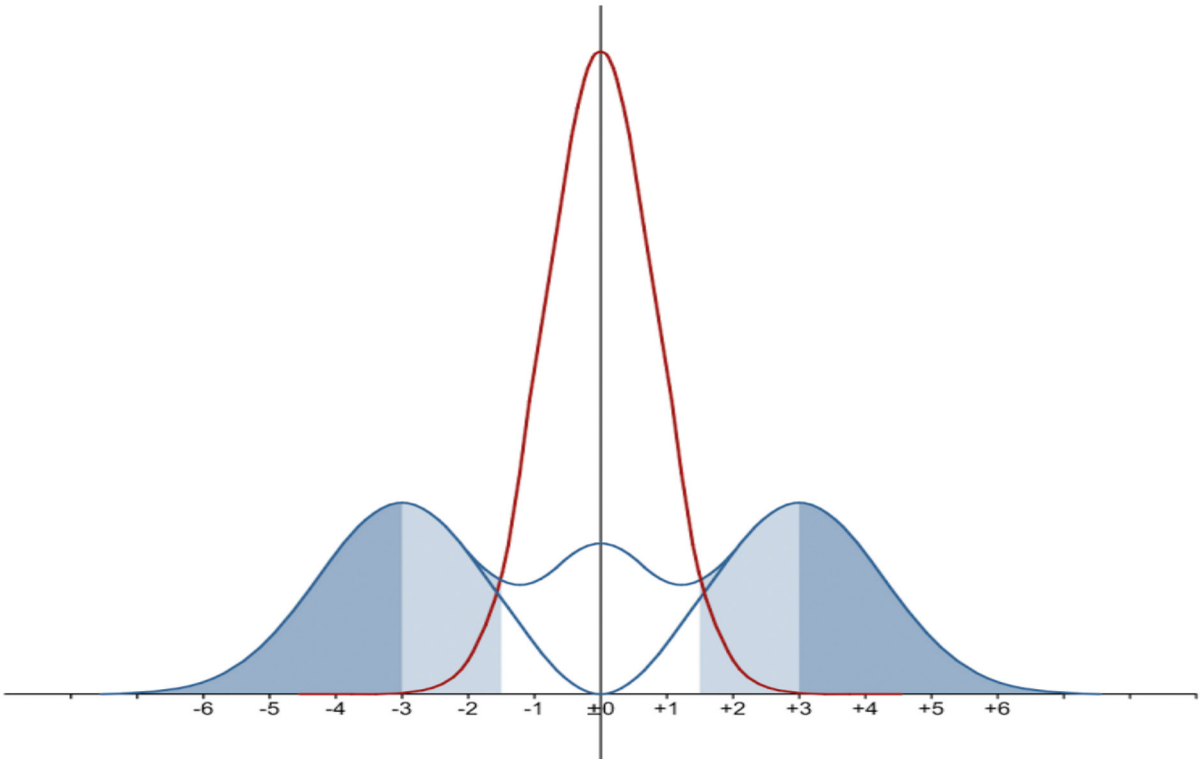
The authors seek to find new connections between recent results of biology and older theories. This paper aims to assemble the jigsaw puzzle. The theoretical background of the hypothesis was described in the previous issue of the journal (Sikter et al. 2017a). Human stress response often coexists with persistent hypocapnia or hypercapnia – developing via psychosomatic pathomechanism – which can lead to mental and psychosomatic illnesses. Chronic hypocapnia mainly generates hyperarousal disorders which may be reversible for an extended time, however, vicious cycles may start when hypoxia and/or severe somatic diseases are simultaneously present (commonly in the elderly), which conditions often end with death without medical help. Chronic hypercapnia devastates the organism initially without symptoms, partly due to neurohumoral contraregulation, consequential dysregulation and metabolic remodeling. Psychosomatic disorders (e.g., diseases of civilization that evolve in people with disadvantaged psychosocial situations) develop over years and decades, causing irreversible changes. Hypercapnia usually occurs in clinical pictures of chronic obstructive pulmonary disease, obesity hypoventilation syndrome, obstructive sleep apnea, and its unobstructed version (sleep-related hypoventilation), generating various organic disorders (hypertension, type 2 diabetes, cardiovascular disorders, immunological diseases, depression, etc.). Because of the above, chronic hypocapnia and hypercapnia cannot be regarded as harmless accompanying phenomena. That is why we have to strive for restoring eucapnia and normalizing the induced ionic changes, which does not appear to be a hopeless task.
(Neuropsychopharmacol Hung 2017; 19(3): 159–169)

Keywords: depression as an extreme hypoarousal, diseases of civilization, idea of restoring the milieu intérieur, remodeling of metabolism

PREVALENCE OF CHRONIC HYPOCAPNIA AND HYPERCAPNIA

When we blame stress for illnesses, we forget that wild animals are regularly life-threatened, but they will not get diseases of civilization unless they are trained or domesticated, (Sapolsky, 1998). What is the difference physiologically between homo sapiens and wild animals (e.g., zebras)? One difference will surely be found: blood gas (Figure 1.). The pCO_2 level changes continuously so for a diagnosis of chronic respiratory disturbance continuous detection of exhaled air ($ETCO_2$) is necessary. Without this, the measuring of pCO_2 should be supplemented with serum bicarbonate (or Base Excess) values (blood gas) – the latter being the result of several days of average (slow variables). On the basis of our estimation, up to half or two thirds of human populations may differ in their rigorous blood gas average (pCO_2: 38-42 mmHg) (Sikter et al., 2017a). According to the available literature, acute

Figure 1. In mammalian populations, blood gas is distributed in a narrow range, while in humans, the large number of hypocapnia and hypercapnia cases strongly pull apart the Gaussian curve. (More preferably, three Gauss curves are hypothesised: Cases of hypocapnia, eucapnia, and hypercapnia.)



BASE EXCESS
Distribution of Blood-gas Parameters in the Population of Homo Sapiens (blue curves) vs. Zebras (red curve).

and chronic hypocapnia is the most common blood gas disorder. It is so common that many respiratory textbooks do not deal with it (Gardner 1996), perhaps due to the misconception that what is general cannot be abnormal. The prevalence of pronounced chronic hypocapnia (<35 mmHg) can reach 15% in the population, and it may have a similar magnitude for mild hypocapnia (35-37 mmHg), too. The causes are wide-ranging, in addition to stress, hypoxia is a significant factor (Bell et al., 2009). Unlike Figure 1, in reality, in the case of hypocapnia the measure of differences is much bigger than in hypercapnia. There is also a strong age and gender difference. In young people and women (below 40 years), the proportion of hypocapnia cases dominate. Above 40-45, the proportion of hypercapnia increases, (Parati et al., 2007) which may also reach 15-30% in the population – depending on how strictly the average values are determined. Over 65 years of age, more than 50% of the population suffer from sleep-related disorders (Punjabi, 2008), which is largely a manifestation of chronic hypercapnia (see later). Hypercapnia is mostly associated with clinical syndromes, most commonly with chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA) and daytime sleepiness (Lindberg et al., 2007). Daytime hypercapnia and sleepiness occur intermittently in OSA (or in its mild form, sleep-related hypercapnia, SRH). (Verin et al., 2001) The incidence of OSA increases steadily to 60-65 years (Punjabi, 2008).

The pCO_2 level of the human population frequently, significantly differs from the average, which is not characteristic of wildlife, such as zebras (Sapolsky, 1998). It is a known difference between civilized people and wild animals, which physiological parameter also affects the "milieu intérieur" (intracellular ion-patterns of the body). According to the hypothesis, the distress can be deduced from this (Sikter et al., 2017a).

There is another factor we should take into account, which can be considered as the consequence of the Second Law of Thermodynamics (Hayflick, 2007,) or commonly referred to as the wear and tear phenomenon. It can be associated with irreversible

damage (e.g., oxidative stress) (Beckman et al., 1998), acidogenic diet and aging mechanism (Epel 2009). One of the constant companions of these damaging agents is intracellular acidosis, or in its complexity the "sick cell syndrome" (Sikter 2007). Metabolic acidosis of various origin may induce insulin resistance, which can lead to a vicious cycle (Souto et al., 2011). As a result, H^+ concentration increases slowly in the aging cells (over decades), which is not evenly distributed in the body due to dysregulation (Sikter et al., 2017a). According to some opinions, (Dhokalia et al., 1998) "… in healthy human subjects, blood pCO_2 decreased progressively with age and was 7% to 10% lower at age 80 years than at age 20." Therefore, the Gauss curve presenting the distribution of the human population pCO_2 level, shown in Figure 1., the zero point of Base Excess should be shifted slightly to the left (in the direction of hypocapnia) with increasing age, as the increasing intracellular metabolic acidosis could only be offset by a decreased pCO_2 (Frassetto, 1996). Measurement of intracellular pCO_2 and pH are currently being developed, so physiological and pathological data are still largely incomplete in this topic (Tresguerres et al., 2010).

Both the profession and the authors have dealt considerably more with the significance of hyperventilation and hypocapnia, so they emphasize hypercapnia in this paper.

PATHOGENETIC SIGNIFICANCE OF ACUTE AND CHRONIC HYPOCAPNIA

A practitioner physician looks for specific signs and symptoms, so they ignore such findings as hypocapnia, hyperventilation – forgetting their physiological and pathogenetic significance (Laffey and Kavanagh, 2002). Many hyperventilating patients having hypocapnia do not have complaints or symptoms at all, and there is also no evidence that this deviation would shorten the life. Being complaint free in chronic hypocapnia is likely to be due to relatively regular respiration, and moderate fluctuation in CO_2 level since the symptom-causing effects of the breathing pattern significantly depends on the degree of breathing irregularity (Wilhelm 2001b; Sikter et al., 2007; Sikter et al., 2009). Another group of chronic hyperventilators has many functional (mostly anxious) complaints or illnesses (Gardner, 1996; Sikter et al. 2009). Medical negligence is multifaceted, on the one hand, to question whether there is any connection between hypocapnia and anxiety and, on the other hand, to doubt that these patients who are extremely complaining and therefore suffer from a significant impairment of quality of life are sick at all (Chenivesse et al., 2014). In the '90s, Gardner (Gardner, 1996), and other hypocapnia-believers were defeated by opinions and studies that questioned the etiopathogenetic significance of chronic hyperventilation (Hornsveld and Garssen, 1996). By contrast, Wilhelm (Wilhelm et al., 2001a) declared that the transcutaneous pCO_2 sensor used by Hornsveld and Garssen (Hornsveld and Garssen, 1996) is not a suitable equipment for pCO_2 real-time analysis due to a delay of 2 minutes. On the other hand, it can not be questioned that "breathing and anxiety are intimately related" (Brouillard et al. 2016., Van Diest et al. 2006). There is also a close relationship between chronic hyperventilation and neuroticism; hypocapnia may be both cause and effect, which can lead to a vicious cycle, which can also help maintain a lasting condition (Decuyper et al., 2012). There is no clear evidence that hypocapnia would cause irreversible changes, organic illnesses unless it is associated with hypoxia or severe organic diseases (Laffey and Kavanagh, 2002). A significant part of women in generic age hyperventilate and also have complaints. One of the main cause of female hyperventilation is progesterone (Bayliss and Millhorn, 1992), and occurs frequently during the premenstrual syndrome. By contrast, the protective effect of gynecological hormones against cardiovascular disorders is also well known.

Since hypocapnia accelerates metabolism, it increases energy demand. That is why if hypocapnia is present vicious cycles often develop in older and weakened organisms (Sikter, 2007), which frequently lead to death without medical intervention (Curley and Laffey, 2014). Therefore, they suggest moderate (permissive) hypercapnia in an emergency: "Acidosis may have direct effects that can protect cells and organs in the setting of acute organ injury." There are a large number of organic diseases where hypocapnia can have a significant pathogenetic role on the progression of the disease: heart failure (Arena et al, 2008), cardiac asthma, bronchial asthma, stroke, delirium associated with dementia, etc.

DISORDERS RELATED TO CHRONIC HYPERCAPNIA AND INTRACELLULAR ACIDOSIS

Most common disorders related to hypercapnia are Obstructive Sleep Apnea + Sleep Related Hypoventilation (OSA+SRH), Chronic Obstructive Pulmonary Disorder (COPD), Obesity Hypoventilation Syndrome (OHS) and significant obesity. Hypoxia is common both in COPD and OSA, which deterio-

rates the situation. There is no uniform terminology in OSA, the authors accept as an etalon the review of Böing and Randerath (Böing and Randerath, 2015): "Chronic hypoventilation with daytime hypercapnia and sleep-related hypoventilation (SRH) do not differ substantially." Sleep-Related Hypoventilation (SRH) is the milder form, and initial stage of OSA (formerly "habitual snoring") and can reach 20% (Parati et al., 2007, Punjabi 2008, Ejaz et al., 2011), while OSA occurs in 2-7% in the US (Park et al., 2011). (A note: only 2% of the sleep apnoea syndromes is driven by chronic hypocapnia and not hypercapnia: namely by the idiopathic central sleep apnea syndrome, Xie A. et al. 1995). Excessive Daytime Sleepiness (EDS) may be associated with all three main hypercapnia-related disorders, coexists with decreased arousal and increased pCO_2 levels. According to Chouri-Pontarollo et al., 2007, hypoventilation is due to reduced CO_2 sensitivity and responsiveness. The higher HCO_3^- level (above 24mmol/L) in OSA may be a sign of chronic hypercapnia, which is initially intermittent and develops primarily during sleep (Berger et al., 2000). OSA has been at the forefront of research over the last decades, although most researchers focused on hypoxia, while moderate hypercapnia was considered less important. This hypothesis puts hypercapnia in the forefront, suggesting that moderate chronic hypercapnia can also be pathogenic if it exerts its effect for decades. This claim is supported by literary data: According to several authors, the presence of an anamnestic "snoring" (SRH) also increases the risk of hypertension, although it does not coexist with hypoxia (Bixler et al., 2000). As claimed by Peppard et al. (Peppard et al., 2000), moderate hypopnea also increases the incidence of hypertension. Although opinions are divided, some researchers say that hypercapnia has blood pressure elevating and vascular resistance enhancing effect – in contrast to hypoxia – and this effect of hypercapnia persists even after the stimulus is over (Cooper et al., 2005).

Previously, genetic defects (e.g., craniofacial abnormalities) were considered to be the main contributors to the development of upper airway collapse and obstruction (Dempsey et al., 2004). In fact OSA is also a manifestation of hypercapnia. An increasingly prevalent view is that upper respiratory tract obstruction and hypoxia are caused by neuromuscular dysregulation due to chronic hypercapnia (Verbraecken and De Backer, 2009). A detailed etiological analysis of Ramirez et al. (Ramirez et al., 2013) found that "OSA is the result of a dynamic interaction between chemo- and mechanosensory reflexes, neuromodulation, behavioral state and differential activation of the central respiratory network and its motor outputs." According to the hypothesis, psychosocial and other psychic stresses cause both disordered breathing and ultimately psychosomatic illnesses (Kim and Dimsdate, 2007). Brouillard et al. (Brouillard et al., 2016) first established an animal model that imitates the enduring psychosocial stress. Due to the persistent psychological stress, bradypnoea developed and lasted for at least ten days, but half of the rats had bradypnoea even some weeks after the stress disappeared. It can be assumed that bradypnoea means hypercapnia as well and, on the other hand, hypoventilation often becomes habitual after the stress is over.

To summarise: to hypothesize that all forms of chronic hypercapnia are pathogenic; there are mainly quantitative differences; the intermittent development and hypoxia are aggravating circumstances, but these phenomena are also the consequences of the existence of hypercapnia plus some genetically coded predisposition. The hypothetical logical chain is Psychosocial stress – Hypercapnia – Dysregulation – Diseases.

As claimed by Verbraecken and McNicholas more than 10% of the population over 40 years of age suffers from COPD, and 10% from OSA (Verbraecken and McNicholas, 2013). 1.5% of the US population is in heavy obese, 10-20% of them suffer from OHS (pCO_2 is above 45 mmHg even during daytime) (Chau et al., 2012). In fact, all sleep-related hypoventilation (SRH) and all obese patients are prone to nightly and intermittent daytime hypercapnia (excessive daytime sleepiness), which is certified by the rise in serum bicarbonate levels. On the other hand, the normal pCO_2 range is too wide (Sikter et al., 2017a) – so we can say that a significant proportion (more than half) of the population over 40 years of age tend to have hypercapnia, which is often manifested in daytime somnolence and nightly snoring. Comorbidity, between COPD, OSA and OHS is very common (overlap syndrome), as are the induced psychosomatic diseases and diseases of civilization (e.g., cardiovascular diseases, stroke, diabetes, obesity) (Verbraecken and McNiholas, 2013; Penninx et al., 2013; Maeder et al. 2016.)..

The etiology and pathogenesis of primary hypertension cannot be considered clear today despite the intensive research. David E. Anderson and his team are pioneers in the topic of behavior- hypercapnia-hypertension, and the team has nearly 100 publications. It has been known for 75 years that chronic inhibition of anger may lead to hypercapnia and (possibly through this) hypertension, at least in women (Scuteri et al., 2001). Anderson et al. (Anderson et

al., 2001) also reported an increased incidence of hypertension in different hypercapnic populations. It is known that angiotensin II (ANG II) and aldosterone activity is often increased in OSA (Moller et al., 2003). It is important that not only the severe form but mild to moderate forms of OSA (that is the SRH) significantly increase the incidence of hypertension (Lavie et al., 2000; Philips and O'Driscoll 2013). Drug resistant hypertension is also extremely common in OSA (Phillips and O'Driscoll 2013). It is a plausible assumption that intracellular acidosis starts counter-regulations, for example, through the angiotensin II (ANG II) system. ANG II potentiates the Na-driven Cl-HCO_3 exchanger, which transports twice more Na^+ into the myocardial and vascular smooth muscle cells (VSMCs) than the Na^+/HCO_3^- -cotransporter (Aiello and De Giusti 2013; see also in Sikter et al., 2017a). Due to the effect of ANG II, affected cells are alkalized and intracellular Ca^{2+} load increases as a result of increased Na^+/Ca^{2+} ion exchange. This leads to hypertrophy of precapillary muscle cells (VSMCs) and hypertension. It should be noted that metabolic acidosis (metabolic stress) such as ammonium chloride, also may cause hypertension, which activates the renin-angiotensin-aldosterone system (Györke et al., 1991).

To sum up, according to the hypothesis the pathogenesis of primary hypertension would be that at first intracellular acidosis occurs as a result of chronic hypercapnia and/or metabolic acidosis, which would be compensated by a variety of different ion-exchanger and acid extruder mechanisms in the VMSCs (Sikter et al., 2017a). ANG II and other stress hormones, such as catecholamines often overcompensate acidosis in VMSCs and myocardium. Over the years, the effects accumulate, and unnoticeable hypertrophy develops in VSMCs with increased tones and increased vascular resistance.

The causes of obesity are partly well-known: welfare, poor physical activity, psychological factors may play a role as well as genetic causes. The genetic factors are often blamed for various diseases of civilization, however, the phenotype of some human populations (European, American) has fundamentally changed over a hundred years in case of diseases such as obesity, hypertension, type 2 diabetes, etc., without significant alteration of the genotype. However, in the spirit of the hypothesis, the alteration in the "milieu intérieur" is able to change the phenotype without changing the genotype (Sikter et al., 2017a). Obesity hypoventilation syndrome (OHS) is not uncommon (Verbraecken and McNiholas, 2013), its incidence can reach 10% -20% in patients with severe obesity (BMI>32). In the background, intracellular acidosis and reduced CO_2-responsiveness can also be present (Chouri-Pontarollo et al., 2007), which may easily lead to a vicious cycle. The classic form of OHS involves daytime hypercapnia, sometimes coexisting with COPD, OSA, or both. Hypercapnic obesity was compared to "obesity with eucapnia" by Chouri-Pontarollo et al. (Choury-Pontarollo et al., 2007). The control group had only obese patients – with alleged eucapnia. Their average serum bicarbonate was 25.9 ± 3.4mmol/L, which is significantly higher than the physiological mean (24±2 mmol/L). The authors of this paper conclude that a significant proportion of obese patients hypoventilate, not only in OHS, but not to the same degree and not continuously (e.g. during daytime sleepiness). According to Chouri-Pontarollo et al. (Chouri-Pontarollo et al., 2007), leptin resistance is the main cause of obesity and the associated hypercapnia. Leptin is a cytokine that physiologically alkalizes certain cells through the Na^+/H^+ exchanger, thus enhancing metabolism, burning fat, and reducing pCO_2 (Konstantinidis et al., 2009). Leptin resistance is analogous to insulin resistance in a sense; both insulin and leptin are fighting against the intracellular acidosis, and both of them suffer defeat.

Sikter (Sikter, 2007) previously dealt with the intracellular electrolyte imbalance in insulin resistance, and with catabolic mechanisms developing in type 2 diabetes (T2DM). Sikter (Sikter, 2007) pointed out that T2DM is a protein (cytoplasm) deficient state since insulin is an anabolic hormone. In the case of insulin resistance, intracellular acidosis (of certain tissues) can be one of the most important pathogenetic deviations, and there may be metabolic as well as respiratory causes in its background. Souto et al. (Suoto et al., 2011) state that acidogenic diet causes diabetes, hypertension, renal and cardiovascular disease, based on epidemiological data. The comorbidity of diabetes is common with OSA (Tasali et al., 2008), COPD, and OHS ((Verbraecken and McNiholas, 2013). Insulin also alkalizes physiologically the cytoplasm of the target organs' cells (the exact mechanism is not yet known), which facilitates glucose transport (Yang et al., 2002). Insulin should overcome and compensate for the (respiratory and/or metabolic) acidosis that is not always successful that is why insulin resistance and type 2 diabetes develops. A Swedish research suggests the pathogenetic role of carbon dioxide retention due to a mild pCO_2 elevation in SRH ("snoring") also raises the incidence of hypertension and type 2 diabetes (Lindberg et al., 2007).

Table 1. Respiratory Type Panic Disorder vs. Major Depressive Disorder

	PD (respiratory type)	MDD
CO_2 sensitivity:	+ + +	– – –
Arousal:	increased	decreased
CO_2 drive:	+ + +	– – –
Catecholamine sensitivity:	increased	decreased
Incidency:	decreases with ageing	increases with ageing
pCO_2 level:	decreased	normal or increased
Heart Rate Variability:	decreased (with lower LF/HF ratio) (Jangpangi et al., 2016)	decreased (with higher LF/HF ratio) (McCraty et al., 2001)
Comorbidity with OSA:	– – –	+ + +
Comorbidity with T2DM, Hypertension, Immun.:	not known	frequent

The authors have already dealt with the relationship between depression and acidosis (Sikter et al., 2009). "Most of the serious aging-associated disorders have a high coincidence with depression, perhaps because of increased basal cytosolic Ca^{2+} and/or H^+ concentration" (Barbagallo et al. 1997 , Sikter et al., 2009). Hyperarousal and hypoarousal states are physiologically well characterized by the response given to carbon dioxide challenge. Anxiety disorders result in hyperreactive responses in both ventilation and also other vegetative sympathetic functions (Van Diest et al., 2009). By contrast, patients having chronic hypopnoea (hypercapnia), suffering from COPD or OHS, usually have decreased carbon dioxide sensitivity and responsiveness (Hartmann et al., 2012). CO_2 sensitivity changes on a wide scale; panic disorder and major depressive disorder are the two extreme poles where the respiratory type panic disorder has the highest CO_2 sensitivity and the MDD the smallest (Freire et al., 2010, Freire et al., 2013). (See also Table 1.) Carbon dioxide sensitivity and responsiveness is important because it may play a role in pathophysiology, and also makes it understandable. Any chronic hypocapnia generates compensation; to compensate extracellular and intracellular metabolic alkalosis metabolic acidosis develops, with different mechanisms and varying degrees. In the case of chronic hypercapnia, the opposite will happen. In chronic hypocapnia, hyperarousal diseases have an increased, while in chronic hypercapnia, hypoarousal diseases have a reduced carbon dioxide sensitivity.

Presently the polyvagal theory is dominant in the pathomechanism of psychosomatic diseases. According to this theory, an increased sympathetic activity and a highly reduced parasympathetic (vagal) tone should exist in depression (Barton et al., 2007; Penninx et al. 2013), but clinicians do not experience such things. Increased tissular level of noradrenaline is confirmed (Barton et al., 2007), but catecholamine sensitivity is significantly reduced in acidosis, in this way the sympathetic effect cannot take to force (Tenney 1960). Vagal tone decreases with only a negligible extent in depression according to Rottenberg (Rottenberg, 2007). These critiques are underpinned by the observed low cardiac frequency (McCraty et al., 2001), and by an extreme hypoarousal in depression, which are difficult to explain with elevated sympathetic tone.

There has long been evidence that there is a reciprocal correlation between severity of depression and OSA (Bardwell et al., 2003). Perhaps it is more important that there is comorbidity even between subclinical SRH ("snoring") and MDD (Deldin et al., 2006; Cheng et al., 2013), i.e., a moderate degree of hypercapnia also predisposes to depression. As claimed by Wientjes (Wientjes, 1992), "slow and shallow breathing is associated with depressed effect." According to Van Diest et al. (Van Dienst et al., 2001, 2006, and 2009) during experimental conditions both pleasant and unpleasant emotions trigger hyperventilation/hypocapnia, with the exception of the suggesting depressive thoughts when breathing goes into the direction of hypercapnia. Observations of Vlemincx (Vlemincx et al., 2015) may also indicate that depression can result in lower minute ventilation. Due to diminished hypercapnic drive, the body is less protected against hypercapnia in depression (Damas-Mora et al., 1982). It seems (and it is not a coincidence) that both the observed breathing pattern and CO_2 responsiveness in OSA is just the opposite of those in observed in hyperarousal disorders, e.g., respiratory type of panic disorder. Their breathing patterns are mirror images of each other. (This is a hypothetical idea.) Reduced or increased CO_2 sensitiv-

ity are indeed related to metabolic compensation and pathogenesis. Intracellular pH is the result of metabolic acidity and pCO_2. CPAP treatment seems somewhat effective also against complications although the results are not conclusive (Schwartz and Karatinos, 2007, Ejaz et al., 2011). Various acidoses may lead to depression, e.g., a reverse correlation between pH and depression was demonstrated in dialyzed uremic patients (Afsar and Elsurer 2015). Lactacidosis may cause depression in tumorous patients. All of these facts suggest that hypercapnia and/or acidosis have an etiopathogenetic role in depression. However, it is not only a symptom of acidosis, but there is a syndrome in which the so-called "cytoplasmic ions" (K^+, Mg^{2+}, Zn^{2+}, phosphates) decrease parallel with the cytoplasmic protein content and ATP concentration, while their antagonistic ions (Na^+, Ca^{2+}, Fe^{2+}, H^+) cumulate in the cytosol (Sikter 2007). In severe long-lasting depression, the affected regions (limbic system, prefrontal area) are atrophied without treatment (Koolshijn et al., 2009). In the background, neuronal and glial cell atrophy can be present and their development can be prevented by antidepressant treatment or (in experimental animals) by eliminating stress (Banasr et al., 2011). It is an important fact that pathophysiological mechanisms (cell atrophy) do not or do not equally affect all parts of the brain or other organs supporting the hypothesis of Sikter (Sikter, 2007) about a sick cell syndrome and locus minoris resistentiae (Place of Less Resistance).

The incidence of many other diseases (cardiovascular, GERD, ulcer, immunology, etc) also increases significantly in SRH. These topics are beyond the frames of this paper.

STRATEGIES TO RESTORE BREATHING AND ELECTROLYTE IMBALANCES CAUSED BY PSYCHIC STRESS

Courtney's (Courtney, 2009) paper could be a summary of the present hypothesis: "Breathing can influence homeostatic functions in other systems including the autonomic nervous system, the circulatory system, chemical regulation and metabolism." She also wrote: There is a "lack of coherent models for explaining the mechanisms of breathing therapies."

The concept of the idea of restoring of the original milieu intérieur can serve as a model for planning treatments. According to the logic of the hypothesis, the following strategies are considered:

A. It is a plausible solution for people to terminate psychic stress with muscular activity (e.g., running), but this is often unviable. Probably physical activity is also useful when delayed (Kozlowska et al., 2015). Although we should titrate the method, scale, and duration of muscular work, indeed the organism can be overloaded.
B. If we accept chronic hypocapnia as an etiopathogenetic factor, it is evident that we should try to restore eupneic ventilation. An early (not-$ETCO_2$-controlled) successful breathing training study was performed by Grossman et al. in 1985 (Grossman et al., 1985). The importance of proper breathing technic already was recognized thousands of years ago (Taoist Yoga) (Courtney 2009). In 1952, Buteyko theorized that hypocapnia has a decisive role in the pathomechanism of asthma. He has created a school which has many followers even today (Bruton and Holgate, 2005). The qualitative change in breathing training is based on the use of real-time capnometry (capnography) of exhaled air ($ETCO_2$) (Davis et al., 1999; Meuret et al., 2004). This provides continuous feedback and signs for the patient when the respiratory technique is correct. The importance of hypocapnia has been debated by a continuous, sharp ideological disagreement for many decades (Meuret et al. 2003), which is still ongoing. Perhaps this solution seems to be too simple, "too vulgar" and perhaps that is why capnometry-assisted breathing training spreads in paramedical but not in the clinical practice. Meuret, (Meuret et al. 2010) pointed out that the ideological misunderstandings of the previous decades have been attributed primarily to the fact that chronic hyperventilation cannot be characterized by a single parameter (pCO_2). It is necessary to sustain monitoring of $ETCO_2$ or examining serum bicarbonate (base excess), which only occasionally happened. Meuret (Meuret et al. 2008) first stated that "our results provide initial evidence that raising end-tidal pCO_2 using capnometry-assisted feedback is therapeutically beneficial for panic patients". First, in a pilot study (Meuret et al. 2008) and after a thorough preparation (Meuret et al. 2010), Ritz (Ritz et al. 2014) completed their first randomized clinical trial. This trial was unexpectedly successful; it ended with positive results. The implementation of the capnometry-assisted biofeedback breathing training took a long time, despite its therapeutic rationality (Ritz et al., 2014).

One of the authors (Roberto De Guevara) has been using capnometry-assisted feedback breath-

ing training for more than ten years. His training, similar to that described above, has achieved excellent results for clients who have experienced habitual chronic hypocapnia with accompanying various complaints. The feedback mechanism of actual breathing patterns and pCO_2 monitoring sets the stage for the client to learn how to regulate and maintain homeostatic breathing in all contexts, whether relaxed or stressed, active or passive. A level as high as 90% efficiency is now achievable in different functional disorders accompanying hypocapnia, using capnometry-assisted breathing training and with the clients' cooperation. This fact is an evidence of the role of chronic hypocapnia (Sikter and De Guevara, 2011).

There is no doubt that capnometry-assisted biofeedback therapy has a future. In view of the fact that there is not enough information without real-time feedback, patients/clients can only guess if they breathe properly. Ritz (Ritz et al., 2014) compared capnometry-assisted, biofeedback-controlled breathing exercises with "slow breathing" without feedback. Both instances proved to be effective, but the latter had a lesser beneficial effect on pCO_2 elevation and respiratory function normalization. There is certainly a connection between the two facts. It is not arguable, however, that the device free breathing training can also bring clinical improvement (Courtney 2009). The "slow breathing" (without capnometry control) may elevate pCO_2 towards the standard level, the breathing might become more regular and, in this way, the slow breathing technique can decrease alteration of neuronal intracellular pH and arousal. Both methods promote synchronization of the nervous system, by minimizing respiratory irregularity, pCO_2 fluctuations, i.e. decreasing anxiety. According to the authors, the Buteyko and other slow breathing respiratory techniques (Courtney 2009) can only be effective if they sometimes control $ETCO_2$ or blood gas. Otherwise, there is a danger that they are using bad techniques which may be even iatrogenic.

On the other hand, capnometry-assisted biofeedback breathing therapy needs many great tools and specialists. This method often requires lots of struggle, much persistence, and exercise of patients/clients. If the body has already adopted the new pathophysiological parameters, hyperventilation has become similar to the addiction or habit of smoking or alcoholism.

C. If habitual hypocapnia or hypercapnia can alter the milieu intérieur (that is the extracellular and intracellular ion pattern), the normalization of the carbon dioxide level will restore the original physiological ion conditions. Results can be achieved by capnometry-assisted biofeedback therapy within 3-4 weeks, but sometimes success has reported after one week. Logically, the opposite also has to be true; If, after the evaluation of the ion-deficiencies, the lacking electrolytes are administered to the patient with chronic hypocapnia or hypercapnia, it can normalize the missing and also unnecessary ion levels in the body (in their proper places). In the longer term (a few weeks or months), this will also normalize the level of pCO_2 (Sikter, 2007). However, these parameters also need controls, similar to the breathing training. The method would have an advantage over breathing training, requires less expertise, less collaboration from the patients ("fewer tears"), so it would be widely applicable. It would be best to combine the two methods. According to the hypothesis, capnometry would be used to measure the achieved results and fine-tune the best condition. The authors do not know of such capnometry-assisted breathing training that could reduce the elevated pCO_2 in hypercapnia. In principle, the electrolyte therapy is possible, but, in practice, these salt-mixtures are not yet available.

The role of breathing training in hypercapnia (COPD, OSA) may also be important. Even though, today's techniques cannot normalize the elevated pCO_2. CPAP may be a potent method (Park et al., 2011, Schwatz and Karatinos 2007), if the decreasing pCO_2 can also reduce the symptoms of complications (depression, hypertension, diabetes, etc.). CPAP treatment in patients with OSA "have revealed promising results" (Maeder et al. 2016). However, other results are controversial and the method is not too physiological. Progesterone derivatives and acetazolamide also have some ventilation enhancing effects, but their clinical use is limited (Wagenaar et al. 2003). It is believable to assume that persistent alteration in the breathing pattern causes diseases through changing the intracellular and extracellular ion patterns in the individual tissues/cells. That is why we should estimate the accurate ion deficiency. As a result, we could try to restore the original state. According to the hypothesis, with the restoration of ion-deficiency pathophysiological anomalies (such as metabolic and neurohumoral changes) would disappear or at least decrease. This topic could be a very fruitful field of research in the future (Sikter 2007).

CONCLUSION

In conclusion, to clarify the difference between wild animal and civilized human stress, we specify the material which can cause psychosomatic disorders. That is nothing more than the persistent lack or surplus of carbon dioxide. The body protects plastically against harm, especially the changes in intracellular pH. However, because the causes do not usually disappear, the neurohumoral protection will generate secondary, tertiary alterations in the body through ripple effects and vicious circles. The organism is defeated after many years or decades. It can be logically justified that the only valid defense can be the restoration of the original conditions, the milieu intérieur of Claude Bernard (the resetting). At least, we should strive for this restoration. In this war, medical assistance is not hopeless, but we must fundamentally change our mindset of not wanting to impose our own will on the body. We should recognize its needs and help it. "Medicus curat, natura sanat."

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A civilizációs betegségek patomechanizmusának egy újabb szemlélete, különös tekintettel a pszichoszomatikus betegségekre.
2.rész. Krónikus hipokapnia és hiperkapnia a klinikumban

A szerzők új összefüggéseket vélnek felfedezni a biológia egyes újabb eredményei és régebbi elméletek között. Jelen írás a „puzzle" összeillesztését célozza meg. A hipotézis elméleti hátterét a folyóirat előző számában ismertették. Az emberi stressz válasz során – pszichoszomatikus patomechanizmussal – gyakran tartós hipokapnia vagy hiperkapnia lép fel, ami mentális és pszichoszomatikus betegségekhez vezethet. A krónikus hipokapnia elsősorban funkcionális hyperarousal kórképeket generál, melyek sokáig reverzibilisek lehetnek, de hipoxia és/vagy súlyos organikus szervi betegségek együttes fennállása esetén (pl. idős korban) circulus vicióusok indíthatnak be, melyek orvosi segítség nélkül gyakran halállal végződnek. A krónikus hiperkapnia kezdetben alattomosan, tünet nélkül rombol, ami jelentős részben a neurohumorális kontrareguláció és az ennek folytán kialakuló diszreguláció, metabolikus remodeling következménye. A pszichoszomatikus betegségek – pl. a hátrányos pszichoszociális helyzetű embereknél kialakuló civilizációs betegségek – évek, évtizedek alatt fejlődnek ki, irreverzibilis változásokat okozva. A hiperkapnia többnyire krónikus obstruktív tüdőbetegség, elhízási hipoventiláció szindróma, obstruktív alvási apnoe és ennek obstrukció nélküli változata (alvási hipoventilációs szindróma) klinikai képében jelentkezik, számos organikus betegséget generálva (hipertónia, 2. típusú diabétesz, kardiovaszkuláris rendellenességek, immunológiai betegségek, depresszió, stb.) A fentiek miatt a krónikus hipo- és hiperkapnia nem tekinthetők ártalmatlan kísérőjelenségeknek, amiért az eukapnia helyreállítására és az indukált ionváltozások normalizálására kell törekedni, ami nem tűnik reménytelen feladatnak.

Kulcsszavak: Anyagcsere remodeling, civilizációs betegségek, depresszió mint extrém hypoarousal, milieu intérieur helyreállításának eszméje