Depression and Burnout (Pathobiochemistry, Pathophysiology, Prevalence, Therapy)

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Foundation for Micronutrients: Research and Education

In late 2013, Prof. Dr. Elmar Wienecke established the Foundation for Micronutrients: Prevention, Health, Quality of Life (SfMPGL) as a non-profit limited liability company (gGmbH). The foundation's goal is to sustainably advance research and education in the field of micronutrient therapy.

A significant milestone was reached in 2017 with the launch of Germany's first master's degree program in Micronutrient Therapy and Regulatory Medicine by Prof. Dr. Elmar Wienecke & Dr. med. Kurt Mosetter at the University of Applied Sciences for Small and Medium-Sized Enterprises (FHM) in Bielefeld.

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1. Depression: a Multidimensional Clinical Picture

Depression is still an underestimated illness. As the most severe and most widespread psychiatric illness, it affects around 500 million people. By the year 2030, with a figure of 34 million impaired years of life, it will overtake both cardiovascular diseases and diabetes in the ranking to become the world's "burden number 1". [1]

Lack of energy, lack of drive, fatigue, sadness, lack of self-worth, feelings of guilt, poor sleep, eating disorders, and suicidality affect not only the patients but also all of their relatives and the social economy.

In the sense of an overarching order, different system levels should be considered. A macro level encompasses psychosocial backgrounds, a meso level the interactions of environment-brain-organism and the ego structure of the individual, and a micro level attempts to capture neuronal and molecular mechanisms in metabolism and in the brain.

The etiology is most certainly not monocausal but multifactorial. Multimodal, interdisciplinary, and cross-disciplinary concepts are therefore required, in which psychotherapists, psychiatrists, physiotherapists, fitness trainers, nutritional physicians, as well as macro- and micronutrient experts work as a team with the patients. From this, demands are derived for a broad interdisciplinary monitoring of sleep parameters, psychological and molecular stress profiles, and personalized concepts. [2]

Bio-psycho-social factors, chronic stress, traumatic burdens, physical inactivity, derailed neurotransmitters and hormonal imbalance, a burdening lifestyle, incorrect nutrition, gut-brain signal cascades, oxidative stress, mitochondrial dysfunctions, and micronutrient deficiency can, in individual biographical scenarios, trigger a multitude of the symptomatologies of this illness.

These correlate with stress response patterns of our hormones and neurotransmitter systems in the various nerve cell network loops. [3]

Whole textbooks discuss the stress axes via CRH-ACTH-cortisol and the wide spectrum of neurotransmitters. Today we know that these effects and ramifications go considerably deeper.

At the system level of physiology and biochemistry, stress is reflected in various phases, and primarily in energy metabolism, the function of the mitochondria, in oxidative stress, in liver metabolism, in the gastrointestinal tract, in the cardiovascular and the neuromuscular system, in immune response behavior, and in the regulation of the inner rhythm. [4]

In this sense, polyetiological pathogeneses, genetic vulnerability and epigenetic factors, and neurobiological and toxicological factors all play equally important roles.

Against this background it becomes understandable why monocausal short-circuits with the concepts of one-dimensional neurotransmitter hypotheses and the prescription of more and more antidepressants could not help. Apart from the limited efficacy, side effects determine the problem of antidepressants:

Agitation, akathisia, dizziness, fatigue, gait unsteadiness, drowsiness, insomnia, nausea, sexual dysfunction, weight gain, suicidality, violent behavior, addiction and dependence, numbness, tingling, constipation.

In view of these connections, it does not appear at all surprising that the prognosis of the illness, the therapeutic successes, and the large number of new cases in all age groups, considered over the last 50 years, deliver very sobering data. [5]

2. Early Detection and Complex Levels of Intervention

In biological medicine it has been revealed for more than 10 years that, through the capture of various patterns of molecular markers, a targeted early detection and early interventions are possible. The basic pattern thereby relates to metabolic parameters which, via the microbiome-metabolome-brain axis and covert insulin resistance conditions in the brain, reflect the neuronal energy metabolism. [6] [7]

Glucose utilization disorders, insulin resistance conditions, silent inflammation, states of energy deficiency, elevated ammonia burdens, and states of exhaustion are in this sense biochemically anchored. [8]

At the same time, a whole spectrum of therapeutic options is derived via these metabolic markers. [3]

3. Cornerstones of Metabolic Monitoring

As a cornerstone of first order of a hemodynamically stable metabolism with a homeostasis optimized in this way and metabolic flexibility, we proposed as early as 2008 a metabolic pattern within a screening for early detection and possible early intervention.

- Ultrasensitive CRP
- Serum cortisol (SC)
- Cortisol in saliva in the morning (CAR)
- HbA1c < 5.5
- Uric acid < 5
- γGT < 20
- ALT < 20
- CK < 150
- Iron > 90
- Ferritin > 120
- Potassium > 4
- Magnesium > 1.2 mmol/l
- Zinc > 110 mg/dl
- TSH > 1.6 and < 2.2
- hsCRP < 2
- Lc Omega 3 Index > 8
- Ammonia < 40 µ/dl or 30 µmol/l
- Insulin < 20 µU/ml
- HOMA index < 1.5
- Triglycerides < 150 mg/dl

For tryptophan, tyrosine, phenylalanine, glutamine, asparagine, serine, leucine, methionine, valine, higher levels should be aimed for.

In considering the system level of a gut profile, the markers zonulin, calprotectin, α1-antitrypsin, kynurenine, and the secretory immunoglobulins A have proven informative. In new research work, ultrasensitive CRP, serum cortisol (SC), the salivary cortisol awakening response (CAR), the brain-derived neurotrophic factor (mBDNF), and the Pittsburgh Sleep Quality Inventory (PSQI) are proposed for evaluation. [9] [10]

4. Extended Causes

In the sense of differentiated etiology research and for individualized and personalized therapy concepts, traumatic burdens, chronic bio-psycho-social stress, accidents, post-infection syndromes, toxicological impacts, dysbioses and silent inflammations in the gut, peripheral metabolic derailments around NAFLD, metabolic syndrome, and diabetes can induce the biochemical bottleneck and corresponding metabolic patterns. In the sense of a “simultaneity” (according to Thure von Uexküll), biochemical markers are, as it were, online synchronized with the psychic dispositions of depression. [11]

Corresponding levels of intervention can be derived via the regulation of neuromuscular tension patterns, via nutritional control and metabolic learning processes, gut-brain health protocols, mitochondrial medicine, targeted supplementation, trauma therapy, and psychotherapy.

A further system level, which is likewise reflected in the end stretch of metabolic markers, revolves around movement behavior, or rather around physical inactivity. Physical inactivity promotes a metabolism of inflammation with low levels of protectively effective myokines such as BDNF, GDNF, PGC-1a, sirtuin, irisin, FGF 21, and elevated levels of pro-inflammatory lipids, myostatin, and inflammatory cytokines. In this way, inactivity and immobilization lead to frailty, loss of autonomy, and depression alike.

At this point, reference should already be made in advance to a very well-documented royal road that can lead out of depression. Effective exercise, training, Myoreflex therapy, KiD (strength in stretching, muscle-fascia length training) can set very positive effects in motion via various interfaces. [3]

That physical activities and the broad spectrum of myokines bring about significantly positive effects has been demonstrated in many studies. A current work summarizes this also with regard to children and adolescents and very clearly. [12] [13]

5. Outlook on the Next Generation

While depressions in childhood and adolescence used to represent a rarity, today more and more children are being signed off sick psychologically. Moreover, more and more children are being treated with antidepressants, which have not been researched and approved for the child and adolescent sector at all. A healthy psyche needs a healthy body. Incorrect nutrition, lack of exercise, too much sitting, chronic school stress, bullying, family conflicts, and an ever faster-moving performance society lead in many children to psycho-mental overloads.

Energy budget crises, supply bottlenecks of omega-3 fatty acids, vitamin and amino acid deficiency, disturbances in the gut, connection disorders in the brain, pollutant burdens, stuck stress in the masticatory muscles, and not least functional disorders in the neuromuscular system, can, as a single burden or in their summation, produce the symptomatology of a depression. [14]

The earlier it is detected and the earlier it is fundamentally treated, the better the prognosis and the lower the risk of a severe depression in adulthood. [15]

6. Depression and Burnout

Depression is an illness of manifold origin. The reasons for the development of depressions are not fully understood and cannot be attributed to a single source. Unlike metabolic disorders, which can express themselves, for example, in a diabetic metabolic state or high blood pressure and can be captured with laboratory parameters, there are no clear measurable parameters for the diagnosis of depression that could unambiguously define this clinical picture. The reasons for the emergence of a severe depression are too manifold for that. In contrast to a metabolic disorder such as diabetes, depression can also involve genetic factors. Further factors for the development of a depression are the psychological constitution and the social environment. To be distinguished from depression, a new term should be considered that was coined in 1975 for the first time in connection with an exhaustion phenomenon in nursing professions (Herbert Freudenberger): burnout.

The term means: being burned out, i.e., the energy reserves are exhausted. Therefore, besides the external triggering moments, one must also look into the energy budget, into the metabolic state, into the status of the mitochondria. Meanwhile, burnout is regarded as a preliminary stage in the development toward a depression if no therapeutic measures are taken. One must probably assume fluid transitions between these two clinical pictures. The acceptance of the diagnosis “burnout” in society is, however, far higher than that of depression, since burnout describes a state of exhaustion whose cause lies mainly in the social environment and can also bear features of self-sacrifice. The tenor is: my psyche is not up to the pressure from society, profession, and family. What burnout actually is, science argues about. There is therefore also no recognized diagnosis for burnout, and it cannot be billed with the health insurers, because in order to find out where “the shoe pinches”, a conversation is required. But doctors are not paid for conversations.

The fact that the diagnosis of depression historically goes back further than that of burnout, although the symptomatology can be similar, opens up a new perspective: it must above all be the living and environmental conditions of the last 50 years that are responsible for the psyche taking damage, and that to an increasing degree. For although genes are co-responsible for the stability or instability of the psyche, no single gene could be identified so far that would be solely responsible for a depression and thus heritable. This would concern a special mutation in the DNA sequence. It has, however, turned out that environmental factors can act on the genetic apparatus in such a way that they do not concern the nucleotide sequence but target the readability of the DNA. Here, in the meantime, a new discipline has established itself that depicts this process: epigenetics. With this it can be explained how traumas can be passed on across generations and can lead to depressive symptoms without the genetic material being directly affected. Excessive stress is one of the most important factors that play a role in this context in the development of depressions.

The connection of psychic experience and physical reaction encompasses the stress axes (sympathetic-adrenal-medullary (SAM) axis, and the hypothalamic-pituitary-adrenal (HPA) axis). In addition to the hormonal system, the immune system is also involved in the response to stress. From this, a connection between stress, hormonal dysregulation, altered immune reaction, and the development of depressive symptomatology can easily be read off. Often there is a connection between psychic stress factors, increased risk of infection, and worsening of the

condition in viral infections. For this connection, the term psychoneuroimmunology was coined [18].

7. Prevalence and Causes of Depression

Depressions, accompanied by states of anxiety, are now regarded as a widespread disease. 5.3 million of adult Germans suffer from depressions, among them 5.1% men and twice as many women at 11.3% (Südkurier 28.2.2020). To this come alarming figures: every 5th school child suffers from anxieties and psychic disorders (Südkurier 4.2.2020). The causes of depression are of genetic origin, go back to traumatic experiences, or are conditioned by environment, nutrition, and psychosocial aspects. Depression has many faces:

The physical causes include chronic illnesses or pains, disorders in the hormone budget, severe illnesses such as cancer. Psychosocial causes can be strokes of fate, permanent stress in profession and family, chronic loneliness. Finally, there can be a hereditary risk of falling ill with depression and an epigenetic legacy that impairs gene regulation. In one study, genome sequences of more than 75,000 Europeans with a diagnosis of depression and 231,000 psychically healthy Europeans were compared. Statistically significant indications were thereby discovered for 15 gene mutations that are likely to be connected with the emergence of depression [16]. From this rather new finding it becomes clear how difficult it is to attest a clearly genetic origin to depression. Even if one could identify a depression gene, the practical-therapeutic benefit would be low. Genes cannot (yet) be manipulated.

The consequences of depression lie in social behavior such as withdrawal from family and circle of friends, in physical signs such as sleep disorder, weakened immune system, loss of appetite, excessive consumption of stimulants (alcohol, cigarettes, sweets), rapid fatigue, and finally psychic signs such as low self-confidence, little capacity for enthusiasm, pessimism, forgetfulness, and concentration disorders.

Whether depressions have increased in recent years cannot be answered unambiguously. On the one hand, the number of psychic illnesses and depressions is increasing, which can also be read off from the rise in prescribed antidepressants; on the other hand, the increase is attributed merely to the higher sensitivity and the willingness to recognize depressions and other psychic disorders as illnesses. What is certain is: psychic disorders are more widespread than was long assumed. According to a study at the TU Dresden (F. Jacobi and H. U. Wittchen), every third EU citizen suffers once a year from a psychic illness. It is also noticeable that younger people show somewhat more psychic illnesses compared to earlier [17].

8. Stress and Depression

Not everything that means stress is unhealthy. It is a physiological reaction to grasp stress as a disturbance variable and to adapt to the challenge. Life is unthinkable without appropriate stressors that promote normal physical and mental development. This is called eustress (ευ, Greek, is always good). Opposed to this is distress (δυσ, bad), which overburdens the body and the soul and, if chronic, makes one ill.

Stress perception originates from the brain, the cortex, from where the stress signals are relayed via the hypothalamus to the pituitary gland. From there, ACTH (adrenocorticotropic hormone) is released, which in turn leads in the adrenal cortex to the release of cortisol and in the adrenal medulla to the release of adrenaline. This pathway is called the hypothalamic-pituitary-adrenal axis, HPA axis. The example is repeatedly cited of how we developed this stress axis in evolution. It is, for instance, the threat from wild animals that either challenged us to fight or let us flee. In both cases the organism is maximally challenged. All available glucose in the blood is claimed by the brain in order to be able to set the body to this situation; it is taken up neither in fat nor muscle cell, insulin resistance prevails. Every anabolic metabolic step (fat synthesis, glycogen synthesis) is inhibited. The mediator of this switching process is cortisol. The described situation is, however, acute and not chronic. For either the flight succeeds or we are eaten. In the former case, excess cortisol switches on a negative feedback effect by binding at the level of the hypothalamus and the pituitary to a glucocorticoid receptor and inhibiting the release of the adrenocorticotropic hormone (ACTH) [19]. Thus a standstill in stress triggering occurs again. The organism can find its way back to its accustomed metabolic state with corresponding insulin sensitivity of all organs.

The disturbance of this axis and its feedback mechanism leads to a preponderance of hormones that counteract insulin and is involved in the development of depressions and post-traumatic disorders (post-traumatic stress disorder PTSD). The disturbed feedback control of the hypothalamic-pituitary-adrenal axis (HPA axis, hypothalamus-pituitary-adrenal system, hypothalamic-pituitary-adrenocortical axis, HPA) is the most conclusive biological signal for severe depression and is part of the pathophysiology of illnesses and of negative emotional states [20]. At the end of the cascade, cortisol is released. This finally puts the body in a position to respond appropriately to a stress signal. After acute stress, cortisol inhibits the HPA axis by feedback. In chronic stress, the feedback slackens and there is a persistent cortisol release with all the associated pathophysiological consequences (insulin resistance, dampening of the immune system, etc.). Stress thus activates the neurohormonal system, such as the HPA axis. At the same time, the release of the “stress peptide”, the “corticotropin-releasing factor”, is activated. The resulting corticosteroids modulate the whole process that plays out peripherally as well as centrally during stress and the development of a depression. The other group of essential substances in this process are the monoamines noradrenaline, adrenaline, dopamine, serotonin, and histamine [38].

The prefrontal cortex developed later in evolution than the areas of hypothalamus and amygdala, which together with nucleus accumbens and hippocampus represent the limbic system. Hypothalamus, amygdala, nucleus accumbens, and hippocampus are the centers for emotions and remembering. The prefrontal cortex, by contrast, is the control center that controls our emotions and impulses. It reacts, however, very sensitively to stress. Acute and above all chronic stress releases biochemical signals that weaken it and rob it of its control function. As a result, older structures gain the upper hand and the control of thoughts and feelings shifts toward the hypothalamus and other archaic structures (amygdala). When these structures dominate, we can feel paralyzing fear and be subject to impulses that we normally keep under prefrontal control. The consequences are unrestrained eating and drinking, excessive drug consumption, or other uncontrolled behaviors such as unbridled shopping and consumption.

The hippocampus is part of the limbic system and generates new neurons throughout life, and here specifically in the gyrus dentatus. There is a close connection between neurogenesis in the hippocampus, chronic stress, and affectively disturbed emotional states. Stress is the principal

factor for depressiveness and states of anxiety, which in each case leads to a decrease in the production and reduced survival of new neurons in the hippocampus. The hippocampus is, however, an important regulator of the HPA stress axis and prevents excessive corticosteroid levels. Chronic stress with the consequence of depressive mood also influences neurogenesis in the hippocampus negatively. If the hippocampus shrinks, there is a lack of inhibitory feedback of the stress axis. The non-decreasing stress further destroys the hippocampus, whereby the vicious circle closes [22]. Chronic stress is thus a risk factor for the development of severe depression. Chronic stress and anxiety reduce the BDNF levels in the prefrontal cortex and in the hippocampus [23]. To this lack of control is added the resistance of the glucocorticoid receptor, which additionally complicates the feedback. Affective disorders are frequently connected with abnormalities of the HPA axis [21].

The lifelong potential neurogenesis is controlled by BDNF ("brain-derived nerve growth factor"). Neurogenesis takes place mainly in the hippocampus. This is all the more significant because in the hippocampus, on the one hand, learning and memory have their structural space, and on the other hand, the hippocampus is extremely susceptible to disturbance and vulnerable through stress. It is therefore not surprising that a severe depression goes along with a reduced hippocampal volume [23]. At the same time, a stress-related decrease in the expression of BDNF in the limbic system is also seen, which underlines the hypothesis of the neurotrophic basis of depression [24]. Fitting to this (anticipating section 9, therapy) is that a therapy with antidepressants intervenes precisely here: the stimulation of neurogenesis. This would at least partly explain why antidepressants do not work immediately but need time.

Prenatal stress has a devastating influence on the psychological health of the child. The mechanism underlying this process is a disturbance of the HPA axis. The glucocorticoid receptor, the main regulator of the HPA axis, is involved here. Prenatal psychological stress results in a lastingly altered methylation pattern (epigenetics!) of the regulatory gene for the HPA axis. This leads to lower responsiveness of the receptor to the cortisol signal, with the consequence of reduced control of the HPA axis in the cycle of catecholamines and glucocorticoids. [25]

9. The Neuronal Network

Depression is an illness, only no one can diagnose it reliably. Therefore it is also difficult to recognize it in the general practitioner environment. It cannot be read off from any blood parameter; no inflammation marker and no liver value gives information about this illness. The severity of the symptomatology that this illness exhibits, with complete lack of drive and paralysis of all will to live, suggests that depression is a disturbance of some important neuronal networks. Here, then, signal transduction between the neurons plays a role. To explain this matter, the physiology of the brain should be addressed in a short section:

The human brain consists of approximately 100 billion neurons and just as many glial cells, the macrophages and immune cells of the brain, and the astrocytes, which essentially supply the neurons with energy. The neurons come into contact with one another via 15 quadrillion (15×10^{15}) synapses. Sensory stimuli (seeing, smelling, tasting, feeling, hearing, pain, heat) meet receptors that conduct these received stimuli as an electrical impulse via dendrites into the neuron, from where they are relayed via the axon. The axon ends in the presynapse, in which the

electrical signal is converted into a chemical signal. Through this signal, messenger substances (transmitters) are released from the vesicles located in the synapses and delivered into the synaptic cleft. The transmitters then meet receptors of the postsynaptic membrane. The occupation of these postsynaptic receptors by transmitters converts the chemical signal back into an electrical potential, which relays the impulse into the dendrites of the next neuron, until it finally arrives at the target organ and there triggers, for example, a muscle contraction. The most important neurotransmitters shall be briefly presented here:

9.1 Acetylcholine

The most important neurotransmitter of the peripheral nervous system is acetylcholine. The messenger substance mediates the transmission of nerve impulses to the musculature. In addition, acetylcholine plays an important role in the autonomic nervous system (which controls respiration, heartbeat, and metabolism).

9.2 Glutamate & GABA

Glutamate is of central importance especially in the brain. The presynaptic glutamate signal meets (besides the AMPA and ACPD receptor) the postsynaptic NMDA receptor. According to the current state of knowledge, glutamate is indispensable for movement control, sensory perception, and also memory. In Alzheimer's patients, the release and uptake of glutamate is impaired. The messenger substance is also likely to be involved in the emergence of epileptic seizures. GABA is an inhibitory neurotransmitter in the brain. If it docks onto the receptor, it lowers the excitability of the nerve cells. Thus GABA is, as it were, the antagonist of glutamate. Alcohol consumption also has an effect on the neurotransmitters, or rather their receptors: through inhibition of the NMDA receptors and simultaneous stimulation of the GABA receptors, the transmission of stimuli is inhibited. Reactions now occur more slowly, less controlled; the reaction speed is slowed and environmental stimuli are no longer correctly interpreted.

9.3 Serotonin

The neurotransmitter serotonin is regarded as the central mood-maker and influences, among other things, appetite, sex drive, and psychic well-being. In depressions, the concentration of this messenger substance is often reduced. Antidepressants act here, among other places, prevent the reuptake of serotonin into the cells, and thus raise the level. There is an imbalance in the serotonin values.

Newer postulate: depressions arise when there is a decrease of neurons because these are not sufficiently renewed (Barry Jacobs). Here the term neurogenesis comes into play, which is treated in the next section. Serotonin is formed from the essential amino acid tryptophan, which must be taken in with food. If tryptophan intake is restricted, not enough serotonin can be formed from it in the brain. Serotonin deficiency is characteristic of depressions. Tryptophan uptake can be impaired by too high fructose concentrations in the gut (fructose intolerance!). If the brain lacks serotonin, it sends out signals that demand sweetness. Here, much sugary food is then eaten, which usually consists of 50% and more of fructose, or fruit, which likewise contains a high proportion of fructose (fruit sugar). Fructose does not serve the satiety center; from this, food cravings develop, which are met with even more fruit, which is well-meant but harmful.

Fructose is taken up via the GLUT5 transporter in the gut. This transporter is only available to a limited extent. In the case of insufficient uptake, the fructose is broken down bacterially in the gut (like xylitol, sorbitol, mannitol), which can lead to flatulence and diarrhea. In malabsorption there

is even less GLUT5. Even normal amounts of fructose become a problem. If fructose reaches the large intestine through a GLUT5 deficiency, it combines with tryptophan, an essential amino acid that must be taken in with food. The tryptophan taken in with food is firmly bound in a fructose-tryptophan complex; it is no longer available for serotonin synthesis. The consequence is a reduced uptake of serotonin with reduced availability of serotonin in the brain.

Some of these neurotransmitters can be brought into connection with drugs. For drug consumption has a particular effect on the function of the neurotransmitters in the brain. Thus the stimulant amphetamine (in scene circles "speed") brings about the release of the neurotransmitters noradrenaline and dopamine. This brings about a stimulation of the sympathetic nervous system, which thereupon contributes to the onset of the "fight-or-flight" reflex. A strong wakefulness, vigilance, and insensitivity to pain and hunger can be observed, only one of the reasons why amphetamine was administered to soldiers as a drug in war. The release of cannabis may be regarded as problematic. Precisely in the age after puberty, in which the brain undergoes a fundamental restructuring and the communication pathways are redesigned, an interference of drugs with neurotransmitters that bind to the same receptors must have effects on psychic development.

9.4 Dopamine & Noradrenaline

Attention, learning ability, motor activity, for all these functions the human brain needs dopamine. In Parkinson's patients, for example, dopamine deficiency in the brain leads to movement impulses no longer being correctly transmitted. At the same time, an excess of acetylcholine and glutamate leads to tremor and the muscle stiffness that is typical of Parkinson's disease. Noradrenaline arises from dopamine and is responsible for the control of attention and wakefulness. In people who suffer from ADHD, medications are used that raise the noradrenaline and dopamine level in the nervous system.

In severe depression, the function of the neurotransmitters is disturbed. There is a close relationship between high cortisol levels and serotonin: chronic stress raises the cortisol levels and reduces serotonin release. This has to do with the fact that, through the elevation of cortisol, the tryptophan breakdown is steered, instead of toward serotonin, in the direction of kynurenine breakdown. This breakdown pathway of tryptophan is catalyzed by an enzyme (indoleamine 2,3-dioxygenase, IDO) that is activated by cortisol and cytokines. Further breakdown pathways of kynurenine point the way to depression and dementia, which exhibits a common biochemical path to these pathologies. In glial cells, these are the macrophages in the neuronal mesh (there are in each case approximately 100 billion neurons and glial cells in the human brain), breakdown products of kynurenine generate, on the one hand, oxidative stress, and on the other hand activate the NMDA glutamate receptor, which leads to an excessive activation of the neuron and finally to apoptosis. This is the path to neurodegeneration [26].

10. Plasticity of the Brain

Plasticity is the property of individual synapses, nerve cells, and whole brain areas to change in dependence on their use. This happens, on the one hand, as a reaction to injuries of the neuronal tissue; on the other hand, it is a natural process that enables the organism to react to changes in its environment and to adapt to them. Plasticity is thus the basis of all learning processes.

Plasticity thereby includes various levels. Functional plasticity plays out at the level of the synapse, i.e., the connections between nerve cells, whereby only the strength of the synaptic transmission, i.e., the amount of the released messenger substance or the receptor density on the receiver cell, is altered. One speaks here also of synaptic plasticity. Synaptic plasticity can, moreover, also cause structural changes. One speaks of structural plasticity when the synaptic contact surface is enlarged or reduced, or whole synapses are built up, broken down, or rebuilt. Structural plasticity can go beyond the synapse when whole axons or dendrite trees are retracted and/or extended in other directions. Finally, this also includes the formation of new nerve cells, neurogenesis. In humans it takes place above all in the gyrus dentatus of the hippocampus, the olfactory bulb, and in the prefrontal cortex through cell division. Thereby stem cells arise that then migrate, when needed, into more distant brain regions.

The history of depression cannot be told linearly; therefore two aspects are considered here that appear again elsewhere. The gyrus dentatus in the hippocampus is the brain area in which learning content is first stored (short-term memory), in order then to be finally deposited in the prefrontal cortex (long-term memory). Chronic psychological stress significantly suppresses cell proliferation in the gyrus dentatus of the hippocampus [27]. The integrity of the hippocampus is decisive for psychic stability. The new formation of the neurons in the hippocampus depends essentially on the presence of a trophic factor, the “brain-derived nerve factor” (BDNF). Chronic stress reduces the BDNF levels in the prefrontal cortex and hippocampus [24]. Chronic stress is a risk factor for the development of severe depression and influences neurogenesis in the hippocampus negatively. Contrary to common opinion, neurogenesis takes place into old age. Positive modulators are social stimulation, learning, making music, dancing, loving, cuddling (oxytocin!). Negative modulators are chronic stress, glucocorticoids, and overactivity of the glutamate NMDA receptor. And of course the process of aging, if it is not countered with sufficient exercise and a healthy lifestyle [28]. The hippocampus is especially vulnerable to oxidative stress (see section 8). This creates a connection between a lifestyle that is to a high degree caused by oxidative stress and characterized by a metabolic state with hyperglycemia and obesity, and a decrease in mental agility and freshness. Here the boundaries to other pathologies become blurred. The bridge to dementia is built here. As the first criterion, the loss of short-term memory applies. There is also a further connection: the diabetic metabolic state (hyperglycemia) raises the risk for the development of dementia and Alzheimer’s several times over; one therefore speaks, in Alzheimer’s disease, of type 3 diabetes [29].

Vital physiological processes such as stimulus conduction, hormone regulation, energy homeostasis, and mental coordination (cognition) are regulated and controlled in the central nervous system through an interplay of the signal molecules mentioned above (not exhaustively). Neurogenesis takes place throughout life. The networking of the brain areas (hippocampus, hypothalamus, amygdala, nucleus accumbens, prefrontal cortex), which is necessary for the coordination of our thinking, feeling, and acting, undergoes a readjustment in puberty. One should therefore not be surprised if, in this developmental phase, the control of feelings, namely the control of the amygdala by the prefrontal cortex, gets out of control. With the knowledge of these physiological processes, the release of cannabis to adolescents appears extremely questionable.

11. Inflammation, Depression and Stress

More and more it is recognized that physiological functions, biochemical parameters, and psychological symptoms are most closely connected with one another. Thus it is no wonder that depression does not represent a purely psychological or even psychiatric phenomenon, but can only be understood in conjunction with the nervous system, the stress-associated hormonal system, and the immune system. Here, first the immune system shall be presented.

The body's own defense system consists of two components: the innate immune reaction and the acquired (humoral, adaptive) immune reaction. The innate immune system mediates a cellular response that can occur immediately and be understood as a primary immune response in an emergency; the humoral immune system is downstream, is acutely activated, and produces antibodies in the end. All cells of the two immune systems derive from stem cells from the bone marrow. From these develop the erythrocytes, the thrombocytes, and the leukocytes. The latter are the cells from which derive, on the one hand, the scavenger cells (macrophages, natural killer cells (NK)) and on the other hand the lymphocytes. In these, the differentiation begins into B lymphocytes, which produce antibodies (humoral immune response), and into lymphocytes that take the passage through the thymus, differentiate there into T lymphocytes, and are regarded as carriers of the cellular immune response.

11.1 The Innate Immune System

The innate immune response is composed of nonspecific components and is directed generally against infections and less against specific threats. The innate immune response represents the body's first line of defense against intruders. It is fast, quickly reaches its peak, and then falls off again, and is above all always available. It is, however, also nonspecific and imprecise. It is the older of the two systems and developed as early as approximately one billion years ago in the first organisms. For even these had to defend themselves against enemies. The innate immune response sets an inflammatory reaction in motion at the site of infection, which is meant to contain and destroy pathogens.

The inflammatory process described here is the part of innate immune defense. It is a nonspecific immune reaction whose main weapon is the oxidative stress in the affected tissue, with which pathogens are killed. One speaks of "oxidative burst", by which it is meant to express what plays out there in an oxidative hell. It includes phagocytosis and breakdown of the fragments. As effective as this immune response is for the eradication of pathogens, it also harbors the danger that, through the inflammation with the associated production of ROS ("reactive oxygen species", oxygen radicals such as O2• or OH•), surrounding tissue is also affected.

The main task of the innate immune system is to immediately recognize intruding pathogens and to organize a fast and effective defense reaction at the site of infection. The components of innate immunity are present from birth and can be called up immediately at any time. Newly arisen cells also react after a second challenge according to the same scheme. The cells of the innate immune system are macrophages, dendritic cells, mast cells, granulocytes, and NK cells. They produce: NO, oxygen radicals, cytokines, complement, antimicrobial peptides. The recognition of damage, pathogens, or molecular triggers such as lipopolysaccharides (e.g., bacteria) takes place via inherited receptors, phagocytosis receptors, Toll-like receptors, and others. The specificity of the innate immune system and its flexibility is low, the reaction fast and immediate. Influencing it is not possible. Above all, however, one thing: it has no memory.

11.2 The Adaptive Immune Response

One speaks of acquired or adaptive immunity in the case of B and T cells, because their action first requires a kind of learning phase. The acquired immune response is composed of specific components. To them belong the cells that are specially adapted to threats. They are pathogen-specific and develop rather slowly after first exposure to a pathogen. The adaptive immune response, which developed later than the innate immune response, runs mainly via so-called T and B lymphocytes. Only late during evolution does this system appear, with the cartilaginous fishes. The T lymphocytes mature in the thymus (which decreases with age, which is why the immune response also turns out weaker in old age), the B lymphocytes experience their maturation in the bone marrow. T and B lymphocytes possess, on the one hand, a large repertoire of receptors that guarantee a great specificity; on the other hand, with long-lived cells an immunological memory is built up. Only T lymphocytes and B lymphocytes carry individual antigen receptors. The adaptive immune response is able to adapt to an environment with a multitude of constantly changing pathogens. The immune system is activated by antigens that are recognized by the body as foreign. To these belong above all the surface proteins of bacteria, fungi, and viruses.

In this figure, the temporal courses of the innate and the adaptive immune response can be read off.

In stress, the immune system reacts in 2 stages. In a first stage, the body reacts to acute stress by the signal from the hypothalamus reaching the adrenal gland via sympathetic nerve fibers. This thereupon secretes adrenaline and noradrenaline. The stress hormones increase the heart rate and blood pressure and activate the immune system. This is important if, in a stress situation, it comes to a fight, which was conceivable in evolutionary times, if the dog bites and an infection sets in, the immune system is ready. Immune cells carry receptors for neurotransmitters. Thus the activated neurons can activate the immune cells. They speak the same language.

In a second stage, the hypothalamic-pituitary-adrenal axis (HPA axis) is activated by the hypothalamus releasing the corticotropin-releasing hormone (CRH), which in turn releases in the pituitary the adrenocorticotropic hormone (ACTH). Via the bloodstream it reaches the adrenal gland, where it occasions the synthesis of cortisol. Cortisol (acutely) finally inhibits the potential immune reaction and leads the immune system back to the normal state [31].

Stress belongs to life, but it must not become chronic, because it then attacks the whole organism. Decisive is that, through the release of cortisol, a feedback occurs that brings the stress back to the starting position. This feedback is, however, put out of force when the receptor responsible for the cortisol, which must be occupied for a physiological response, no longer reacts adequately. In investigations in patients with post-traumatic stress disorder, which can be a cause of depression, an epigenetic change (methylation) of the gene coding the receptor was identified, which led to the inactivation of the receptor signal. If, therefore, a feedback response turns out only weak or not at all, cortisol continues to be released. This disturbs the entire metabolic state [25]. Stress-related fatty acids are released from their depots (fat tissue), which leads in the end to insulin resistance. Insulin resistance is, however, the pathobiochemical basis of the metabolic syndrome, which encompasses high blood pressure, type 2 diabetes, fatty liver, and coronary cardiovascular illnesses. There therefore leads a direct path from stress (triggered by, e.g., traumas, experiences of violence) directly to depression and a disturbed metabolic state.

In recent years, however, the view has been directed to the interplay of brain and peripheral organs, whereby changes in the endocrine and in the immune system play a main role in the emergence of depressions. Here, on the one hand, the products of the cellular (native) immune response with the release of cytokines play a role. In the last 40 years it has been clearly shown that the cellular (and the humoral, see below) immune response is out of balance in severe depression. Interleukin-6 (IL-6) is elevated as one of the most important inflammation-promoting cytokines in the blood of depressive patients. The pro-inflammatory cytokine interferon-alpha (IFN) developed in patients during a therapy (e.g., hepatitis) a depression that could be abolished again by discontinuing IFN. Pro-inflammatory cytokines modulate the release of biogenic amines (neurotransmitters). Cytokines redirect the breakdown of tryptophan to serotonin into the breakdown to kynurenines, whereby the function of serotonin during a depression is weakened. At the same time, the dopaminergic system is also weakened by inflammation. IFN (a body's own cytokine) reduces the synthesis of dopamine and activates the synthesis of NO. This neurotransmitter activates the glutamatergic system, which, when it overshoots (occupation of the glutamatergic postsynaptic NMDA receptor with glutamate), leads to apoptosis (programmed cell death) and neurodegeneration. Cytokines increase the reuptake of neurotransmitters (monoamines such as serotonin and dopamine) and thus reduce the functionally important concentrations of these neurotransmitters in the synaptic cleft, which inhibits neuronal transmission.

Since dopamine stands for reward, its decrease must lead to the lack of desire and joylessness typical of depressions. If cytokines such as IFN and lipopolysaccharides (LPS, bacterial outer walls) are administered to subjects, they show symptoms such as dejection, states of anxiety, anorexia, fatigue, psychomotor slowing, poor sleep, and cognitive malfunction, as they normally occur in severe depressions. (Pro-inflammatory cytokines also contribute to the development of depressions by activating the HPA axis, this in turn by increasing the corticotropin-releasing hormone (see fig.). This leads to hypercortisolemia and consequently to chronic stress, which triggers changes in the serotonergic system and finally plays a critical role in the development of a depression. When then the glucocorticoid receptor becomes resistant, inhibitory feedback signals are no longer registered, with the consequence of permanent flooding of the organism with cortisol, as was shown above. Hypercortisolemia plays a devastating role in the brain as in the periphery, starting from chronic stress with its consequences, above all with the insulin resistance affecting the whole organism.

Figure: Stress raises in the limbic system the "corticotropin-releasing factor", which activates the HPA axis, which leads to the elevation of circulating glucocorticoids. The fundamental result of stress is the release of fatty acids and cytokines from the visceral fat, which leads to the development of insulin resistance. The chronic elevation of cortisol (hypercortisolemia) lowers the threshold for the development of a depression, activates the release of pro-inflammatory cytokines, and desensitizes the glucocorticoid receptor on immune cells, hypothalamus, and neurons, which leads to glucocorticoid resistance. This leads to permanently elevated cortisol levels with increased release of fatty acids, which in turn release cytokines such as, among others, interleukins and resistin. The result is the development of insulin resistance.

The inflammatory process plays a decisive role in the psychopathology of depression. Nevertheless, the question arises why the inflammation status in depression is elevated, although the cortisol levels are also elevated. The answer could be that the glucocorticoid resistance in the brain and in the periphery no longer leads to any suppression of the immune cells, and these thus

continue to produce cytokines. The stress-induced activation of the HPA axis in combination with the glucocorticoid resistance leads to the activation of the microglia, the cytokine-producing macrophages in the brain. The result is an elevated inflammation status. The above-mentioned connection of depression and metabolic syndrome harbors no surprise. The question is only that of the chicken and the egg. Stress leads to both, depression and insulin resistance; conversely, the disturbed metabolic state, with the consequence that, e.g., cytokine-producing fat tissue (visceral fat) leads to elevated cytokine levels, which in turn are typical of the inflammatory process affecting the whole organism. Even mild acute stressors, e.g., public appearances, can lead to an elevation of NFκB activity (NFκB is a transcription factor that is part of an inflammatory cascade, at the end of which stands the production of, e.g., TNFα, a strong pro-inflammatory cytokine).

In severe depression there is a protracted activation of the inflammatory network in the brain. The signal transmission of the trophic nerve factor neurotrophin is weakened, which leads to reduced repair performance on neurons, and neurogenesis is, its main site is the hippocampus, reduced. In addition, there is an increased activation of the glutamatergic (excitatory) pathway, which leads to neuronal apoptosis, oxidative stress, and also to apoptosis in glial cells and astrocytes, which supply the neuron with energy. Summarized at this point: in addition to the pro-inflammatory cytokines (IL-6, TNFα, and others), nitric oxide (NO), cortisol, and glutamate play a decisive role in the pathological process that is connected with depression [30].

The structural changes in the brain of patients with chronic depression finally lead to the hypothesis that depression also has a neurodegenerative background. The shrinkage of the hippocampus in patients with severe depression, the decrease in the number of astrocytes, and the loss of neurons in the prefrontal cortex and striatum are described. These changes can be the result of elevated levels of pro-inflammatory cytokines, nitric oxide (NO), prostaglandin E2, and other inflammation-promoting mediators [26].

11.3 The Function of the T Cells

Not only the native but also the adaptive immune system seems to play an important role in the development of a depression. CD4+ T cells of depressive patients show a spontaneous apoptosis. In depressive patients, T cell function is inhibited by glucocorticoids. Elevated cortisol levels are a characteristic of depression. This is the result of receptor resistance (on the one hand reduced expression of the receptor and on the other hand epigenetically modified receptor). A normal functional capacity of the T cell system seems indispensable for neuronal integrity and for learning functions. T cells facilitate the expression of BDNF and neurogenesis in the hippocampus. The inhibition of T cell functions by stress and depression therefore has fundamental consequences for essential immunological elements of a healthy activity in the brain.

11.4 Acute and Chronic Stress

Psychological stress modulates the immune system. Chronic stress can lead to fewer B and T cells circulating. It likewise leads to the decrease of a proliferating response of lymphocytes to various mitogens that normally activate an immune response, and also to the decrease of natural killer cells. Thereby the susceptibility to infections increases and additionally complicates illness processes such as cancer. In contrast, acute stress such as an examination situation is able rather to stimulate the parameters of the immune system [32].

12. Oxidative Stress

Each individual one of the common theories on the development of severe depressions explains only insufficiently all the reasons for this illness. Besides the monoamine hypothesis and the cytokine-inflammation hypothesis, a further one would come: oxidative stress. The main source for oxidative stress are the mitochondria, whose production at the oxygen radical O2• proceeds under normal conditions within physiological limits, but in the case of an unhealthy way of life gets out of hand. Then O2• reacts with NO•, which is of various origins (there is a neuronal (nNOS), an endothelial (eNOS), and an inducible (iNOS) NO synthesis), to peroxynitrite (ONOO-). For in the inflammatory process as in chronic stress, through activation of NO production by the inducible NO synthase, nitric oxide, NO, is generated, which means nitrosative stress. The iNOS is activated to excess by xenobiotics, medications, infections, vaccinations, chronic stress, and others. Nitrosative stress inhibits the function of the mitochondria, whereby energy production is impaired. The consequence is ATP deficiency. A reduced ATP production correlates significantly with the severity of the depression. The purely psychiatric view of depression must be expanded by the view of the imbalances in cellular energy production in the mitochondria. Thus other pathologies that themselves rest on mitochondrial dysfunction, such as migraine, likewise intervene in the depressive process. Migraine raises the risk of depression; conversely, depressions increase the migraine risk [33]. Chronic stress is the trigger for nitrosative stress and therefore the cause for mitochondriopathies, i.e., for pathologies that arise on the basis of weakened mitochondria.

13. Multitasking

A certain belief has spread that says multitasking is a superior ability to do several things at once. This ability is gladly attributed to women. Unfortunately, however, the brain is not able to do or pursue even just two things or processes at the same time. Joachim Bauer (University of Freiburg) justifies this in terms of brain physiology. Whoever drives a car and at the same time telephones or checks their mobile phone for messages drives as if with an alcohol level of 0.8 to 1 per mille. When the reason for the increase of depressions is asked about (worldwide around 300 million people live with depressions, which corresponds to an increase of 18% between 2005 and 2015 [37]), then surely the use of multitasking in the media (simultaneous use of telephone, e-mail, television, and others) can also be regarded as a decisive factor for an overburdening of the capacity for perception. An increased “media multitasking” is brought into connection, in a regression analysis, with an increase in depression and symptoms of anxiety. The ability for multitasking is gladly attributed to women: children, household, job. This would mean that the brains are gender-specifically different with regard to working and short-term memory, but they are not. The claim and compulsion to have to accomplish many things at the same time inevitably lead to stress, which logically can issue into a depression. Since many women see themselves in this situation, the hypothesis can at least be set up that in this may lie the reason why the depression rate in women is twice as high as in men.

14. Therapies

The therapy against depression rests on several approaches. On the one hand it is based on the monoamine hypothesis, which states that the lack of serotonin in the synaptic cleft, and thus an insufficient occupation of the postsynaptic receptor with serotonin, is responsible for the depression. The common antidepressants were developed on the basis of the "monoamine hypothesis", which regarded a disturbed order within the biogenic amines (serotonin, dopamine, adrenaline, noradrenaline) in the limbic and cortical circuit as the main cause of depressions. Antidepressants are meant here to restore order. The therapeutic success of the so-called serotonin reuptake inhibitors (SSRI = selective serotonin reuptake inhibitor) is, however, limited. A good third of all patients do not react at all; in others, the effect, with attenuated symptomatology, sets in only after weeks. That speaks against a pure receptor pharmacology. The reason for this is that it is not the inhibition of the reuptake of serotonin from the synaptic cleft that constitutes the actual effect of the SSRIs or the monoamine oxidase inhibitors (MAO) and the tricyclic or tetracyclic antidepressants, but the influence on the native as well as the acquired immune system. The antidepressants of the monoamine oxidase type inhibit the cytokine release that, as a product of the native immune system in the case of stress, floods the organism and negatively influences the interplay of the neurotransmitters.

Other mechanisms could, however, also come into play. One mechanism is the activation of neurogenesis in the limbic system with the hippocampus, which under the conditions of a depression undergoes a shrinkage, and which can explain the temporal delay of the pharmacological effect. It could be shown that fluoxetine, an SSRI (selective serotonin reuptake inhibitor), acts positively on processes of neurogenesis in the hippocampus and, in a neurogenesis-dependent process, restores the control on the stress axis in the hippocampus [31]. It seems that the multitude of effects of the antidepressants in the end rests on the activation of BDNF and thus activates neurogenesis in the hippocampus [34]. Nevertheless, a complete remedy of the symptoms is rarely achieved. Causes and involved mechanisms in the neuronal mesh of the limbic system are too interwoven for the depression to be tackled with a single causality and corresponding therapy. To this belongs the therapy that inhibits the action of the cytokines, i.e., reduces the inflammatory process overall. It has turned out that the common antidepressants lower the inflammation markers [30]. Cytokines influence the metabolism of serotonin, noradrenaline, and dopamine and alter the neuroendocrine functions overall. Cyclooxygenase inhibitors (e.g., celecoxib), which specifically inhibit the production of inflammation-promoting prostaglandins, are discussed for the therapy, even if only partial relief is achieved. Aspirin too was tested in studies with a similar effect. These therapy approaches rest clearly on the anti-inflammatory effect of the substances in question [26].

But it is also the lifestyles that promote depressions. Everyday stress in profession, family, and elsewhere generally cannot be switched off. But there are conditions and possible changes in lifestyle that can mitigate the symptomatology of depression and act preventively against a possible development of a depression. Nutrition belongs without doubt to the factors that decide over well-being or illness. One of the most striking correlations and bidirectional relationships exists between depression and obesity. 70% of adults with depression develop an obesity; conversely, obese people carry a 40% higher risk of becoming depressive [35]. This correlation is more pronounced in women. Obesity in turn has to do with nutrition, too much of the wrong things, and lack of exercise due to a mainly sitting way of life. Among the components that

promote overweight and obesity belong, first, the high carbohydrate load and wrong fats (too much palmitic acid and trans fatty acids). Both lead to insulin resistance. Insulin resistance is, however, not only a problem of the periphery but is also a central problem. Through the glucose transport prevented by insulin resistance, there is in any case a lack of energy supply, above all in the brain. This promotes the dying off of the nerve cells. One way to supply the brain with healthy nutrition lies in the ketogenic diet. This consists of few carbohydrates, protein, and medium-chain fatty acids such as from coconut fat or avocado. Ketone bodies (acetoacetate, hydroxybutyric acid) are formed in hunger and fasting (interval fasting) in the liver from stored fat and thus, under these conditions, provide for the necessary energy supply. Ketone bodies also raise the amounts of the growth factor BDNF, which promotes the survival of nerve cells and stimulates the formation of synapses. Ketone bodies are also active in the hippocampus, the structure for learning and memory [36].

Indispensable for the functional capacity of the neurons with their communication with one another is the membrane quality, since it is decisive whether signals can be relayed. For this, the membranes must preserve their mobility, for receptor function and ion transport. Decisive for these concerns is the content of omega-3 fatty acids. These are absolutely underrepresented in today's food. They must urgently be replenished through supplementation. Physical activity likewise increases the activation of BDNF. Martin Korte recommends, for the preservation of balanced brain structures and for mental recovery, the 5 L factors:

- Learning (ongoing activation of the hippocampus)
- Running (Laufen) (activation of BDNF)
- Laughing (Lachen) (balancing effect on the neurotransmitters in the limbic system)
- Love (Liebe) (oxytocin, the cuddle hormone, promotes neurogenesis)
- Salmon (Lachs) (omega-3 fatty acids)

15. Healing Pathways of Regulation

On the path to helping people under the suffering pressure of depressions, the concepts of therapeutic action should contain a broad spectrum of solution options. In the sense of a therapy that begins close to the individual experience of those affected, several medical and life concepts can be used alongside one another in the sense of the simultaneity of physicality, stress physiology, and psychic feeling. Psychotherapy, psychiatric support, sport, nutritional factors, and targeted personalized supplementations support one another in the best possible way.

A set of 20 healing key factors which can set the body's own self-regulation pathways in motion.

15.1 Glycoplan & "Natural Eating"

An anti-inflammatory nutrition according to Glycoplan, with few bad carbohydrates, valuable proteins, and valuable fats, has a very positive effect on a healthy psyche. Natural Eating moreover creates, via the right dietary fibers, a healthy gut with superfoods for energy metabolism and the brain. Filling the repair toolbox for a succeeding neuro-metabolic psycho-health. The less sugar, the more moderate the long-term blood sugar value, the better. Hyperglycemias, insulin resistance, hidden metabolic inflammations fetter the immune system, cause inflammations, burden performance, inhibit regeneration, and weigh heavily on the psyche. Dinner cancelling or

meals with protein, vegetables, nuts, and moderate evening sport can be helpful in getting the metabolism going. With this, the rules of the game for the physiological cortisol activities for morning wakefulness with a drive for activity are also guaranteed.

The ability laid down in us humans to switch over to fat burning in the mitochondria we can activate and train according to Glycoplan rules of the game. At night, fat burning reigns. This homeostasis guarantees stable functions of melatonin, serotonin, growth and sex hormones. Therefore the experts are agreed: sugar, short-chain carbohydrates, and trans fats should therefore be avoided especially in the evening. [39] [40] [41]

15.2 A Healthy Gut

A healthy gut shapes a harmonious gut-brain-psyche axis. The healthy gut feeling is grounded on micro-creatures and bacteria in the gut. Pre- and probiotics can today be regarded as essential for this regulation. In the health of the microbiome and the gut flora lie hidden the remote control and the driving force for our psychic health, a healthy brain, a strong immune system, a high-performance mobile musculoskeletal system, a strong cardiovascular system, a healthy inner rhythm, and a good regeneration. In the gut, the setting of the course for the sufficient synthesis of melatonin, serotonin, GABA, NPY, kynurenic acid, SCFA such as butyrate, and NAD+ takes place. These guarantee the proper timing between calming, regeneration, and good performance in everyday life. [42]

15.3 Probiotics and Prebiotics

Probiotics and prebiotics can influence the gut-brain-psyche axis regulatively via signal pathways of the microbiome-metabolome communication pathways. The spectrum of effects ranges over anti-inflammatory, neuroreparative processes, up to the strengthening of the mitochondria and the autophagosome. An improvement of the homeostasis of the GIP, the regulation of the signal pathways of the enteric and autonomic nervous system, the metabolization of the amino acids, as well as the synthesis of the superfoods NAD+, butyrate, biotin, vitamin B3, folic acid, and the SCFA opens up effective help. We recommend rotating through various pre- and probiotics according to a rotation principle: Sakara, Omni Biotic, Symbiolact, Daily, colon formula, etc. [43]

15.4 Thyroid in Balance

Thyroid overfunctions generate stress, poor sleep, poor regeneration, and end in a thyroid underfunction with lack of drive, fatigue syndrome, and depression. A good supply with the essences for the thyroid, i.e., selenium, zinc, iodine, vitamin E, vitamin D, and the amino acid L-tyrosine, can guarantee a good basis. Further amino acids such as cysteine, methionine, arginine, and lysine likewise prove helpful. Via the strengthening of the energy system and the mitochondria, the performances of the thyroid can be economized. As the ideal target value for the TSH, we aim for the range between 1.6-2.2. [44]

15.5 The Support of the Mitochondria

The support of the mitochondria strengthens the brain, the body and emotional landscape, and guarantees energy on all levels. High-performance mitochondria can, corresponding to the need, guarantee all requirement profiles in everyday life. Ribose, galactose, creatine, coenzyme Q10, NADH, and the B vitamins can render very good services. Also for the immune defense behavior against viruses, the mitochondria are part of the orchestra. [45]

15.6 Antioxidative Protective Orchestra

The orchestra of physiologically antioxidative substances can unfold antidepressive effect spectra across several system levels. These molecular natural substances act anti-inflammatorily, relieve several mitochondrial functions, act regulatively in the equilibrium systems of the neurotransmitters, and they can improve the ATP availability as well as the cellular energy balance. [46]

15.7 Sunlight

Sun, light, and vitamin D nourish the balance of all steroid hormones, promote activity in the morning, and help the inner rhythm to find rest also in the evening. Light is the best-known stimulus for the central pacemaker nucleus suprachiasmaticus. That sufficient exposure to natural sunlight can markedly improve the quality and the sleep time is demonstrated by a current study of the American Academy of Sleep Medicine. [47]

15.8 Radiation and Light Hygiene, Blue Light Filter

Since scientific data clearly demonstrate that blue light and the blue light receptors ipRGC (intrinsically photosensitive retinal ganglion cells) trigger wakefulness and hyperarousal via several signal pathways, it is advisable to switch off electronic devices at the latest around 9 p.m., to use a blue light filter, and to provide in the bedroom for a lamp with a sufficient red component.

15.9 Vitamin D and B

Besides the milieu in the gut and a sufficient tryptophan supply, a supporting role falls to the vitamin D level. Sufficient levels of the sun hormone are essential for the work of the mitochondria, for every regeneration, all molecular repair processes, the synthesis of growth and sex hormones, for a strong immune system, and for neuronal learning processes. [48] The family of the B vitamins is woven just as essentially into a multitude of metabolic processes, the guarantee of a stable energy budget of the mitochondria, the synthesis of neurotransmitters and the hormonal balance in the organism, a stable psychoneuroimmunology, as well as a harmonious inner rhythm.

15.10 Omega-3 Fatty Acids

As a landing place for the hormone vitamin D, with clearly demonstrated anti-inflammatory effects, as an important tool in the molecular toolbox, good supplies with a balanced spectrum of omega-3 fatty acids are essential for performance and regeneration. In particular, the spectrum of the DHA can strengthen the psyche. [49]

15.11 Amino Acids and Proteins

Within the last years, the scientific data situation regarding nutrition has fundamentally improved. Proteins and amino acids play a central role for psychic health. Rich in protein and relatively poor in carbohydrates proves decisive for regeneration, performance, and a healthy psyche. Amino acid deficiency states can today be measured unambiguously and very reliably, qualitatively and quantitatively. Especially the amino acids tryptophan, tyrosine, phenylalanine, methionine, asparagine, glycine, GABA, valine, leucine, isoleucine, methionine, glutamine are strongly reduced in depression illnesses. Tryptophan shall be emphasized: L-tryptophan belongs to the group of essential amino acids and must be supplied with food. Tryptophan serves as the basic substance for vitamin B3, for the neurotransmitters serotonin and melatonin, and is essential for the circadian rhythm as well as for the calming systems of the body. Tryptophan can

thus act antidepressively, pain-regulatingly, sleep-promotingly, cardiovascular-regulatingly, anxiety-relievingly, and activatingly on the economy of energy metabolism.

15.12 Galactose: a Bypass System for the Energy Budget

In order to avoid the chronic stress patterns with insulin resistance, neuronal energy crisis, pathological insulin secretions in the brain, and to bypass the wide spectrum of dysfunctional insulin signal cascades, the insulin-independent monosaccharide galactose offers manifold solutions for the brain and its performances. Galactose is taken up equally well by liver and brain. After uptake via GLUT1 and GLUT3, galactose is metabolized intracellularly via the famous Leloir metabolic pathway to glucose and finally ATP. In addition, galactose induces the intestinal release of glucagon-like peptide-1 (GLP-1) and of the glucose-dependent insulinotropic polypeptide (GIP), which can both regulate insulin secretion. GLP-1 thereby improves, via central pathways, memory and learning performance. Via the regulative effect of galactose, the acetylcholine neurotransmitter system in the nucleus basalis of Meynert can also be influenced regeneratively. As one effect principle, the improvement of aerobic oxidative phosphorylation and of the mitochondrial functions under galactose turned out. [50] [51]

Within the broadly fanned-out effect spectrum of galactose, the parallel effects in peripheral and central energy metabolism are striking. Thus galactose improves fat burning in the mitochondria and can support weight regulation. [52] In clinical studies, both cognitive performance and physical performance could be markedly improved via oral galactose administrations. In more than seven years, extensive investigations confirmed that streptozotocin and insulin resistance conditions can be regulated and restored via galactose. Thus orientation behavior, cognitive performances, stress tolerance, and balanced behavior patterns improve. [53] The positive effects of orally administered galactose could be shown via the induction of the expression, in particular of GLUT3, which enable the overcoming of the intracellular energy deficiency. Via this pathway, the excess extracellular glucose can now reach the cell in the bypass system of the new GLUT3, insulin-independently. The simultaneous reduction of ammonia with the biosynthesis of amino acids via the citrate cycle makes possible the overcoming of the toxic ammonia effect. [54]

15.13 Myoreflex Therapy

Myoreflex therapy, craniosacral therapy, acupuncture, and regulations in the region of the upper cervical spine can correspondingly calm and, to a healthy degree, prepare the ground for physiological activities. The physiological erection of the cervical spine, the stable neuromuscular synchronization around the head joints, can help us physically and psychically to come into balance. Via sympatholytic effects in the cervical ganglia and stimulation of the vagus ramifications, areas of the ventromedial hypothalamus (VMH), the periventricular nuclei (PVN), the nucleus arcuatus, and the dorsomedial hypothalamus can be reached regulatively and de-stressed. At the same time, via the balance of interoception, rest, relaxation, calming, and a feeling of happiness can unfold. [3]

Regulation of the masticatory musculature, the jaw region, and the trigeminal stress activity patterns: Myoreflex therapy, osteopathy, craniosacral therapy, acupuncture. The interconnections of the activities of the masticatory musculature are, as it were, online coordinated between the stress directors in the head, the trigeminal nuclei, and nuclei of the hypothalamus (VMH, PVN, nucleus arcuatus) as well as thalamus nuclei. The treatment and regulation of the tonus conditions of the masticatory and jaw joint musculature opens the neuroanatomical paths to central mechanisms of de-stressing. [3]

15.14 Vagus Nerve Stimulations

Vagus nerve stimulations: ear acupuncture, sound therapy, light therapy, neural therapy, Myoreflex therapy. The parasympathetic nervous system and the rest nerve vagus resemble a kind of treasure chamber of the organism. Regeneration can be strengthened just as much as the body-emotional landscape. [55]

15.15 Neuronavi

Neuronavi applications are based on frequency modulations and their effect on the autonomic nervous system. Imbalances arise when, through permanent stress and overload, one component of the nervous system, the sympathetic, is permanently fired up. The acoustic applications stimulate the autonomic nervous system for regulation. Frequency-modulated music can render very good support in regeneration in cases of stress burdens, tensions, and sleep difficulties, in burnout, and in depressiveness.

15.16 Meditation

A good stress management, mindfulness, meditation, sufficient sleep, breathing exercises, sauna, a well-timed cold bath, and “everything that makes one feel happy” can show very positive effects. A whole series of research works could show that these procedures of mindfulness can reduce the burdening stress level and “destructive emotions”. At the same time, cognitive control operations can be set in motion via activation patterns of the PFC. De-stressing and regeneration can profit considerably from these approaches and act antidepressively. [56]

15.17 HRV and Biofeedback Training

Via HRV, derailments and asymmetries of the autonomic nervous system can be detected and made visible just as well as depression-associated disorders of the sleep architecture. Even more, via biofeedback procedures, (otherwise autonomously organized) stress patterns can, via neuro-training, become cognitively controllable and surmountable. [57]

15.18 Movement & Myokines

Training and the activation of muscle hormones helps and protects against depressions. In addition, training helps to break down the activities of immunosuppressive stress hormones, to strengthen the potential immune activity of the mitochondria, and to improve the aerobic oxygen availability. Finally, there are also positive psychoneuroimmunological effects for the immune behavior. As an original source and resource of such factors, the musculature and its muscle hormones, the so-called myokines, could meanwhile be identified as the largest hormone gland of the human being. Meanwhile, in fact, 3,000 myokines are known. Very many of the neurohormones previously known for the brain, such as BDNF, GDNF, IGF-1, are also produced in the muscles and secreted, on the one hand, directly into the surrounding tissues, but also for the brain. This group of the known neurohormones is supplemented by a wide spectrum of neurotrophic messenger substances. Substances such as NGF, neurotensin, and neuropeptide Y belong to the classic candidates. A whole family of further myokines such as IL-6, irisin, STAT3, PGC-1a, AMPK can both crank up and fine-tune these known factors, but also become active directly in the brain for neurogenesis, neuroplasticity, neuronal repair, and optimized cognitive performance. Irisin can, in these processes, act with the transcription factor FNDC5 in several neuroactive mechanisms. [58] [59]

Training can repair derailments of the central rhythm and the peripheral clocks. Moderate training in the evening can be efficient and sensible. Muscle training activates the physiological fat burning. Here an important detail on this: after physical exertion it is important, afterwards, to eat the right thing. To go hungry afterwards brings, apart from extreme exceptions, little. Fish or a small steak, vegetables, soups, chickpea and lentil dishes, or simply just a protein shake. Training in the morning helps the metabolism get going and activates fat burning. Before breakfast, on an empty stomach? Yes, but knowing how! Running at low intensity for 45 minutes helps to train the metabolism toward economy. Afterwards a protein shake, egg dishes, low-carb muesli with amaranth popcorn, buckwheat, berries, nuts, almond milk, coconut milk, goat or sheep yogurt. Well-timed endurance training also helps to bring an inner rhythm that has gotten out of step back into harmony. It is important to pay attention not to start too fast, because otherwise the organism nibbles at its glycogen stores and the training effect is starved. [60] Galileo, a special training that is very suitable to overcome physical inactivity and, besides a multitude of positive effects, also opens up antidepressive effect spectra. [61]

15.19 Sleep Training and Melatonin

Sleep is trainable. Muscle training in the evening, midday sleep, targeted going to sleep earlier, the elimination of disturbance fields such as blue light, etc., can considerably improve the architecture of sleep and the recovery, and help to free again the inner rhythm originally, naturally anchored in us. Melatonin and serotonin can unfold pain-inhibiting, anxiety-relieving, antidepressive, relaxing, sleep-promoting, and appetite-regulating effects. Both hormones support the circadian rhythm. High insulin levels in the evening and at night inhibit the synthesis of growth hormones just as much as the synthesis of serotonin and melatonin. Metabolic stress and pro-inflammatory tissue with elevated levels of IL-6, TNFα, CRP, and IFNγ lead to reduced synthesis of tryptophan to melatonin. Frequently the important coenzymes magnesium and vitamin B6 are too low and IDO enzymes, which break down tryptophan increasingly dysfunctionally into kynurenine, are elevated. Serotonin and melatonin deficiency additionally bring about hunger and eating attacks. Melatonin is at the same time lacking as the body's own antioxidative protective system. In these dysregulations, 5-HTP, melatonin, and Orthomed Cannabis Plus in the evening can promote the regenerative sleep architecture. [62]

15.20 Social Togetherness

Social togetherness and "being integrated" into nourishing communities can be regarded as an essential precondition for the development of homo sapiens and his healthy psyche. Dynamic equilibrium systems shaped and guaranteed a brain ecology. The situation circle originally described by Thure von Uexküll and the bio-psycho-social environment-ego model encompasses all aspects of human development. In relationship and a trusting and understanding dialogue, the experience of the clients can change considerably in a psychotherapeutic working alliance. In the face of the other, the life of people with psychic suffering pressure can become worth living again. In the sense of a simultaneity, the homeostasis in physiology, biochemistry, biology, and neurobiology can help precisely this ecology of the human body and his psyche to come back into balance and to unfold antidepressive effects. [3] [63]