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Perspective on Environmental Influences Causing Nitro-Oxidative Stress and Modulating Neuroendocrine-Immune Function

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Abstract

Since the evolution of single-celled organisms, the development of defense and tolerance mechanisms in relation to other cells, as bacteria and viruses, became a existential goal. Mitochondria were the organizers to reach that target. The increase in atmospheric oxygen facilitated the process. Generating nitro-oxidative stress proved to be an essential step in this direction. Next step consisted in creating the innate immune system to allow identification of the targets of defense reactions. Nuclear-Factor-kB became the activator of pro-inflammatory cytokines. Inflammation is associated with mood disorders. Inducers of this cascade are infections, autoimmune reactions, allergies, as well as toxic, and neurotoxic substances. The question is, can environmental conditions and environmental toxicants likewise stimulate this cascade. The data described here demonstrate that physical and chemical substances in subtoxic levels are, capable of interacting and of triggering such reactions, and also may be a cause for mood-disorders.

Keywords: Environmental pollutants; Electromagnetic fields; Nitro-oxidative stress; Defense mechanisms; Neuroinflammation; Cytokines; Electroencephalogram

Introduction

The significance of specific environmental factors such as noise (from vehicular traffic, aircraft, bars, etc.) as well as occupationally-relevant factors like working in shifts, under pressure or in particularly unpleasant workplaces due to dampness, cold, heat, or dust have long been recognized as relevant stressors of humans. If one accepts Hans Selye's definition of stress [1], according to which stress is the *unspecific reaction of the body to every form of challenge*, then a more intensive consideration of such environmental factors is justified. Selye borrowed the term *stress* from metallurgy. There the term refers to alterations of metals due to external forces. Similar alterations to human health from such external forces forms the basis of clinical environmental medicine, which deals specifically with how chronic exposition to environmental factors affects the structures and/or functions of the human body.

Throughout evolution, the development of our ability to react to stress was essential to surviving the most challenging and dangerous situations. Without this ability, our remarkable achievements in such varied fields of arts and science, music and sport would never have been possible. The problem is not in the reaction to stress itself but in its restriction to an absolute minimal, indispensible degree. The diversity of environmental stress factors affecting humans is extensive [2,3] and may be

- of a physical nature such as intense heat or cold, insufficient food and water, noise, light, radioactivity, electromagnetic fields, or

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- caused by psychosocial factors such as strained personal relationships, loss of a loved one, time pressure, deadlines, conflicts in school, in other educational institutions, or in the workplace, or

- the result of dysfunctioning of the neuroendocrine-immune system (NEIS) cycles or their essential structures such as membranes, receptors, or organelles as mitochondria.

Never before in the past 150 years has man exerted so much influence on the environment and consequently on his own well-being. The most significant and consequential results of this are the unavoidable bioavailability to the human population of persistent lipophilic chlorinated hydrocarbon not only from products but also from contaminated air, water, and food and the extension to the spectrum of naturally occurring electrical and electromagnetic fields by artificially-produced ones [4] (Figure 1). The assumption that the diseases induced by these new, previously unknown influences are likewise caused by new mechanisms is principally false. Instead, long-established mechanisms will be utilized to solve new problems. This creates stress for the relevant systems, since they did not evolve for these new challenges and their involvement is a biological necessity, even when the organism attempts to select the most appropriate mechanism. The biggest problem resulting from environmental stressors is the loss of established entropy due to these dominating, hitherto unknown influences.

In a study of the European Union (EU) on the prevalence of diseases caused by environmental factors, the authors conclude that 7% of all diseases in the participating countries (Belgium, Germany, Finland, France, Italy, The Netherlands) are caused by environmental effects [5]. The study analyzed only nine environmental stressors: benzene, lead, dioxins/furans/polychlorinated biphenyls (one chemical group), formaldehyde, noise, ozone, passive smoking, and particles. Thus the study is unlikely to reflect reality, since of the more than 4 million known substances, approximately 365,000 are in daily use [6] and for the risk assessment only toxicological methods were applied. Despite these limitations, the frequency of diseases considered to be due to environmental factors was in the area of that for well-recognized common illnesses. It is not surprising that The Lancet Commission lists the death rate due to environmental factors as 25% [7]. Furthermore, during the last decades, a growing body of data has indicated that environmetal stressors can cause elevated levels of free radicals, nitro-oxidative stress, chronic inflammation (especially silent or smoldering inflammation) and even mood changes.

Possiblities and Limitations of Toxicology

Our understanding of the consequences of environmental influences and their tolerance limitations has up until now been defined almost exclusively by the *dose-effect principle*, according to which a linear relationship exists between the affecting substance and the resulting risk. The conclusions based on this principle were and are derived from short, at most a few months-long animal experiments and then extrapolated to humans under consideration of safety factors. The assumption is made that all people react to such substances in the same way. Such studies fail to recognize that individuals can react differently and that exposure to

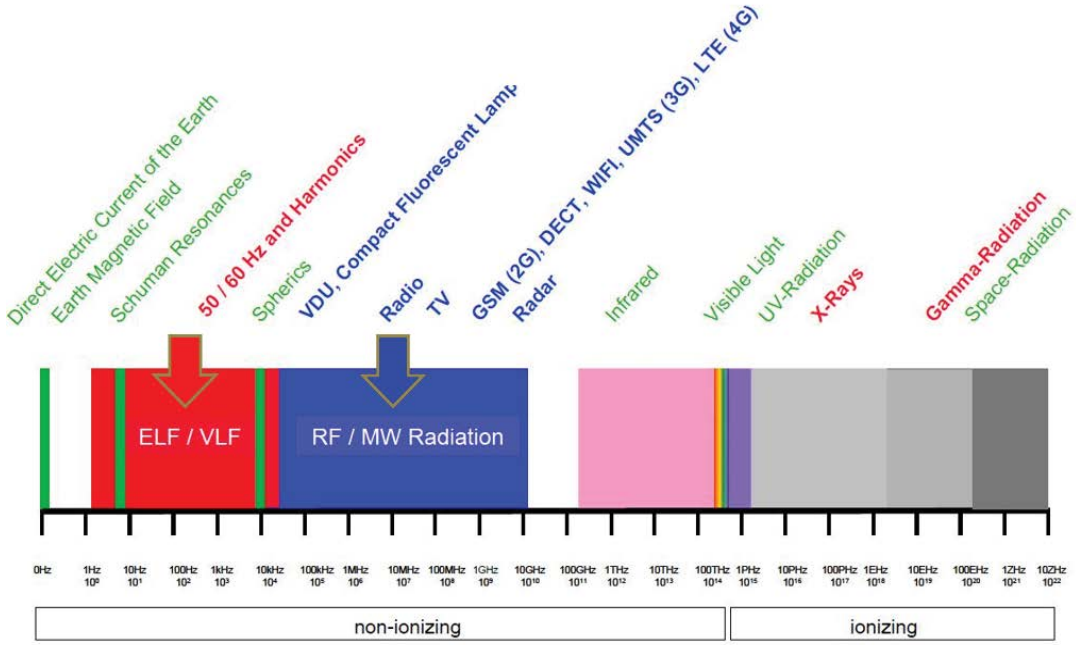

Figure 1: Natural and artificial electromagnetic non-ionizing spectrum. The red and blue columns marked with an arrow are man-ade and new. With the other non-ionizing fields we are familiar since millions of years.

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certain substances can alter an individual's ability to respond. Additionally, chronic exposition can affect individual organs differently. A typical example is the uptake of mercury in the human body. Dental amalgam represents the main source of elemental mercury [8]. It is transported to organs by erythrocytes and can traverse the placenta. In organs it is oxidized by catalases and stored with various half-lives. While its half-life in the kidneys of 0.5 to 1 year is relatively short, it is significantly higher – 6-8 years – in the liver and thyroid gland and exceeds 20 years in the brain. Chronic exposition of even small amounts poses a significant risk of accumulation in the brain [9]. In addition, mercury binds strongly to the S-hydroxyl-groups important for detoxification and disrupts the disulfide bridges required for the three-dimensional structure of proteins. The longer the exposition, the more the protective capacities are diminished. At the same time, the risk of autoimmune reactions increases due to the structural alterations of proteins. This was confirmed by studies showing a significant increase in the formation of antibodies to particles of the cell nucleus, tissues of the thyroid, kidney, and nerves, as well as serotonin [10,11].

For a number of chemicals, monotone dose-response curves could not be shown, especially when they had hormonal effects which could be estrogenic and androgenic, antiestrogenic and antiandrogenic and influencing the sexual differentiation of central nervous sytem (CNS) [12]. In the first publication on this problem of chemicals with a hormonal effect, the authors coined the term *endocrine disruptors* [13]. This initiated a wave of similar publications so that today such effects have been confirmed for a plethora of chemicals. Their greatest influence is in the embryonal stage or early developmental phases of youth. These phases are described as *effective window of action***.** In summary, the complex interaction of the organism with its environment cannot be viewed as a simple dose-effect mechanism. In cases of chronic exposure to small amounts of harmful substances, the dynamic changes in the body resulting from such exposure play as significant a role as genetic predisposition [14-17].

Environmental Chemicals as Modulators of NEIS

Although the genotypes of humans are 99% identical, a huge variety of phenotypes exist, despite the apparently small number of differences in the genome. So besides the genome it is these differences that determine the individual variability of responses to environmental influences. This variability results from epigenetic modulations of the function of enzymes for which environmental factors, especially chemicals, play a significant role. Researchers from the Humboldt University in Berlin succeeded back in the 60s of the last century in demonstrating that various concentrations of hormones, neurotransmitters and cytokines occurring during critical developmental phases and altered by environmental factors can have functionally teratogenic effects [18-21,22]. Since the CNS controls the interactions of the NEIS [19,23], harmful substances that pass the blood-brain-barrier can affect the organization of the brain and consequently alter its ability to respond to various challenges. Lipophilic chemicals that affect membrane function such as dioxins, furans, and polychlorinated biphenyls (PCBs), among others, play a crucial role in the development of such damage. Persistent chemicals in the environment were identified as culprits. Furthermore, results from an Israeli research group demonstrated that the invasion of immune cells from the choroid plexus is a prerequisite for the development of reparative and cognitive capacities of the CNS [24]. However, since the chemicals mentioned above are also immunotoxic, it would appear unlikely in view of these results that such crucial steps in the regulation of the NEIS would generally proceed with no physiological affects. The possibility of an *unavoidable background burden* must, therefore, be reconsidered. The near future will clarify to what degree such influences are the (partial) cause of increasing cognitive brain dysfunction and mood disorders and why even during normal everyday challenges efficient brain function is possible only after concomitant activation of stress reactions. The results of this research group also suggest that the risk of neurodegenerative diseases is similarly influenced [24].

Genetic polymorphisms of detoxification enzymes

The mechanisms of detoxification were not developed throughout evolution to compensate for exogenous pollutants but rather to break down reactive, toxic, and sometimes even carcinogenic byproducts of our manifold metabolic processes. The implementation for these purposes of the same enzyme systems required for the detoxification of ubiquitous environmental toxicants creates competition between the detoxification of endogenous and exogenous substances. The greater the demand for detoxification of exogenous substances, the fewer molecules are available for the treatment of endogenously occurring intermediates. Detoxification proceeds principally in two phases. Phase I serves to convert non-polar lipophilic substances through oxidation, reduction, and hydrolysis into polar hydrophilic compounds. Often the resulting intermediates are more toxic than the original substances. The requisite enzymes belong to the complex cytochrome P450 enzymes, of which two essential ones should be mentioned here: cytochrome P450 3A4 (CYP3A4) and cytochrome P450 2D6 (CYP2D6, following chapter). Both enzymes are important in endogenous physiological regulations, for detoxifying lipophilic exogenous toxicants, and for the metabolism of medications. Their function is required by more than half of all drugs. Cytochromes are themselves inductors of free radicals [25]. The increasing exposure to humans in the last 150 years to lipophilic chemicals has led to significant detoxification stress (Figure 2).

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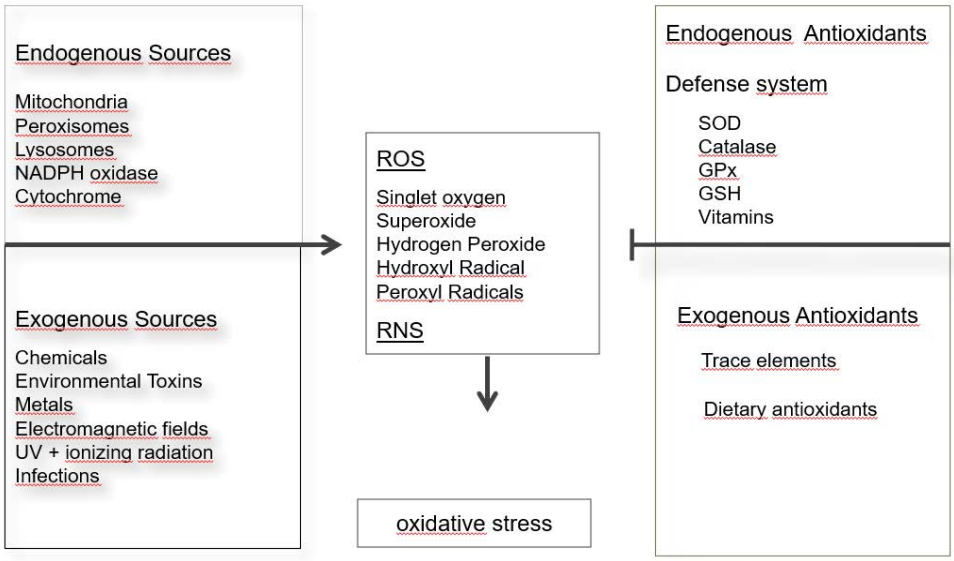

Figure 2: Endogenous and increasing types and amounts of exogenous sources of ROS and RNS. Compensation by the defense system and exogenous antioxidants.

In Phase II of detoxification, the polar hydrophilic substances are conjugated. The essential mechanisms for this are glucoronidation, sulfonation, acetylation, conjugation to amino acids, and methylation (Figure 3). Here we can discuss only a few examples of environmentally relevant enzymes and their respective polymorphisms. It was found, for example, that the polymorphism of UDP-glucuronidase associated with the relatively benign regarded Gilbert's Syndrome is a significant risk factor (odds ratio 8.6) for Multiple Chemical Sensitivity (MCS) [26]. The same enzyme is required to neutralize two carcinogenic byproducts of a polymorphism of catecholamine-O-methyltransferase (COMT), quinones and semiquinones, which result from insufficient compensation of the stress reaction induced by catecholamines caused by a polymorphism of COMT. In the case of pentachlorphenol, glucoronidation detoxifies the body, whereas conjugation to glutathione with the help of glutathione-S-transferase P1 (GSTP1) is the detoxification pathway for the brain. Such factors determine not only who will get ill but also which organs will be affected and which not.

Cytochrome P450 2D6

Among the myriad of enzymes of the cytochrome P450 system, the polymorphism of the cytochrome P450 2D6 gene (CYP 2D6) stands out because of its role in neurotransmitter regulation, in Phase I detoxification of pollutants, as well as in metabolism and activation of medication. It is also an important cause of oxidative stress [25]. It consists of nine exons and is located on chromosome 22q13.1. The enzyme encoded, a polypeptide with 497 amino acids, is expressed in a number of various neurons. Genetic mutations can cause transcription errors (splicing defects) leading to amplification or deletion of the gene and/or interruption of transcription (altered stop codons) as well as polypeptides with missing

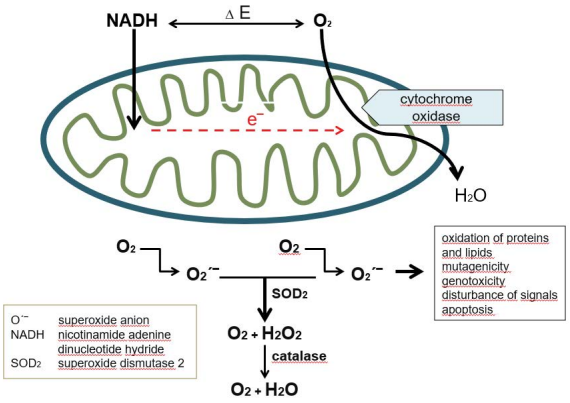

Figure 3: ΔE is the engine of mitochondria for the synthesis of ATP. It is also the producer of free radicals and superoxide, which may become uncontrollable when oxygen is high.

or substituted amino acids. Four types of enzymatic activity are produced, termed poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM), and ultrarapid metabolizer (UM). The UM type, with extremely reduced function in many drugs, has a low incidence in northern Europe (1-2% of the population) and a somewhat higher incidence in western Europe (5.5%). In the Asian population, this type does not occur at all [27]. In the approximately 3.3 million people with this genotype in Germany, the desired therapeutic effect with normal doses of drugs metabolized by this step cannot be expected. The PM type is found in 5-10% of the Caucasian population. Since in addition to the detoxification of lipophilic harmful substances and the metabolism of medication CYP 2D6 also has the task of controlling the regeneration of serotonin from 5-methoxytryptamin, in 4-8 million German people this function is significantly restricted and may lead to a competing situation between xenobiotics, drugs and regeneration of serotonin in the use of this enzyme [28].

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The enzyme serves as a substrate for antidepressants, neuroleptics, beta blockers, antiarrhythmics, and acid inhibitors. In two studies, an increase in psychotic disturbances in persons with the PM genotype was described [29,30]. When a drug is both a substrate and an inhibitor of CYP 2D6, problems similar to the IM type can occur. There is far too little awareness that medical therapeutic applications can lead to metabolic stress in combating environmental influences, that environmental substances can diminish the efficacy of drugs, and that both effects can limit the regeneration of serotonin.

Mitochondrial function and nitro-oxidative stress

Mitochondria are the crucial organelles of energy production. Molecular biochemical mechanisms like glycolysis and the citrate cycle, position, transport and binding of protons for ATP production, and the use of substances such as cobalamine and carotinoid, had already been developed, as was the important ubiquinone. Since then, the regulation of both extra- and intra-cellular oxygen plays an essential role [31]. This regulation was coupled initially with the interaction with the free oxygen radicals thus produced, followed by the resulting superoxide ($\cdot O_2^-$), and finally with the associated oxidative stress. Its use as a defense mechanism is known as *oxidative shielding* [32]. In addition, mitochondria were also the organizers of the innate immune system in order to better identify the target of defense [33]. The nitric oxide axis had been developed early, initiating together with superoxide the cascade peroxynitrite, oxidative stress, and activation of nuclear factor-*kB (*NF-kB). This cascade remains significant to this day.

Mitochondrial structure and function is affected by many commonly occurring toxic substances as well as their own metabolic activities. Here the non-compensated extensive production of free radicals called reactive oxygen species (ROS) plays a crucial role. They can induce structural alterations in the membranes of the mitochondria, especially of the inner membrane, or even damage the ribosomes and DNA. The lipid and protein content of mitochondrial structures plays an essential role in determening the location of damage caused by hydrophilic and/or lipophilic pollutants [34]. ROS activate inducible nitric oxide synthase (iNOS) and stimulate the production of nitric oxide ($\cdot NO$), which forms with $\cdot O_2^-$ peroxinitrite ($\cdot ONOO^-$). Mitochondrial oxidases and the availability of oxygen are the main sources of superoxide. Artificial respiration increases $\cdot O_2^-$ dangerously, thereby potentiating the lethality of such actions [35]. $\cdot ONOO^-$ activates the immunological inflammatory reaction through NF-kB and stimulates the further production of ROS, resulting in a vicious circle that can end in an oxidative burst and cytokine storm. If the process is limited, postviral fatigue or depression may result.

Manganese superoxide dismutase 2 (Mn-SOD2), catalase, and glutathione peroxidases (GPx) can exert a regulating protective effect against this. If these enzyme activities are diminished due to a polymorphism and/or high consumption by pollutants, the mitochondria will not compensate the high amount of generated $\cdot O_2^-$ and induce their own damage [36-38]. The wild type T/T is present in approximately 20% of the Caucasian population. Fifty percent have a heterozygote (C/T) and over 25% have a homozygote (C/C) reduced enzyme activity. A relevant performance reduction is generally accepted for a homozygous altered gene, while the effect of a heterozygous polymorphism remains controversial. The $\cdot NO$ production is enhanced by damage to the mitochondria, whereby the transition metals of the citrate cycle and of the respiration chain are inhibited. In the short term, this represents a useful functional limitation. If this effect occurs because of chronic exposure to pollutants or long-term intake of medication, the reduction in ATP can be associated with chronic fatigue [39]. Since the catecholamine controlled stress regulation via S-adenosyl methionine is dependant on ATP [40], the capacity to regulate stress decreases to a time in which an effective stress control is especially necessary as ATP level is low. An optimal mitochondrial function is an essential prerequisite for the function and regulation of the catecholamines of the stress axis. This mechanism plays a crucial role in the greater than 11-fold escalation of burnout in AOK-medically insured Germans in the period between 2004 and 2011 [41].

Today's lifestyle does not permit sufficient regeneration of the mitochondria from the lost ATP. In conjunction with a deficiency of micronutrients especially in stress situations and the increasingly significant deficiency in the respiration chain of ubiquinone due to its reduction by multiple therapeutic applications of medication [42], this constant loss of energy ends up causing exhaustion of the neuroendocrine stress axis and induces what is now commonly recognized as burnout. The stress situations in which this problematic becomes clinically manifest are not inducers of the functional basis of the problem but rather of the moment in which the deficient capacity to compensate becomes noticeable for the first time. In such cases, psychotherapeutic therapy is neither preventive nor curative. Due to the functional damage to the mitochondria, the organism loses its ability to rapidly regulate stress and to economize the control loops of the NEIS. Both the necessary maintenance of a stress situation as well as the control of the extent and termination of the stress reaction are energy demanding processes which dephosphorylate ATP completely [40]. The remaining adenosine is immunosuppressive, which explains the high susceptibility to infections following intensive mental or physical stress. Inflammation and stress reactions activate, as mentioned above, Indolamine-dioxygenase (IDO) and tryptophan-dioxygenase (TDO) increasing kynurenine synthesis from

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L-tryptophan up to 90% and down regulating synthesis of serotonin down to 10%. This manifests in depression due to the ATP-deficiency induced exhaustion as well as associated fatigue [39]. On the other hand, down regulation of serotonin had been an evolutionary advantage as affected individuals were forced to limit their activity. This step enhanced their chance to survive. In the case of chronic inflammation, this effect is maintained by the production of NF-kB, interferon-y (IFN-y), interleukin-1ß (IL-1ß) and tumor necrosis factor-α (TNF-α). Microglia become inflamed, and kynurenine is transported by LAT1 through the membrane into the brain where it is metabolized to kynurenic acid and quinolinic acid. The latter stimulates together with glutamate the N-methyl-D-aspartat (NMDA) receptor, thereby triggering inflammation-associated depression [43].

Nitro-oxidative stress

Whereas immunological reactions resulting from the immune system's defense against foreign agents and toxicants are based on specific genetic or acquired mechanisms, oxidative stress represents an unspecific reaction with both beneficial and detrimental potential. Oxygen plays the dominant role. It is an essential element for all life on earth and occurs in both a diatomic (O_2) and triatomic (O_3) form. Through its ability to take up electrons from reduced substrates, it has a remarkable oxidative capacity [25].

Free oxygen radicals are strong oxidants. These include singlet oxygen ($^1O_2$), superoxide radicals ($\cdot O_2^-$/ $HO\cdot_2$), hydrogen peroxide (H_2O_2), hydroxyl radicals ($OH\cdot$), peroxyl radicals ($ROO\cdot$), and reactive nitrogen species (RNS). Physiological markers of oxidative stress are: 8-hydroxydeoxyguanosine, 8-nitroguanine, protein carbonyl, iNOS, nitrotyrosine, malondialdehyde, F2-isoprostane, oxidative sugar products, redox-ratio of the glutathion system, NF-kB, cyclooxigenase-L, glutathione-S-transferase pi, and hem-oxigenase 1. Sources of oxidative stress include mitochondria, cellular oxidases (NOX), metal-catalyzed reactions, myeloperoxidase (MPO), NO-synthases (NOS), oxidases of the endoplasmic reticulum, cytosolic enzymes and DNA methylating enzymes. From today's perspective, the presence of oxygen is no longer required. Oxidative stress is considered a chemical reaction in which an atom or molecule donates electrons. Its oxidation number is thereby increased. The substance receiving the electrons is reduced. Both reactions are part of the redox reaction [42].

Free radicals also have useful functions. For example, they carry out lytic functions in the lysosomes of macrophages. They play a crucial role not only in interactions with tumors and infectious microorganisms but also with environmental pollutants. Endogenous sources of free radicals are mitochondria, peroxisomes, lysosomes, nicotinamide adenine dinuleotide phosphate (NADPH) oxidases and cytochrome enzymes. Exogenous sources include chemicals and toxins, UV- and ionizing radiation, and mutagens (Figure 2). Their effect can cause fatigue [44] and may be accompanied by inflammation. My own, not yet published data, suggest that this applies similarly to electromagnetic fields. Postinflammatory tissue damage results from the action of free radicals. Local inflammatory processes were believed to have only a local impact. In the meantime, it has become clear that even minor local irritations (*silent inflammation*) can exert a systemic effect if they are chronic. These result in alterations in neurotransmitters, cortisol levels, gonad functions [3], energy levels [37,38], endothelial function, gene activation and inactivation, and protein structure. The primary therapeutic goal is not to stop or at least reduce the oxidative stress by applying antioxidants but rather to terminate it by identifying the cause. To accomplish this, interdisciplinary cooperation is essential. In addition, an important challenge in the future will be to recognize when oxidation plays a protective role and when its elimination would only increase risk (*antioxidant paradox*) and not minimize it [32].

Although $\cdot NO$ is structurally an inorganic compound and not a typical cytokine, it nevertheless fulfills the function of a cytokine [45]. On the one hand, it has the function of directing the blood flow to the location of the inflammation to allow rapid transport of necessary substances. On the other hand, it has the function of destroying intracellular pathogens directly [32,45]. In doing so, the production of the highly reactive and oxidative stress inducing $\cdot ONOO^-$ from the reaction of $\cdot NO$ with $\cdot O_2^-$ is initially advantageous, since oxidative stress controls the activation of NF-kB, which accelerates the inflammatory process [36,46-49]. Proinflammatory cytokines as well as nitric oxide can induce the activity of nitrogen monoxide synthase (iNOS). This can occur both in neurogenic tissue through the activation of neurogenic nitrogen monoxide synthase (nNOS) and along the endothelium [36,50] through the production of endothelial nitrogen monoxide synthase (eNOS). As long as the process is short-lived, the advantages of the $NO\cdot/ONOO^-$-cascade outweigh the disadvantages. The situation becomes more dangerous when the inflammatory processes are chronic, when for example the chronic effect of xenobiotics in one's private and occupational sphere or the use of alloplastic materials or chronic infections are the rule and not the exception. Oxidative stress has been reported to be an important cause of chronic fatigue syndrome (CFS) [51].

Nitro-oxidative stress in COVID-19

The first defense reaction to viruses is not immunological but physical: oxidation fulfills this function as a defense reaction. It is also termed *oxidative shielding* [32]. Evolutionarily this mechanism is more than two billion years old and basically the same now as then. The mitochondria remain the place where the action is. For this defense reaction the cell utilizes the electrons remaining from the generation

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of ATP by protons [52,53] In combination with oxygen (O_2), free oxygen radicals like $\cdot O_2^-$, singlet oxygen, H_2O_2, OH radical, and peroxyl radicals are produced [42,54] These ROS are utilized even today for the defense against a wide variety of infectious organisms [32]. The method is rapidly available, since the mechanisms are active at a low level even in healthy people. The activation time is considerably faster than that of the immune system. If $\cdot O_2^-$ is not required, it is catabolized in the first step by Mn-SOD$_2$ to hydrogen peroxide, which is still an oxydative radical. In the second step, it is catabolized to water (H_2O) by catalases (Figure 3, 4). This step is particularly relevant for the development of edema of the lungs (*fluid lung*) in patients with COVID-19 [55].

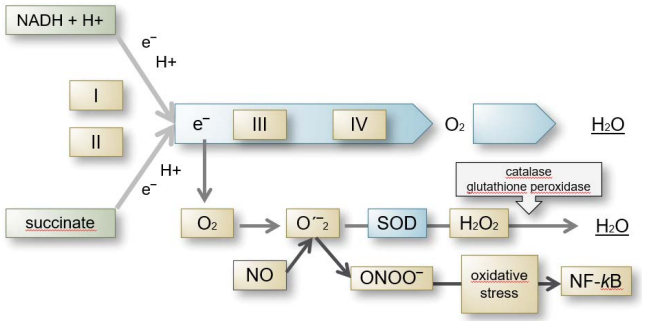

Figure 4: Leakage of electrons between complex II and III when O2 induces high ΔE. Superoxide rises and elevates peroxinitrite by binding to nitric oxid. The resulting oxidative stress activates NF-kB which stimulates the production of proinflammatory cytokines.

In the case of an infection, the organism increases the production of nitric oxide [56]. As an inducer of the NO·/ ONOO⁻ cascade, NO· is also bactericidal and virucidal and dilates blood vessels in order to direct the blood flow to the location of infection [57,58]. The latter effect is, among others, one of the reasons for the increased risk of embolisms in COVID-19 patients. As mentioned before, nitric oxide reacts easily with $\cdot O_2^-$ to ·ONOO⁻, the strongest biological inducer of oxidative stress [56-61]. In the defense mechanism of the innate immune system, oxidative stress activates the complement cascade, cytotoxic CD8+-T cells, and antibody synthesis of B cells. NF-kB is activated by oxidative stress [36,54]. From then on the production of proinflammatory cytokines begins (IFN-y, IL-1ß, IL-6, TNF-α, etc.). The release of cytokines stimulates inducible nitrogen synthase (iNOS), which amplifies NO· production (*vicious cycle* according to Pall 2007). A cycle is closed (Figure 5). The influx of calcium can additionally activate the eNOS and the neuronal NOS (nNOS) causing inflammation in nerve tissues and endothelium [36,55]. Tuning oxidative stress to its lowest effective level is essential to avoid causing serious risks when uncontrolled. Ubiquinol plays a crucial role here [42]. In addition, cholesterol has to be available in adequate amounts since it is the basic molecule in the production of cortisol and of the "mother hormone" of all sex hormones pregnenolon, the only sex hormone synthesized in mitochondria [62]. If this process remains adequate and controlled, clinically mild or low level symptoms will develop. Complications or long-term effects would not be expected. The application of exogenous antioxidants in this phase is counterproductive. They should be used only in the recovery phase of the infection. Vitamin B12 especially should be avoided since it inhibits the beneficial activation of NO·. Chronic activation of the cascade iNOS --- ·NO --- $\cdot O_2^-$ --- ·ONOO⁻ --- oxidative stress --- activation of NF-kB --- proinflammatory cytokines plays a crucial role in environmental syndromes multiple chemical sensitivity (MCS), chronic fatigue syndrome (CFS), fibromyalgia (FM), electromagnetic hypersensitivity (EHS), Gulf War Syndrome (GWS9, sick building syndroem (SBS), posttraumatic stress disorder (PTSD) [36,²-65] as well as in psychic disorders [43,46-49,66]. It is therefore not surprising that postviral fatigue and depression (*long haul COVID-19*) can be a consequence of the infection even in young people.

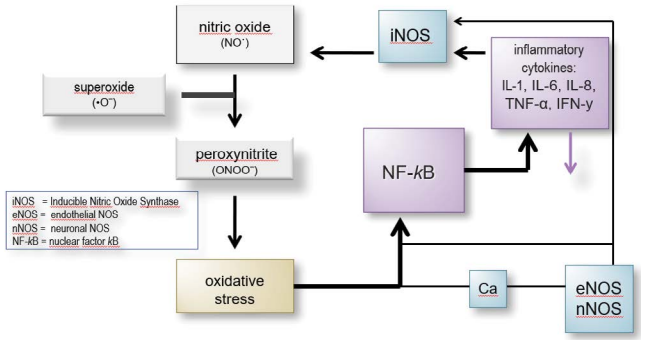

Figure 5: "Vicious cycle" of nitric oxide, superoxide, and peroxinitrite causing inflammation by expression of NF-kB and proinflammatory cytokines. INOS, eNOS and nNOS keep the process running [36].

Oxidation of lipids and proteins

The development of ROS and free radicals in the organism is a physiological process that is in itself not pathological. What is decisive is whether free radicals can be sufficiently compensated by radical scavengers. A radical strives to fill incompletely filled electron orbitals with electrons that are freed by collision with other molecules. The reaction begins on the membrane phospholipids by the removal of hydrogens from the effect of a OH radical. It continues by producing conjugated dienes, over a peroxyl radical, hydroperoxid, and alkoxyl radical and on to malonaldehyde (MDA), which can be measured as a marker substance of lipid peroxidation. Hardly noteworthy in nature but since the introduction of chlorine chemistry ubiquitous existent toxicants cause the oxidative destruction of lipids and proteins. Another important factor is that chemicals such as polychlorinated biphenyls, dioxins, furans, bisphenol A and others are structurally very similar

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to the antioxidants ubiquinone and vitamin E. The chemicals displace these out of the lipids, thereby diminishing the oxidative protection they guarantee. The resulting increased production of ROS and inhibition of oxidative protection amplifies the toxic effect considerably. The problem of denaturizaton of membrane lipids has been known for years but received too little attention and is the result of structural and functional stress caused by environmental influences. This effect can be found at the membranes of receptors as well. The damage to membranes of postsynaptic dopamine D_2 receptors by mercury, formaldehyde, and pentachlorphenol (PCP) has been reported [67,68].

Proteins can be oxidatively altered in a general and widespread way or locally and selectively. The latter type of protein oxidation is the most common and significant. This effect occurs when ROS are produced locally thereby inducing structural changes in the proteins leading to denaturation, aggregation, or desintegration. Basically no amino acid residue is excluded from such alterations, although cysteine, methionine, phenylalanine, tryptophan and tyrosine are most often affected. Thus, the amino acids required for the synthesis of neurotransmitters are frequently involved. Chemicals, non-physiological metals, radiation, and electromagnetic fields play a similar role.

In a review [32]. the increased production of ROS is viewed not as the reason for illness but rather a consequence of it. Metabolic damage to cells is considered the initiating mechanism. Oxidation of surface structures leads to protective structural changes that shield the cell and other structures from damaging effects (*oxidative shielding*). Evolutionarily, this mechanism renders cells impenetrable to infectious organisms. The author recommends choosing not antioxidative therapy but instead to treat those metabolic influences that cause the disease. Unfortunately, in addition to infections, a myriad of environmental causal factors have to be considered. Whether the goal of protecting the cells can still be achieved is questionable. Lipophilic substances can damage the membrane structure and render it permeable to hydrophilic xenobiotic compounds that can cause serious damage. An example of such a cascade of reactions were the wood preservatives dissolved in solvents with their lipophilic toxic contaminants. The therapeutic principle of minimizing exposure, well-known in environmental medicine, remains the basis for all other therapeutic interventions even in the case of oxidative shielding.

Pollutants as Regulators of Immune Function

In 1681 John Dryden wrote the remarkable sentence: "Self-defense is nature's oldest law" and in doing so revealed an amazingly advanced understanding of biological life for his time [69]. The critical principle in achieving this goal in evolution was learning to differentiate between substances against which one has to fight (*defense*) and those which one can accept or even cooperate with (*tolerance*). The nitro-oxidative stress system, which developed early, is too biased towards defense and was at best only capable, through oxidation of own structures, of maintaining the current state in the sense of oxidative shielding [32]. In order to better determine when defense and when tolerance is appropriate, the innate immune system had to be developed. It utilized hereby the surface structures of biological substrates such as lipopolysaccharides, lipoproteins, lipoarabinomannan, lipoteichoic acid, polyanions, formyl peptides, muramyl peptides, and peptidoglycan [45]. A perplexing problem today is that environmental pollutants seldom possess such surface structures that would permit a clear differentiation between defense and tolerance. Often they bind to tissue structures, denature them, and make them targets of defense as well as inducing inflammation. Already in 2002 a shift from classical infectious diseases to allergic and autoimmune disorders was recognized [70] (Figure 6).

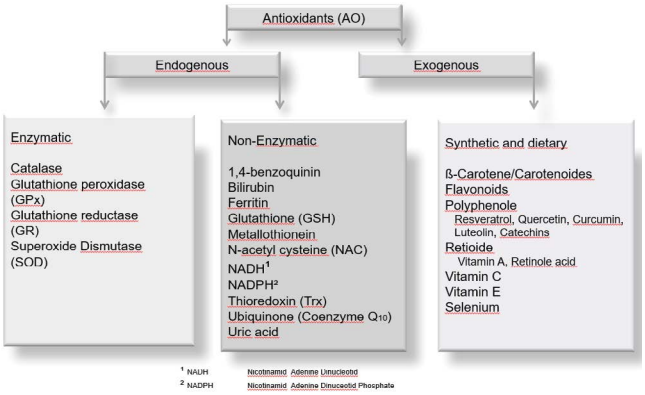

Figure 6: Enzymatic and non-enzymatic endogenous and exogenous synthetic and dietary antioxidants for regulation of oxidative stress.

It was long believed that the classical four types of allergy (Type I, II, III, IV) represented the only form of pathological immune reaction to environmental noxen. Later the granulomatous intolerance reaction was added as Type V. Since Type I (immediate-type, IgE-mediated allergy) and Types IV and V (delayed-type, T-cell mediated) can be distinguished by allergy tests, these are the most common ones tested diagnostically in cases of hypersensitivity. The significance of unspecific inflammatory immunologic reactions as well as the loss of immune tolerance as relevant additional mechanisms was recognized only much later [3].

Already in 2001 a textbook of immunology mentioned that susceptibility of immune cells to intracellular pathogens was significantly enhanced by the presence of IFN-y: *IFN-y makes cells susceptible to intracellular pathogens* [45].The concomitant influence of lipophilic (e.g. dioxines, furans, PCB) and hydrophilic toxicants (e.g. water soluble solvents) favors intracellular penetration considerably. Chemicals can induce inflammatory immune reactions, as shown by

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phthalate, which is also considered to be an endocrine disruptor (Figure 7). Basically all chemicals as well as non-physiological metals in the body can cause this. This explains why, in contrast to allergic reactions, clinical symptoms can be caused by a myriad of compounds [36,50,71]. Chemically different substances can induce the same symptoms in the same person, even in low, previously tolerated doses. This fulfills the definition of Multiple Chemical Sensitivity as represented in the criteria of Cullen [72].

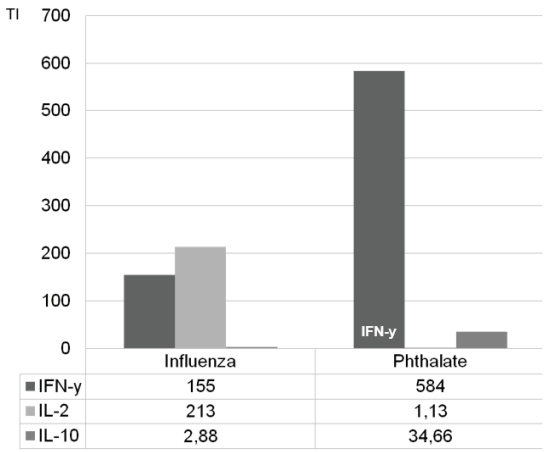

Figure 7: Normal immune reaction to influenza antigen. Highly elevated IFN-y expression caused by phthalate. Low IL-2 to phthalates., and therefor no T- cell proliferation. Unspecific inflammation caused by phthalates. No immune reaction to phthalates in the control person.

The immune system utilizes preferentially the strategy with the best chances of success. Since the industrial revolution, environmental pollutants have been exerting more and more havoc on a larger and larger population. It is unreasonable to expect that in this short time, new immunological mechanisms for these novel expositions could be developed. Instead, the immune system applies the old, well-established reactions for these new challenges. It utilizes logically the immunological mechanism with the greatest chance of success. Unfortunately, as mentioned earlier, these non-infectious environmental pollutants lack the typical membrane surface structures, so that measureable fever reactions, for example, do not occur, although the affected individual subjectively feels feverish. Compared to infections, inflammation is often less apparent but more often chronic (*silent* or *smoldering inflammation*). Conventional diagnostic approaches have little chance in resolving such situations. More comprehensive diagnostics, however, can reveal an increase in pro-inflammatory cytokines and mediators [3].

The combination of lipophilic and hydrophilic substances facilitats the penetration into the intracellular space. IFN-y expression is responsible for lymphocytic inflammation and thus for the activation of T-helper cells (TH_1-cells), as is the pro-inflammatory IL-17. The enhanced proliferation of T lymphocytes is regulated by IL-2. In the case of myelomonocytic leukemia, organ-specific macrophages, which develope from the monocytes in the blood, play a central role. TNF-a, IL-1, IL-6, and IL-8 then represent the dominating cytokines. In all of these cases, the nitro-oxidative stress mechanism is involved. Ongoing, not yet published studies on the immunological effects of the electromagnetic fields of 5G show that after only 30 minutes a significant increase in IL-1b occurs which remains measureable for 2 hours (Figure 8). TNF-a rises more slowly but continuously and after 1.5 hours is also increased (Figure 9). IL-6 and IL-8 do not change in the same time period. The alterations in EEG will be presented in the next chapter.

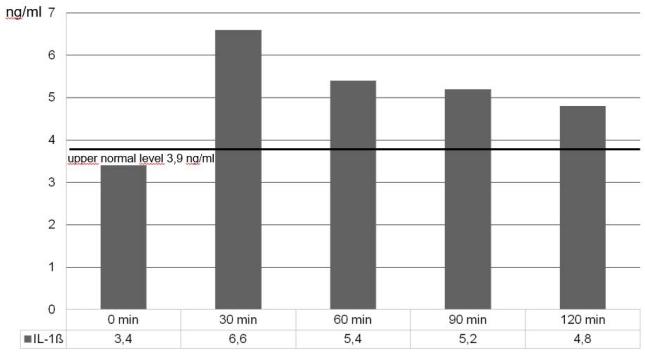

Figure 8: Expression of IL-1ß during 120 min exposure to 5G by a common mobile phone.

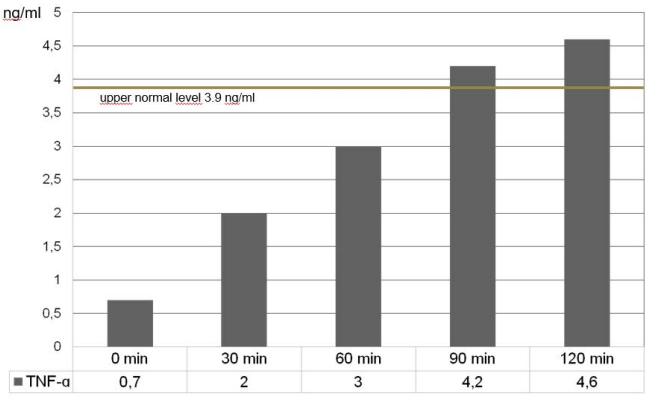

Figure 9: Expression of TNF-α during 120 min exposure to 5G by a common mobile phone.

The expression of IL-4 and IL-10 is controlled by TH_2 cells. The sequential shift to this cell type was described nearly 20 years ago [70]. Environmental pollutants can trigger this trend, too. My own studies showed that exposure to chemicals can substantially increase the expression of IL-10 (Figure 10). None of these patients mounted a normal immune response in the control of the infuenza antigen. The same effect has been described in patients having survived severe craniocerebral trauma caused by accidents.

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They developed a persistent IL-10 expression and often died months after the trauma from simple infections. A comparable deficit is probably responsible for the severe course of some COVID-19 patients. It could be demonstrated quite early that environmental burdens affect the severity of disease [73]. Mast cell activation also goes hand in hand with the activation of TH_2-cells. The clinical results are Type I allergies, pseudoallergies, mast cell disorders, and histamine intolerances. Histamine, leukotriene, tumor growth factor-ß (TGF-ß), and serotonin are important cytokines and mediators. The TH_2-cell system is especially activated by strong catecholamine expression during stress or physical exhaustion [74]. The consequences are fatigue due to ATP deficiency, immune suppression from adenosine generated by the complete dephosphorylation of ATP, the risk of chronically persisting viral infections from the immune suppression, and an elevated risk for autoimmune reactions.

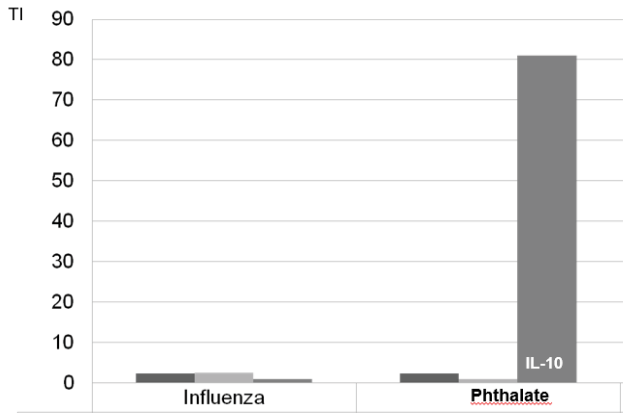

Figure 10: High IL-10 expression caused by phthalates. Suppression of adequate immune reaction to influenza antigen. No immune reaction to phthalates in the conrol persons.

In the end, even previously mentally and physically fit people suffer fatigue, depression, and the *Overtrained Athlete Syndrome* (OAS). This handicap is even more likely in the presence of a polymorphism of catecholamine-O-transferase (COMT) with reduced enzyme activity. NF-kB induces a similar effect with strong inflammation from the TH1-cells. It also inhibits catechol-*O*-methyltransferase (COMT) and compounds the effect of catecholamines [75,76]. While the will to fight for one's life is strengthened, the high energy consumption limits the process. I observed similar effects in patients with psychoses and tumors.

Electromagnetic Field Exposure as a Risk Factor for the Development of Neuropsychiatric Symptoms: Evidence from EEG studies

Current literature shows that electromagnetic field (EMF) exposure induces a wide range of psychophysiological changes and neuropsychiatric symptoms. In humans, a relation of EMF exposure with a widespread range of neuropsychiatric disorders such as depression (for a meta-analytic overview see [77]), sleep disorders [78,79], disorders of concentrational performance [80,81], memory disorders [82], desorientation [83], provocation of cramps in epilepsy patients [84], increases of symptoms in ADHD patients [85], disturbance of motor memory consolidation when exposed to EMFs during sleep [86], and development disorders in children (see meta-analysis [87]). Further, changes in brain development in prenatal exposure is shown up to two years after birth [88]. Evidence comes from studies that exposure to EMFs increase the risk for neurodegenerative disorders such as Alzheimers disease (AD) and Parkinsons disease [89]. As the underling mechanisms for the development of these disorders oxidative stress in the brain [90,91], and the development of heat shock proteins [92] due to EMF exposure are discussed.

Investigating the underlying neurophysiological mechanisms studies using electroencephalography (EEG) reveal that EMF exposure induces patterns in brain activity that are similar to that of a range of neuropsychiatric disorders, mostly characterized by a lack of alpha activity with an increase in beta and gamma frequencies during resting state. Further, changes in sleep architecture are observed similar to patterns of sleep architecture in patients with major depression and burnout symptoms.

Several EEG studies have demonstrated systematic changes in EEG brain activity induced by electromagnetic field exposure in healthy subjects. Most of these studies showed systematic increases in the EEG high-frequency range (beta and gamma activity) with a simultaneous reduction of low-frequencies (delta, theta, and alpha activity) when subjects were exposed to mobile phone radiation [93-98]. Further, changes in sleep architecture with reduction of deep sleep phases and increases of waking phases were observed in EMF exposure during night sleep [99,100].

As technologies for mobile communication are developing towards higher power and transmittability of signals their effects on brain activity is subject to changes. While in most previous studies rather superficial activations of the neocortex during EMF exposure were observed, the newest smartphone developments and the newly introduced 5G standard in mobile communication induces changes in the neocortex as well as in deeper brain layers such as the limbic system. In recent studies, it was shown that a ten-minute use of the iPhone X near the head activated not only the temporal lobes of the neocortex but also parts of the limbic system such as the hippocampus [100]. Using bluetooth headsets caused similar patterns in brain activity as smartphones with even stronger increases in the temporal lobes and hippocampus. Further, recovery phases from EMF exposure displayed a

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longer duration compared to smartphone use [101]. In further studies, 5G exposure by a smartphone and in the car was shown to induce widespread activations in the beta and gamma range with simultaneous reduction of overall alpha activity of the frontal, temporal, parietal, and occipital brain regions as well as parts of the limbic system. More specifically, changes in hypothalamic activity and the epiphysis were observed as well as in healthy [102,103] and electrosensitive subjects [104].

In a recent study, the interrelations between EMF exposure in the 5G range by a smartphone, changes in EEG brain activity, and the role of neuroinflammation were investigated [105]. Subjects were tested. Subjects were exposed for 30 minutes to smartphone (iPhone 12, Apple) emitted EMFs that transmitted in the 5G range. Further, a control condition was tested for 30 minutes without EMF exposure. The smartphone was applied 1.0 cm from the right ear of the participants. Data were recorded before, during, and after each experimental condition with a mobile high density EEG device from 256 electrodes. Results showed increases in EEG beta and gamma activity in central, temporal, and occipital brain areas, and in deeper brain layers such as the limbic system, compared to the control condition (Figure 11). More specifically, hypothalamic, and epiphysal structures were activated by the smartphone call, compared to the control condition. Further, results revealed an overall decrease of alpha activity in parietal and occipital brain regions during and after the smartphone EMF exposure (Figure 12). Results of the immunological parameters mirror the findings of the EEG results. Espaciallly the elevation of **IL-1ß** demostrates the connection between inflammation in the **periphery** and **neuroinflammation**. This cytokine also is named as gatekeeper of inflammation [106]. In CNS the proinflammatory effect focuses in hypothalamus as electromagnetic fields from 5G do.

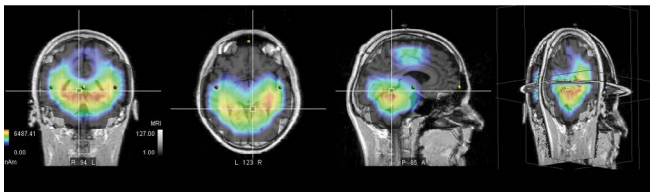

Figure 11: EEG source localization in a 30-minute EMF exposure by iPhone12 in the 5G range. Results show strong brain activations in temporal, parietal, occipital areas, and in deeper brain layers such as in parts of the limbic system.

EEG studies show that brain activity in MDD is characterized by reduced alpha activity [107,108]. Furthermore, a recent study shows a correlation between reduced EEG alpha activity, increased neuroinflammatory response, and depressive symptoms [109]. Additionally, data show involvement of parts of the limbic system in 5G exposure with involvement of the hypothalamus and epiphysis that regulate essential neuroendocrine circuits in the human body. We hypothesize that changes or disturbances in frequency activity in these brain areas lead to a wide range of effects on regulatory circuits in the brain and human body. The problem is that part oft the chemicals and all frequencies can not be avoided and that their interaction inreases the effect. The whole endocrino-immune system is involved. The developing individual problems will depend from individual susceptiblity, age and sex and the possibilities to compensate the influences.

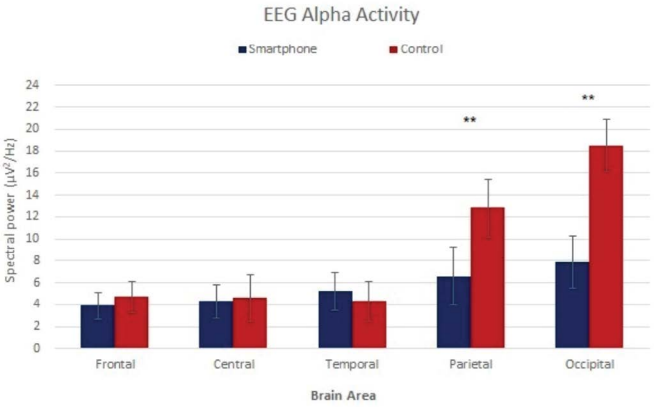

Figure 12: EEG alpha activity in the neocortex during EMF exposure and in the control condition. Results show decreases in EEG alpha activity in parietal and occipital brain areas in smartphone exposure compared to the control condition.

In summary, these results support the hypothesis that EMFs induce changes in EEG brain activity and immunological parameters that cause vulnerability and therefore are a risk factor for the development of neuropsychiatric symptoms, and mood disorders, including depressive symptoms.

Summary

The development of a rapidly changing environment with the introduction of substances and electromagnetic fields that never existed previously has induced never-before seen alterations in the immune system which in turn affect the neuroendocrine system. The consequence of this development is the appearance worldwide of novel health disorders. Diseases resulting from the body's defense against membrane-bound microorganisms have shifted to inflammation to foreign substances, intolerance reactions, and allergies as well as autoimmune disorders. The immune system's ability to distinguish foreign from self is now less reliable. Mitochondrial functions are more in demand, and the resulting oxidative stress due to the increase in free radicals is often uncontrollable. It attacks own body structures rather than organizing the defense against foreign substances. Through denaturation, the body's own membranes lose their protective function and instead become a target of oxidative stress and lipidperoxidation. Enzyme functions become inhibited or overloaded, and apoptosis loses its regenerative capacity.

Instead silent inflammation manifests itself, interacting with neurotransmitters and apparently inducing psychogenic reactions. It has long been recognized that chronic exposure to chemicals and non-physiological metals can induce such effects. Own data show that comparable effects can also be caused by the electromagnetic fields that in the last 50 years slowly appeared on the scene and since then have become unavoidable. Individual variations in susceptibility to such influences lead to significant variations in clinical manifestations. The process of developing illness due to exhaustion of adaptive mechanisms to combat the effects of a rapidly changing environment has further accelerated. In dealing with environmental toxicants, the body utilizes all the regulatory circuits originally developed in evolution to combat infections. These include nitro-oxidative stress, inflammation, allergic reactions, and autoimmune reactions. The results are neurodegenerative and neuroinflammatory processes as well as mood disorders. The data show that chemical, biochemical, and electrophysiological effects, such as those caused by environmental influences, are involved. This can lead to alterations in the functional regulatory systems of embryos, newborns, and later even children and adults. To what degree illness results depends on individual susceptibility and compensatory abilities. This means that very different clinical manifestations can be observed after contact with the same substance. Thus the tried-and-true toxicological dose-effect principle does not apply here. Disorders resulting from genotoxic and epigenetic alterations will manifest themselves over generations.

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Conflict of Interests

The authors declare that there is no competing interest.

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