



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Toxicology issues related to the COVID–19 outbreak

Ronald N. Kostoff¹, Michael B. Briggs² and Alan L. Porter³

¹*School of Public Policy, Georgia Institute of Technology, Gainesville, VA, United States,* ²*Independent Consultant, Roscommon, MI, United States,*

³*Search Technology, Inc, and Georgia Institute of Technology, Atlanta, GA, United States*

31.1 Introduction

A 2020 review of the role of toxicology in the COVID–19 pandemic concluded (Kostoff et al., 2020b) that “Coronavirus disease 2019 (COVID–19) and previous pandemics have been viewed almost exclusively as virology problems, with toxicology problems mostly being ignored. This perspective is not supported by the evolution of COVID–19, where the impact of real-life exposures to multiple toxic stressors degrading the immune system is followed by the SARS–CoV–2 virus exploiting the dysfunctional immune system to trigger a chain of events ultimately leading to COVID–19. This immune system degradation from multiple toxic stressors (chemical, physical, biological, psychosocial stressors) means that attribution of serious consequences from COVID–19 should be made to the virus-toxic stressors nexus, not to any of the nexus constituents in isolation. The leading toxic stressors (identified in this study as contributing to COVID–19) are pervasive, contributing to myriad chronic diseases as well as immune system dysfunction. They increase the likelihood for comorbidities and mortality associated with COVID–19.

For the short-term, tactical/reactive virology-focused treatments are of higher priority than strategic/proactive toxicology-focused treatments, although both could be implemented in parallel to reinforce each other. However, for long-term pandemic prevention, toxicology-based approaches should be given higher priority than virology-based approaches. Since current COVID–19 treatments globally ignore the toxicology component almost completely, only limited benefits can be expected from these treatments.”

Given the importance of the toxicology-based component of immune system dysfunction stated in the above summary, the present chapter will focus mainly on the immune system toxicology component. The chapter starts by presenting evidence that a dysfunctional immune system is the main characteristic of COVID–19 mortality. Once the central role of a dysfunctional immune system in COVID–19 mortality has been established, then the immune system toxicology will be addressed in three sections. The first section contains the contributing factors shown most frequently to increase immune system dysfunction. The second section examines a few specific contributing factors from this list in greater detail, and discusses their impacts on the immune system. The third section addresses vaccine toxicology in some detail, because of the prominent role of vaccines as potential preventatives of COVID–19 or similar infectious diseases.

Finally, the myriad treatments for COVID–19 being developed and tested will be addressed.

31.2 Centrality of immune system dysfunction in pandemics

31.2.1 Immune system dysfunction

Viruses, especially those considered pathogenic, appear to be operating in a continual mode of probing and challenging immune system defenses. When the virus encounters an immune system whose functionality has been degraded through hereditary/genetic means or through exposure to immune-degrading substances (immunosuppressive drugs, pesticides, wireless radiation, perfluorooctanesulfonate (PFOS), perfluorooctanoic acid (PFOA), polychlorinated biphenyls (PCBs),

etc., as will be demonstrated later in this chapter), the virus then exploits the weakness of this dysfunctional immune system, and enables the adverse health effects we associate with viral infectious diseases.

The virus is not a toxic stimulus intrinsically in the sense of the immune-degrading substances (toxic stimuli) listed above, but rather is exploiting a target of opportunity. If the immune system had not been degraded by these toxic stimuli, and not compromised by other means, the virus would have had little/no effect. If the immune system were partially compromised for nontoxic exposure reasons (e.g., heredity), exposure to the virus would have more adverse impacts than the healthy immune system case. Additional toxic stimuli exposures would further compromise the immune system and exacerbate the severity of the infectious disease. That would not be true for the immune-degrading factors listed above. For example, pesticide exposure will enhance immune system dysfunction, whereas viral exposure will have minimal effect on a healthy immune system.

The immune-degrading substances listed above also trigger a positive feedback mechanism. These substances degrade the immune system (Kostoff et al., 2020a), which in turn increases vulnerability to infection. Infections, in turn, degrade the immune system further, which again enhances vulnerability to infection. The intervention under our control to disrupt this feedback loop is to reduce/eliminate exposure to these immune-degrading substances.

31.2.2 Pandemic characteristics

Over the past two decades, there have been at least three major coronavirus-based infectious disease outbreaks/epidemics/pandemics (Severe Acute Respiratory Syndrome (SARS), 2002–2003; Middle East Respiratory Syndrome (MERS), starting in 2012; COVID–19, starting in December 2019), and annual influenza outbreaks. There are a number of biomarker/symptom similarities among these three infectious coronavirus diseases and influenza, including abnormal values of selected biomarkers (e.g., neutrophils, lymphocytes, albumin, CRP, TNF-alpha, etc.), pulmonary inflammation, pulmonary damage. From the perspective of corrective measures, the most important similarities among these infectious diseases are (1) dysfunctional immune systems and (2) the demographic affected most severely (the elderly, with comorbidities) (Huang et al., 2020; Liu et al., 2020; Mo et al., 2020; Qian et al., 2020; Qin et al., 2020; Tian et al., 2020; Han et al., 2020; Yun et al., 2020; Medetalibeyoglu et al., 2020; Docea et al., 2020; Petrakis et al., 2020), with comorbidity being a stronger predictor of impaired immunity than chronological age in older adults (Castle et al., 2005, 2007). Further, as stated in a comparison of COVID–19 and Influenza (<https://www.hopkinsmedicine.org/health/conditions-and-diseases/coronavirus/coronavirus-disease-2019-vs-the-flu>): “Neither virus is treatable with antibiotics, which only work on bacterial infections; both are treated by addressing symptoms, such as reducing fever; severe cases may require hospitalization and support such as mechanical ventilation.”

31.3 Immune system toxicology

The most severe consequences from the above infectious diseases stem primarily from a dysfunctional immune system, and secondarily from the exploitation of the dysfunctional immune system by the virus. The virus is unable to overcome the strong defenses of a healthy immune system, and will be neutralized, with minimal adverse effects.

31.3.1 Isolated toxic stimuli

Most of the laboratory experiments that led to identification of immune-degrading substances/behaviors [shown in the 2020 COVID–19 monograph (Kostoff et al., 2020a) and summarized in Section 31.3.3 of the present chapter] were a product of single stressor experiments. The laboratory animals were exposed to one toxic stimulus at a time. While such experiments allow for sharp links to be drawn between a stimulus and its potential toxicity to the immune system, they do not reflect the real-life exposures of multiple toxic stimuli, with interactive effects among these stimuli.

31.3.2 Toxic stimuli mixtures

31.3.2.1 Difficulties in testing toxic mixture effects

To ascertain immune-degrading effects of real-life exposures, either epidemiological studies or multistressor laboratory experiments are required. Two problems with the former are: (1) identifying the full spectrum of toxic stimuli to which the test subjects were exposed over their lifetimes, and (2) separating the contributions of the myriad toxic stimuli to a dysfunctional immune system, even if the full spectrum of toxic stimuli were known. While multistressor laboratory experiments would allow the marginal effects of each constituent on the immune

system to be ascertained, the numbers of experiments required (to simulate the massive numbers of combinations possible with thousands of stimuli potentially toxic to the immune system) would be prohibitive because of time, funding, and other resource requirements.

Many biomedical studies have shown that combinations of stressors can enhance the adverse effects of any one of their constituents (relative to its effects when acting in isolation) (Kostoff et al., 2018b, 2020c). Only a relatively few combinations of potentially toxic stimuli decrease the adverse effects of any constituent. For toxic stimuli, including those leading to a dysfunctional immune system, stimuli combinations/mixtures typically allow less of each mixture component to cause damage compared to the levels obtained when examining the (single stressor) toxicity of each component in isolation (Kostoff et al., 2020c).

31.3.2.2 Examples of toxic mixture effects

The following examples show some of these multistressor combinations, and the resultant enhancement of adverse effects on the test subjects. For these examples, each of the items tested in isolation was essentially benign (in the parameter range selected), yet in combination contributed to harmful effects on the test subjects:

“Synergistic toxicity produced by mixtures of biocompatible gold nanoparticles and widely used surfactants” (Ginzburg et al., 2018).

“Synergistic action of the nephrotoxic mycotoxins ochratoxin A and citrinin at nanomolar concentrations in human proximal tubule-derived cells” (Schulz et al., 2018). Only concurrent but not individual exposure to ochratoxin A and citrinin at nanomolar concentrations led to (1) an increase of TNF protein and mRNA, (2) a decrease of COX-2 protein and mRNA, (3) a decrease of E-cadherin protein and (iv) an increase of vimentin and alpha-SMA protein.

“DNA damage in rat lymphocytes treated in vitro with iron cations and exposed to 7 mT magnetic fields (static or 50 Hz)” (Zmyslony et al., 2000). Lymphocyte exposure to magnetic fields (MF) at 7 mT did not increase the number of cells with DNA damage in the comet assay. Incubation of lymphocytes with 10 µg/mL FeCl₂ did not produce a detectable damage of DNA either. However, when the FeCl₂-incubated lymphocytes were simultaneously exposed to 7 mT MF the number of damaged cells was significantly increased and reached about 20% for static MF and 15% for power frequency MF.

What are the contributing factors to a dysfunctional immune system? There are some immune systems that are intrinsically dysfunctional due to genetic/hereditary/congenital factors. However, for most people, other factors may play a much stronger role in determining the health of the immune system.

31.3.3 Contributing factors to dysfunctional immune system

A 2020 study examined the adverse impacts of toxic Lifestyle, Iatrogenic, Biotoxic, Environmental/Occupational, and Psychosocial/Socioeconomic factors on the health of the immune system (Kostoff et al., 2020a). Depending on how one aggregated the results, there were anywhere from 1000 to 2000+ factors that contributed to a dysfunctional immune system, and that number was viewed as a gross underestimate [see Table A4 – 1 of Kostoff et al. (2020a) for the full list of contributing factors to a dysfunctional immune system]. Some of the factors in this recent study that were shown repeatedly to increase immune system dysfunctionality include:

- Lifestyle (e.g., smoking, excess alcohol, substance abuse, high-fat diet, protein-deficient diet, high-cholesterol diet, Western-style diets, chronic sleep restriction, etc.)
- Iatrogenic (e.g., immunosuppressive drugs, gamma radiation treatments, nanomedicinal products, adjuvanted vaccines, acetaminophen, nonsteroidal antiinflammatory drugs (NSAIDs), surgical stress, serotonin reuptake inhibitors, selected anesthetics, selected antibiotics, highly active antiretroviral therapy drugs, etc.)
- Biotoxins/Biomaterials (e.g., aflatoxin, ochratoxin, T-2 toxin, anatoxin-A, mycotoxins, microcystin-LR, dietary toxic cyanobacteria, yessotoxin, scorpion venom, *Streptomyces californicus*, *Pseudomonas aeruginosa*, Rhinovirus, respiratory syncytial virus, etc.)
- Occupational/Environmental (e.g., microplastics, endocrine-disrupting chemicals, heavy metals, pesticides/insecticides/herbicides, nanoparticles, PFOA, PCBs, polyaromatic hydrocarbons (PAHs), PFOS, fine particulate matter, air pollution, acrylamide, aromatic halogenated disinfection byproducts, benzene, benzo(a)pyrene, crude oil, corexit, ultraviolet (UV) radiation, wireless radiation-cell phones/cell towers/WiFi, sodium fluoride, etc.)
- PsychoSocial/SocioEconomic (e.g., depression, chronic stress, restraint stress, social isolation, stressful life events, childhood adversity, etc.)

Eliminating/ameliorating these toxic exposures/behaviors will require a combination of individual motivations/efforts and government efforts, especially at the regulatory level.

The factors in the Lifestyle category mainly require motivation and willpower to eliminate, although government regulation would be beneficial for controlling food additives and labeling contents of processed foods.

For the Iatrogenic category, government regulation is necessary for ensuring treatment safety. There is room for individual motivation in eliminating excessive or unnecessary use of painkillers, such as NSAIDs or opioids, and unnecessary/elective surgeries.

Members of the Biotoxin/Biomaterial category (especially the Biotoxin component) are more difficult for individuals to eliminate. As we are seeing with COVID–19, virus exposure is difficult to control (as is bacterial exposure). There are many mycotoxins listed in the above-referenced Table A4 – 1. Those found in food may result from improper storage and insufficient processing to eliminate mycotoxins. Those in indoor environments may result from insufficient moisture/humidity control. Some of these problems can be addressed by stricter government regulations.

The Occupational/Environmental category could benefit substantially from more rigorous government regulation. Most of the exposures are beyond the control of the individual; in fact, the individual most likely does not he/she is being exposed to these substances.

For example, the Occupational Safety and Health Administration (OSHA) has responsibility for regulating most workplace toxic exposures. Out of the more than 85,000 chemicals registered with the EPA, OSHA only issues federally enforceable Permissible Exposure Limits (PELs) for about 500 of these chemicals. In 2018, the first author published a study of the adequacy of OSHA's PELs (Kostoff, 2018a), using a sampling technique. Of those substances that were sampled, their PELs were one to four orders of magnitude higher than exposures shown in the biomedical literature to cause damage.

As another example, the radiation exposure limits for wireless radiation (cell phone/cell towers/WiFi, etc.) approved by the FCC are from three to six orders of magnitude higher than exposures shown in the biomedical literature to cause damage (Kostoff et al., 2020f), the discrepancy varying with the level of damage (Sage and Carpenter, 2019).

But, even in this category, individual choice and motivation play a role. People who want to strengthen their immune systems can choose (especially in the home environment, and partly in the work environment) to reduce exposure to wireless radiation, water with sodium fluoride, strong pesticides, strong disinfectants, etc.

The PsychoSocial/SocioEconomic category could benefit from some government interventions that reduce stressful situations for the individual (e.g., providing economic/health/occupational security, providing more protections for the most vulnerable (very young, elderly, disabled), etc.). Some of the types of adverse events and stresses are beyond the control of government or the individual, but here again, individuals can take steps to improve their responses to many of these types of stress.

31.3.4 Specific examples of increased immune system dysfunctionality by toxic stimuli

Because of space limitations, only a handful of the more well-known, and perhaps ubiquitous, immune-degrading toxic stimuli will be examined in somewhat more detail. To provide some context for the details that follow, Table 31.1 contains biomarkers from the immune dysfunction database closely associated with inflammation, and Table 31.2 contains biomarkers closely associated with oxidative damage. Inflammation and oxidative damage were highlighted, since these are two fundamental general markers associated strongly with immune system dysfunctionality. For inflammation, the emphasis is on the pro-inflammatory cytokines and the innate immune system cells, while for oxidative stress, the emphasis is on reactive oxygen species/products of peroxidation and antioxidant defenses. There is overlap between inflammation biomarkers and oxidative stress biomarkers.

Tables 31.3–31.8 present more detail about the selected immune-degrading toxic stimuli, in the following format. Each table contains three segments: top, middle, bottom. The top segment contains the toxic stimulus name; the middle

TABLE 31.1 Biomarkers closely associated with inflammation.

AHR; apoptosis; CD4 + ; CD8(+); C-reactive protein; cytokines; dendritic cells; eosinophils; fibrosis; granulocytes; IFN-gamma; IgE; IgG; IL-1beta; IL-4; IL-5; IL-6; IL-8; IL-10; IL-12; IL-13; IL-17; infection; iNOS; leukocytes; lipid peroxidation; lymphocytes; macrophages; mast cells; microglia; monocytes; necrosis; neutrophils; NF-kappaB; nitric oxide; oxidative stress; p38; pro-inflammatory cytokines; spleen; T cells; Th1; Th1/Th2; Th17; Th2; THP-1 cells; thymus; TNF-alpha

TABLE 31.2 Biomarkers closely associated with oxidative stress.

acetylcholinesterase; alanine aminotransferase; alkaline phosphatase; apoptosis; Bax; Bcl-2; caspase-3; catalase; CD4 + ; cell death; glutathione; glutathione peroxidase; glutathione reductase; glutathione S-transferase; heat shock protein; HSP70; hydrogen peroxide; hypertension; IFN-gamma; IL-1beta; IL-2; IL-4; IL-6; IL-8; IL-10; IL-12; iNOS; lipid peroxidation; lymphocyte; malondialdehyde; myeloperoxidase; N-acetylcysteine; NF-kappaB; nitric oxide; NRF2; reactive oxygen species; splenic; superoxide dismutase; Th1; thymocytes; thymus; T-lymphocyte; TNF-alpha

TABLE 31.3 Immune system degradation related to nanoparticles.

Nanoparticles

Biomarkers impacted: apoptosis; cytokines; DNA damage; genotoxicity; IFN-gamma; IgM; IL-1beta; IL-2; IL-6; IL-8; IL-10; immune response; immunosuppression; immunotoxicity; inflammation; innate immune; lipid peroxidation; lymphocytes; macrophages; neutrophils; NF-kappaB; nitric oxide; oxidative stress; phagocytosis; proteins; reactive oxygen species; spleen; T cells; Th2; thymus; TNF-alpha

Sample article titles

- Acute exposure to ZnO nanoparticles induces autophagic immune cell death.
- Aggravating impact of nanoparticles on immune-mediated pulmonary inflammation.
- Copper nanoparticles induce early fibrotic changes in the liver via TGF-beta/Smad signaling and cause immunosuppressive effects in rats.
- Deleterious effects in reproduction and developmental immunity elicited by pulmonary iron oxide nanoparticles.
- Direct effects of carbon nanotubes on dendritic cells induce immune suppression upon pulmonary exposure.
- Maternal exposure to silver nanoparticles are associated with behavioral abnormalities in adulthood: Role of mitochondria and innate immunity in developmental toxicity.
- Mechanisms for how inhaled multiwalled carbon nanotubes suppress systemic immune function in mice.
- Oxidative stress and immunotoxicity induced by graphene oxide in zebrafish.

Nanoparticle damage is reflected in inflammation and oxidative damage, and results in immunosuppression and immunotoxicity.

TABLE 31.4 Immune system degradation related to high-fat-diet.

High-fat diet

Biomarkers impacted: apoptosis; B cells; body weight; fatty acids; glucose; glutathione; hepatocytes; IL-2; IL-4; IL-10; immune dysfunction; immune response; immunoreactivity; immunosuppression; inflammation; innate immune responses; insulin resistance; leukocytes; lipid peroxidation; lymphocytes; macrophages; NF-kappaB; oxidative stress; phagocytosis; reactive oxygen species; T cells; TNF-alpha; weight gain

Sample article titles

- Alginate oligosaccharide (AOS) improves immuno-metabolic systems by inhibiting STOML2 overexpression in high-fat-diet-induced obese zebrafish.
- Bacteroides uniformis CECT 7771 ameliorates metabolic and immunological dysfunction in mice with high-fat-diet induced obesity.
- High-fat diet-derived free fatty acids impair the intestinal immune system and increase sensitivity to intestinal epithelial damage.
- Immune dysfunction and increased oxidative stress state in diet-induced obese mice are reverted by nutritional supplementation with monounsaturated and n-3 polyunsaturated fatty acids.
- Impaired immune response in old mice suffering from obesity and premature immunosenescence in adulthood.
- Lipoic acid attenuates high fat diet-induced chronic oxidative stress and immunosuppression in mice jejunum: a microarray analysis.
- Western-style diets induce oxidative stress and dysregulate immune responses in the colon in a mouse model of sporadic colon cancer.

High-Fat-Diet damage is reflected in both inflammation and oxidative stress, and results in obesity and insulin resistance, which in turn are associated with many chronic diseases such as cancer.

TABLE 31.5 Immune system degradation related to immunosuppressants.

Immunosuppressants

Biomarkers impacted: CD4 + ; antibodies; antibody production; apoptosis; atrophy; autoimmune; B-cell; bone marrow; CD8 + ; cytokines; Erythrocytes; glutathione; host resistance; humoral immune; hypersensitivity; IFN-gamma; IgG; IgM; IL-2; IL-4; IL-6; IL-10; immune response; immunosuppression; immunotoxicity; infection; inflammation; lymph; lymphocytes; macrophages; NK cell; oxidative stress; phagocytosis; reactive oxygen species; red blood cells; spleen; splenic; splenocytes; T cells; thymus; TNF-alpha

Sample article titles

- Calcineurin inhibitor tacrolimus impairs host immune response against urinary tract infection.
- Cancer immunotherapy with anti-ctla-4 monoclonal antibodies induces an inflammatory bowel disease.
- Carboplatin-induced immune hemolytic anemia.
- Cutaneous immunopathology of cyclosporin-A-induced autoimmunity in the rat.
- Development of a lymphocytic lymphoma during immunosuppressive therapy with azathioprine for systemic lupus erythematosus with renal involvement induced by phenylbutazone.
- Enhancement of metastasis of prostate adenocarcinoma cells by immune-suppressive cyclosporine A.
- Exacerbation of allergic contact dermatitis during immunosuppression with cyclosporine A.
- Hepatic veno-occlusive disease following sirolimus-based immune suppression.
- Hepatotoxicity induced by new immunosuppressants.
- Hypertension induced by immunosuppressive drugs: a comparative analysis between sirolimus and cyclosporine.
- Immunosuppressant prograf (tacrolimus) induces histopathological disorders in the peritubular tissue of rat testes.
- Immunosuppression-induced leukoencephalopathy from tacrolimus (FK506).
- Immunosuppressive drug-induced diabetes.
- Immunosuppressive therapy exacerbates autoimmunity in NOD mice and diminishes the protective activity of regulatory T cells.

Immunosuppressant damage is reflected in both inflammation and oxidative stress, adversely impacts both the innate and adaptive immune systems, and can increase vulnerability to infections and more serious chronic diseases.

TABLE 31.6 Immune system degradation related to pesticides.

Pesticides

Biomarkers impacted: apoptosis; autoimmune; B cells; bone marrow; CD4; cytokines; endocrine disruption; humoral immune; IFN-gamma; IL-1beta; IL-2; IL-4; IL-6; immune response; immunosuppression; immunotoxicity; infection; inflammation; innate immune; leukocytes; lipid peroxidation; lymphocytes; macrophages; malondialdehyde; oxidative stress; phagocytosis; reactive oxygen species; spleen; T cells; thymus; TNF-alpha

Sample article titles

- Apigenin reverses lung injury and immunotoxicity in paraquat-treated mice.
- Apoptosis in immunocytes induced by several types of pesticides.
- Bifenthrin induces developmental immunotoxicity and vascular malformation during zebrafish embryogenesis.
- Cadmium and chlorpyrifos inhibit cellular immune response in spleen of rats.
- Cis-bifenthrin causes immunotoxicity in murine macrophages.
- Deltamethrin-induced immunotoxicity and its protection by quercetin: An experimental study.
- Developmental immunotoxicity of atrazine in rodents.
- Dietary exposure to low pesticide doses causes long-term immunosuppression in the leopard frog (*Rana pipiens*).
- Exposure to bifenthrin causes immunotoxicity and oxidative stress in male mice.
- Immunotoxicity in mice induced by short-term exposure to methoxychlor, parathion, or piperonyl butoxide.
- Suppression of humoral immunity following exposure to the perfluorinated insecticide sulfluramid.

Pesticide damage is reflected by oxidative stress and inflammation to some degree, and results in immunotoxicity and immunosuppression, impacting both the innate and adaptive immune systems.

segment contains the major immune biomarkers impacted by the toxic stimulus; the bottom segment contains selected descriptive title names of articles showing adverse effects of the toxic stimulus.

Most of the studies that produced the above findings are based on single stressor experiments. In real-life, where many of these toxic stimuli occur in concert, additive/synergistic effects will occur, increasing immune system dysfunction further, perhaps substantially.

TABLE 31.7 Immune system degradation related to fluoride.

Fluoride

Biomarkers impacted: apoptosis; B lymphocytes; catalase; cytokines; DNA damage; IL-1beta; IL-6; IL-8; immunotoxicity; infections; lymphocytes; macrophages; neutrophils; oxidative stress; reactive oxygen species; spleen; superoxide dismutase; T cells; TNF-alpha

Sample article titles

- Dental Fluorosis and Catalase Immunoreactivity of the Brain Tissues in Rats Exposed to High Fluoride Pre- and Postnatally.
- Fluoride exposure abates pro-inflammatory response and induces invivo apoptosis rendering zebrafish (*Danio rerio*) susceptible to bacterial infections.
- Fluoride-induced immunotoxicity in adult male albino rat: a correlative approach to oxidative stress.
- Sodium fluoride exposure triggered the formation of neutrophil extracellular traps.
- Sodium fluoride impairs splenic innate immunity via inactivation of TLR2/MyD88 signaling pathway in mice.
- The role of PERK and IRE1 signaling pathways in excessive fluoride mediated impairment of lymphocytes in rats' spleen invivo and invitro.

Fluoride damage is reflected by oxidative stress and inflammation, results in immunotoxicity, and impacts both the innate and adaptive immune systems. Its main importance derives from sodium fluoride being a central component of fluoridated drinking water in many parts of the world.

TABLE 31.8 Immune system degradation related to wireless radiation.

Wireless radiation

Biomarkers impacted: amnesia; anemia; antibodies; apoptosis; autoimmune; calcium homeostasis; DNA damage; genomic instability; genotoxic effects; headache; IgA; IgG; IgM; immune response; immunoreactive; immunoreactivity; infections; inflammation; lipid peroxidation; lymphocytes; macrophages; neutrophils; oxidative stress; reactive oxygen species; T8 cell count; thymus

Sample article titles

- Calcium-binding proteins and GFAP immunoreactivity alterations in murine hippocampus after 1 month of exposure to 835 MHz radiofrequency at SAR values of 1.6 and 4.0 W/kg.
- Electromagnetic fields may act via calcineurin inhibition to suppress immunity, thereby increasing risk for opportunistic infection: Conceivable mechanisms of action.
- 954 MHz microwaves enhance the mutagenic properties of mitomycin C.
- Exposure to 900 MHz radiofrequency radiation induces caspase 3 activation in proliferating human lymphocytes.
- Exposure to radiation from single or combined radio frequencies provokes macrophage dysfunction in the RAW 264.7 cell line.
- Gene expression changes in the skin of rats induced by prolonged 35 GHz millimeter-wave exposure.
- Immunosuppressive effect of the decimeter-band electromagnetic field.
- Impact of radiofrequency radiation on DNA damage and antioxidants in peripheral blood lymphocytes of humans residing in the vicinity of mobile phone base stations.
- Increased levels of numerical chromosome aberrations after in vitro exposure of human peripheral blood lymphocytes to radiofrequency electromagnetic fields for 72 hours.
- Study of low-intensity 2450-MHz microwave exposure enhancing the genotoxic effects of mitomycin C using micronucleus test and comet assay in vitro.
- Terahertz radiation increases genomic instability in human lymphocytes.

Wireless radiation damage is reflected by genotoxic effects/DNA damage/apoptosis as well as inflammation and oxidative stress and enhances immunoreactivity and autoimmunity.

31.3.5 Vaccine toxicology

Numerous mid- and longer-term potential adverse effects from vaccines have been identified (Kostoff et al., 2020). These include: (1) Antibody-Dependent Enhancement (where enhanced virus entry and replication in a number of cell types is enabled by antibodies) (Huisman et al., 2009; Taylor et al., 2015); (2) Vaccine-associated Virus Interference (where vaccinated individuals may be at increased risk for other respiratory viruses because they do not receive the non-specific immunity associated with natural infection) (Wolff, 2020; Cowling et al., 2012); (3) Vaccine-Associated Imprinting Reduction (where vaccinations could also reduce the benefits of “imprinting,” a protection conferred upon children who experienced infection at an early age) (Skowronski et al., 2019; Kelvin and Zambon, 2019); (4) Non-Specific Vaccine Effects on Immune System (where previous infections can alter an individual’s susceptibility to

unrelated diseases) (Benn et al., 2013; Rakebrandt and Joller, 2019); (5) Impact of Infection Route on Immune System (where immune protection can be influenced by the route of exposure/delivery) (Demars et al., 2019; Pascual et al., 2018); and (6) Impact of Combinations of Toxic Stimuli (where people are exposed over their lifetime to myriad toxic stimuli that may impact the influence of any vaccine) (Kostoff et al., 2018b, 2020c). Each of these effects will be addressed in more detail.

31.3.5.1 *Antibody-dependent enhancement*

The following amplifies further the concern about vaccine-induced enhancement: “Examples of vaccine-induced enhancement of susceptibility to virus infection or of aberrant viral pathogenesis have been documented for infections by members of different virus families. Several mechanisms, many of which still are poorly understood, are at the basis of this phenomenon . . . Certain experimental lentiviral vaccines even proved to be counterproductive: they rendered vaccinated subjects more susceptible to infection rather than protecting them. For vaccine-induced enhanced susceptibility to infection with certain viruses like feline coronavirus, Dengue virus, and feline immunodeficiency virus, it has been shown that antibody-dependent enhancement (ADE) plays an important role . . . Consequently, vaccine-induced enhancement has been a major stumble block in the development of certain flavi-, corona-, paramyxo-, and lentivirus vaccines. Also recent failures in the development of a vaccine against HIV may at least in part be attributed to induction of enhanced susceptibility to infection” (Huisman et al., 2009).

For another perspective on the ADE mechanism:

“for a number of viral pathogens, under certain conditions, antibodies provide an attractive means of enhanced virus entry and replication in a number of cell types. Known as ADE of infection, the phenomenon occurs when virus-antibody immunocomplexes interact with cells bearing complement or Fc receptors, promoting internalization of the virus and increasing infection. Frequently associated with exacerbation of viral disease, ADE of infection presents a major obstacle to the prevention of viral disease by vaccination and is thought to be partly responsible for the adverse effects of novel antiviral therapeutics such as intravenous immunoglobulins.” (Taylor et al., 2015). These effects are confirmed further in numerous studies (Tirado and Yoon, 2003; Smatti et al., 2018; Shmelkov et al., 2014; Gu et al., 2015; Rajao et al., 2016).

31.3.5.2 *Vaccine-associated virus enhancement*

In addition to ADE, the effect of vaccine-associated virus interference (vaccinated individuals may be at increased risk for other respiratory viruses because they do not receive the nonspecific immunity associated with natural infection) (Wolff, 2020) need to be addressed. Consider the following examples:

“We identified a statistically significant increased risk of noninfluenza respiratory virus infection among TIV {trivalent inactivated influenza vaccine} recipients, including significant increases in the risk of rhinovirus and coxsackie/echovirus infection . . . Receipt of TIV could increase influenza immunity at the expense of reduced immunity to noninfluenza respiratory viruses” (Cowling et al., 2012).

“Prior receipt of 2008–09 TIV was associated with increased risk of medically attended pH1N1 illness during the spring-summer 2009, with estimated risk or odds ratios ranging from 1.4 to 2.5” (Skowronski et al., 2010).

“Among children there was an increase in the hazard of ARI {acute respiratory illness} caused by noninfluenza respiratory pathogens post-influenza vaccination compared to unvaccinated children during the same period.” (Rikin et al., 2018).

“When influenza type A hit early, RSV {respiratory syncytial virus} outbreaks tended to be delayed, coronavirus outbreaks tended to be intensified” (Van Asten et al., 2016).

“Examining noninfluenza viruses specifically, the odds of both coronavirus and human metapneumovirus in vaccinated individuals were significantly higher when compared to unvaccinated individuals (OR = 1.36 and 1.51, respectively) . . . the laboratory data in our study showed increased odds of coronavirus and human metapneumovirus in individuals receiving influenza vaccination . . . While influenza vaccination offers protection against influenza, natural influenza infection may reduce the risk of noninfluenza respiratory viruses by providing temporary, nonspecific immunity against these viruses . . . On the other hand, recently published studies have described the phenomenon of vaccine-associated virus interference; that is, vaccinated individuals may be at increased risk for other respiratory viruses because they do not receive the nonspecific immunity associated with natural infection” (Wolff, 2020).

“Here we show that reported influenza vaccination coverage rates for 29 OECD countries are associated significantly with recently observed SARS–CoV–2 infection rates in these countries. This early result, which merits further investigation, suggests that during the current coronavirus outbreak an influenza vaccination background might be a relevant factor for SARS–CoV–2 infection” (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3558270).

31.3.5.3 *Vaccine-associated imprinting reduction*

Vaccination could also reduce the benefits of “imprinting,” a protection conferred upon children who experienced infection at an early age, as the following shows:

“Imprinting by the first childhood influenza infection is known to confer long-lasting immunity focused toward priming epitopes. Our findings suggest vaccine mismatch may negatively interact with imprinted immunity. The immunological mechanisms for imprint-regulated effect of vaccine (I–REV) warrant investigation” (Skowronski et al., 2019).

“we suggest that the potential impact of distant influenza immune imprinting on current vaccination outcomes should be considered in the design of next generation or universal vaccine candidates” (Kelvin and Zambon, 2019).

31.3.5.4 *Nonspecific vaccine effects on immune system*

“Vaccines against infectious diseases have nonspecific effects on the ability of the immune system to handle other pathogens. For instance, in randomized trials tuberculosis and measles vaccines are associated with a substantial reduction in overall child mortality, which cannot be explained by prevention of the target disease. New research suggests that the nonspecific effects of vaccines are related to cross-reactivity of the adaptive immune system with unrelated pathogens, and to training of the innate immune system through epigenetic reprogramming ... diphtheria-tetanus-pertussis (DTP) vaccine, although protective against the three target diseases, increases female mortality from other infectious diseases ... and it turned out that DTP vaccine administered after the measles vaccine was the explanation for the increased female mortality observed in the high-titer measles vaccine trials ... The effects of vaccines on the immune system may be modulated by other immune-modulating factors. Interactions are found between vaccines and high-dose vitamin A supplementation ... and two vaccines may have completely different effects when administered simultaneously ... We need to explore systematically what is likely to happen when our effective interventions are administered with other vaccines, drugs, or micronutrients and in different sequences” (Benn et al., 2013).

“Epidemiological data suggest that previous infections can alter an individual’s susceptibility to unrelated diseases ... Substantial research efforts have expanded the classical concept of immune memory to also include long-lasting changes in innate immunity and antigen-independent reactivation of adaptive immunity. Collectively, these processes provide possible explanations on how acute infections might induce long-term changes that also affect immunity to unrelated diseases ... This heightened state of alert enhances the ability of the immune system to combat even unrelated infections but may also increase susceptibility to autoimmunity. At the same time, infection-induced changes in the regulatory compartment may dampen subsequent immune responses and promote pathogen persistence” (Rakebrandt and Joller, 2019).

31.3.5.5 *Impact of infection route on immune system*

Vaccine-based infections have different routes of exposure from natural exposure, and this could lead to different impacts on the immune system. The typical vaccine is injected directly into the bloodstream, thereby bypassing much of the innate immune system, while the naturally acquired infection evolves through the time-consuming process of delay and resistance by the innate immune system. Studies have been performed examining the effects of different routes of exposure. For example:

“Our study demonstrates that the identification of candidate LAVs {live attenuated viruses} and immune protection markers in an animal model can be strongly affected by the route of infection used” (Demars et al., 2019.)

“Vaccine formulation and route of delivery can influence outcomes as suggested by our studies ... Consideration of alternative methods rather than reliance on parenteral methods for vaccination can lead to vaccination strategies that produce improved efficacy and long-term memory response. Such improvements in protection came about by considering brucellosis as a mucosal disease, rather one that solely produces a systemic disease. Empowering mucosal approaches could harness additional lymphocytes to protect against infection, particularly since most infections occur following a mucosal exposure” (Pascual et al., 2018).

31.3.5.6 *Impact of combinations of toxic stimuli*

In the combination case, where people are exposed over their lifetime to myriad toxic stimuli that may impact the influence of any vaccine, typically less of each constituent of the combination is required to cause damage compared to the amount determined from single stressor experiments. Thus exposure limits based on single toxic stimulus experiments are inadequate for setting limits for stressor combinations. (Kostoff et al., 2018b, 2020c).

Many more specific potential vaccine adverse effects in the mid-term are presented in a 2020 COVID–19 monograph (Kostoff et al., 2020a).

31.4 Treatments for COVID–19

There are myriad approaches to categorizing COVID–19 treatment types. For the present chapter, treatments are divided into immune-augmenting and immune-strengthening. The immune-augmenting approaches are virology-centric, and the immune-strengthening approaches are toxicology-centric. The immune-augmenting approaches tend to be reactive/tactical in nature, and the immune strengthening approaches tend to be proactive/strategic. The immune-augmenting approaches tend to be short-term, while the immune-strengthening approaches tend to be long term. Vaccines tend to straddle both categories, since they contain a proactive component.

31.4.1 Immune-augmenting

31.4.1.1 Reducing viral exposure

The most immediate reactive/tactical approach used for past pandemics and COVID–19 is restriction of exposure to the virus. This approach is most beneficial to the most vulnerable demographic; its value to those not in the vulnerable category is questionable. It consists of quarantine (both physical isolation and social distancing) and good hygiene (including frequent hand-washing and wearing masks). Its downsides (as evidenced by its application to COVID–19) are that (1) economic activity collapses with extreme restrictions on assembly and gatherings and (2) fear and associated stress that accompany/fuel the lockdown are themselves factors that contribute to immune system dysfunction.

31.4.1.2 Applying newly developed or repurposed treatments

The next reactive/tactical approach is application of treatments to reduce viral loads and attenuate related symptoms. These treatments can be newly developed or repurposed. Given the time required for new treatment development, safety testing, manufacturing (if a substance), and wide-scale distribution, almost all the treatments applied during a pandemic, including during COVID–19, will be repurposed.

As of early July, 2020, there were 250 + treatments being examined for application to COVID–19 (<https://milkeninstitute.org/covid-19-tracker>). These included, but were not limited to: Actemra/Tocilizumab; Avigan/Favipiravir; Azithromycin; Baricitinib/Olumiant; Bevacizumab/Avastin; Calquence/Acalabrutinib; Chloroquine; Colcrys/Colchicine; Convalescent Plasma; EIDD-2801; Fingolimod/Gilenya; Galidesivir; Hydroxychloroquine; Ilaris/Canakinumab; Ivermectin; Jakafi/Ruxolitinib; Kaletra/Lopinavir/Ritonavir; Kevzara/Sarilumab; Kineret/Anakinra; Leronlimab; Mavrilimumab; Methylprednisolone; Olumiant/Baricitinib; Otezla/Apremilast; Remdesivir; Tamiflu/Oseltamivir; Umifenovir/Arbidol; Xeljanz/Tofacitinib (<https://www.drugs.com/condition/covid-19.html>; <https://www.goodrx.com/blog/coronavirus-treatments-on-the-way/>).

The trials of candidate treatments have met with mixed results, and, in any case, do little, if anything, to strengthen the dysfunctional immune systems of the most vulnerable. After such reactive/tactical treatments for one viral infection, people with dysfunctional immune systems will again be vulnerable to serious infectious consequences from exposure to the next harmful virus they encounter, unless they take active measures to strengthen their immune systems.

31.4.1.3 Vaccines

Vaccines are the third approach to augmenting the immune system. Their purpose is to prevent, or at least attenuate, the infection. They do not strengthen a dysfunctional immune system intrinsically, but, if effective, act as a crutch to the immune system's capability to neutralize the virus.

As of early July, 2020, there were 170 + vaccines under development for COVID–19 (<https://milkeninstitute.org/covid-19-tracker>). The myriad types of vaccines being developed include:

- DNA-based (e.g., DNA With Electroporation/Chula Vaccine Research Center; DNA Plasmid, Needle-Free Delivery/ Immunomic Therapeutics/Epivax/Pharmajet; Bactrl-Spike/Symvivo)
- Inactivated Virus (e.g., (Inactivated + Cpg 1018)/Sinovac/Dynavax; Inactivated/Beijing Minhai Biotechnology Co., Ltd.)
- Live Attenuated Virus (e.g., Measles Virus (S, N Targets)/Dzif – German Center For Infection Research; Codon Deoptimized Live Attenuated Virus/Indian Immunologicals Ltd/ Griffith University)

- Nonreplicating Viral Vector (e.g., Adeno-Based/Gamaleya Research Institute; Stabilitech Biopharma Ltd/Oral Ad5 S); Dendritic Cell-Based Vaccine/(University of Manitoba)
- Protein Sub-Unit (e.g., Recombinant S1-Fc Fusion Protein/Anygo Technology; Subunit Protein, Plant Produced/Ibio/Cc-Pharming; RBD-Based/Kentucky Bioprocessing (British American Tobacco))
- Replicating Viral Vector (e.g., Attenuated Influenza Expressing An Antigenic Portion Of The Spike Protein/Fundacao Oswaldo Cruz and Instituto Buntantan; VSV–S/Israel Institute for Biological Research/ Weizmann Institute Of Science)
- RNA-based Vaccine (e.g., mRNA In Targeted LPNS (Langerhans Cell Specific)/Max Planck Institute Of Colloids And Interfaces; Self Amplifying RNA, Self-Assembling Delivery System/Chimeron Bio/ George Mason University’s National Center for Biodefense and Infectious Disease)
- Virus-Like Particle (e.g., VLPS Peptides/Whole Virus/University of Sao Paulo; VLP; Plant-Derived VLP/Medicago Inc.)
- Other (e.g., Gene-Encoded Antibody Vaccine, Non-Viral Nanoparticle Delivery/Smartpharm Therapeutics/Sorrento Therapeutics; Artificial Antigen-Presenting Cells Modified with Lentiviral Vector Expressing Synthetic Minigene Based on Domains of Selected Viral Proteins/Shenzhen Geno-Immune Medical Institute)

A 2020 study examined myriad COVID–19 vaccines under development (Calina et al., 2020). As stated in this reference: “Normally, the period of development of a vaccine is 12–15 years.” Against this backdrop, SARS–CoV–2 vaccines are being targeted for accelerated development by an order of magnitude. Each of the accelerated steps listed in this reference (Calina et al., 2020) has drastically reduced the time required. Strongly accelerated development and implementation (relative to standard vaccine development times) is the goal; bypassing some critical steps in the vaccine development process is troubling. While much of the vaccine development and testing effort focuses on efficacy, it is difficult to see how true long-term safety can be validated within these limited time scales (Kostoff et al., 2020).

Section 31.3.3 addressed different aspects of vaccine toxicology. These myriad potential adverse impacts of vaccines cannot be identified in short-term tests characteristic of efficacy testing, but require long-term testing under real-life conditions (exposures to multiple toxic stimuli). Therefore it is difficult to see how vaccines validated for short-, mid-, and long-term safety can be brought to market anytime soon.

31.5 Strategic/proactive

31.5.1 Contributors to strong immune system

31.5.1.1 *Eliminate factors that enhance immune system dysfunctionality*

One approach to strengthening the immune system is to identify those factors that increase immune system dysfunctionality, then eliminate them as widely, deeply, and rapidly as possible. A 2020 monograph (Kostoff et al., 2020a) presented a method to identify those factors that contribute to a dysfunctional immune system, and, as stated in Section 31.3.1, identified 1000–2000 such factors, depending on how one aggregated these factors. Any individual wanting to strengthen his/her immune system and reduce vulnerability to infectious disease would need to eliminate those factors contained in the list relevant to his/her daily life.

31.5.1.2 *Add factors that strengthen immune system*

A second approach to strengthening the immune system is identifying those factors that contribute to a stronger immune system, then adding them to daily life. A number of studies have identified factors (especially related to diet, nutrition, exercise, and sleep) that can strengthen the immune system. A 2020 article summarized the dietary component as follows: “Evidence indicates that a diet that positively impacts immune function contains adequate amounts of protein, particularly including glutamine, arginine and branched-chain amino acids (BCAAs); high omega-3 versus lower saturated, trans fat, and omega-6 fatty acids, low refined sugars, high fiber content such as whole grains, and micronutrients including vitamin A, vitamin D, vitamin C, vitamin E, B vitamins, zinc, selenium and iron, as well as phytochemicals” (Iddir et al., 2020). Table 31.2 in this reference provides many examples of foods rich in these desirable immune-strengthening factors. Other favorable factors for enhancing immune system performance can be found in the following references: Nilashi et al. (2020); Cunningham-Rundles et al. (2005); Mainardi et al. (2009); Jahns et al. (2018); Majde and Krueger (2005); Chandra (1996); Briguglio et al. (2020); Marcos et al. (2003); Langley-Evans and Carrington (2006); Yang et al. (2020); Saeed et al. (2016); Davison et al. (2016); Skalny et al. (2020).

31.6 Conclusions

The underlying causes of the present pandemic have been both misrepresented and camouflaged. Causes that are mainly toxicology-based have been ignored relative to virology-based causes. This has resulted in treatments and “protective” measures that (1) address virology issues to the exclusion of toxicology issues, (2) are of questionable effectiveness, (3) do little, if anything, to prevent future pandemics, and (4) have produced disastrous effects on the global economy. To correct this situation, and offer intrinsic protection against future pandemics, both (1) tactical/reactive responses to survive the immediate threat and (2) strategic/proactive responses to prevent the problem and damage from reoccurring are required (Kostoff et al., 2020). Strategic responses could be initiated in parallel with the tactical responses; synergies between the two cannot be ruled out at this point.

References

- Benn, C.S., Netea, M.G., Selin, L.K., Aaby, P., 2013. A small jab—a big effect: nonspecific immunomodulation by vaccines. *Trends Immunol.* 34, 431–439.
- Briguglio, M., Pregliasco, F.E., Lombardi, G., Perazzo, P., Banfi, G., 2020. The malnutritional status of the host as a virulence factor for new coronavirus SARS-CoV-2. *Front. Med.* 7, 146.
- Calina, D., Docea, A.O., Petrakis, D., Egorov, A.M., Ishmukhametov, A.A., Gabibov, A.G., et al., 2020. Towards effective COVID-19 vaccines: updates, perspectives and challenges (Review). *Int. J. Mol. Med.* 46, 3–16.
- Castle, S.C., Uyemura, K., Rafi, A., Akande, O., Makinodan, T., 2005. Comorbidity is a better predictor of impaired immunity than chronological age in older adults. *J. Am. Geriatr. Soc.* 53, 1565–1569.
- Castle, S.C., Uyemura, K., Fulop, T., Makinodan, T., 2007. Host resistance and immune responses in advanced age. *Clin. Geriatr. Med.* 23, 463–479.
- Chandra, R.K., 1996. Nutrition, immunity and infection: from basic knowledge of dietary manipulation of immune responses to practical application of ameliorating suffering and improving survival. *Proc. Natl. Acad. Sci. USA* 93, 14304–14307.
- Cowling, B.J., Fang, V.J., Nishiura, H., Chan, K.-H., Ng, S., Ip, D.K.M., et al., 2012. Increased risk of noninfluenza respiratory virus infections associated with receipt of inactivated influenza vaccine. *Clin. Infect. Dis.: Off. Publ. Infect. Dis. Soc. Am.* 54, 1778–1783.
- Cunningham-Rundles, S., Mcneeley, D.F., Moon, A., 2005. Mechanisms of nutrient modulation of the immune response. *J. Allergy Clin. Immunol.* 115, 1119–1128.
- Davison, G., Kehaya, C., Jones, A., W.Y.N., 2016. Nutritional and physical activity interventions to improve immunity. *Am. J. Lifestyle Med.* 10, 152–169.
- Demars, A., Lison, A., Machelart, A., Van Vyve, M., Potemberg, G., Vanderwinden, J.-M., et al., 2019. Route of infection strongly impacts the host-pathogen relationship. *Front. Immunol.* 10, 1589.
- Docea, A.O., Tsatsakis, A., Albuлесcu, D., Cristea, O., Zlatian, O., Vinceti, M., et al., 2020. A new threat from an old enemy: re-emergence of coronavirus (review). *Int. J. Mol. Med.* 45, 1631–1643.
- Ginzburg, A.L., Truong, L., Tanguay, R.L., Hutchison, J.E., 2018. Synergistic toxicity produced by mixtures of biocompatible gold nanoparticles and widely used surfactants. *ACS Nano* 12, 5312–5322.
- Gu, W., Guo, L., Yu, H., Niu, J., Huang, M., Luo, X., et al., 2015. Involvement of CD16 in antibody-dependent enhancement of porcine reproductive and respiratory syndrome virus infection. *J. Gen. Virol.* 96, 1712–1722.
- Han, H., Ma, Q., Li, C., Liu, R., Zhao, L., Wang, W., et al., 2020. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. *Emerg. Microbes Infect.* 9, 1123–1130.
- Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., et al., 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, 395, pp. 497–506.
- Huisman, W., Martina, B.E.E., Rimmelzwaan, G.F., Gruters, R.A., Osterhaus, A.D.M.E., 2009. Vaccine-induced enhancement of viral infections. *Vaccine* 27, 505–512.
- Iddir, M., Brito, A., Dinguo, G., Fernandez Del Campo, S.S., Samouda, H., La Frano, M.R., et al., 2020. Strengthening the immune system and reducing inflammation and oxidative stress through diet and nutrition: considerations during the COVID-19 crisis. *Nutrients* 12.
- Jahns, L., Conrad, Z., Johnson, L.K., Whigham, L.D., Wu, D., Claycombe-Larson, K.J., 2018. A diet high in carotenoid-rich vegetables and fruits favorably impacts inflammation status by increasing plasma concentrations of IFN-alpha2 and decreasing MIP-1beta and TNF-alpha in healthy individuals during a controlled feeding trial. *Nutr. Res.* 52, 98–104.
- Kelvin, A.A., Zambon, M., 2019. Influenza imprinting in childhood and the influence on vaccine response later in life. *Eurosurveillance* 24.
- Kostoff, R.N., 2018a. OSHA Permissible Exposure Limits (PELs) Are Too Permissive. Georgia Institute of Technology PDF. Available from: <http://hdl.handle.net/1853/60067>.
- Kostoff, R.N., Goumenou, M., Tsatsakis, A., 2018b. The role of toxic stimuli combinations in determining safe exposure limits. *Toxicol. Rep.* 5, 1169–1172.
- Kostoff, R.N., Briggs, M.B., Porter, A.L., 2020a. COVID-19: Preventing Future Pandemics. Georgia Institute of Technology PDF. Available from: <https://smartech.gatech.edu/handle/1853/62907>.
- Kostoff, R.N., Briggs, M.B., Porter, A.L., Hernández, A.F., Abdollahi, M., Aschner, M., et al., 2020b. The under-reported role of toxic substance exposures in the COVID-19 pandemic. *Food Chem. Toxicol.*

- Kostoff, R.N., Aschner, M., Goumenou, M., Tsatsakis, A., 2020c. Setting safer exposure limits for toxic substance combinations. *Food Chem. Toxicol: Int. J. Publ. Br. Ind. Biol. Res. Assoc.* 140, 111346.
- Kostoff, Ronald N, Briggs, Michael B, Porter, Alan L, Aschner, Michael, Spandidos, Demetrios A, Tsatsakis, Aristidis, 2020d. [Editorial] COVID-19: Post-lockdown guidelines. *Int J Mol Med* 1791-244X46 (2), 463–466. Available from: <https://doi.org/10.3892/ijmm.2020.4640>. 32626934.
- Kostoff, Ronald N, Briggs, Michael B, Porter, Alan L, Spandidos, Demetrios A, Tsatsakis, Aristidis, 2020e. [Comment] COVID-19 vaccine safety. *Int J Mol Med* 1791-244X46 (5), 1599–1602. Available from: <https://doi.org/10.3892/ijmm.2020.4733>. 33000193.
- Kostoff, Ronald N, Heroux, Paul, Aschner, Michael, Tsatsakis, Aristides, 2020f. Adverse health effects of 5G mobile networking technology under real-life conditions. *Toxicol Lett* 1879-3169323, 35–40. Available from: <https://doi.org/10.1016/j.toxlet.2020.01.020>. 31991167.
- Kostoff, Ronald N, Kanduc, Darja, Porter, Alan L, Shoefeld, Yehuda, Calina, Daniela, Briggs, Michael B, Spandidos, Demetrios A, Tsatsakis, Aristidis, 2020g. Vaccine- and natural infection-induced mechanisms that could modulate vaccine safety. *Toxicol Rep* 2214-75007, 1448–1458. Available from: <https://doi.org/10.1016/j.toxrep.2020.10.016>. 33110761.
- Langley-Evans, S.C., Carrington, L.J., 2006. Diet and the developing immune system. *Lupus* 15, 746–752.
- Liu, Y., Yang, Y., Zhang, C., Huang, F., Wang, F., Yuan, J., et al., 2020. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci. China. Life Sci.* 63, 364–374.
- Mainardi, T., Kapoor, S., Bielory, L., 2009. Complementary and alternative medicine: herbs, phytochemicals and vitamins and their immunologic effects. *J. Allergy Clin. Immunol.* 123, 283–294. quiz 295–6.
- Majde, J.A., Krueger, J.M., 2005. Links between the innate immune system and sleep. *J. Allergy Clin. Immunol.* 116, 1188–1198.
- Marcos, A., Nova, E., Montero, A., 2003. Changes in the immune system are conditioned by nutrition. *Eur. J. Clin. Nutr.* 57 (Suppl 1), S66–S69.
- Medetalibeyoglu, A., Senkal, N., Capar, G., Kose, M., Tukek, T., 2020. Characteristics of the initial patients hospitalized for COVID-19: a single-center report. *Turkish J. Med. Sci.*
- Mo, P., Xing, Y., Xiao, Y., Deng, L., Zhao, Q., Wang, H., et al., 2020. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clin. Infect. Dis.: Off. Publ. Infect. Dis. Soc. Am.*
- Nilashi, M., Samad, S., Yusuf, S.Y.M., Akbari, E., 2020. Can complementary and alternative medicines be beneficial in the treatment of COVID-19 through improving immune system function? *J. Infect. Public Health* 13, 893–896.
- Pascual, D.W., Yang, X., Wang, H., Goodwin, Z., Hoffman, C., Clapp, B., 2018. Alternative strategies for vaccination to brucellosis. *Microbes Infect.* 20, 599–605.
- Petrakis, D., Margina, D., Tsarouhas, K., Tekos, F., Stan, M., Nikitovic, D., et al., 2020. Obesity—a risk factor for increased COVID-19 prevalence, severity and lethality (review). *Mol. Med. Rep.* 22, 9–19.
- Qian, G.Q., Yang, N.B., Ding, F., Ma, A.H.Y., Wang, Z.Y., Shen, Y.F., et al., 2020. Epidemiologic and clinical characteristics of 91 hospitalized patients with COVID-19 in Zhejiang, China: a retrospective, multi-centre case series. *QJM: Monthly J. Assoc. Phys.* 113, 474–481.
- Qin, C., Zhou, L., Hu, Z., Zhang, S., Yang, S., Tao, Y., et al., 2020. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. *Clin. Infect. Dis.: Off. Publ. Infect. Dis. Soc. Am.* 71, 762–768.
- Rajao, D.S., Sandbulte, M.R., Gauger, P.C., Kitikoon, P., Platt, R., Roth, J.A., et al., 2016. Heterologous challenge in the presence of maternally-derived antibodies results in vaccine-associated enhanced respiratory disease in weaned piglets. *Virology* 491, 79–88.
- Rakebrandt, N., Joller, N., 2019. Infection history determines susceptibility to unrelated diseases. *BioEssays: News Rev. Mol. Cell. Develop. Biol.* 41, e1800191.
- Rikin, S., Jia, H., Vargas, C.Y., Castellanos De Belliard, Y., Reed, C., Larussa, P., et al., 2018. Assessment of temporally-related acute respiratory illness following influenza vaccination. *Vaccine* 36, 1958–1964.
- Saeed, F., Nadeem, M., Ahmed, R.S., Nadeem, M.T., Arshad, M.S., Ullah, A., 2016. Studying the impact of nutritional immunology underlying the modulation of immune responses by nutritional compounds—a review. *Food Agric. Immunol.* 27, 205–229.
- Sage, C., Carpenter, D.O., (Eds.) 2019. BioInitiative report: a rationale for biologically-based public exposure standards for electromagnetic radiation. <http://www.bioinitiative.org>, December 31, 2012, last updated 2019.
- Schulz, M.-C., Schumann, L., Rottkord, U., Humpf, H.-U., Gekle, M., Schwerdt, G., 2018. Synergistic action of the nephrotoxic mycotoxins ochratoxin A and citrinin at nanomolar concentrations in human proximal tubule-derived cells. *Toxicol. Lett.* 291, 149–157.
- Shmelkov, E., Nadas, A., Cardozo, T., 2014. Could vaccination with AIDSVAX immunogens have resulted in antibody-dependent enhancement of HIV infection in human subjects? *Hum. Vaccin. Immunother* 10, 3013–3016.
- Skalny, A.V., Rink, L., Ajsuvakova, O.P., Aschner, M., Gritsenko, V.A., Alekseenko, S.I., et al., 2020. Zinc and respiratory tract infections: perspectives for COVID-19 (Review). *Int. J. Mol. Med.* 46, 17–26.
- Skowronski, D.M., De Serres, G., Crowcroft, N.S., Janjua, N.Z., Boulianne, N., Hottes, T.S., et al., 2010. Association between the 2008–09 seasonal influenza vaccine and pandemic H1N1 illness during Spring-Summer 2009: four observational studies from Canada. *PLoS Med.* 7, e1000258.
- Skowronski, D.M., Sabaiduc, S., Leir, S., Rose, C., Zou, M., Murti, M., et al., 2019. Paradoxical clade- and age-specific vaccine effectiveness during the 2018/19 influenza A(H3N2) epidemic in Canada: potential imprint-regulated effect of vaccine (I-REV). *Eurosurveillance* 24.
- Smatti, M.K., Al Thani, A.A., Yassine, H.M., 2018. Viral-induced enhanced disease illness. *Front. Microbiol.* 9, 2991.
- Taylor, A., Foo, S.-S., Bruzzone, R., Dinh, L.V., King, N.J.C., Mahalingam, S., 2015. Fc receptors in antibody-dependent enhancement of viral infections. *Immunol. Rev.* 268, 340–364.
- Tian, S., Hu, N., Lou, J., Chen, K., Kang, X., Xiang, Z., et al., 2020. Characteristics of COVID-19 infection in Beijing. *J. Infect.* 80, 401–406.
- Tirado, S.M.C., Yoon, K.-J., 2003. Antibody-dependent enhancement of virus infection and disease. *Viral Immunol.* 16, 69–86.

- Van Asten, L., Bijkerk, P., Fanoy, E., Van Ginkel, A., Suijkerbuijk, A., Van Der Hoek, W., et al., 2016. Early occurrence of influenza A epidemics coincided with changes in occurrence of other respiratory virus infections. *Influenza Other Respir. Viruses* 10, 14–26.
- Wolff, G.G., 2020. Influenza vaccination and respiratory virus interference among Department of Defense personnel during the 2017–2018 influenza season. *Vaccine* 38, 350–354.
- Yang, H., Sun, Y., Cai, R., Chen, Y., Gu, B., 2020. The impact of dietary fiber and probiotics in infectious diseases. *Microb. Pathog.* 140, 103931.
- Yun, H., Sun, Z., Wu, J., Tang, A., Hu, M., Xiang, Z., 2020. Laboratory data analysis of novel coronavirus (COVID-19) screening in 2510 patients. *Clin. Chim. Acta* 507, 94–97.
- Zmyslony, M., Palus, J., Jajte, J., Dziubaltowska, E., Rajkowska, E., 2000. DNA damage in rat lymphocytes treated in vitro with iron cations and exposed to 7 mT magnetic fields (static or 50 Hz). *Mutat. Res.* 453, 89–96.