COMMUNICABLE DISEASES ARE NOT COMMUNICABLE!

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ABSTRACT

Communicable disease is a misnomer. The disease is not communicable; the microbe mainly associated with the disease is communicable. Whether the recipient of the microbe develops the disease depends on the health of the recipient's immune system. Our model of COVID-19 development starts with real-life exposures to multiple toxic stressors degrading the immune system. This is followed by the SARS-CoV-2 virus exploiting the degraded immune system to trigger a chain of events ultimately leading to COVID-19.

To prevent or treat infectious disease, the health of the immune system must be maintained or improved. One major component of maintaining and improving immune system health is removal of those factors that contribute to immune system degradation. A previous monograph identified many factors that contribute to immune system degradation (Contributing Factors (CFs)). It was hypothesized that many of these CFs to immune system degradation were identical to those that past studies have shown were CFs to chronic diseases.

To test this hypothesis, a proof-of-principle demonstration was performed to identify the commonality between CFs to immune system degradation and CFs to Parkinson's Disease (PD). A very streamlined approach was used, and approximately 500 CFs were found in common between the two diseases. Since COVID-19 (and other infectious diseases) results from immune system degradation in our model, this means COVID-19 and PD are enabled by many of the same toxic exposures and toxic behaviors. Thus, many of the measures required to strategically treat and prevent infectious diseases are similar to those required to strategically treat and prevent chronic diseases. This is a major paradigm shift for orthodox Western medicine, but is required to achieve major advances in global population health.

TABLE OF CONTENTS

INTRODUCTION

<u>Definitions</u>

Diseases are generally divided into two classes: communicable and non-communicable [1].

Communicable diseases may be defined as follows: "Communicable diseases, also known as infectious diseases or transmissible diseases, are illnesses that result from the infection, presence and growth of pathogenic (capable of causing disease) biologic agents in an individual human or other animal host" [2].

Examples of communicable diseases include COVID-19, Severe Acute Respiratory Syndrome (SARS), influenza, etc.

Non-communicable diseases may be defined as follows: "A noncommunicable disease (NCD) is a medical condition or disease that is by definition non-infectious and non-transmissible among people" [3].

Examples of non-communicable diseases include cancer, chronic kidney disease (CKD), Parkinson's disease (PD), Alzheimer's disease (AD), etc.

<u>Misrepresentation of Communicable Diseases</u>

Despite widespread usage of the term, "communicable disease" is a misnomer. The disease is not communicable, the virus(es)/microbe(s) mainly associated with the disease is communicable. Whether the disease results from the transmitted virus/microbe, and most especially whether serious consequences result from the transmitted virus/microbe, depends on the health of the virus/microbe recipient's immune system [4-5].

The distinction between communicable disease and communicable virus goes well beyond semantics, and is extremely important for prevention and treatment of these diseases. For a virus-associated disease (such as COVID-19), if the disease were actually communicable, then prevention/treatment would have to be virology-focused, such as quarantine, face masks, anti-viral drugs, antiviral vaccines, etc. [4-6].

In our model, COVID-19 results from the effective exploitation of a degraded immune system by the SARS-CoV-2 virus, with the exploitation process outlined as follows: COVID-19 development starts with real-life exposures to multiple toxic stressors degrading the immune system. This is followed by the inability of the degraded immune system to neutralize the SARS-CoV-2 virus, thereby allowing the virus to enter and replicate in the cell and trigger a chain of events ultimately leading to COVID-19 [4-6].

If immune system degradation is a/the major factor in the severity of disease, then prevention/long-term treatment requires eliminating those factors that contribute to the degradation of the immune system. The virology-centric approach used currently would need to be strongly supplemented by a toxicology-centric approach, whose evidentiary basis would require going beyond current single-stressor laboratory experiments to more comprehensive stressor combination experiments [4, 7].

<u>Over-Emphasis on Virology; Under-Emphasis on Toxicology</u>
        Unfortunately, much of communicable disease medical research sponsored by the government and industry, and some foundations, focuses on the virology and ignores the toxicology aspects. The research attempts to find 'magic bullets' that will suppress viral transmission and resultant infection without producing severe side-effects. From a toxicology-centric perspective, so-called communicable and non-communicable diseases are intrinsically almost identical when it comes to prevention and reversal. Consider Alzheimer's disease (AD) or Parkinson's disease (PD) and Coronavirus Disease 19 (COVID-19), for example, since our group has studied these diseases in some detail [6, 8]. AD and PD are driven by degradation of the neural system (Cognitive functioning for AD, and Motor functioning for PD), and COVID-19 is driven by degradation of the immune system. Essentially the same factors that contribute to the degradation of the neural system also contribute to degradation of the immune system, as the next section will show for the example of PD and immune system degradation.

COMMONALITY OF CONTRIBUTING FACTORS (CFs) TO PD AND COVID-19 (IMMUNE SYSTEM DEGRADATION)

Background
        Our group has been developing protocols to prevent and reverse chronic diseases [8-10]. The central component of our approach is identification and elimination of CFs to these myriad chronic diseases. The question arises: can our central component for preventing and reversing chronic diseases be applied successfully to preventing and reversing so-called communicable diseases, such as COVID-19?
        In our model, COVID-19 results from the effective exploitation of a degraded immune system by the SARS-CoV-2 virus; therefore, CFs to a degraded immune system are CFs to COVID-19. In the present section, we identify CFs to PD (which we are studying at present) and immune system degradation (which we are also studying presently), and show their commonality using a very streamlined approach. The importance of this commonality means that many of the factors that are contributing to PD are also contributing to COVID-19, and elimination of these common factors (as well as other CFs not in common) would contribute substantially to preventing or reversing these serious diseases. In this respect, these two superficially different diseases are in actuality two heads of the same Hydra (a multi-headed serpentine water monster from Greek mythology)!
        It should be noted that CF commonality between PD and COVID-19 is one of potentially multiple commonalities between the two diseases, although it is an extremely important commonality from the perspective of prevention and treatment. In 2014, the first author published a study showing theme commonalities between PD (neurodegenerative) and Crohn's Disease (autoimmune) using phrase matching between the two disease literatures and bibliographic coupling between the two literatures (shared references) [11]. Because of the strong emphasis on shared references, the commonality at a more fundamental mechanism level was demonstrated. Combining these two approaches for identifying commonality (CF commonality and bibliographic coupling/phrase matching) could provide deeper understanding at different levels of commonality. The present study focused on CF commonality only.

Methodology
        The streamlined method used for this study is termed a dot-product approach. Lists of known toxic substances were aggregated from myriad (mainly) government agencies, and combined with lists of CFs identified in our previous disease studies. This produced a final list of over 14,000 potential CFs to disease. While this is certainly a large number of potential CFs, it undoubtedly omits additional CFs that a well-resourced study could have identified.
        A core literature query was defined for PD, applied to Pubmed, and the resultant retrieval was imported into VantagePoint software [12]. The title and abstract phrases of the retrieved records were parsed, resulting in lists of many phrases. The same procedure was followed for the immune degradation core literature [6, app. 4].
        The external list of >14,000 phrases of potential CFs was intersected with the parsed list of abstract phrases in the PD and immune degradation core literatures. These two intersected lists were compared, and the CFs in common were identified. Over 500 CFs in common were identified, albeit some being variants of the same concept. However, this is a very conservative estimate of CFs in common, for the following reasons.

First, only CFs that occurred within the PD and immune system degradation core literatures were used. Thus, if a candidate CF was shown to enhance oxidative stress, and enhanced oxidative stress was a marker of PD or immune degradation, the candidate CF became a confirmed CF if the article that showed the linkage to CF was in the PD or immune degradation core literature. If the candidate CF enhanced, say, "oxidative stress," but the article(s) that showed this linkage was not in the PD or immune degradation core literature, then the candidate CF did not become a confirmed CF. Given that "oxidative stress" occurs in 2200 abstracts in the PD literature used for the present study, and about 230,000 abstracts in the total Medline database, these indirect impacts that require merging of two records (impact of CF on oxidative stress; impact of oxidative stress on PD) have the potential to expand the number of records in common substantially.

Some of the more general biomarkers in common between PD and immune degradation include inflammation, apoptosis, oxidative stress, cell death, pro-inflammatory cytokines, anemia, lipid peroxidation, plaque, oxidative damage, reduced glutathione, DNA fragmentation, insulin resistance, NF-kappaB activation, hypertrophy, free radicals, ROS generation, neurodegeneration, mitochondrial dysfunction, demyelination, caspase-3 activation, microglial activation, neuronal loss, tyrosine phosphorylation, cellular damage, gliosis, arterial hypertension, mitochondrial damage, astrogliosis, brain damage, excitotoxicity, protein phosphorylation, hyperphosphorylation, membrane permeability, nitrosative stress, protein degradation, axonal degeneration, mitochondrial depolarization, mitochondrial fragmentation, cholinergic deficits, metabolic stress, neurofibrillary degeneration, nigrostriatal degeneration, protein folding, etc. If indirect impacts, as defined above, had been included, much larger numbers of both CFs and commonalities would have resulted.

Second, the core immune degradation literature (as defined by our query) was relatively small compared to the PD core literature (and other chronic disease core literatures we have retrieved). A more comprehensive query would have retrieved a much larger literature, with many hundreds more CFs to immune degradation.

Third, all the matching and dot product operations required *exact phrase matching*. The slightest difference between any two phrases meant neither phrase survived the dot product process. Given the disagreements on phrase representations among the toxic substance list providers for identical concepts, especially chemical formulas, and the subsequent disagreements between the external phrases and the parsed phrases of the Pubmed retrievals, we estimate many hundreds of phrases in common were lost. The fact that ~500 common phrases survived is testament to the potentially large commonality between the CFs to PD and COVID-19. We would expect similar results between COVID-19 and most (if not all) chronic diseases, based on the findings in our Pervasive Causes of Disease eBook [13].

Fourth, in order for a toxic substance or behavior to have been included in the core literature for PD or COVID-19, it had to have been researched and reported in Medline. Given the large number of potential toxic substances and behaviors possible [13], and the limited number of biomarkers used in experiments to identify their adverse effects, the limited number of toxic substance/behavior-disease combinations studied will limit the number of potential CFs that enter any disease core literature, and therefore will limit the number of CFs in common between any two diseases.

Results and Discussion

Results
Fifty of the ~500 common CFs were selected for validation, and are presented in Table 1, at the end of the present section. They span the five-category taxonomy we have developed for classifying CFs to disease: Lifestyle, Iatrogenic, Biotoxins, Occupational/Environmental, Psychosocial/SocioEconomic [8]. We do not include Genetics, since the CFs in our definition are viewed as foundational, meaning they are somewhat under our control.

The fifty CFs in Table 1 were validated as follows. To validate a CF to PD, the candidate CF was intersected with the PD core literature query in Pubmed, and the retrieved records were examined. If a record's title or abstract showed a link between the candidate CF and some representation of PD, the CF and reference were entered into Table 1. The same procedure was followed with a slightly generalized version of the immune degradation core literature query. The detailed record excerpts showing these linkages are presented in Appendix 1.

What is a 'representation' of PD or immune degradation, as mentioned above? 'Representations' of PD are biomarkers characteristic of PD (e.g., Parkinson's disease; Parkinson Disease; alpha-synuclein; Lewy bodies; Subthalamic Nucleus; neurodegenerative; dyskinesia; Degeneration; Neurodegeneration; Neurotoxicity; Movement Disorders; cognitive impairment; supranuclear palsy; oxidative stress; dystonia; essential tremor; freezing of gait; cell death; apoptosis; mitochondrial dysfunction; dopaminergic neurodegeneration; Autonomic dysfunction; cognitive dysfunction; motor impairment; olfactory dysfunction; Motor Dysfunction; dopaminergic degeneration; dopaminergic neurotoxicity; dopaminergic dysfunction; memory impairment; tau pathology; phosphorylated tau, etc.). While some of these biomarkers apply to other diseases, it should be remembered they were located in records that had PD as their main theme, so their use was in the context of PD.

'Representations' of immune degradation are biomarkers characteristic of immune degradation or components of the immune system that are being degraded (e.g., immunotoxicity; immunotoxic; spleen; immunosuppression; lymphocytes; immunosuppressive; inflammatory; cytokines; infection; macrophages; T cells; apoptosis; immunoglobulin; Thymus; hypersensitivity; oxidative stress; T-cell; cytotoxicity; cytotoxic; autoimmune; splenocytes; T cell; bone marrow; reactive oxygen species; immune suppression; neutrophils; cell death; neurotoxicity; immunodeficiency; thymocytes; lipid peroxidation; autoimmunity; pro-inflammatory cytokines; T-lymphocyte; natural killer cell; oxidative damage; immune dysfunction; white blood cell; red blood cell; cell apoptosis; impaired immune; immune alterations, etc.). Again, while some of these biomarkers apply to other diseases, it should be remembered they were located in records that had immune degradation as their main theme, so their use was in the context of immune degradation.

Discussion
Alteration of natural and pathological autoimmunity appears to be the thread connecting processes/agents related to PD and immune degradation. This is in keeping with the fact that PD has a tight connection with a long list of autoimmune diseases, such as type 1 diabetes, Crohn disease, ulcerative colitis, rheumatoid arthritis, celiac disease, psoriasis, multiple sclerosis, amyotrophic lateral sclerosis, Graves/hyperthyroidism, Hashimoto/hypothyroidism, pernicious anemia, and polymyalgia rheumatic [14-15]. Such PD autoimmune context appears to underlie

and link together, one-by-one, CFs and immune degradation as listed in Table 1. A few examples from Category 1 are:

Advanced Glycation End Products (Table 1, Row 1)
- advanced glycation end (AGE) products may activate NLRP3 inflammasome [16]. Altered NLRP3 inflammasome may lead to autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis, and ankylosing spondylitis [17].

Cocaine (Table 1, Row 3)
- cocaine may interfere with immune recognition of α-synuclein by anti-α-synuclein natural autoantibodies (NAAbs). Under physiological conditions, anti-α-synuclein NAAbs prevent aggregation and clumping of α-synuclein, a protein that, when aggregated, accumulates as Lewy bodies in the brains of people with PD [18-19]. Consequently, naturally occurring α-synuclein autoantibody levels are lower in patients with Parkinson disease [20]. Possible interference of cocaine with the immune protection of α-synuclein by NAAbs derives from the fact that cocaine binds tightly to N-terminus of intrinsically unstructured α-synuclein that adopts a more compact folded conformation, thus increasing the likelihood of α-synuclein structure misfolding [21-22], immune mis-recognition, and clumping.

Gluten (Table 1, Row 4)
- gluten toxicity might extend to the nervous system and contribute to PD via cross-reactive autoimmunity. As a matter of fact, gliadin protein – a component of gluten protein complex - presents a single amino acid repeat (QQQQQQQQQQQQ) that is also present in numerous human proteins related to neurodegeneration (ie, Voltage-dependent P/Q-type calcium channel subunit alpha-1A, Huntingtin, DNA polymerase subunit gamma-1, Ataxin-1, Ataxin-8, Atrophin-1 among others) and alterations of which lead to spinocerebellar ataxia, frontotemporal degeneration, Huntington disease, cognitive impairment, aphasia and oculomotor apraxia, inter alia [23].

High-Fat Diet (Table 1, Row 5)
- an autoimmune link between high fat diet and immunity degradation emerges from the fact that a high fat diet rich in saturated fatty acids induces inflammation in part by mimicking the actions of lipopolysaccharide (a very potent stimulus of inflammatory responses), with bioactivity in the microgram per liter concentration range [24]. Of interest, lipopolysaccharide is an adjuvant that stimulates autoimmune responses [25] and has been used to establish a bacterial endotoxin-based experimental model of PD [26].

Methamphetamine (Table 1, Row 7)
- methamphetamine has a double link with immune degradation, PD, and autoimmunity. Firstly, methamphetamine has a secondary amine that can start the Maillard reaction and lead to methamphetamine-conjugated AGE products [27], with consequent NLRP3 inflammasome activation and consequent autoimmune pathologies as described above [16-17]. Then, in addition, methamphetamine can bind to α-synuclein and cause a more compact conformation [28] with consequent immune mis-recognition and α-synuclein clumping. In this way, methamphetamine reproposes the cocaine pathological scheme: a drug binding to α-synuclein

that increases the likelihood of misfolding and, possibly, interferes with the protective solubilization activity of anti- α-synuclein NAAbs [18-20]. As a direct consequence, this would increase the incidence of PD.

The commonality of the broad spectrum of contributing factors presented in Table 1 shows that many of the factors responsible for the emergence of PD are also responsible for degrading the immune system and enabling the broad panorama of infectious diseases, including COVID-19. A larger and more well-resourced study that included more potential CFs than the 14,000+ used for the present study, and allowed for a concept-matching approach rather than a phrase matching approach, would identify many hundreds more CFs in common.

TABLE 1 – Common Contributing Factors to PD and Immune Degradation/COVID-19

CONTRIBUTING FACTOR	CATEGORY	PD REF	IMM DEGR REF
Advanced Glycation End Products	1	[29]	[30]
Alcohol Abuse	1	[31]	[32]
Cocaine	1	[33]	[34]
Gluten	1	[35]	[36]
High Fat Diet	1	[37]	[38]
Malnutrition	1	[39]	[40]
Methamphetamine	1	[41]	[42]
Sedentary	1	[43]	[44]
Vitamin D Deficiency	1	[45]	[46]
Bleomycin	2	[47]	[48]
Carboplatin	2	[49]	[50]
Cyclophosphamide	2	[51]	[52]
Halothane	2	[53]	[54]
Isoflurane	2	[55]	[56]
Thalidomide	2	[57]	[58]
Borrelia Burgdorferi	3	[59]	[60]
CMV	3	[61]	[62]
Epstein-Barr Virus	3	[63]	[64]
2,3,7,8-tetrachlorodibenzo-p-dioxin	4	[65]	[66]
Acrolein	4	[67]	[68]
Air Pollution	4	[69]	[70]
Aluminum	4	[71]	[72]
Arsenic	4	[73]	[74]
Atrazine	4	[75]	[76]
Cadmium	4	[77]	[78]
Carbon Monoxide	4	[79]	[80]
Carbon Tetrachloride	4	[81]	[82]

Chlorpyrifos	4	[83]	[78]
Cobalt	4	[84]	[85]
Copper Sulfate	4	[86]	[87]
Dichlorodiphenyltrichloroethane	4	[88]	[89]
Hexachlorobenzene	4	[90]	[91]
Inorganic Dust	4	[92]	[93]
Lead	4	[94]	[95]
Manganese	4	[96]	[97]
Mercury	4	[98]	[99]
N-hexane	4	[100]	[101]
Nitrogen Dioxide	4	[102]	[103]
Polychlorinated Biphenyls	4	[104]	[105]
Perchloroethylene	4	[81]	[106]
Polybrominated Diphenyl Ethers	4	[107]	[108]
Power Frequency EMF	4	[109]	[110]
Radiofrequency EMF	4	[111]	[112]
Radiotherapy	4	[113]	[114]
Silica	4	[115]	[116]
Titanium Dioxide	4	[117]	[118]
Trichloroethylene	4	[119]	[120]
Chronic Restraint Stress	5	[121]	[122]
Depression	5	[123]	[124]
Life Stress	5	[125]	[126]
Posttraumatic Stress	5	[127]	[128]

CATEGORY CODE: 1=LIFESTYLE; 2=IATROGENIC; 3=BIOTOXINS;
4=OCCUPATIONAL/ENVIRONMENTAL; 5=PSYCHOSOCIAL/SOCIOECONOMIC

NEW PARADIGM REQUIRED FOR PREVENTING AND TREATING INFECTIOUS AND CHRONIC DISEASES

Mainstream Medical Approach for "Magic Bullets" to Cure Disease
        The mainstream medical focus on PD/AD and COVID-19 is searching for a 'magic bullet' that will "cure" the patient. For PD/AD, it's some sort of 'magic drug', whereas for COVID-19, it's some sort of a 'magic vaccine'. As Bredesen (AD expert) stated: "In the case of Alzheimer's disease, there is not a single therapeutic that exerts anything beyond a marginal, un-sustained symptomatic effect, with little or no effect on disease progression. Furthermore, in the past decade alone, hundreds of clinical trials have been conducted for AD, at an aggregate cost of billions of dollars, without success. This has led some to question whether the approach taken to drug development for AD is an optimal one [129]." That statement could apply in different degrees to myriad chronic diseases. In fact, it is challenging to identify a chronic disease to which that statement does not apply! Bredesen's statement is applicable to some (perhaps many) infectious diseases as well. For example, since the initial SARS outbreak in 2002, many coronavirus vaccine developments have been attempted, and none have succeeded [6].
        For PD/AD and COVID-19, the researchers/politicians have the belief that some 'magic bullet' can compensate for the adverse effects produced by hundreds of CFs to the disease. Conceptually, how is this possible? The symptoms of PD/AD and COVID-19 are warning signals that something is out of kilter, similar to the oil warning light on a car's dashboard. Addressing only the symptoms with some drug or vaccine in isolation (akin to altering the oil warning light without addressing the underlying reasons why it is lit) can only lead to more serious consequences, if the fundamental causes are not addressed. Addressing the fundamental causes in parallel with a drug or vaccine would increase the efficacy of each; in fact, addressing the fundamental causes could potentially preclude the necessity for drugs or vaccines in preventing/treating these diseases.

Major Medical Paradigm Shift Required
        The findings of the present study suggest a paradigmatic shift in medical approaches to disease. The current approach to both 'communicable' and non-communicable diseases is mainly (not exclusively) external-treatment-based; i.e., taking some additive action (providing a drug, vaccine, radiation, surgery, etc.) to alleviate/reduce symptoms/abnormal biomarkers without sufficiently addressing the myriad factors that enabled the disease to emerge. The approach suggested by the findings in the present study is centered on identifying the factors that contributed to the disease, and eliminating these factors as comprehensively, thoroughly, and rapidly as possible. If CF elimination by itself is insufficient to prevent/reverse the disease completely, then some type of external treatment may be included, and in fact may be more efficacious with the elimination of the CFs. But, in both cases, healing must center around CF elimination, with external treatment used if healing does not proceed as rapidly as desired (e.g. the first step to heal a burn is to remove the heat source prior to treatment).

SUMMARY

Communicable disease is a misnomer. The disease is not communicable; the microbe mainly associated with the disease is communicable. Whether the recipient of the microbe develops the disease depends on the health of the recipient's immune system.

Thus, to prevent or treat infectious disease, the health of the immune system must be improved. One major component of increasing immune system health is to remove those factors that contribute to immune system degradation. A previous monograph identified many CFs to immune system degradation [6]. It was hypothesized that many of these CFs to immune system degradation were identical to those that past studies have shown were CFs to chronic diseases [8-10].

To test this hypothesis, a proof-of-principle demonstration was performed to identify the commonality between CFs to immune system degradation and CFs to PD. A very streamlined approach was used, and approximately 500 CFs were found in common between the two diseases. Since COVID-19 (and other infectious diseases) results from immune system degradation, this means COVID-19 and PD are enabled by many of the same toxic exposures and toxic behaviors (some toxic behaviors, such as choosing to smoke cigarettes, also involve toxic exposures, whereas others, such as sedentary living, do not). Thus, many of the measures required to strategically treat and prevent infectious diseases are similar to those required to strategically treat and prevent chronic diseases. This is a major paradigm shift for orthodox Western medicine, but is required to achieve major advances in global population health.

Realistically, very few people are willing to make the sacrifices required to eliminate the CFs to these myriad diseases, and thereby prevent or reverse these diseases. Decision-makers realize this, and continue to promote and sponsor the non-toxicology approaches for preventing and reversing both communicable and non-communicable diseases, even though these approaches have had very limited success.

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15

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APPENDIX 1

Commonality of Contributing Factors between PD and Immune System Degradation – Details

Category 1

Advanced Glycation End Products

PD: "Immunolocalization of advanced glycation end-products and a marker of oxidative stress response induction provides evidence that glycoxidation and oxidative stress may be an important pathogenic factor in diseases characterized by Lewy body formation, and furthers the evidence that cytoskeletal proteins and their inclusions are susceptible to oxidative stress." [29]

ID: "Advanced glycation end products impair NLRP3 inflammasome-mediated innate immune responses in macrophages" [30]

Alcohol Abuse

PD: "A history of an alcohol use disorder conferred an increased risk of admission with a diagnosis of Parkinson's disease in both women and men. In particular, the risk seemed higher at lower ages of first admission with Parkinson's disease." [31]

ID: "Alcoholism causes alveolar macrophage zinc deficiency and immune dysfunction" [32]

Cocaine

PD: "found that exposure to cocaine both in utero or as adults did not affect substantia nigra cell number, but did make these neurons more susceptible to the parkinsonian toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine." [33]

ID: "based on in vivo experiments with the protozoan Tetrahymena, suggests the compromised immune response in cocaine addicts and assures the reported effects of cocaine on immune cell function." [34]

Gluten

PD: "Dramatic improvement of parkinsonian symptoms after gluten-free diet introduction in a patient with silent celiac disease" [35]

ID: "CGM negatively affected the gut health of turbot by inducing enteritis and by decreasing intestinal immunity and antioxidant capacity" [36]

High Fat Diet

PD: "Neurodegeneration in an animal model of Parkinson's disease is exacerbated by a high-fat diet" [37]

ID: "High-fat diet-derived free fatty acids impair the intestinal immune system and increase sensitivity to intestinal epithelial damage" [38]

Malnutrition

PD: "Under-nutrition is a problem for around 15% of community dwelling people with PD" [39]

ID: "Malnutrition is the primary cause of immunodeficiency worldwide and profoundly affects immune responses." [40]

Methamphetamine

PD: "Studies have implicated methamphetamine exposure as a contributor to the development of Parkinson's disease." [41]

ID: "METH exposure results in altered T cell cycle entry and progression." [42]

Sedentary

PD: "data suggest that treadmill exercise throughout life can markedly reduce the chances of dopamine decrease, reinforcing studies that showed a lower incidence of Parkinson's disease in patients who were active during life." [43]

ID: "Sedentary lifestyle leads to the accumulation of visceral fat. This is accompanied by the infiltration of immune cells with pro-inflammatory characteristics in adipose tissue, causing an increased release of cytokines and generating a low-grade inflammatory state." [44]

Vitamin D Deficiency

PD: "Reduced exposure to sunlight and low food intake can lead to vitamin D deficiency. Increasing evidence highlights the impact of vitamin D deficiency as a favoring factor in various central or peripheral neurological diseases, especially multiple sclerosis and several neurodegenerative diseases, such as amyotrophic lateral sclerosis, Parkinson's disease and Alzheimer's disease." [45]

ID: "Vitamin d deficiency reduces the immune response, phagocytosis rate, and intracellular killing rate of microglial cells" [46]

Category 2

Bleomycin

PD: "Removal of alpha-synuclein in human cells leads to increased DNA double-strand break (DSB) levels after bleomycin treatment and a reduced ability to repair these DSBs" [47]

ID: "Increased bleomycin-induced chromosome damage in lymphocytes of patients with common variable immunodeficiency indicates an involvement of chromosomal instability in their cancer predisposition" [48]

Carboplatin

PD: "Progression of Parkinson's disease with impairment of vision under carboplatin/cyclophosphamide therapy for ovarian cancer" [49]

ID: "Carboplatin-induced immune hemolytic anemia" [50]

Cyclophosphamide

PD: "Our cases of chemotherapy-induced parkinsonism occurred after exposure to…..cyclophosphamide …by alkylating and cross-linking DNA…..Cyclophosphamide and ara-C are the most commonly implicated agents" [51]

ID: "Cyclophosphamide did not affect body mass or packed cell volume. However, spleen to body mass ratios and the number of viable spleen cells were lower in CY-treated birds when compared to controls. Peripheral white blood cell numbers were reduced in CY-treated starlings, and the decrease affected all cell types. Phagocytic ability of macrophages cultured from peripheral blood monocytes was impaired in cells from CY-treated birds. Additionally, CY treatment resulted in decreased lymphocyte blastogenesis to the T-cell mitogen Concanavalin A. The hemagglutination response to sheep erythrocytes was lower in birds that had received CY. Thus, these immunological methods detected chemically-induced immune dysfunction in starlings" [52]

Halothane

PD: "Numerous recent mechanistic studies (in vitro essays and in vivo short-term studies) strengthened the association between exposure to anesthetic gases (nitrous oxide, halothane, isoflurane, levoflurane) and PD." [53]

ID: "halothane anesthesia potentiates the suppression of cell-mediated immunity observed in tumor-bearing hosts." [54]

Isoflurane

PD: "Because the transport of dopamine by synaptosomes is impaired during and after exposure to halothane or isoflurane, [19] there may be decreased dopaminergic transmission as well as accumulation of extracellular dopamine during inhalational anesthesia because of simultaneous dopaminergic receptor blockade and depressed neuronal release and reuptake of dopamine." [55]

ID: "isoflurane anesthesia disrupts hippocampal neuroimmune mediator gene expression in the old brain and suggests a potential mechanism by which general anesthesia can contribute to disordered neuronal homeostasis and post-anesthesia cognitive disability in older subjects." [56]

Thalidomide

PD: "Thalidomide induced acute worsening of Parkinson's disease") [57]

ID: "thalidomide prevents antiplatelet antibody-mediated platelet destruction in ITP mouse possibly through reducing the number of macrophages" [58]

Category 3

Borrelia Burgdorferi

PD: "IB consisting of CMV, EBV, HSV-1, B. burgdorferi, C. pneumoniae and H. pylori is associated with PD. This study supports the role of infection in the etiology of PD." [59]

ID: "B. burgdorferi induced significantly greater monocyte activation and inflammatory cytokine production than did borrelial lysates or T. pallidum, and only B. burgdorferi elicited gamma interferon (IFN-gamma) from NK cells" [60]

CMV(Cytomegalovirus)

PD: "found higher frequencies of myeloid DCs with a pro-inflammatory CD16+ILT2(high) phenotype in CMV-positive PD patients than controls, suggesting the potential involvement of CMV in exacerbating PD." [61]

ID: "HIV-infected individuals are almost universally co-infected with cytomegalovirus (CMV) and both viruses are associated with inflammation-related morbidities." [62]

Epstein-Barr Virus

PD: "Postencephalitic parkinsonism and basal ganglia necrosis due to Epstein-Barr virus infection" [63]

ID: "Epstein-Barr virus strain heterogeneity impairs human T-cell immunity" [64]

Category 4

2,3,7,8-tetrachlorodibenzo-p-dioxin

PD: "TCDD induces UbcH7 expression and synphilin-1 protein degradation in the mouse ventral midbrain" [65]

ID: "A review of 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced changes in immunocompetence: 1991 update" [66]

Acrolein

PD: "data suggests acrolein likely plays an important role in inducing PD pathology following bTBI by encouraging α-synuclein aggregation." [67]

ID: "Acrolein in cigarette smoke attenuates the innate immune responses mediated by surfactant protein D" [68]

Air Pollution

PD: "Traffic-related air pollution increased the risk of Parkinson's disease in Taiwan: A nationwide study" [69]

ID: "air pollutants can affect different immune cell types such as particle-clearing macrophages, inflammatory neutrophils, dendritic cells that orchestrate adaptive immune responses and lymphocytes that enact those responses. Common themes that emerge are of the capacity of air pollutants to stimulate pro-inflammatory immune responses across multiple classes of immune cell. Air pollution can enhance T helper lymphocyte type 2 (Th2) and T helper lymphocyte type 17 (Th17) adaptive immune responses, as seen in allergy and asthma, and dysregulate anti-viral immune responses." [70]

Aluminum

PD: "Aluminum-containing antacids as a cause of idiopathic Parkinson's disease" [71]

ID: "Aluminum as a CNS and Immune System Toxin Across the Life Span" [72]

Arsenic

PD: "Arsenic Induces Accumulation of α-Synuclein: Implications for Synucleinopathies and Neurodegeneration" [73]

ID: "Arsenic immunotoxicity and immunomodulation by phytochemicals: potential relations to develop chemopreventive approaches" [74]

Atrazine

PD: "Identification of miRNA-7 as a regulator of brain-derived neurotrophic factor/α-synuclein axis in atrazine-induced Parkinson's disease by peripheral blood and brain microRNA profiling" [75]

ID: "Long-term Immunotoxic Effects of Oral Prenatal and Neonatal Atrazine Exposure" [76]

Cadmium

PD: "Cadmium toxicity has been associated with learning disabilities and Parkinsonian symptoms in humans." [77]

ID: "Cadmium and chlorpyrifos inhibit cellular immune response in spleen of rats" [78]

Carbon Monoxide

PD: "Increased risk of Parkinson disease in patients with carbon monoxide intoxication: a population-based cohort study" [79]

ID: "Chronic prenatal exposure to carbon monoxide results in a reduction in tyrosine hydroxylase-immunoreactivity and an increase in choline acetyltransferase-immunoreactivity in the fetal medulla: implications for Sudden Infant Death Syndrome" [80]

Carbon Tetrachloride

PD: "Ever exposure to trichloroethylene (TCE) was associated with significantly increased risk of PD…..exposure to perchloroethylene (PERC) and carbon tetrachloride (CCl(4)) tended toward significance (respectively: OR, 10.5; 95% CI, 0.97-113; p = 0.053; OR, 2.3; 95% CI, 0.9-6.1; p = 0.088). Results were similar for estimates of exposure duration and cumulative lifetime exposure.." [81]

ID: "Carbon tetrachloride is immunosuppressive and decreases host resistance to Listeria monocytogenes and Streptococcus pneumoniae in female B6C3F1 mice.)" [82]

Chlorpyrifos

PD: "Chlorpyrifos-induced parkinsonian model in mice: Behavior, histopathology and biochemistry" [83]

ID: "Cadmium and chlorpyrifos inhibit cellular immune response in spleen of rats" [78]

Cobalt

PD: "The neurotoxicity of iron, copper and cobalt in Parkinson's disease through ROS-mediated mechanisms" [84]

ID: "dermal sensitization to cobalt may increase the susceptibility of the lungs to inhaling cobalt. Mechanistically, this enhanced susceptibility involves changes in pulmonary DCs and ILCs." [85]

Copper Sulfate

PD: "Enhancement of cytotoxicity and clastogenicity of l-DOPA and dopamine by manganese and copper" [86]

ID: "Immunotoxicity of copper nanoparticle and copper sulfate in a common Indian earthworm" [87]

Dichlorodiphenyltrichloroethane

PD: "Dichlorodiphenyltrichloroethane (DDT) induced extracellular vesicle formation: a potential role in organochlorine increased risk of Parkinson's disease" [88]

ID: "Exposures to the environmental toxicants pentachlorophenol (PCP) and dichlorodiphenyltrichloroethane (DDT) modify secretion of interleukin 1-beta (IL-1β) from human immune cells" [89]

Hexachlorobenzene

PD: "Although associations with other compounds were weaker, hexachlorobenzene (P = 0.003) and α-chlordane (P = 0.007) were also related to Lewy pathology." [90]

ID: "Oral exposure of rats to HCB showed stimulatory effects on spleen and lymph node weights and histology, increased serum IgM levels, and an enhancement of several parameters of immune function." [91]

Inorganic Dust

PD: "Exposure to inorganic dust was associated with increased risk of Parkinson's disease and Parkinsonian disorders" [92]

ID: "immunologic aberrations occur in several inorganic dust diseases" [93]

Lead

PD: "The immunohistochemical approach has revealed that Pb-intoxicated Meriones show a significant increase of Tyrosine Hydroxylase (TH) levels within the Substantia Nigra compacta (SNc), Ventral Tegmental Area (VTA), Locus Coeruleus (LC), Dorsal Striatum (DS) and Medial Forebrain Bundle (MFB)," [94]

ID: "Lead exposure can result in impaired immune function of T lymphocytes and erythrocytes in preschool children." [95]

Manganese

PD: "Manganese-induced parkinsonism and Parkinson's disease" [96]

ID: "SNc of the Mn-exposed animals showed an important decrease (67.58%) in the number of TH-immunopositive neurons." [97]

Mercury

PD: "Mercury may play a role in the etiology of Parkinson disease and Grover's disease." [98]

ID: "Diphenyl diselenide protects against hematological and immunological alterations induced by mercury in mice" [99]

N-hexane

PD: "Chronic exposure to n-hexane contributes to induce onset of Parkinson's disease" [100]

ID: "Severe testicular atrophy involving the seminiferous tubules with loss of the nerve growth factor (NGF) immunoreactive germ cell line was found. Total loss of the germ cell line was found in a fraction of animals up to 14 months post-exposure, indicating permanent testicular damage. ... . Toluene and xylene were thus found to protect from n-hexane induced testicular atrophy." [101]

Nitrogen Dioxide
PD: "In logistic regression models, long-term exposure to NO2 increased PD risk overall (odds ratio (OR)=1.06 per 2.94μg/m3 increase, 95% CI=1.00-1.13)." [102]
ID: "Acute nitrogen dioxide (NO2) exposure enhances airway inflammation via modulating Th1/Th2 differentiation and activating JAK-STAT pathway" [103]

PCBs
PD: "These quantitative data demonstrate an association between brain PCB levels and Parkinson's disease-related pathology. Furthermore, these data support epidemiological and laboratory studies reporting a link between PCB exposure and an increased risk for Parkinson's disease, including greater susceptibility of females." [104]
ID: "Exposure to PCBs suppresses the immune system, thereby increasing the risk of acquiring several human diseases." [105]

Perchloroethylene
PD: "Ever exposure to trichloroethylene (TCE) was associated with significantly increased risk of PD (odds ratio [OR], 6.1; 95% confidence interval [CI] 1.2-33; p = 0.034), and exposure to perchloroethylene (PERC) and carbon tetrachloride (CCl(4)) tended toward significance (respectively: OR, 10.5; 95% CI, 0.97-113; p = 0.053; OR, 2.3; 95% CI, 0.9-6.1; p = 0.088)." [81]
ID: "The mechanism of enhancing the PCA reaction is assumed to be that PCE increases IL-4 production and PCE causes T helper (Th) 1/Th2-type helper T-cell imbalance and increases histamine release from excessively accumulated mast cells." [106]

Polybrominated Diphenyl Ethers
PD: "isobaric tags for relative and absolute quantitation (iTRAQ) proteomics study of the striatum, which is the part of brain that is most intensively studied in PD pathogenesis, revealed that BDE-47 could induce neurotransmitter system disturbance, abnormal phosphorylation, mitochondrial dysfunction and oxidative stress." [107]
ID: "The results showed that after 24h of exposure, BDE-47 (>5 μM) and BDE-209 (>20 μM) induced cell apoptosis, increased intracellular reactive oxygen species (ROS) formation and depleted glutathione." [108]

Power Frequency EMF
PD: "We finally demonstrate that ELF-MFs alter the expression of the alpha-synuclein, which is specifically stimulated upon ELF-MFs exposure via both direct miR-34 targeting and oxidative stress. Altogether, our data highlight the potential of the ELF-MFs to tune redox homeostasis and epigenetic control of gene expression in vitro and shed light on the possible mechanism(s) producing detrimental effects and predisposing neurons to degeneration" [109]
ID: "The data demonstrate that MF in vivo exposure of female rats induces complex effects on the mitogenic responsiveness of T cells, which may lead to impaired immune surveillance after long-term exposure." [110]

Radiofrequency EMF
PD: "GSM radiation seems to contribute to the Alzheimer's and Parkinson's disease pathogenic mechanisms…..changes in monomeric α-syn accumulation and multimerization, as well as induction of oxidative stress and cell death, were documented" [111]
ID: "After 30 days of exposure time, 1 h/day EMF exposure resulted in significant decrease in immunoglobulin levels (IgA, IgE, IgM, and IgG); total leukocyte, lymphocyte, eosinophil

and basophil counts; and a significant increase in neutrophil and monocyte counts. These changes were more increased in the group exposed to 2 h/day EMF." [112]

Radiotherapy

PD: "Occupational exposure to chronic ionizing radiation increases risk of Parkinson's disease incidence in Russian Mayak workers" [113]

ID: "various degrees of cognitive deficit can develop after much lower doses of ionizing radiation, as well…..A permanent deficit in neurogenesis, chronic microvascular alterations, and blood-brain barrier dysfunctionality are considered among the main causative factors. Chronic neuroinflammation and altered immune reactions in the brain, which are inherent complications of brain irradiation, have also been directly implicated in the development of cognitive decline after radiation." [114]

Silica

PD: "the in vivo injury of neurochemicals occurred as the SiO2-NPs appeared to induce depleted dopamine in the striatum, and the down-regulation of tyrosine hydroxylase protein was the main contribution. These data demonstrate that SiO2-NPs possibly have a negative impact on the striatum and dopaminergic neurons as well as a potential risk for neurodegenerative diseases." [115]

ID: "toxicity of SiNPs to the immune system has received an increasing amount of attention. SiNPs may have toxic effects on phagocytes, particularly macrophages, dendritic cells (DCs) and T-lymphocytes. Additionally, the immunotoxicity of SiNPs to tissues and organs has been investigated in vivo." [116]

Titanium

PD: "Our findings indicated that TiO2, depending on dose, can cause the destruction of dopaminergic neurons and consequently increase the risk of Parkinson's disease" [117]

ID: "these results indicated that TiO2 could induce hematotoxicity, genotoxic, and immunotoxic alterations with exposure for long durations" [118]

Trichloroethylene

PD: "mice were intoxicated with trichloroethylene and tyrosine hydroxylase immunoreactivity was used to measure neuronal death in the substantia nigra pars compacta. Treated mice presented significant dopaminergic neuronal death in comparison with control mice (50%)." [119]

ID: "Differential immunotoxicity induced by two different windows of developmental trichloroethylene exposure" [120]

Category 5

Chronic Restraint Stress

PD: "Chronic restraint stress triggers dopaminergic and noradrenergic neurodegeneration: Possible role of chronic stress in the onset of Parkinson's disease" [121]

ID: "Toll-like receptor 4 mediates chronic restraint stress-induced immune suppression" [122]

Depression

PD: "patients with depression are at risk of developing PD later in life." [123]

ID: "Both stress and depression were associated with the decreased cytotoxic T-cell and natural killer cell activities affecting the processes of the immune surveillance of tumours, and the events that modulate the development and the accumulation of somatic mutations and genomic instability." [124]

Life Stress

PD: "Exposure to Early Life Stress Results in Epigenetic Changes in Neurotrophic Factor Gene Expression in a Parkinsonian Rat Model" [125]

ID: "Chronic life stress alters sympathetic, neuroendocrine, and immune responsivity to an acute psychological stressor in humans" [126]

Posttraumatic Stress

PD: "Our study was the first to demonstrate that both TBI and PTSD are independently associated with increased relative PD risk in a diverse nationwide cohort of military service veterans, and the first to suggest a potential modest synergistic excess risk in those with comorbid TBI/PTSD" [127]

ID: "Posttraumatic stress and immune dissonance" [128]

AUTHOR BIOS

Ronald Neil Kostoff received a Ph. D. in Aerospace and Mechanical Sciences from Princeton University in 1967. He has worked for Bell Laboratories, Department of Energy, Office of Naval Research, and MITRE Corp. He invented the Wake Shield for producing high vacuum in low orbit, and used in manned space missions for research and development. He has published over 200 peer-reviewed articles, served as Guest Editor of four journal Special Issues since 1994, obtained two text mining system patents, and presently is a Research Affiliate at Georgia Institute of Technology.

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  - Raynaud's Phenomenon,
  - Cataracts,
  - SARS,
  - Vitreous Restoration,
  - Peripheral Neuropathy/Peripheral Arterial Disease
  - Alzheimer's Disease, and
  - Chronic Kidney Disease;
- potential causes of Chronic Kidney Disease;
- potential causes of Alzheimer's Disease;
- potential causes of Peripheral Neuropathy/Peripheral Arterial Disease;
- potential impacts of Electromagnetic Fields on health;
- synergistic effects of toxic stimuli combinations, and
- COVID-19 prevention strategies and vaccine safety issues.

His recent publications in toxicology have shown that regulatory exposure limits to toxic stimuli are, on average, orders of magnitude too high compared to exposures shown to cause damage in the biomedical literature, and are not protecting the public from harmful substances.

He is listed in:
- Who's Who in America, 60th Edition (2006),
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Michael B. Briggs is an independent research consultant. He received a B.S. and M.S. in Nuclear Engineering, and an M.E. in Radiological Health Engineering from the University of Michigan. He has worked in high-impact organizations at the cutting edge of high-tech disciplines as an end-user, integrator, and developer of Science & Technology (S&T) driven capabilities using multi-disciplinary approaches to exploit signatures, detection, and measurements in multiple modalities. He is currently using a multi-disciplinary approach to explore novel text mining techniques to enhance S&T discovery and innovation.

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