The position of geochemical variables as causal co-factors of diseases of unknown aetiology

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Abstract

The term diseases of unknown aetiology (DUA) or idiopathic diseases refers to diseases that are of uncertain or unknown cause or origin. Among plausible geoenvironmental (co-)factors in causation of DUA, this article focusses on the entry of trace elements, including metals and metalloids into biological systems, and their involvement in humoral and cellular immune responses, representing potentially toxic agents with implications as co-factors for certain DUA. Several trace elements/metals/metalloids (micronutrients) play vital roles as cofactors for essential enzymes and antioxidant molecules, thus, conferring protection against disease. However, inborn errors of trace element/metal/metalloid metabolisms can occur to produce toxicity, such as when there are basic defects in the element transport mechanism. Ultimately, it is the amount of trace element, metal or metalloid that is taken up, its mode of accumulation in human tissues, and related geomedical attributes such as the chemical form and bioavailability that decisively determine whether the exerted effects are toxic or beneficial. Several case descriptions of DUA that are common worldwide are given to illustrate our knowledge so far of how trace element/metal/metalloid interactions in the immune system may engender its dysregulation and be implicated as causal co-factors of DUA.

Introduction

An excerpt from Marcus Haase's paper in JAMA, "Etiology Unknown", written way back in 1923 runs as follows: "*I doubt seriously whether there is a more humiliating moment in the life of a medical man, either as teacher or practitioner, than when asked by a student or patient, 'What is the cause of this?' and he is forced to say, 'I do not know.'"* Despite the enormous advances made by modern medicine, there are many diseases whose causes are still unknown (See examples in Table 1). These diseases are generally referred to as *diseases of unknown aetiology* (DUA), and as recently as 2020, an estimated seventy-six percent of unknown disease outbreaks remained undiagnosed (Mao et al., 2020). Rappaport had earlier (2012) noted that: "Although *chronic* diseases are primarily environmental (i.e., not genetic) in origin, the particular environmental causes of these diseases are poorly understood."

A recent World Health Organisation (WHO) study of worldwide cancer mortality identified ten diverse environmental *risk* factors, including some with links to the geological environment, such as air pollution and ionising and ultraviolet radiation (WHO, 2018a). But, on the whole, it appears that the influence of geoenvironmental factors in disease causation, in particular, the effects of involvement of trace elements/metals/metalloids in human metabolisms that produce disease, have been somewhat underestimated.

In this paper, it is argued that greater consideration should be given to the contribution of the geoenvironmental co-factor in a multi-factor explanation and diagnosis of DUA; in particular, the entry of trace elements including metals and metalloids into biological systems, and their involvement in humoral and cellular immune responses. Possible ways in which trace elements/metals/metalloids can contribute towards shaping developmental metabolic frameworks and pathways in DUA progression are described. The expectation is that a firm understanding of the role of geoenvironmental co-factors, more especially trace element/metal/metalloid perturbations that produce errors or disturbances in metabolic processes will help greatly in unravelling the aetiology of DUA when this knowledge is applied in a circumspective way.

Rationalisation of such knowledge falls within the compass of the Medical Geologist who, according to Bundschuh et al. (2017), can provide "... a more holistic understanding of the occurrence, mobility, bioavailability, bio-accessibility, exposure and transfer mechanisms of *geochemicals* to the food-chain and humans, and the related ecotoxicological impacts and health effects." To these parameters, can be added the chemical form of the element, a parameter that, in turn, greatly influences mobility, bioavailability and the mechanism that either transports the element to the centres (of the body) where it is needed for vital reactions, or be involved in interactions that result in disease (*cf.* DUA). Such an integrative approach recognises that most DUAs and other enigmatic diseases have multifactorial causes, engendering a complex interplay between genetic factors (polygenic), immunological mediators (trace elements/metals/metalloids) and various other (geo)environmental factors, none of which factors would cause the disease on its own.

This approach is further buttressed by Panelli's (2017) statement: "The focus on multisystem diseases of unknown cause highlights not only the immediate need in medicine to research the origin of an unknown disease with multiple symptoms, *but also the necessity to find novel ways to diagnose and discriminate diseases that have no clear aetiology* but represent a dramatic reality affecting large populations of patients."

Methodology

An iterative approach was adopted in a comprehensive internet search using Google search engine through August 26, 2021. Initial searches used broad terms: 'geo-environmental factors', 'unknown aetiology' and 'disease X'. Inclusion criteria were studies carried out in humans and animals and reported observational designs. The documents returned from these searches were used to identify narrower search terms, such as 'risk factors', 'nutritional and toxic elements/metabolic imbalances', 'immune system', 'geo-climatic variables and health', and 'disease clusters'. Over one thousand documents were retrieved (including some duplicates), out of which the conclusions of about six hundred and eighty were studied in detail. These included peer reviewed journal articles and conference proceedings, authentic book chapters, published and unpublished theses and reports, and selected web references.

Main Text

Contributions made

This paper has advanced reasons why a keener look at co-factors linked to the geoenvironmental milieu, especially geochemical variables, deserves greater attention in understanding causality of DUA. The medical profession, environmental health practitioners and allied scientists, relevant government officials and other stakeholders should now be aware of the huge potential contribution of Medical Geologists in teams investigating the causes of DUA and sudden disease outbreaks. The discourse fosters, in particular, an understanding of the relationship of certain trace elements/metals/metalloids and the immune system and presents examples of current critical evidence of associations between environmental risk factors such as geographical variables and climate change, and immune system impairment. The work buttresses the hypothesis that errors (or disturbances) in trace element/metal/metalloid metabolism negatively affect immune response and can provide useful clues in the unravelment of DUA causality. Consequently, it is possible to proffer that a proper understanding of the dynamics/imbances of trace element/metal/metalloid interactions in metabolic processes may one day be found to play a far greater role in deciphering DUA aetiology than has hitherto been realised.

Finally, a list of some of the more recent research (as at 2021) is assembled, supporting the thesis that greater consideration of geoenvironmental factors would enhance efforts in unravelling DUA aetiology. It is considered that this reference list would also prove useful as an aid to the search process of researchers interested in continuing with work on this important and exciting subject.

A NOTE ON CAUSALITY

In the field of medicine, *cause*, also sometimes referred to as *aetiology* is the [reason](#) or origination of a disease, or of a *pathology* (essential nature of disease) (Ross, 2018). The word 'aetiology' is derived from the [Greek](#) αἰτιολογία, *aítiologia*, "giving a reason for" (αἰτία, *aitia*, "cause"; and -λογία, *-logia*) (Simpson and Weiner, 2002).

The search for the aetiologies of human diseases can be traced back to antiquity. [Hippocrates](#), a Greek physician of the 4th and 5th centuries BCE, is credited with being the first to adopt the concept that [disease](#) is not a visitation of the gods but rather is caused by earthly influences (Britannica, 2020). Medieval [European](#) doctors were generally of the view that disease was related to the *air* and adopted a [miasmatic approach](#) to disease aetiology (Berry, 2007). Scientists have since continually searched for the causes of disease and, indeed, have discovered the causes of many. Where no aetiology can be ascertained, the disorder is said to be [idiopathic](#) (CMD, 2010).

Traditional accounts of the causes of disease may point to the [evil eye](#), a phenomenon elucidated by Abu-Rabia in 2005, in describing the rituals of diagnosis, treatment and prevention among the Bedouin tribes of the Negev in the Middle East.

Aetiological discovery in medicine also has a history in [Robert Koch's](#) demonstration that the tubercle bacillus (*Mycobacterium tuberculosis* complex) causes the disease [tuberculosis](#), *Bacillus anthracis* causes [anthrax](#), and *Vibrio cholerae* causes [cholera](#) (Cambau and Drancourt, 2014). This line of thinking and evidence is summarised in [Koch's postulates](#). In the epidemiology of infectious diseases, proof of causation is limited to individual cases where experimental evidence of aetiology can be advanced. In order to infer causation, we require several lines of evidence, taken together.

Chain of causation and correlation

We need to [distinguish between causation and association or statistical correlation](#). Events may occur simultaneously simply due to [chance](#), [bias](#) or [confounding](#) (See: "Glossary of Terms" for definitions), instead of one event being precipitated by the other. It is also necessary to decipher which event is the cause. [Confounding](#) is said to occur when exposure to a probable disease causative agent or cofactor and an outcome have an apparent but false correlation (Fig. 1). It is important to control for the confounder, otherwise, there would seem to be a link between the exposure and the outcome, when in fact both are due to the confounding effect and bear no relationship at all (or no strong relationship). Careful sampling and analyses should be the *sine qua non*, rather than complex statistical analysis to establish causation. Evidence from experimental studies involving interventions (providing or removing the supposed cause) provides the most convincing evidence of aetiology.

It is also necessary to state that there are times when several symptoms appear together, sometimes more than what could be expected; though it is known that one cannot cause the other. These situations are referred to as *syndromes* (See “Glossary of Terms”, this article). The assumption is that an underlying condition exists that explains all the symptoms. Quite often, however, a single cause for a disease cannot be found, but rather, we find a *chain of causation* from an initial trigger to the development of the clinical disease. An aetiological agent of disease may require an independent co-factor and be subject to a *promoter* (See “Glossary of Terms”, this article) to cause disease.

Role of genetics as causality co-factor

A *gene* is the basic physical unit of heredity. Genes are made up of *DNA* (deoxytribonucleic acid) and act as instructions to synthesise molecules called *proteins*. Many proteins are actually *enzymes*, and are responsible for carrying out all cellular functions. Salzberg (2018) estimated the number of genes in the *human genome* (genetic complement) to be 20,000 to 25,000. Genes are passed on from parents to offspring, and contain the information needed to specify traits.

Certain human diseases result from *mutations* in the genetic complement contained in the *DNA* of chromosomes. Although mutations occurring in the DNA of somatic (body) cells cannot be inherited, they can cause *congenital malformations* (existing at birth) and cancers. However, mutations that occur in germ cells - i.e., the *gametes*, ova and sperm - are passed on to offspring causing inherited diseases.

Studies on how environmental exposures modify the expression of genes without directly changing the genetic code stored in DNA were appraised by Rappaport in 2016, and more recently by Perera et al. (2019). Such studies belong to the field of *environmental epigenetics*, a field that is currently being actively researched by the United States National Institute of Environmental Health Sciences (US NIEHS) (US NIEHS, 2020).

THE GEO-ENVIRONMENT AS AN AGENT OF ILLNESS

In 2000, Kroll-Smith et al. noted that: “Struggles over environmentally induced diseases are struggles over the very nature of what exists and how we know the nature of the phenomenon”.

Suggestions that the geoenvironmental milieu (geographical and climatic patterns, seasonal variations, geological and geochemical variables) can have a significant influence on the occurrence and development of disease, has for long captivated scholarly attention across a number of disciplinary and policy domains. Mehri (2020), for instance, discuss how geoenvironmental conditions work in concert with infectious agents that activate *innate* and *adaptive* immune system (See “Glossary of Terms”, this article) and provoke DUA in genetically susceptible patients.

Writing on one of the more well-known DUAs (*chronic kidney disease*, CKD: Table 1), Hara et al. (2016) remarked on the significance of the contribution of environmental factors compared to genetic factors in the development of CKD among individuals with the same ethnicity. In 2017, Senanayake and King, reviewing recent research done on emerging health-environment relationships, categorised the studies done into three themes, viz: complexity, uncertainty, and bodies. Although there have been robust contributions to these thematic areas from geography and the social sciences, Senanayake and King (2017) construe that integrating them into an analytical framework can extend geographical perspectives on scale, knowledge production, and human-environment relations, while also incorporating valuable insights from cognate fields.

The cardinal thesis here is that proper consideration of geoenvironmental co-factors can significantly contribute to resolution of causation of DUA, probably to an extent greater than what has hitherto been conceived (Table 1). Some examples of probable geoenvironmental and related co-factors to be considered are:

(i) The immune-modulatory effect of geochemical variables (e.g., chemical form and the mechanism of element transport) that underline nutritional and potentially toxic element (PTE) perturbations in metabolic processes.

(ii) Water, soil and air pollution emanating from diverse sources that include volcanic emissions, mining, naturally contaminated groundwater, agriculture and industry. A substantial part of the pollution load from these sources often comprises the PTEs (e.g., As, F, Hg, Pb) having a propensity to enter the food chain (through consumption of food crops, drinking water and through other intake pathways such as inhalation and direct contact) [cf., (i) above]. Initially undetected release of a chemical from the Earth's sub-surface into the groundwater system can occur, such as when CO₂ gas was released in the Lake Nyos (Cameroon) disaster of the 1980's (See, e.g., Rouwet *et al.*, 2016).

(iii) Geogenic dust particles (from mining, ore processing and vehicular transportation on untarred roads).

(iv) Over-exposure to ionising radiation and radionuclides in the water, soil and air environments during mining, ore processing and tailings handling of U, Au and other radiogenic ores.

(v) Geographical patterns (e.g., locality, altitude) and seasonal variations.

(vi) Climate change and *geoclimatic* effects.

(vii) Factors of *geopathic stress* and *heat stress*.

PLEASE INSERT TABLE 1 HERE

Geogenic contaminants

Geochemicals such as metals, metalloids, radionuclides and isotopes as well as transuraniums, referred to as *geogenic contaminants* (GCs) by Bundschuh *et al.* (2017), occur naturally in geogenic sources (minerals, rocks, ground- and surface waters, volcanic emanations). Their accelerated release globally has been attributed to rapid population rise and economic growth, and the associated increase in demand for water, energy, food, and mineral resources. When GCs occur in near-surface environments, their release can be triggered into the environment by natural biogeochemical processes and/or by anthropogenic activities such as mining and oil exploitation, fossil fuel combustion as well as exploitation of geothermal resources. The result is the contamination of soil, water, air and biota, and their subsequent entry into the food chain with often deleterious health consequences that are mostly underestimated and poorly recognised; not to say that other categories of co-factors of environmental pollution are to be discounted, when studying environmental toxicology and pathogenesis. Indeed, Garchitorena *et al.* (2017) demonstrate clearly that: "Control of environmentally transmitted diseases can be more effective when human treatment is complemented with interventions targeting the environmental reservoir of the pathogen."

Geographical patterns, seasonal variations and climate change

As recently as 2008, Dummer recapitulated the intrinsic link between geography and health, and went on to posit that, where we were born, where we live, where we work, the food we eat, the viruses we are exposed to, among other circumstances, all directly influence our state of health; and should be the key determinants driving any research on the geography of disease. Buttressing this observation was a noteworthy study by NCSV in 2010 that factored climate and geographical variables, population data, disease-control data, pathogen data and human history data into statistical models that attempted to show which factors had stronger correlations to disease.

The "place factor"

The spatial location (the geographic context of places and the connectedness between places) plays a major role in shaping environmental risks as well as many other health effects. As Ruiz noted in 2017, carefully designed geographical investigations of the spatial variation of diseases can provide useful clues on what contributes to disease outcomes and options for disease prevention. *The occurrence of diseases in some places but not in others, or the variation of disease rates from place to place, should lead the Medical Geologist and others in disease investigation teams to having a closer look at the characteristics that differentiate those places in providing clues to aetiology* (See Section on: "Investigation of disease clusters", this article). The importance of the "place factor" in unravelling DUA is well illustrated in the study of *spastic paraparesis* in Mozambique by Cliff *et al.* (1984) (Fig. 2).

PLEASE INSERT FIG. 2 HERE.

Again too, apart from accounting for the diseases themselves, teams investigating the geographical drivers of disease must take cognisance of the characteristics and dynamics of pathogens, vectors and host populations, the presence of xenobiotic chemicals or other toxic agents (See: Ruiz, 2017). This would lend to a more holistic approach in the aetiological characterisation of enigmatic diseases.

Seasonality/spacio-temporal associations of disease

Seasonal change in the incidence of infectious diseases is a common phenomenon worldwide, particularly in continents having temperate or tropical climates. *However, the mechanisms responsible for seasonal disease incidence, and the epidemiological consequences of seasonality are, with only a few exceptions, poorly understood* (See: Grassly and Fraser, 2006).

The several mechanistic hypotheses that have been advanced to explain seasonality of various directly transmissible diseases include: human activity, pathogen infectivity, seasonal variability in human immune system function, seasonal variations in vitamin D levels and seasonality of *melatonin*. The influence of these factors in the seasonal patterns of infectious diseases, and whether or not seasonal immune modulation takes place in humans, have been discussed by Grassly and Fraser (2006); Fisman (2012); Fares (2013); and Payntner (2015).

According to Ruiz (2017), geographical factors of disease are related to the weather and geohydrology of a region, the built and natural environment, and population differences in age and cultural and social habits. Spatial patterns are often linked to temporal factors. Seasonal differences in rainfall and temperature, as well as agricultural activities can affect disease patterns and transmission rates (US NRC, 2001; Ruiz, 2017). Under these circumstances, Ruiz (2017) observed that: "When the number of cases of a disease changes across time periods, spatiotemporal analysis can reveal the direction and speed that the disease has spread, and declining disease rates may indicate the effect of preventative actions or development of immunity." MacGillivray and Kollmann had earlier (2014) noted that though an individual may remain geographically constrained, their environmental exposures may vary dramatically depending on seasonality. However, changing temperature, rainfall, exposure to PTEs, food availability, diet, and exposure to infectious agents may also be compounded or alleviated by local cultural and lifestyle practices.

Sometimes, also, disease occurs only after long exposure and can even be absent in ensuing generations; and prior immunity, nutritional health, and genetic differences can have significant impacts on the spatial patterns of diseases. Given this variety, interdisciplinary effort is vital in research aimed at tackling complex disease problems. Ruiz (2017) attempts a presentation of methodological and theoretical threads across a variety of disease systems that are all related to the geography of diseases.

Climate change and health

The relationship between climate change and health is becoming increasingly clear (Fig. 3) and current knowledge, well documented. Developments in this area of research can be followed up in a multitude of recent publications, and many scientific journals are devoted exclusively to this subject or have whole sections addressing it. *With DUA, specifically, however, the relationship with climate is much less clear and relatively few studies or publications exist on the subject.*

PLEASE INSERT FIG. 3 HERE.

According to WHO (2003; 2018b), climate change affects many of the social and environmental determinants of health - clean air, safe drinking water, sufficient food and secure shelter, and so on (Fig. 3). The US Centers for Disease Control and Prevention (US CDC) have warned that: "Climate change threatens human health and well-being in many ways, including impacts from increased extreme weather events, wildfire, decreased air quality, and illnesses transmitted by food, water, and diseases carriers such as mosquitoes and ticks." (US CDC, 2020).

In recent years, attempts in grappling with the challenges of global climate change have revealed unexpected findings on immune system mediation by toxic trace elements, infectious disease (re)emergence, and the expanding field of epigenetics. These findings have helped us recast the environment as an agent of illness. Reflecting this shift, leading international bodies assessing the science related to **climate change**, such as the WHO and the Intergovernmental Panel

on Climate Change (IPCC) [e.g., through its Fifth Assessment Report], respectively, have begun to focus attention on contingent, non-linear, and cross-scalar cause and effect relationships between the environment and human health (WHO, 2011; Smith et al., 2014; IPCC, 2019).

The IPCC Report (Smith et al., 2014) along with several other parallel and subsequent studies on climate change (e.g., Denton et al., 2014; Copeland et al., 2017; Morris et al., 2017; NRC, 2019; Aleuy and Kutz, 2020) has revealed that the possible effects of climate change on health and well-being would be realised *via* multiple, overlapping, and often unpredictable pathways. As Portier et al. noted earlier (2010), climate related health issues would include increased risks of injury, disease, and death from extreme weather events. Added to these effects are those that are wrought by biophysical systems such as the distribution of disease vectors, water-borne diseases, and air pollution (e.g., Smith et al., 2014).

Predicting the impact of climate change impacts on health and disease is beset by confounding variables, is context dependent, and is fraught with uncertainties regarding the drivers and outcomes of change. In this connection, Rohr et al. (2011) suggest that: “... *forecasts of climate-change impacts on disease can be improved by more interdisciplinary collaborations, better linking of data and models, addressing confounding variables and context dependencies, and applying metabolic theory to host-parasite systems with consideration of community-level interactions and functional traits, ...*”.

The links between climate change and infectious disease (Fig. 3) are manifold *but are still not well understood* (US NRC, 2001; Garcia-Solache and Casadevall (2010); Wu et al., 2016; Ogden, 2018; Boukerche and Mohammed-Roberts, 2020; Casadevall, 2020; El-Sayed and Kamel, 2020); and according to Hofer (2019), these links are both complex and multifactorial. We do know, however, that as pathogens get attuned to gradually warmer temperatures in the natural world, they become better able to withstand the high temperature inside our body. This concurs well with Boukerche and Mohammed-Roberts observation in 2020, that: “As global temperatures rise, long-term changes in climate and wildlife habitat could have a significant effect on human health and increase the risk of infectious diseases like the coronavirus (COVID-19).” (Fig. 3).

The spectrum of illness during *heat waves* and *heat stress*

The increasing frequency, duration and magnitude of heat waves have been noted as one category of extreme temperature events (WHO, 2021). **Heat wave** or **heatwave** refers to a period of sustained, abnormally high, surface temperatures relative to those normally expected (Robinson, 2001). This phenomenon is observed worldwide and is associated with **climate change** (Smoyer-Tomic et al., 2003; WHO, 2021). Human exposure to heat waves can lead to a wide range of physiological impacts such as heat exhaustion, **dehydration** and **heatstroke** (Kilbourne, 1999; Ye et al., 2012). Heat waves may be characterised by **low humidity**, which may precipitate **drought**, or high humidity, which may amplify the health effects of *heat-related stress*. Existing health conditions may also be exacerbated, causing premature death and disability.

Heat stress occurs when the body cannot cool down properly through sweating, to maintain a healthy temperature (37 °C). It can take the form of relatively mild conditions such as heat rash and heat cramps to more serious conditions such as heat exhaustion (Li et al., 2020). Some authors have noted that increase in global temperatures *wrought by climate change* will increase the prevalence of *heat stress* (WHO, 2018b; Li et al., 2020).

Glaser et al. (2016) have considered the effect of heat stress (resulting from climate change) on the emergent epidemic of chronic kidney disease (CKD) in rural communities. These authors propose that “... heat stress nephropathy (HSN) may be a major cause of CKD, representing an overlooked disease in neglected populations in hot communities.”

Geopathic stress

It is now fairly well established that *stress* is a factor in ill health, as it can affect the body's ability to perform certain functions (Freshwater, 1997). These functions include those that rely on the body's subtle energy system (*the etheric body, chakras* and *meridians*) (See “Glossary of Terms” for definitions) and the body's electrical system (brain, heart and muscles), thus delaying healing and recovery.

The original definition of *geopathic stress* (GS) is: “... the study of Earth energies and their effect on human health.” (Dovjak and Kukec, 2019). The word “geopathic” is derived from two Greek words: *geo*, meaning “of the Earth” and *pathos*, meaning “suffering” or “disease”. Interest in the phenomenon was first generated in Germany back in the 1920s (Freshwater 1997). In the early days of study of geopathic stress, it was noted that very few people were aware of its

association with specific localities, and how a careful selection of locations for civilisations and sites for construction of structures and dwellings were important in avoiding GS (Dharmadhikari et al., 2011). The rationale for judicious site selection for construction purposes was that certain localities overlay *geopathic stress zones* (GSZ), defined as: ‘places on the surface of the Earth having a natural frequency of Earth’s magnetic field, and known to cause health problems.’ The term also encompasses other weak electromagnetic fields produced by innate geological features like underground water streams or deposits of coal, oil or gas. Man-made structures such as roads, bridges, railways, electricity, water mains and sewers can also cause disruption in the Earth’s electromagnetic field, resulting in **geopathic stress**.

The spectrum of causes of geopathic stress, however, is still not yet well defined, and Freshwater’s 1997 account challenges all professionals in health care who are dedicated to the development of holistic care to “... further their understanding and awareness of this phenomenon.”

GEOCHEMICAL VARIABLES AND THE HUMAN IMMUNE SYSTEM

Numerous geoenvironmental factors can modulate human immunity; and it is necessary to understand their interactions in development of the immune system. Such an understanding enables us to address specific aspects of diseases, such as in unravelling the aetiology of DUA, but also, to identify the strategies needed to change trajectories toward long-term, life-long protection from disease. Here, an attempt is made to amalgamate existing data into a cohesive vision that illustrates how exposure to geoenvironmental variables, more especially, the geochemical-, can leave a lasting impression on the human immune system, and how this impression can either have beneficial or potentially deleterious effects.

Cells of the immune system

The immune system is a complex network of cells and proteins that finds and attacks infectious agents such as bacteria, viruses and fungi (Nicholson, 2016). The three broad categories of immune system cells are: *lymphocytes* (T-cells, B-cells and NK cells), which are a type of white blood cells; *neutrophils*, and *monocytes/macrophages*. Each cell type has specialised functions. For instance, *neutrophils* are important in fighting bacteria and fungi, while *lymphocytes* generally fight viruses. The distribution of metal- and metalloid species within a cell or tissue type, referred to as the *metallome*, constitutes an important study in the context of DUA.

Principles of infection and immunity

According to Galask et al. (2008), virtually any organism may behave as a pathogen under the right set of conditions; and therefore, it is more instructive to place organisms along a continuum from lesser to greater virulence, rather than classifying them as either pathogens or nonpathogens. Galask et al. (2008) also contended that: “... among individual human hosts, there is a continuum in the intrinsic ability of each host to resist infection.”

As long ago as 1934, Theobald Smith suggested, in what is now, perhaps the most insightful statement of the relationship between microbial virulence and host resistance to infection, that: disease was a function of the number of organisms with which a host is initially infected multiplied by the virulence of the organism. This relationship is considered to accurately reflect the nature of the infectious process today, despite modern changes in the ecology of infections.

Smith’s equation states:

$$\text{Number of organisms} \times \text{Virulence of organisms}$$

$$\text{Disease} = \frac{\text{Number of organisms} \times \text{Virulence of organisms}}{\text{Host's resistance to infection}} \quad \text{..... Equation 1.}$$

One can see from Equation 1 that the result of a host’s encounter with an infectious agent, even a proven pathogen, will not necessarily be an infectious disease. However, if the host’s immunity becomes lowered for some reason, or if the host becomes overwhelmed by an increasing number of organisms, disease may appear, even with an organism of relatively low virulence. Another noteworthy point about Equation 1, is its practical significance, which contributes to the clinician’s knowledge about the role of the individual host in infectious disease (Galask et al., 2008).

Immune system mechanisms

There are numerous mechanisms by which trace elements/metals/metalloids are absorbed, distributed, modified and stored in the body, and subsequently eliminated. Only a very brief look at immune system mechanisms is presented here, and only with reference to its interactions with trace elements, including

metals and metalloids. Readers interested in further details should consult the many excellent publications on the topic (such as: Failla, 2003; Keen et al., 2004; Plumlee and Ziegler, 2006; Plumlee et al., 2006; Galask et al., 2008; Chaplin, 2010; Winans et al., 2011; Nicholson, 2016; Marshall et al., 2018 and Paludan et al., 2020).

Toll-like receptors (TLRs) which are located either on cell surfaces or within *endosomes* (See: “Glossary of Terms”, this article), are type I integral transmembrane receptors involved in the recognition and conveyance of pathogens (including trace elements/metals/metalloids) to the immune system (El-Zayat et al., 2019). Some micronutrients (vitamins and trace elements) may be considered as important TLR regulators, as they have immunomodulatory functions. Vitamins D, B12 and A, Zn, Cu and Fe, for instance, have important roles on innate immune responses (El-Zayat et al., 2019).

Thurnham’s 2004 review summarises work on, *inter alia*, “... interactions between nutrients and genes, the influence of gene polymorphisms on micronutrients, the impact of immune responses on micronutrients and specific interactions of antioxidant micronutrients in disease processes to minimise potential pro-oxidant damage.” Mineral deficiency-induced abnormalities in the immune system are particularly profound when they occur during early development (Keen et al., 2004).

In addition to the effect of trace elements on immune function, several studies have shown that, at certain levels, some of these elements, such as Se can influence the genetics of a viral pathogen. Thus, trace element nutrition influences not only the host response to a pathogen but also the pathogen itself (See e.g., Beck, 1999; Lingamaneni et al., 2015).

Factors that influence the toxicities of substances that encounter the body in *bioaccessible* form (those that are readily released from Earth materials into the body fluids) include: *the exposure route, the dose, the chemical form of the substance at exposure, and the processes that chemically transform the substance during absorption, transport, and metabolism* (Plumlee et al., 2006; Finkelman et al., 2018; Hasan, 2020). *Sometimes, immanent errors of trace element metabolism occur to produce disease, such as when there are basic defects in the trace element transport mechanism* (See e.g., Danks, 1985; Ferreira and Ghal, 2017).

CRITICALITY OF THE ‘OPTIMAL RANGE OF INTAKE’ AND THE OCCURRENCE OF NUTRIENT TOXICITIES

Writing on the criticality of the optimal range for the micronutrient elements, Mao et al. (2020), remarked: “The dietary requirement for an essential trace element is an intake level which meets a specified criterion for adequacy and thereby minimises risk of nutrient deficiency or excess. Disturbances in trace element *homeostasis* may result in the development of pathologic states and diseases.”

Many nutrients have an antagonistic relationship to one another, which can mean that when one is too high, it causes the other to become too low; and this could increase one’s susceptibility to infectious disease which may be acute or chronic. No pair of elements better exemplify this relationship than Cu and Zn, which is as a result of their complex interactions in metabolic processes. A high intake of Cu may adversely affect the absorption or utilisation of Zn, and *vice versa*. In other words, when your Cu to Zn ratio becomes out of balance, many health problems can occur.

Excesses or deficiencies of **trace elements/metals/metalloids** and **infectious diseases** often co-occur and are the result of complex metabolic interactions. Most of our essential nutrient intake is from our diet, though, thankfully, this portion alone is unlikely to bear excessive element intake levels. However, the consumption of fortified foods or supplements can also raise the level of trace elements/metals/metalloids and hence increase the chance of toxicity.

Environmental or occupational exposure to potentially toxic levels of elements/metals/metalloids can induce concentrations that are bioavailable to immune cells, high enough to affect their function. Such an imbalance of the immune system caused by pollutants may play a significant role in the incidence of infectious diseases (See e.g., Erickson et al., 2000; Chaturvedi et al., 2004; Hara et al., 2016). In any case, our bodies have an elaborate system for managing and regulating the amount of key trace elements and limiting or eliminating the PTEs circulating in blood and stored in cells (Osredkar and Sustar, 2011). It is when this system fails to function correctly that metabolic disturbances occur, with abnormal levels and ratios of trace elements/metals/metalloids developing and paving the way for occurrence of infectious disease (See e.g., Danks, 1985; Ferreira and Ghal, 2017).

The concept of *nutritional immunity* in the context of host defense against pathogens (Djoko et al., 2015) perceives a role for mechanisms by which a host organism sequesters trace elements/metals/metalloids to limit invading pathogens during infection. *Calprotectin*, for example, can restrict the acquisition of Zn or Mn (Kehl-Fie et al., 2011). The question remains however, as to whether the host is able to exploit the toxic properties of transition metal ions and use them as bactericides? (See Djoko et al., 2015).

Immunotoxicity due to metals

According to Nriagu and Skaar (2015): “Many parts of the world in which common infectious diseases are endemic also have the highest prevalence of trace metal deficiencies or rising rates of trace metal pollution. Infectious diseases can increase human susceptibility to adverse effects of metal exposure (at suboptimal or toxic levels), and metal excess or deficiency can increase the incidence or severity of infectious diseases.”

Metals and metalloids influence the function of immunocompetent cells by a variety of mechanisms. Several of these metals and metalloids are known to be *immunotoxic*, including: Al, As, Be, Cd, Co, Cr, Cu, Fe, Hg, Mg, Mn, Ni, Pb, Se, Sn, Va and Zn. Depending on the particular metal, its speciation, concentration and bioavailability, and a number of other interdependent factors, a continuous metal/metalloid exposure will result in an *immunosuppression* or *immunoenhancement effect* (Kakuschke and Prange (2007)).

Immunotoxicity occurs: “... either direct action of the free metal on the cell membrane or other organs of immunocytic components or by catalysis or inhibition of numerous enzyme reactions that are essential to cellular metabolism” (Cabassi, 2007). These interactions interfere with expression of the immune response. In this connection, Cabassi (2007) notes that: “... certain metals at a low exposure concentration manifest immunopotentiating effects, while at high concentrations they cause immunosuppression.” Theron et al. (2012) affirmed this observation and went on to point out that it held true particularly for toxic metals such as Cd, Hg and Pb, due to their cytotoxic effects which induce *apoptosis* and/or *necrosis* of immune cells with consequential weakening of the immune defences to infection.

Cabassi (2007) describes some of the immunosuppression effects earlier identified by Descotes (1999) that xenobiotics (including trace elements/metals/metalloids) can produce. Effects described include: “... changes in leucocyte cellularity, lymphocyte sub-population, reduced resistance of the organism to immune specific alterations, immunosuppression with increased susceptibility to infection and tumour development, immunostimulation with hypersensitivity and development of autoimmune diseases.” (See Fig. 4).

As Wang et al. stated in 2020, in any discussion on the role of the ‘metallome’ in the aetiology of dementias of unknown aetiology (*cf.*, Alzheimer’s Disease and Parkinson’s Disease), “The *homeostasis* of metal ions is critical for the physiological functions of the brain. In AD (*Alzheimer’s Disease*) patients or the animal models, the imbalanced metal ions and their transporters have been widely observed. The deposition of metal ions in different brain regions impairs mitochondrial functions and thus causes oxidative stress, which can result in cascade pathological reactions.” [Sic]

PLEASE INSERT FIG. 4 HERE.

Autoimmune diseases

Autoimmune diseases (ADs) are a heterogeneous group of chronic conditions that affect specific target organs or multiple organ systems. Among the different environmental factors that are known to influence the development of ADs are: infections, low vitamin D levels, UV radiation, and *melatonin* (Smith and Germolec, 1999; Watad et al. (2017)), which factors are also known to exhibit seasonal variation patterns that could influence disease development, severity and progression. Autoimmune disorders may cause destruction of body tissues, abnormal organ development, or changes in organ function.

In 2004, Descotes recapitulated on the importance of autoimmunity as an important area of immunotoxicology, especially because autoimmune diseases are frequent diseases in the general population, and some experimental data suggest a possible link between *chemical exposures* and autoimmunity.

Many questions remain as to how pathogenic challenge, for instance, may interfere with immune system regulation and give rise to *autoimmunity*; and it is likely that other apparently novel immune modulatory mechanisms (e.g., trace element/metal interaction) also contribute to clinical ADs (Fig. 4). *But, till quite recently, the exact etiopathogenesis of ADs is still not well-defined* (See: Getts et al., 2020).

Dopico et al. (2015) give, as an example of evolutionary adaption of humans to different environments, the loss of skin pigmentation as humans migrated out of Africa to more temperate and colder zones to increase sunlight-driven vitamin D production. *Despite such observations, however, the mechanisms by which seasons might more broadly influence the underlying molecular details of human physiology remains unknown* (See e.g., Nelson, 2004). Watad et al. (2017) discuss further the effects of seasonality on the onset, relapses and activity of various ADs.

Effect of sunlight on the incidence of autoimmune diseases

Sunlight, the radiation and heat from the sun [ultraviolet radiation (UVR)], is an essential source of light and warmth for all living organisms. It can however have a number of undesirable effects on the health of man “... such as promoting the malignant transformation of skin cells and suppressing the ability of the human immune system to efficiently detect and attack malignant cells.” (Gonzalez Maglio et al., 2016).

However, consideration of seasonal influences on both disease incidence and clinical course as well as recent analytical studies at the individual level have lent support for a possible protective role for UVR in certain diseases (See e.g., Moozhipurath et al., 2020, in relation to the novel corona virus). But Ponsonby et al. (2002) had earlier noted that the available data upon which such notion is made are largely inconclusive.

González Maglio et al. (2016) have put forward some ideas in perspective and have posed some questions within the field of photoimmunology based on established and new information. These authors presume that their ideas may lead to new experimental approaches and hence, to a better understanding of the effects of sunlight on the human immune system.

DISEASE CLUSTERS

The term *cluster* (as used in epidemiology) has been defined in various ways (See e.g., Last, 1988; US CDC, 1990; Antó and Cullinan, 2001; Porta, 2008; Dolk et al., 2015; PHE 2019). Taken together, these definitions incorporate the following features: (i) An unusually large aggregation, real or perceived, of events or diseases, over and above the number that could be expected by chance; (ii) The events or diseases are grouped together in time and space (i.e., a particular geographical location, the place of residence, or the location used for a common activity, e.g., workplace). The definition of Porta et al. 2008 singly encapsulates all of these features, i.e.: “Aggregations of relatively uncommon events or diseases in space and/or time in amounts that are believed or perceived to be greater than could be expected by chance. Putative disease clusters are often perceived to exist on the basis of anecdotal evidence, and much effort may be expended by epidemiologists and biostatisticians in assessing whether a true cluster of disease exists.”

Recognition of a cluster depends on its size; being reckoned to be greater than would be expected by the [play of chance](#). According to Kumar et al., (2004), ‘clustering’ may provide clues about the underlying aetiology of a disease (*cf.*, DUA), though this may have initially been based on [anecdotal evidence](#). It is therefore incumbent

on [epidemiologists](#) and [biostatisticians](#) to assess whether or not the suspected cluster corresponds to an actual increase of disease in the area (See e.g., Song and Kulldorff, 2003). Usually, when clusters are recognised, they are reported to [public health](#) authorities in the local area, who may then re-evaluated them as [outbreaks](#), if they (the clusters) are of sufficient size and importance. [John Snow](#)’s pioneering investigation of the [1854 cholera outbreak in Soho, London](#) (Tulchinsky, 2018), is considered as a classic example of the study of ‘disease clusters’.

Investigating disease clusters

Whenever disease clusters are identified and reported to local or public health authorities by concerned citizens or health care professionals, a response team is usually set up and sent immediately to investigate the cluster. Such an investigation follows a well-established process based on national, regional or international guidance.

What is the value of investigating disease clusters?

There is hardly any doubt regarding the desirability for disease cluster investigations (including those that are potentially related to environmental or occupational exposures) to be conducted, and for the outcomes of these investigations to be transmitted to relevant public health authorities. There are many inherent gains in performance of a good cluster investigation, but also challenges, too.

The investigation starts with the determination of whether a suspected cluster is a true cluster or not (See, e.g., Kulldorff and Nagarwalla, 1995; Gómez-Rubio et al., 2005; McAfferty, 2015). Epidemiologists then go on to identify the appropriate scientific approach and organise a data collection plan that synthesises the available health data in the cluster domain. In this way, the identification of clusters and small outbreaks may eventually lead to the isolation of relevant risk factors and provide clues about the underlying aetiology (*cf.*, DUA).

Despite early views that there is little scientific value in cluster investigations e.g., Rothman (1990), there are several researchers who today, contend that 'clusters' should be looked upon solely from their scientific merit.

Multimorbidity disease clusters

The term *disease clusters* is often used in another sense, differing from that described in the foregoing sections. *Multimorbidity* refers to the (co-)occurrence of two or more medical conditions simultaneously in an individual, although some health care professionals sometimes use the more intuitive term "*multiple health conditions*" (See: Aiden, 2018). Morbidities that cluster together are referred to as *concordant multimorbidities*, since they can share a common aetiology. Conditions such as: depression, cardiometabolic disorders, cerebrovascular disease and musculoskeletal disorders are most commonly present within multimorbidity clusters (Willadsen et al., 2016).

Co-occurrences of cases often come up in cluster research and are frequently reported as potential clusters. Various environmental exposures, such as can occur in the community or in the workplace, are frequently reported as sources of potential clusters. However, not all co-occurrences of disease cases are clusters *per se* (Aiden, 2018). Preliminary analytical work, if performed systematically, can often resolve the question of whether a true cluster exists, or not. This may involve comprehensive epidemiological and statistical measurements and thorough assessment of the exposure characteristics to confirm whether a true cluster exists.

According to the UK 'Research and Innovation/National Institute for Health' Research Project Working Group, *multimorbidity has received limited scientific attention to date* (2020), having previously been regarded as a random assortment of diseases; and hence, difficult to address (UKRI/NIHR, 2020). The call for more research on *multimorbidity* is justified by the knowledge that the proportion of patients who have two or more medical conditions simultaneously is rising steadily in all age groups in Africa and worldwide (Osakunor et al., 2018; Whitty et al., 2020). Such research would need the application of new multi-disciplinary approaches to mapping and tackling these conditions at scale (UKRI/NIHR, 2020). This kind of research was proposed and sponsored by UKRI/NIHR in 2019 (See: UKRI/NIHR, 2020).

Finally, writing on the *modus operandi* of effectively tackling 'multimorbidity', Whitty et al. (2020) contend that "Clustering of diseases, and how we might better tackle management of coexisting physical and mental health problems, should be embedded into medical training and continuous professional development, including for specialists ..."

Clusters of diseases of unknown aetiology

In 2016, Rodo et al. reviewed the relevance of environmental factors to health outcomes of ailments whose causes are still poorly understood; and listed several examples of emerging diseases belonging to this category, and surprisingly sharing some common epidemiological features, "... such as their appearance in 'clusters' (grouped geographically; and temporarily progress in nonrandom sequences that repeat every year in a similar way). They also show concurrent trend changes within regions in countries and among different world regions.)" Rodo et al.' (2016) list included: rheumatic diseases such as vasculitides, some inflammatory diseases, or even severe childhood acquired heart diseases, Kawasaki disease (KD), Henoch-Schönlein purpura, Takayasu's aortitis, and ANCA-associated vasculitis.

In Africa, clusters of DUA do occur occasionally in various geographical localities (e.g., See: Darikwa and Manda, 2020). However, there hardly exists the requisite framework in many African countries for undertaking disease cluster investigations that might contribute towards unravelling the underlying causes of DUA.

Assessment of disease clusters

In recent years, there has been considerable progress in the use of modern methods for the assessment of clusters. The magnitude of such development has resulted in the recognition of *epidemiological and statistical analysis of clusters* as a specialised field that has found a place in several journals. Some of the more recent cluster assessments reports are given in: Gómez-Rubio et al. (2005); Coory and Jordan (2013); Forouzanfar et al. (2016); Kronenfeld and Wong (2017) and Stanaway et al. in (2018).

One of the largest and most comprehensive studies of disease clusters known so far was undertaken by the Natural Resources Defense Council (NRDC) and the National Disease Clusters Alliance (NDCA) of the US using information from federal, state and local officials (Navarro et al., 2011). Forty-two disease clusters were found in 13 US states. These institutions subsequently urged federal coordination in order to better investigate these clusters, determine their causes, and work to protect residents in the affected areas.

THE VALUE OF ENVIRONMENTAL RISK MAPS

According to Lahr and Kooistra (2010), "Risk maps help risk analysts and scientists to explore the spatial nature of the effects of environmental stressors such as pollutants." Environmental risk maps are used as a means for conveying the results of complex environmental risk assessments to public health authorities, policy makers, urban planners, and other stakeholders such as the general public.

In 2014, Pinto et al. wrote: "Geochemical mapping is the base knowledge to identify the regions of the planet with critical contents of potentially toxic elements from either natural or anthropogenic sources. Sediments, soils and waters are the vehicles which link the inorganic environment to life through the supply of essential macro and micro nutrients. The chemical composition of surface geological materials may cause metabolic changes which may favor the occurrence of endemic diseases in humans." [Sic].

In the above context, it is possible to suggest that, for us to create a better understanding of the relationship between surficial geochemistry and public health it is necessary, first, to construct complete geochemical maps at appropriate scales across national boundaries, depicting the surficial distribution of all non-gaseous chemical elements (See: Darnley et al., 1995). Such maps have already been drawn for China [(See: Wang et al., 2007; Xie et al., 2008; Cheng et al., 2014), England and Wales (See: Rawlins et al., 2012), Australia (See Reimann and de Caritat, 2017) the USA (See: Smith et al., 2019), and a few other countries]. An overlay of epidemiological maps (of disease distribution) on these geochemical maps would make possible the depiction of areas where disease clusters overlie anomalous element distribution (in water or soil), and so permit an evidence-based statistical assessment of the magnitude of any geochemical component in the disease causative web.

Conclusions

1. There is currently an increasing worldwide trend in environmental geochemistry research towards determining the circulation of both nutritional elements and PTEs in the water-soil-food crop nexus, that enters the food chain. The prime motivator of this approach has been the increasing realisation of the significance of the entry - largely through the diet - of varying concentration levels of elements that may be bioavailable for negative interactions in metabolic processes that produce diseases, some of whose diagnoses are still ill-defined (the DUA). It is clear that most DUA's are multifactorial diseases, caused by a complex interplay between genetic factors (polygenic), immunological mediators (trace elements/metals/metalloids) and various environmental factors, none of which factors would cause the disease on its own.

2. The human immune system is complex, with numerous environmental factors modulating it early in life. As such, the system is constantly in a state of flux, trying to adapt to various local constraints and conditions imposed by selective pressures of our environment. This inherent plasticity means that our exposure to different geochemicals and pathogenic organisms can result in undesirable outcomes.

3. After decades of research on the complexity and developmental trajectory of the foetal-neonatal immune system (See e.g., Amarasekera et al., 2020; Jain, 2020; Scanlon, 2020), we are only just beginning to acquire knowledge and insights on the participation of trace elements/metals/metalloids in the selection, maturation and early activation events of the immune cells. Judicious use of modern analytical tools in cell biology- and molecular genetics research, and array technology, will no doubt hasten our understanding of outcomes in these metabolic processes. The position of the “metallome” in the aetiology of SIDS and that of many other DUA needs urgent research!

4. A functional immune system able to prevent or limit infections of the host, is particularly important for many rural populations where exposure to novel infectious occur frequently. From the abundance of evidence adduced in this article, it is becoming increasingly clear that the amount of trace elements/metals/ metalloids taken up largely through the diet, and its outcome in metabolic processes (leading either to accumulation or to deficiency in human tissues), has a significant control on whether the exerted effects are toxic or beneficial. As we gradually begin to fully understand these processes, food safety regulators will have the important and urgent task of re-considering, harmonising and updating current legislative regimes regarding the concentrations of trace elements/metal/ metalloids in food and in drinking water.

5. In order to promote immune-mediated health for life, we must consider the importance of our exposure to geoenvironmental variables and the dynamics of pathogen invasion in immune programming. To do this, however, we still need to seek knowledge on several aspects of immune system programming that starts in early life, and its influence on the risk of developing various DUA. Such research would generate information needed for articulation of future public health initiatives and for drawing renewed attention to the vulnerability of children in early life.

6. The reasons for differences in host immune responsiveness between human populations are now becoming clearer (See: e.g., Quach et al., 2016; Barreiro and Quintana-Murci, 2020), as a result of our greater understanding of evolutionary theory. **Such explanations have major implications for the protection of the organism against pathogens and** offer clues that can help explain the reason why some populations are particularly susceptible to diseases such as the novel COVID-19, which is more common among the Western nations than it is in Africa (See also: Onyilagha and Uzonna, 2019 and Alfituri et al., 2020).

7. On the other hand, Bentwich et al.' explanation of the difference in HIV diffusion rates between Africans and western populations, back in 1995, lies in the "... over-activation of the immune system in the African population, owing to the extremely high prevalence of infections, particularly helminthic, in Africa. Such activation shifts the cytokine balance towards a T helper 0/2 (Th0/2)-type response, which makes the host more susceptible to infection with human immunodeficiency virus (HIV) and less able to cope with it."

8. Despite the unprecedented rate of global climate change, links between weather and infectious disease have not received much research attention even in high income countries. Improved knowledge on the linkages between environment and infection risk would help sensitise national authorities, policy makers and other stakeholders on the need for investment in robust public health surveillance systems that are able to detect changing disease burdens. An understanding of the diverse effects of climate change on the immune system, coupled with recent results from the emerging science of epigenetics would help unravel the aetiology of DUA, which can never be explained or resolved by isolating independent cause and effect relationships.

9. Determinants of disease emergence and persistence interact in a highly complex way within the environment-ecosystem network. Consequently, model-based projections, as useful as they may be, are fraught with great uncertainty; and so must be designed in a highly circumspective way.

10. Cluster investigations are an important public health strategy for responding to public concern about possible associations between disease and environmental exposures. A proper investigation of a non-communicable disease cluster may help generate hypotheses that can be tested in another study population and time period. It is submitted that the efficiency of cluster investigation teams would be enhanced by inclusion of Medical Geologists, from whom significant geoenvironmental exposure information can be obtained, as well as for an increased potential for unravelment of environment and disease relationships.

11. Increase in public awareness and concern about environmental exposures will continue to spur the need to follow up on reported clusters of disease. This is an important task that we need to carry out within a customised and systematic framework in the light of glowing publicity and under pressing and stressful circumstances. The overarching need for development of techniques for recognising the grouping of cases of a particular disorder in space and time (disease clusters), is that this may provide clues about the underlying aetiology (*cf.*, DUA).

12. There is little doubt that GIS technology will continue to find widespread application in cluster investigations for non-infectious diseases registries, and by cluster responders. However, to achieve optimal results, new developments such as including more systematic approaches to cluster investigations, improved accuracy in data acquisition, and consideration of geoenvironmental co-factors in disease incidence, may be necessary.

13. It is suggested that correlation maps featuring complete geochemical databases analogous to what exists for China (See: Wang et al. 2007), England and Wales (See: Rawlins et al. 2012), the USA (See: Smith et al. 2019), and a few other countries, would, among other applications, enable the depiction of areas where disease clusters overlaid anomalous element distribution (in water, soil or air), and so permit an evidence-based statistical assessment of the magnitude of any geochemical component in the disease causative web.

14. Finally, it is proffered that further intensive research is warranted on the effects of errors/disturbances in metalloid metabolism to help us better understand the importance of this attribution as co-factors in causation of DUA, particularly the neurodegenerative diseases: Alzheimer's disease, autism, Parkinson's disease, and SIDS.

Glossary Of Terms

- *Acute disease/illness* is any disease or illness that develops quickly, is intense or severe and lasts a relatively short period of time, or, any condition, e.g., infection, trauma, fracture - with a short (often less than 1 month) clinical course.
- *Apoptosis* refers to an orderly process of cell breakdown that occurs in multicellular organisms.
- *Bias*: In the field of statistics, *bias* refers to the tendency of a *statistic* to overestimate or underestimate a parameter.
- *Calprotectin* is a protein biomarker released by a *neutrophil* when there is inflammation in the gastrointestinal (GI) tract, resulting in an increased level in the stool.
- *Chakra* (pl. *chakras*), a concept is found in the early traditions of Hinduism, refers to various focal points used in a variety of ancient meditation practices, collectively denominated as Tantra, or the esoteric or inner traditions of Hinduism. [Wikipedia, 2021. <https://en.wikipedia.org/wiki/Chakra> (accessed 20.01.2021)].
- A *chronic condition* is a human health condition or disease that is persistent or otherwise long-lasting in its effects or a disease that comes with time. The term chronic is often applied when the course of the disease lasts for more than three months.
- *Communicable diseases* are those that can be spread from person to person *via* an infectious agent, such as bacteria, viruses, fungi or parasites. *Non-communicable diseases* (NCDs) are the conditions or diseases which are not caused by transmission of infections like that in communicable diseases.
- A *confounding factor* also called a *confounding variable*, or *confounder* is a third variable in a study examining a potential cause-and-effect relationship. A *confounding variable* is related to both the supposed cause and the supposed effect of the study.
- *Correlational research* is a type of non-experimental research method in which a researcher measures two variables, understands and assesses the statistical relationship between them with no influence from any extraneous variable. "*Correlation* is not *causation*" means that just because two things *correlate* does not necessarily *mean* that one causes the other.
- *Endosomes* are membrane-bound vesicles, formed via a complex family of processes collectively known as endocytosis, and found in the cytoplasm of virtually every animal cell.

- The *etheric body*, *ether-body* or *æther body*, is a name given by neo-Theosophy to a vital *body* or subtle *body* coined by esoteric philosophers to describe the first or lowest layer in the "human energy field" or *aura*. It is thought to be in immediate contact with the physical *body*, to sustain it and connect it with "higher" *bodies*.
- *Gametes*, also referred to as *sex cells*, are an organism's reproductive cells.
- *Homeostasis*. In biology, the tendency towards a relatively stable state (equilibrium) - internal, physical, and chemical conditions - maintained in physiological processes while adjusting to changing external conditions. *Dyshomeostasis*, on the other hand, refers to an imbalance or other breakdown of a homeostasis system.
- *Infectious diseases* are disorders caused by organisms such as bacteria, viruses, fungi or parasites. Many organisms live in and on our bodies. They are normally harmless or even helpful. But under certain conditions, some organisms may cause disease.
- The *immune system* is a series of complex defence mechanisms found in humans and other vertebrates, that helps to combat and destroy pathogenic organisms such as bacteria, fungi, viruses, and parasites. The immune system consists of two types of response mechanisms: (i) An *antigen-specific adaptive immune response mechanism*, also referred as the *acquired immune system*, which is composed of specialised, systemic cells and processes that eliminate pathogens by preventing their growth; and (ii) The *innate immune system* is a collection of cells and proteins that are functionally diverse and that defend against invasion by foreign organisms. An *innate immune response mechanism*, also called *natural*, is the set of processes that operate to protect the host from the surrounding environment in
- *Immunosuppression* refers a state of decreased immunity.
- *Lymphocytes* are white blood cells that are also one of the body's main types of immune cells.
- *Macrophages* are large, specialised cells that detect, engulf and destroy bacteria and other harmful organisms.
- *Melatonin* (sometimes referred to as the sleep hormone) is a natural hormone made by the *pineal* gland (a pea-sized gland situated just above the middle of the brain). It plays a central role in the body's sleep-wake cycle. With its production rising with evening darkness, it promotes healthy sleep and helps orient our *circadian rhythm* (natural internal processes that follow a 24-hour cycle).
- *Meridian* (as used in acupuncture and Chinese medicine) refers to each of a set of pathways in the body along which vital energy is said to flow.
- *Metallome*: In biochemistry, the *metallome* is the distribution of metal ions in a cellular compartment.
- *Monocytes* are the largest type of leukocyte (white blood cells). As a part of the vertebrate innate immune system monocytes also influence the process of adaptive immunity.
- *Mutations* are permanent changes in the DNA sequence, and they are a main cause of diversity among organisms.
- *Myalgia*: Pain in a muscle or group of muscles.
- *Necrosis* refers to the premature death of cells in living tissue when too little blood flows to them as a result of disease or injury.
- *Neutrophils* are a type of white blood cell. Most of the white blood cells that lead the immune system's response are neutrophils.
- *Neurodegenerative disorders* are illnesses that involve the death of certain parts of the brain.
- *Pathogenesis* refers to the way (biological mechanism) in which a disease develops. *Pathogenicity* is the ability of an agent to cause disease (i.e., to harm the host).

● In **genetics**, a *promoter* is a sequence of **DNA** (deoxyribonucleic acid) to which proteins bind that initiate **transcription** of a single **RNA** (ribonucleic acid) from the DNA downstream of it. [Wikipedia, 2021. Promoter (genetics).

[https://en.wikipedia.org/wiki/Promoter_\(genetics\)](https://en.wikipedia.org/wiki/Promoter_(genetics)) (accessed 26.01.2021).

● *Reactive oxygen species* (ROS): An unstable molecule that contains oxygen and that easily reacts with other molecules in a cell. ROS are the contributors of oxidative stress which leads to various diseases and disorders.

● *Shank proteins* are multidomain scaffold proteins of the postsynaptic density that connect neurotransmitter receptors, ion channels, and other membrane proteins to various metabolic pathways.

● A *syndrome* is a set of **medical signs** and **symptoms** which are correlated with each other and often associated with a particular **disease** or disorder. [Wikipedia, 2020. Syndrome. <https://en.wikipedia.org/wiki/Syndrome> (accessed 10.01.2021)].

● *Toll-like receptors* (TLRs) are a class of proteins (receptors) that constitute the first line of defence system against microbes.

● A *xenobiotic* is a chemical substance found within an organism that is not naturally produced or expected to be present within the organism. It can also cover substances that are present in much higher concentrations than are usual." [Wikipedia, 2020. <https://en.wikipedia.org/wiki/Xenobiotic> (accessed 26.01.2021)].

Declarations

1. Funding and/or competing interests

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2. Ethics approval

No ethical approval was required for this study since no human participants, their data or biological materials were involved. No experimental work involving animals was conducted in this study.

3. Data availability

No data pertaining to human tissues were reproduced from articles reviewed in this study, obviating the need for ethical approval.

4. Author contribution

All contributions to the manuscript were made by the sole author.

5. Consent to participate

The work reported in this manuscript did not involve human subjects, and informed consent to participate was not required.

6. Consent to publish

The work reported in this manuscript did not involve human subjects, and informed consent to publish was not required.

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Tables

.. Examples from the global literature on diseases of unknown aetiology (DUA) having one or more possible or suspected geochemical other geoenvironmental variable(s) as causal cofactor

Figures

Figure 1
The structure of confounding. Source: Jager et al., 2008.

DUA	Presentation	Incidence/Geographical Distribution/Demographical Pattern	Geochemical variable (Including Trace Element Mediated Immune Response)	Geoclimatic and Seasonal Variations	Remarks
1. Acrocyanosis	<i>Acrocyanosis</i> is a peripheral vascular disorder which presents as a persistent bluish or cyanotic discolouration of the extremities, most commonly occurring in the hands	Geographical locale (latitude; urban versus rural setting) uncertain - Kurklinsky et al., 2011	<i>Chronic</i> As toxicity - Grobe, 1976; Tseng, 1977; Mak, 1988; Kurklinsky et al., 2011	Cold climate - Crocq, 1896; Carpentier, 1998; Cold environments - Das and Maiti, 2013; Kent and Carr, 2020	"Diagnosis remains mostly clinical, and pathological mechanisms vary, suggesting that acrocyanosis may not be a single entity" - Kurklinsky et al., 2011
2. Acute Febrile Illness	<i>Acute Febrile Illness</i> (AFI) is characterised by malaise, <i>myalgia</i> (pain in muscle or group of muscles) and a raised temperature that is a nonspecific manifestation of <i>infectious diseases</i> in the tropics (Bashkaran et al., 2019)	Sub-Saharan Africa; Tropics and Sub-Tropics	Viral respiratory tract infections - Crump et al., 2013; D'Acremont et al., 2014; Significantly lower serum Zn levels in febrile seizure group than in the afebrile group - Lee and Kim, 2012; No significant relationship observed between febrile convulsion and the elements: Fe, Zn, Mg and Ca - Amouian et al., 2013	Clear seasonal trend observed - Kaboré et al., 2020	Further research is warranted on trace element metabolism in relation to the development of AFI - See: Amouian et al., 2013
3. Acute Severe Asthma	<i>Asthma</i> is characterised by chronic airway inflammation, resulting in periodic wheeze, cough and breathlessness (See: Carlsson and Bayes, 2020)	Worldwide prevalence. The Global Asthma Report of 2017 recorded a figure of approximately 334 million for the number of people in the world suffering from asthma, thus making this condition the most prevalent chronic respiratory disease (Soriano et al., 2017)	Respiratory tract infections - Johnston et al., 1995; Jackson and Johnston 2010; Air pollution - Guarnieri and Balmes, 2014; Shmool et al., 2014; Decrease in antioxidant capacity in bronchial asthma as serum Se and Zn levels decrease, leading to further increase in oxidant stress and resulting enhanced inflammation and hyperreactivity in the airways - Uzuner et al., 2001; Low Se and Cu levels may have a role in bronchial asthma in Sudan, north-central Africa - Hussein et al., 2008	Recent global rise in asthma, an early health effect of anthropogenic climate change - Beggs and Bambrick, 2005; Cecchi et al., 2010; Weather changes/cold weather - Hyrkäs et al., 2016; D'Amato et al., 2018	The precise mechanisms by which these environmental stimuli and viruses initiate asthma or cause worsening of the disease are still unknown - Kostakou et al., 2019
4. Alzheimer's Disease	<i>Alzheimer's Disease</i> (AD) is the most common neurodegenerative disorder and the leading cause of dementia (i.e., the particular group of symptoms shown). It becomes worse with time (degenerative). The symptoms expressed are as a result of the damage or destruction of nerve cells (neurons) in parts of the brain involved in thinking, learning and memory (cognitive function)	By 2009, the global prevalence of dementia was estimated at 3.9 % in people aged 60+ years, with the regional prevalence being 1.6 % in Africa, 4.0 % in China and Western Pacific regions, 4.6 % in Latin America, 5.4 % in Western Europe, and 6.4 % in North America (Qui et al., 2009); Geographical variation (latitude) plays key role in dementia risk (e.g., Russ et al., 2016)	Significantly different ($p < 0.05$) mean concentrations of Br, Cl, Ce, Hg, N, Na, P, and Rb were observed in AD bulk brain samples compared to controls - Ehmann et al., 1986; Varying trace element relationships with AD severity, with Al deposits greater in severely affected AD brain - Jagannatha Rao et al., 1999; Loeff and Walach, 2012; Biometal <i>dyshomeostasis</i> and toxic metal accumulations - Chapman, 2008; Greenough et al., 2013; Li et al., 2017; Bagheri et al., 2018; Liu et al., 2019; Mocanu et al., 2020; Cilliers, 2021; Anomalous concentration levels of metals in metal-binding proteins have growth inhibition functions on neurons - Constantinidis, 1991; Richarz and Brätter, 2002; Trace metals and abnormal metal metabolism influence protein aggregation, synaptic signalling pathways, mitochondrial function, oxidative stress levels, and inflammation, ultimately resulting in synapse dysfunction and neuronal loss in the AD brain - De Benedictis et al., 2019; Wang et al., 2020	Air pollution, <i>cf.</i> , long-term exposure to O ₃ and PM _{2.5} above the current [2015] US EPA standards (US EPA, 2021) are associated with increased risk of AD - Jung et al., 2015; Association between high altitude exposure, cognitive decline and dementia mortality rate - Thielke et al., 2015; Hu et al., 2016; Lall et al., 2019; Koester-Hegmann et al., 2019; Calderón-Garcidueñas, 2021; Associations with seasonal temperature - Wei et al., 2019; Global warming and <i>neurodegenerative disorders</i> - Habibi et al., 2014	"Environmental risk factors for Alzheimer dementia are not well understood" (Thielke et al., 2015), nor are those having links with the geological milieu. In 2019 Alzheimer's Disease International (ADI) estimated that there are over 50 million people living with dementia globally, a figure set to increase to 152 million by 2050 - ADI, 2019. In both developed and developing nations, Alzheimer's disease has had tremendous impact on the affected individuals, caregivers, and society [See, e.g., Taylor et al. (2017)], for some relatively recent figures for Alzheimer's mortality in the US). Because developing countries are projected to see the largest increase in absolute numbers of older persons, their share of the worldwide aging population will increase from 59 % to 71 % - Qui et al., 2009. "Because occurrence of AD is strongly associated with increasing age, it is anticipated that this dementing disorder will pose huge challenges to public health and elderly care systems in all countries across the world" - Qui et al., 2009
5. Autism Spectrum Disorder	<i>Autism Spectrum Disorder</i> (ASD) refers to a diverse group of developmental conditions caused by differences in the brain, and is characterised by some degree of impaired	Worldwide prevalence. About 1 in 160 children have ASD - Elsabbagh et al., 2012; A geographical pattern is observed in ASD prevalence study in the US - Hoffman et al., 2017. ASD	Several environmental factors mentioned in the development of ASD, include: air pollutants, fragrances, glyphosate and toxic metals, especially Al used in vaccines as adjuvant - Sealey et al., 2016; Existence of mechanistic link between genetic mutations in <i>Shank proteins</i> and Zn deficiency in the aetiology of ASD - Ha et al., 2018; Significantly	Season of birth as a risk factor for ASD - Lee et al., 2019	-

	social behaviours, speech and nonverbal communication	certainly prevalent in Africa, but prevalence rate is unknown, e.g., for South Africa - See: Pillay et al., 2021; and, by 2021, very little research has been done within the school systems in South Africa	lower concentrations of Ca, Cu, Cr, Mn, Fe and Co in hair samples of children with ASD compared to normal children - Al-Ayadhi, 2005; Genetic heavy element toxicity - Chapman, 2008; Zn deficiency, excess Cu levels, and low Zn/Cu ratio, common in children diagnosed with ASD - Bjørklund, 2013; Hair concentrations of Cr, Co, I, Fe and Mg in ASD patients significantly lower than those of control subjects - Saghazadeh et al., 2017; Ca deficiency and toxic metal (As and Pb) overload - Filon et al., 2020; Children with ASD present a reduced ability of eliminating toxic metals, leading to these metals accumulating in the body - Baj et al., 2021; The levels of Hg, Li, Pb and Se in the hair of autistic children were higher than those of healthy children, while the levels of Zn in the blood were lower - Zhang et al., 2021; Children exposed to O ₃ , CO, NO ₂ , and SO ₂ in polluted air during the preceding 1 year to 4 years may be amenable to increased risk of ASD diagnosis - Jung et al., 2013		
6. Chronic Fatigue Syndrome/ <i>Myalgic Encephalomyelitis</i>	<i>Chronic Fatigue Syndrome/Myalgic Encephalomyelitis</i> (CFS/ME) is a disabling, debilitating and complex disease characterised by profound fatigue, sleep abnormalities, pain and other symptoms that are worsened by exertion	Worldwide prevalence (Panelli, 2017; Lim et al., 2020), with 17 to 24 million people having the disease (EME CFS, 2020)	Metal hypersensitivity - Manousek et al., 2014; Some nutrient deficiencies (vitamin C, vitamin B complex, Na, Mg, Zn, folic acid, L-carnitine, L-tryptophan, essential fatty acids, and coenzyme Q10) appear to be important in the severity and exacerbation of CFS - Bjørklund et al., 2019; Ca associated with some of the neurological findings described in ME/CFS - Pacini et al., 2012; Insufficient Ca inflow into cells that perform intracellular functions - Nguyen et al., 2017	-	<p>“Researchers have not yet found what causes ME/CFS, and there are no specific laboratory tests to diagnose ME/CFS directly” - US CDC, 2018. It cannot be fully explained by an underlying medical condition.</p> <p>“There is a need for more epidemiologic studies on the prevalence and sociodemographic characteristics of CFS in developing countries.” - Njoku et al., 2007.</p> <p>Sierpina and Carter (2002) suggested that 200 mcg of chromium picolinate (taken with meals) may have the potential to reduce any reactive hypoglycaemia that may aggravate symptoms</p>
7. Chronic Kidney Disease of Unknown Aetiology	<i>Chronic Kidney Disease of unknown aetiology</i> (CKDu) has, as its predominant feature, tubular atrophy and interstitial fibrosis (thickening and scarring of the tiny air sacs and interstitial tissues in the lungs)	Reported in many parts of the world, especially among rural farming communities. High incidence in low- and middle-income countries over last two decades - Mills et al., 2015; Bikbov et al., 2020; “In 2017, the global prevalence of Chronic Kidney Disease (CKD) was 9.1% (95% uncertainty interval [UI] 8.5 to 9.8), which is roughly 700 million cases” - Cockwell and Fisher, 2020	Synergistic reaction between Cd and diabetic-related hyperglycaemia - Edwards and Prozialeck, 2009; Consumption of (polluted) well water suggested; need for investigating role of Cd - Wanigasuriya et al., 2011; Too high Ca intake? - Schiffrin et al., 2007; “Geographical mapping showed that villages with a high prevalence of CKDu are often related to irrigation water sources and/or located below the level of the water table” (Jayasekara et al., 2013); Toxins/heavy metals - Jha et al., 2013; Groundwater geochemistry (high levels of F ⁻ , Cd, As) - Wijetunge et al., 2015; Exposure to low levels of Cd - Redmon et al., 2014; High ionicity of drinking water due to fertiliser runoff - Dharma-Wardana et al., 2015; Rajapakse et al., 2016; Toxic metal exposure; water pollution - Lunyera et al., 2016; Synergistic reaction between fluoride and water hardness - Sengupta, 2013; Wickramaratna et al., 2017; Balasooriya et al., 2020; Chemical species such as Ca, phosphate, oxalate, and F ⁻ form intra-renal nanomineral particles initiating the CKD of multifactorial origin (CKDmfo) - Wimalawansa and Dissanayake, 2020; Total dissolved solids and As in drinking water have a positive correlation with CKDu - Gobalarajah et al., 2020	Altitude - Almaguer et al., 2014; Heat stress nephropathy due to global warming - Glaser et al., 2016; Sorensen and Garcia-Trabanino, 2019; Floris et al., 2021; Climatic patterns - Wimalawansa and Dissanayake, 2020; A quintessential climate-sensitive disease - Salas et al., 2019	<p>“There have been several global epidemics of CKDu. Some, such as Itai-Itai disease in Japan and Balkan endemic nephropathy, have been explained, whereas the aetiology of others remains unclear” - Gifford et al., 2017. “Those affected do not have common risk factors or underlying conditions that lead to CKD, such as diabetes, immune-mediated glomerulonephritis, or structural renal disease” - Caplin et al., 2019</p>
8. Endomyocardial fibrosis	<i>Endomyocardial Fibrosis</i> (EMF) is a form of restrictive cardiomyopathy of unknown aetiology, characterised by endocardial fibrosis of the apices and inflow tracts of the right ventricle, left ventricle or both (Khalil, 2020)	Most prevalent in the tropical regions of Africa, Asia, and South America, and mainly affecting young adults of lower socioeconomic status in those regions	Significantly elevated Ce levels ($p < 0.05$) in serum of EMF patients compared to controls - Eapen et al., 1997; Ce contamination in soil and water - Bhatti et al., 2021; High levels of Ce; Deficiency of Mg promotes the absorption of Ce and enhances its toxicity forming the basis for the initial injury of the heart (Smith et al., 1998; Thakaran and Bohora, 2009; Mocumbi et al., 2019)	-	In 2014, Mocumbi wrote: “EMF is probably the most neglected disease in cardiovascular medicine. Despite constituting a big burden to the families and health systems in endemic areas, due to its preponderance in poor sectors of the society, few human and material resources are made available for research onto its mechanisms.”

					Today (2021), the exact aetiology and <i>pathogenesis</i> of EMF remains unknown (See e.g., Bhatti et al., 2021; Khalil, 2020)
9. Fibromyalgia	<i>Fibromyalgia</i> is a rheumatic condition characterised by chronic pain, fatigue, and tenderness of muscles, tendons, and joints; often accompanied by fatigue, sleep, memory and mood issues	<i>Fibromyalgia</i> has a <i>worldwide</i> prevalence ranging from 0.2% to 6.6% in the general population; in women between 2.4 and 6.8%; in urban areas between 0.7 and 11.4% in rural areas (Marques et al., 2017)	An imbalance of the trace element status in human tissues and body fluids - Rosborg et al., 2007; Sendur et al., 2008; Metal-induced oxidative stress contributes to the severity of FMS (Stejskal et al., 2013; Shukla et al., 2021); Elevated blood Pb and Cd levels in FMS patients, compared with control group; Serum Ca and Mg levels significantly reduced ($p < 0.05$) in FMS patients compared to control group - Al-Khalifa et al., 2016; Women with FM have lower dietary intake of Ca, Mg, Fe and Mn in comparison with women who did not have the condition - Kim et al., 2011; Andretta et al., 2019	Fors and Sexton's 2002 study did not reveal any statistically significant relationship between fibromyalgic pain and the weather, although it is possible that certain patients with less chronic fibromyalgia might be weather sensitive	The aetiology and <i>pathogenesis</i> of fibromyalgia till today (2021), remain a mystery. Several proposed co-factors such as dysfunction of the central and autonomic nervous systems, neurotransmitters, hormones, immune system, external stressors, psychiatric aspects, and others are still being researched (See e.g., Siracusa et al., 2021). The recent literature clearly shows that the role of the <i>metallome</i> in FMS aetiology deserves far more attention
10. Geographic Tongue	<i>Geographic tongue</i> (also known as <i>benign migratory glossitis</i>) is an inflammatory disorder that usually appears in a map-like (geographic) pattern on the dorsum and margins of the tongue. Typically, affected tongues have a bald, red area of varying sizes that is surrounded, at least in part, by an irregular white border	A common condition, affecting 2-3% of the adult general population, <i>worldwide</i> (Ship et al. 2003; Picciani et al., 2020)	Fe and Zn deficiency; Vitamin B12 - Ogueta et al., 2019; Nandini et al., 2016; Picciani et al., 2016; Picciani et al., 2017; Low levels of salivary Zn in affected individuals compared to control groups - Khayamzadeh et al., 2019	-	-
11. Ill-thrift or 'Unthriftiness' as it is called in South Africa	<i>Ill-thrift</i> or <i>Unthriftiness</i> is an ill-defined condition of young sheep. Affected animals show mild to severe depression of growth rate and anaemia	In South Africa, the disease occurs in the coastal areas of the Eastern Cape Province. The condition has been reported from a number of other countries, including Australia, New Zealand, France and Norway (Stewart and Burroughs, Undated)	Cu, Co, Se and I, being essential components of the diet of beef cattle for maintaining their health and productivity, their deficiency in these elements can cause ill-thrift and infertility, among other causes - Crawshaw and Caldow, 2005; A state of sub-optimal growth (ill-thrift) in buffalo-calves was largely attributed to trace element deficiency, in particular Cu, Co, Fe, Se and Zn deficiency that may cause reduction in the total antioxidant capacity, with a lower ability to reduce oxidative compounds - Ali et al., 2015; Ismael et al., 2015; MLA, 2020	Mainly reported from coastal areas of high rainfall - Examples are found in Australia (MLA, 2020) and South Africa (Stewart and Burroughs, Undated)	-
12. Kawasaki Disease	<i>Kawasaki Disease (KD)</i> is an acute, self-limited <i>vasculitis</i> (inflamed blood vessels) of infants and children, with unknown aetiology. Signs of KD include prolonged fever associated with rash, red eyes, mouth, lips and tongue, and swollen hands and feet with peeling skin. The disease causes damage to the coronary arteries in a quarter of untreated children and may lead to serious heart problems in early adulthood	KD occurs worldwide; most prominently in Japan, Korea, and Taiwan, reflecting increased genetic susceptibility among Asian populations (Rowley and Shulman, 2018). The epidemiology of KD in Africa is very ill-defined, which inevitably leads to misdiagnosis and the reporting of very few cases. This gives the impression that the condition is rare in Africa - Badoe et al., 2011; Animasahun et al., 2017; Noorani and Lakhani, 2018. The presentation of KD is similar to that of measles (which is very prevalent in Africa), so the exact prevalence (of KD in Africa) is difficult to ascertain - See e.g., Badoe et al., 2011; Davaalkham et al., 2011	Environmental exposure to Hg - Orłowski and Mercer, 1980; Mutter and Yeter, 2008; Yeter et al., 2016; Portman et al., 2018; Airborne pathogens or toxins - Rodo et al., 2014; Rodo et al., 2016	Seasonality of KD, with winter peaks and winter-spring predominance in Japan and the US, respectively, and in many other temperate areas - Rowley and Shulman, 2018; Decades of research have been unable to unearth the cause of the disease, but its distinct seasonality can hardly be in doubt - UCSDH, 2013; Lin and Wu, 2017; Rypdal et al., 2018; Kim, 2019; Elakabawi et al., 2020	(i) "... Thus, these twin studies suggest that environmental factors contribute more to the development of KD than genetic factors among individuals with the same ethnicity." - Hara et al., 2016. (ii) The temporal association between the COVID-19 pandemic and the results of RT-PCR and antibody testing suggest a causal link between Kawasaki disease and COVID-19 - Toubiana et al., 2020. As Rowley and Schulman remarked in 2018, "The occurrence of epidemics and geographic wave-like spread of KD during epidemics supports a presently unknown single agent or closely related group of agents as the etiology." [Sic.]
13. Lupus Erythematosus	<i>Systemic Lupus Erythematosus (SLE)</i> is a chronic inflammatory autoimmune disease of multifactorial origin (Pedro et al., 2019)	Worldwide. Highest prevalence rate in North America (Rees et al., 2017). Once thought to be of low prevalence rate in Sub-Saharan Africa (due to	Low serum levels of albumin, Zn, Se and Zn/Cu ratio; negative correlation between serum Cu levels and lupus disease activity - Sahebari et al., 2014; SLE patients have different profiles of trace elements and toxic metals compared to healthy controls - Pedro et al., 2019	"Active SLE has the characteristics of seasonal distribution and is associated with temperature. The mechanism remains to	The aetiology of SLE is complex, and incompletely understood (See; Justiz Vaillant et al. - Updated 2020).

		under-reporting?) SLE prevalence rate is now found to 1.7% (Essouma et al., 2020), as a result of availability of improved diagnostic capacity		be further studied" - Hua-Li et al., 2011	"More epidemiological studies in Africa are warranted." - Rees et al., 2017
14. Multiple Sclerosis	<i>Multiple Sclerosis</i> (MS) is a demyelinating disease (a nervous system disease in which the insulating covers of nerve cells in the brain and spinal cord are damaged). This damage disrupts the ability of parts of the nervous system to transmit signals, resulting in a range of signs and symptoms, including physical, mental, and sometimes psychiatric problems (Compston and Coles, 2002; Compston and Coles, 2008; Murray et al., 2012). Kister et al. (2013) list 11 specific symptom domains commonly affected in multiple sclerosis: mobility, hand function, vision, fatigue, cognition, bowel/bladder function, sensory, spasticity, pain, depression, and tremor/coordination	Distribution is worldwide. Distinct geographical pattern of prevalence with high prevalence rates between 45 degrees and 65 degrees north (Wade, 2014). The age-standardised MS prevalence estimate per 100,000 population for eastern Sub-Saharan Africa is put at 3.3 by WGBD (2019); but such an estimate would always be influenced by misdiagnosis and under-reporting (e.g., Bhigjee et al., 2007)	Metabolic imbalance of trace elements/metals - Rieder et al., 1983; Smith et al., 1989; Melo et al., 2003; Tamburo et al., 2015; Bredholt and Frederikson, 2016; Janghorbani et al., 2017; Sarmadi et al., 2020; the therapeutic potential of antioxidant [<i>reactive oxygen species</i> (ROS)] protection in the pathogenesis of MS - van Horssen et al., 2011; Tavassolifar et al., 2020; Effect on the immune system of Al toxicity and Cu, Zn, and Se toxicity and deficiency, followed by neuron inflammation and degeneration - Hesamian and Eskandari, 2020	People living in higher geographical latitudes may receive lower levels of sunlight, and therefore have lower vitamin D levels which probably explains the reason for a higher incidence of MS in countries with higher latitudes - MS International Federation, 2016; "There is a striking latitudinal gradient in multiple sclerosis (MS) prevalence ..." - Simpson Jnr. et al., 2011, Simpson Jnr. et al., 2019; See also: Warren and Warren, 2001; Staples et al., 2003; Sabel et al., 2021	-
15. Nodding Disease (ND)/Nodding syndrome (NS)	<i>Nodding Disease</i> is characterised by an occasional nodding of the head, as in epilepsy, with seizures, stunted growth, and with mental retardation sometimes occurring	This is an emerging disease occurring in <i>clusters</i> in South Sudan, southern Tanzania, northern Uganda and possibly also other countries of Sub-Saharan Africa. The exact prevalence and geographic distribution of the disease in the affected countries is still unknown - Korevaar and Visser, 2013	Deficiency of vitamin B6 (pyridoxine) and other micronutrients such as vitamin A, Se, and Zn - GU/WHO, 2012; Foltz et al., 2013	Climate change - Donnelly, 2012; Cold weather - Kaiser et al., 2000; Nyungura et al., 2011; Living in the vicinity of fast-flowing streams, the breeding habitat of the black fly - Donnelly, 2012	"Nutritional toxicity remains a possible cause of nodding syndromes." - Dowell et al., 2013. As at 2020, "Much about NS remains unclear. That we do not know the cause of the disorder is perhaps least surprising - the number of acquired neurological diseases whose aetiology is well understood is not large. ..." Olum et al. (2020).
16. Noma	<i>Noma</i> (<i>cancrum oris</i> or <i>gangrenous stomatitis</i>), is a severe and progressive gangrenous infection (body tissues die as a result of infection or inadequate blood supply) that affects the mouth and face	Mainly observed in tropical countries, particularly those in Sub-Saharan Africa. True global incidence unknown; but estimated incidence of 30,000 - 40,000 has been suggested by Srour et al. (2017)	Deficiencies of trace elements and amino acids influencing the efficacy of the immune system: Fe, Zn, cysteine, methionine, serine, and glycine - Baratti-Mayer et al., 2003; Deficiency of micronutrients in the diet - Srour et al., 2017; Srour and Baratti-Meyer, 2020; Farley et al., 2021	-	Patients generally live in extremely poor conditions, frequently located in remote rural areas
17. Parkinson's Disease	<i>Parkinson's Disease</i> (PD) is a progressive heterogeneous, multisystem and neurodegenerative nervous system disorder that affects movement. The cardinal features of Parkinson's disease are (i) tremor, mainly at rest; (ii) muscular rigidity, which leads to difficulties in walking, writing, speaking and masking of facial expression; (iii) <i>bradykinesia</i> , a slowness in initiating and executing movements; and (iv) stooped posture and instability (Sian et al., 1999). Parkinson's disease occurs when nerve cells, or dopamine-rich neurons in an area of the brain that controls movement called the <i>substantia nigra</i> , become impaired and/or die. But the complete series of steps leading to this cell death is still vague, and the underlying causes remain one of medicine's greatest mysteries	Worldwide occurrence. According to the 2016 Dorsey and GBD Collaborators Study published in 2018, 6.1 million (95% uncertainty interval [UI] 5.0 - 7.3) individuals had Parkinson's disease globally, compared with 2.5 million (2.0 - 3.0) in 1990; Geographical variation (<i>cf.</i> latitude) plays key role in dementia risk (e.g., Russ et al., 2016)	High concentrations of Al and low levels of Mg observed in the pathogenesis of CNS (central nervous system) degeneration and PD - Yasui et al., 1992; Association with metal and trace element concentration in urine, serum, whole blood and cerebrospinal fluid - Bocca et al., 2004; Forte et al., 2004; Gellein et al., 2008; Zhao et al., 2013; Raj et al., 2021; Very high or very low levels of Se - Ellwanger et al., 2016; Combination of Mo deficiency and purine ingestion - Bourke, 2018; Significant association between the PD mortality rates and soil concentrations of Se, Sr, and Mg - Sun, 2018; Adani et al., 2020; Lemelle et al., 2020; Elevated trace metals (namely, Cu, Zn, Mg and Fe) found compared to controls ($p < 0.001$) in Nigerian Parkinson's Disease patients (Ogunrin et al., 2013)	Existence of seasonality (related to temperature) in Parkinson's disease symptoms - Rowell et al., 2017; Improvement of PD symptoms at high altitude - Capcha et al., 2018; Thomas, 2019; several risk factors in development of PD at high altitude - Cao et al., 2021	Regional maps depicting correlations between the distribution (clusters) of PD and soil geochemistry which would be helpful in this aetiological debate, are very rare in the published literature (See an example in: Sun, 2018 for PD distribution in the United States). To date (2021), "... the fundamental molecular mechanisms of PD etiology and pathogenesis is still obscure, metals toxicity have been documented in the implication of PD pathogenesis by several epidemiological studies with several potential mechanisms. In many cases, the metals equilibrium is disturbed, which leads to deleterious effect on the entire body including the

					brain.” [Sic.] (Ullah et al., 2021).
18. Sarcoidosis	<p><i>Sarcoidosis</i> is a multisystem, granulomatous, inflammatory disease that affects one or more organs, but most commonly affects the lungs and lymph glands. The inflammation may change the normal structure and possibly the function of the affected organ(s)</p>	<p><i>Sarcoidosis</i> is observed throughout the <i>world</i> and affects all races and ages, with an average incidence of 16.5 per 100,000 in men and 19 per 100,000 in women (Patil et al., 2015).</p> <p>Race and geographical location are considered as factors in the incidence and prevalence of sarcoidosis, which has consistently been observed to be highest in Nordic countries and in African Americans (Arkema and Cozier, 2018).</p> <p>Sarcoidosis is not a rare condition in Africa (Awotodu et al., 1987; Kaloga et al., 2015), the apparent infrequency of reporting being probably a result of misdiagnosis (as, e.g., tuberculosis) (Morar and Feldman, 2015a; Morar and Feldman, 2015b). Further research is therefore necessary in Africa to unravel the various clinical aspects of this mysterious and complex disease</p>	<p>Exposure to toxic metals and rare earth elements (REEs) in the environment - Newman, 1998; Beijer et al., 2020; Denisova et al., 2020; Metal dusts - Judson, 2020; Crystalline silica - Arkema and Cozier, 2018; Industrial exposure to Be - Culver et al., 2007.</p> <p>Since low dose metal particles can induce <i>monocyte/macrophage</i> survival (See e.g., Lacey et al., 2009), as recently as 2021, Lepzien et al. (2021) went on to show that <i>monocytes</i> could be a vital marker in understanding the inflammatory process of sarcoidosis.</p>	<p>Geographic clustering of disease in many parts of the world has long been noted [e.g., in the US (Sartwell and Edwards, 1974)], and has ignited further speculations concerning weather, soil, and foliage in the pathogenesis of sarcoidosis.</p> <p>More recently (2019), Ramos-Casals et al. asserted that local weather is a key environmental factor influencing the incidence of sarcoidosis in a specific geographical area, with the peak of diagnosed cases following a specific seasonal distribution pattern</p>	<p>The causes of sarcoidosis are still unknown and epidemiological data are often discordant (Pietra et al., 1988; Beghè et al., 2017).</p> <p>“Although the etiology of this condition is unclear, environmental and genetic factors may be substantial in its pathogenesis.” [Sic.] - Ganeshan et al., 2018.</p> <p>According to Ahmadzai et al. (2013), in sarcoidosis, conventional sampling techniques or cultures of non-caseating granulomas cannot detect tissue micro-organisms; although as Newman earlier (1998) proposed, clinicians should use a systematic approach to investigating the occupational and environmental history and immunologic responses of patients with sarcoidosis, for discriminating metal-induced granulomatosis from sarcoidosis</p>
19. Spastic Paraparesis	<p><i>Hereditary Spastic Paraparesis</i> (HSP) or the <i>Strümpell-Lorrain Syndrome</i> refers to a heterogeneous group of disorders in which the main clinical feature is progressive lower limb spasticity or gait disorder.</p> <p>HSP is also known as <i>familial spastic paraplegia</i> (US NINDS, 2014); however, “<i>paraparesis</i>” indicates weakness in both legs, and is of lesser severity than “<i>paraplegia</i>”</p>	<p>The prevalence of all hereditary spastic paraplegias combined is estimated to be 2 to 6 in 100,000 people (US NIH, 2019)</p>	<p>Nutritional disorders, including Cu deficiency, vitamins B₁₂ and E deficiencies - Mitchell et al., 1986; Hedera, 2016; Hedera, 2018</p>	<p>High intake of HCN⁻ engendered by drought conditions (Cliff et al., 1984)</p>	<p>See Taibo et al. (2017) for report of a real-life outbreak of spastic paraparesis investigation undertaken in northern Mozambique in 1981</p>
20. Sudden Infant Death Syndrome	<p><i>Sudden Infant Death Syndrome</i> (SIDS) is the sudden and unexplained death of a baby younger than 1 year old, after thorough case investigation (Duncan and Byard, 2018)</p>	<p>Global distribution (Müller-Nordhorn et al., 2020); A significant cause of mortality in Africa (See: Ogbu, 2003; Ndu, 2016; Dempers et al., 2018)</p>	<p>Genetic heavy element toxicity - Chapman, 2008; Elevated Pb burden (blood samples) in SID babies compared with control babies - Drasch et al., 1988; Increased tissue Pb levels in SIDS infants - Erickson et al., 1983; K levels significantly lower in less than 6-month-old SIDS infants than in non-SIDS infants - Steele et al., 1984; Soft water with low Mg and Ca and with high concentration of Na, linked to higher SIDS rates - Caddell, 1992; Recharge of groundwater which increases its nitrate content - George et al., 2001</p>	<p>Cold wet weather - Deacon and Williams, 1982; Overheating or disordered thermoregulation - Sawczenko and Fleming, 1996; Exposure to increased ambient temperature associated with an increased risk of SIDS - Schluter et al., 1998; Jhun et al., 2017</p>	<p>“Despite decades of investigation and millions of dollars spent, the cause of sudden infant death syndrome (SIDS) eludes researchers. It is timely therefore to reconsider the reasons for this failure and to explore how research might go forward with better prospects.” [Sic.] (Goldwater, 2017).</p> <p>In deciphering the causes of SIDS, we must remember that a <i>baby’s immune system</i> is immature when they are born, making newborns particularly at risk of illness (See e.g., Goenka and Kollmann, 2015; Simon et al., 2015). It is therefore critically important that their</p>

potential contact with geoenvironmental factors of disease, especially the “*metallome*”, be given particular attention by caregivers.

In Africa, many of the risk factors of SIDS exist, and the syndrome may well be widespread (See, e.g., Ogbu, 2003; Ndu, 2016); but scarce attention is given to research on it

Figure 2

Map of Mozambique, showing the affected area and incidence rates of “mantakassa” (spastic paraparesis) per 1000 inhabitants. Source: Reproduced from Cliff et al., 1984.

Figure 3

Impact of climate change on human health. Credit: George Lubet, CDC. Source: Ebi et al., 2017.

Figure 4

Schematic illustration of the link between (trace element interactions in-) organs of the immune system and development of autoimmune diseases. The probable role of trace elements in the incidence of systemic lupus is described under this disease in Table 1. Image by the U.S. National Institute of Environmental Health Sciences.