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# THE ROLE OF GEO-ENVIRONMENTAL VARIABLES IN UNDERSTANDING CAUSAL CO-FACTORS OF DISEASES OF UNKNOWN AETIOLOGY AND OTHER ENIGMATIC DISEASES IN AFRICA: A NARRATIVE REVIEW.

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## ABSTRACT

Idiopathic diseases (ID) or diseases of unknown aetiology (DUA) are poorly understood diseases. These diseases are widespread in Africa and other regions of the world. In Africa, we also experience occasional outbreaks in a population, or a *cluster* of diseases appears for which the causes are unclear. Until now, there has been a lack of literature linking geo-environmental variables with DUA, perhaps due to under- and misdiagnosis of these diseases. However, some of the few existing reports have implicated geo-environmental variables as inducers of a wide spectrum of pathophysiological responses including apoptosis, fibrosis, inflammation, molecular damage, and oxidative tissue injuries. The present review therefore seeks to explore the critical role that these variables may play as co-factors or risk factors in the incidence and progression of a range of DUA in Africa.
A comprehensive online search of journal databases (Google Scholar, ScienceDirect, PubMed, Scopus, and SpringerLink) was mounted to obtain requisite data that would enable tangible deductions to be drawn on the extent to which geo-environmental variables act as co-factors or *risk factors* in unraveling the mysteries of unknown aetiology; and to demonstrate the importance of including the geo-environmental component in a multi-factor explanation of the disease causative web. The databases were used to obtain reports related to DUA, disease clusters, and geo-environmental variables as disease risk factors in Africa.
Findings from the present study help us understand and interpret unexpected DUA aetiological data, which are prerequisites for developing accurate and effective diagnosis, prevention, and improved management strategies for these diseases.
It became clear from the present study that for us to fully understand the pathogenesis and progression of DUA, healthcare professionals investigating disease clusters should, perhaps team up with Medical Geologists, a research collaboration that rarely exists in most developing countries today.

***Keywords:*** *Africa, Geo-environmental variables; Idiopathic diseases, Disease clusters*
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## INTRODUCTION

*Idiopathic diseases* (ID) or *diseases of unknown aetiology* (DUA) are a group of illnesses, multisystem diseases, and *syndromes* with poorly understood aetiology (Ardissino et al. 2019). The diagnoses and management of DUA are daunting tasks, and their widespread occurrence in Africa poses a huge socio-economic burden, particularly on countries with poorly-resourced medical facilities (Njoku et al. 2007).

Diseases epidemics often occur due to a new or modified pathogen, a naturally occurring toxin, or the release of geo-chemicals initially undetected. In investigating the causes of such enigmatic outbreaks, there is a need to deeply consider, in addition to other possible aetiological co-factors, geological/geochemical/biochemical phenomena in the localities concerned, such as sudden changes in soil, water or air composition, over-exposure to ionizing radiation or organic compounds from mining or other geogenic sources. Carefully recording the history of the episode and conducting a thorough epidemiological study, may reveal plausible causes which could then provide leads for further, more specialized investigations. Among the geo-environmental factors examined in this study are: geo-materials such as geogenic dust and radioactive particles, long and short-term changing weather patterns, heat stress, and the geo-pathic stress phenomena. This review also examines the impacts of long and short-term changes in weather patterns on the biology and ecology of pathogens associated with DUA.

Generally, DUA is diagnosed by excluding all other possible diseases exhibiting similar clinical symptoms, a phenomenon known in medical circles as a *diagnosis by exclusion* (Wakwaya et al. 2019). Diagnosis by exclusion

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commonly occurs where scientific knowledge about the disease is generally scarce and there are no objective methods to confirm the diagnosis (Drossman 1999). The causes of DUA are no doubt multifactorial, with no single biological or environmental factor directly linked to their pathogenesis and progression. An understanding of the source of the antigen/pathogen, including trace elements/metals/metalloids, their migration pathways into the body, and interactions within the body are required for credible diagnosis to be made, as well as to guide management strategies (Alberts et al. 2002, WHO 2001). These considerations underline the need for the Medical Geologist's inclusion in a multidisciplinary team in such investigations, to enable the design of optimum research and possible management strategies.

The methodology involved a comprehensive online search of journal databases (Google Scholar, ScienceDirect, PubMed, Scopus, and SpringerLink), to obtain results of pertinent studies by using keywords: 'Africa', 'diseases', 'unknown aetiology' 'idiopathic diseases' and 'geo-environmental variables. Climate change, seasonal variations in weather patterns, geopathic stress, heat stress, ionizing radiation, and geochemical perturbations emerged as prominent geo-environmental variables whose dynamics of action outside the human body and/or associated interactions within it may contribute to the development and progression of DUA.

## RISK FACTORS

The phrase 'risk factor', was first defined by Kannel et al. (1961) as variables that determine the onset and/ or progression of a particular medical disorder (infectious / non-infectious disease or injury) (Parritz et al. 2013, Ambo et al. 2010, Sabel et al. 2007, IPCC 2014). Risk factors can encompass attributes such as family history, age, sex or ethnicity, the presence of a prior health condition, or exposure to an environmental variable, such as ionizing radiation exposure (WHO 2017).

### Causal attribution of risk factors

When conscripting effective disease and injury prevention strategies, one must have reliable and comparable health risk analysis tools (Ezzati et al. 2002). Indeed, significant proportions of the worldwide disease burden are attributable to some primary risk factors, even to a level greater than has recently been projected (Ezzati et al. 2002). In almost all listings of primary risk factors responsible for the worldwide and regional burden of disease, unsafe water, and micronutrient deficiency (Ezzati et al. 2002, Lopez et al. 2006) as well as the place factor (geographical location) (Cluver 2019, Toms et al. 2019) and environmental toxins, are all considered as having links to geo-environmental variables. In their work on disease causation, Ezzati et al. (2002) noted that African countries and other developing nations suffer the most from the burden of diseases due to the pervasion of many primary risk factors. However, disease management approaches that target such factors provide considerable, but often undervalued public health benefits.

Among the determinants that are most commonly encountered in epidemiological associations are: age, gender, and race; these are also the determinants that are most commonly controlled by confounders (Bovbjerg 2019, Filardo et al. 2011). Other important equally important determinants include genetic profiles, income, geographic location, profession, diet, physical activity, smoking, and alcohol consumption. Many other determinants are not usually adjusted for possible confounders, among which is 'genetic predisposition'.

### Geographical patterns, seasonality, and spatial-temporal associations of disease

Dummer (2008) reiterated the importance of relationships between geography and health and further asserted that the geographical area where one is located (live or work), the pathogens present, and diet are among the factors, which directly influence health experiences. Indeed, spatial locations have a strong bearing on several environmental risks, as well as many other health effects; therein lies the key focus of any scientific inquiry on the geography of diseases, *viz*., determination of the extent to which health is influenced by geographical factors. Buttressing these observations was a noteworthy study by the North Carolina State University (NCSV) that factored climate, disease control, population, pathogen, and human history data into systematic models to determine relationships between geo-environmental factors and human diseases (NCSV 2010). In this connection, it is necessary to state that the geography of disease in Africa is quite different from that in the Western world which is highly industrialized, wealthy, and with a higher literacy rate and relatively secure community. Most of the population of Africa is still rural and many parts of the continent are not yet at an advanced stage of development. Malnutrition, illiteracy, poverty, and access to clean water and air are still realistic challenges in these areas.

As Ruiz (2017) noted, carefully designed epidemiological studies can reveal factors contributing to disease outcomes and provide options for disease prevention. The spatial and temporal distribution of diseases should lead medical and geology experts to critically examine features that differentiate such areas to determine possible aetiological factors. The significance of "place factors" in understanding DUA was demonstrated by Cliff et al. (1984) in a study on *spastic paraparesis* in Mozambique (Fig. 1).

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In addition to the aforementioned factors, research groups investigating the geographical drivers of disease outbreaks must also take into consideration the characteristics and dynamics of pathogens, vectors, and host populations, as well as the presence of xenobiotic chemicals and toxic agents (e.g., As, Hg and Pb) in the environment (Ruiz 2017). Such an approach would lend to a more holistic approach in the aetiological characterization of ‘mysterious’ diseases in Africa.

Geographical factors of a given disease are linked to the weather and geo-hydrology of a given region, the natural environment, as well as demographical factors which include age differences, and social and cultural behaviors (Ruiz 2017). Although a group of people may be constrained to a given geographical location, their response to prevailing environmental factors and seasonality differs considerably (MacGillivray et al. 2014). However, the effects of changing geo-environmental factors, diet, and exposure to infectious agents may also be exacerbated or alleviated by local cultural and lifestyle practices.

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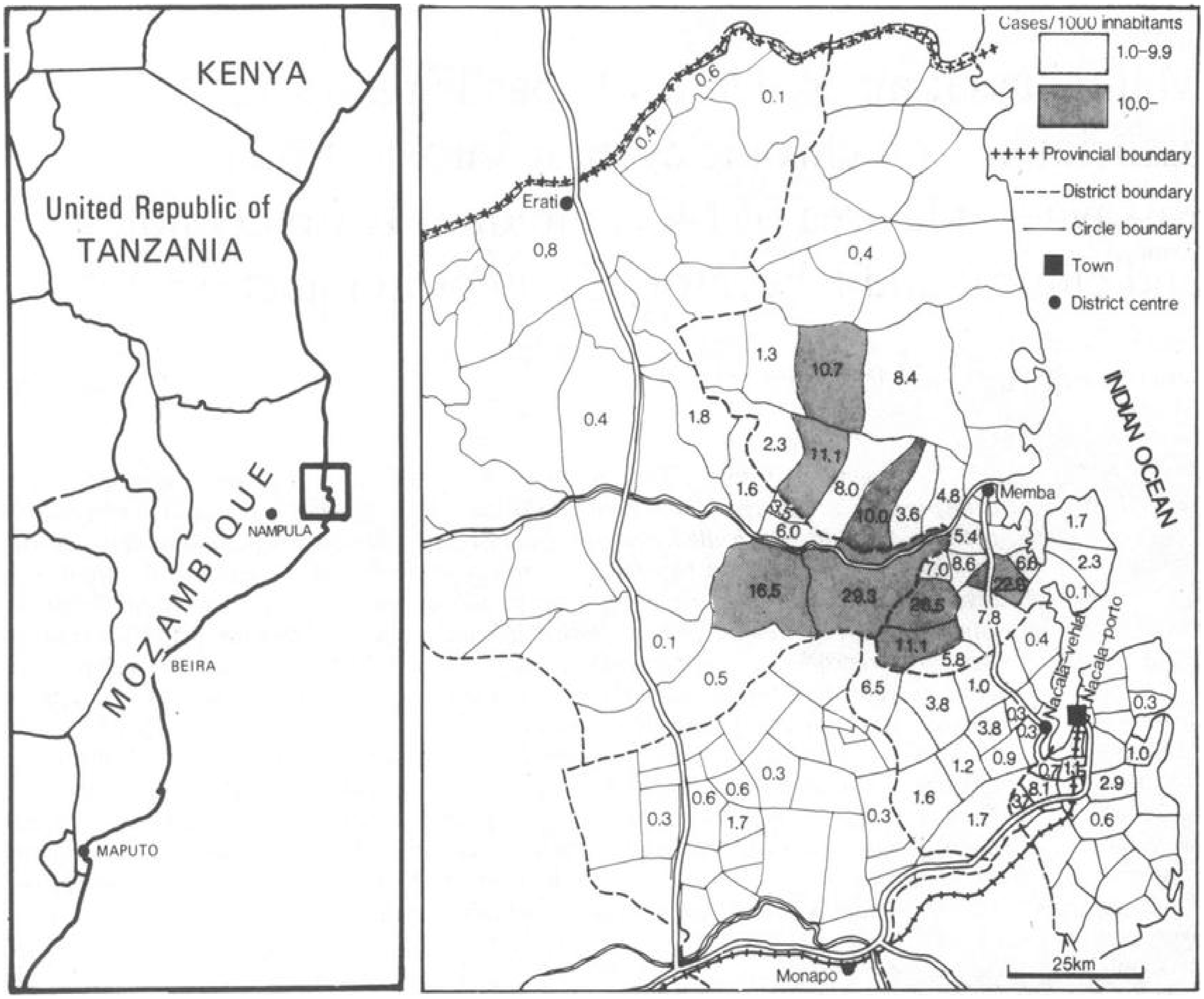


**Fig. 1. A Map showing the geographical distribution and prevalence of "mantakassa" (spastic paraparesis) per 1000 inhabitants in Mozambique, Africa [Reproduced from Cliff et al. (1984) (With permission)].**

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## Seasonal variations of disease

Martineau et al. (2011) provided an assessment of the influence of infectious diseases, seasonal variations, and vitamin D on tuberculosis (TB) in South Africa. The study revealed correlations between seasonal variation in serum 25(OH)D concentration and TB notification. The study also emphasized the need for consideration of 'seasonality', now known to be a multifactorial parameter, in studies of human immunity. According to Behrman et al. (2018), a proper understanding of swift and cyclic responses to seasonal environmental pressure is urgent, since it will provide a broader perception of the multifaceted ecological and genetic relationships that determine the development of immune defense in natural populations.

Seasonal changes in the prevalence of communicable diseases are not an uncommon phenomenon in Africa and other continents with temperate or tropical climates. However, the mechanisms responsible for seasonal disease occurrence, and resultant epidemiological outcomes are generally not yet well known (Grassly et al. 2006).

Seasonal variations in the prevalence and severity of some DUA including idiopathic epistaxis, juvenile idiopathic arthritis, idiopathic club foot, idiopathic sudden sensorineural hearing loss, and idiopathic pulmonary fibrosis (IFP) have been closely linked with seasonal variations in the frequency of some bacterial and viral infections, too (Rundgren et al. 2008, Berkun et al. 2010, Gerceker et al. 2011, Olson et al. 2009).

Several systematic theories proposed to explain the seasonality of various directly communicable diseases include pathogen infectivity, human activity, seasonal variations in vitamin D levels, seasonality of melatonin (See: "Glossary of terms" for definition), and seasonal differences in human immune system function. The impacts of these variables on seasonal patterns of transmittable diseases, and whether or not seasonal immune modulation takes place in humans, were discussed in detail by Grassly et al. (2006), Fares (2013), and Paynter et al. (2015).

## Spacio-temporal associations

Spatial disease patterns are often linked to chronological factors. Seasonal changes in rainfall and temperature patterns, as well as agricultural activities often influence disease trajectories (Mistry et al. 2015, Ruiz 2017). Ruiz (2017) noted that: "When the number of cases of a disease change at any given time, spatial-temporal 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." (*Sic*).

Sometimes a disease may occur only after a prolonged exposure to specific risk factors and can even be absent in successive generations. Earlier immunity, nutritional health, and genetic differences can therefore have significant impacts on the spatial distribution of the disease (Davies et al. 2008). Multi-disciplinary research efforts are therefore key in tackling complex disease problems (Davies et al. 2008).

## Effect of climate change on the geo-environmental determinants of health

The interaction between climatic changes and human health is increasingly becoming clear (Fig. 2), and the available knowledge is well documented. New findings in this area of research are documented in several recent publications, and it is worth noting that some scientific journals have been devoted exclusively to this subject, or have entire sections addressing it (e.g. the journal Environmental Geochemistry and Health). However, interactions between DUA and climate are poorly understood, as evidenced by the scanty information in the literature.

According to the World Health Organisation (WHO 2003, WHO 2018), changing climatic conditions affect several socio-environmental factors related to pollution, shelter and food security, to mention but a few (Fig. 2). The US Centre for Disease Control and Prevention (USCDC) has cautioned that: "Climate change threatens human health and well-being in many ways, including impacts from increased extreme weather events (heat waves, floods, snow, hail, etc.), wildfire, decreased air quality, food and water-borne illness, and diseases transmitted by carriers such as mosquitoes and ticks" (USCDC 2020a).

## Relationship of climate change and DUA in Africa

Because of its unique environmental setting and other variables in its life support system, there are indications that Africa would be the most susceptible to health effects emanating from climate change (Ilevbare 2019).

According to Rohr et al. (2011), observations estimating the impact of climate change on human health and disease in Africa, as in other developing regions, are plagued by confounding variables. Depending on the context, there are a lot of uncertainties regarding the actual drivers of climate change and the resultant epidemiological effects. Furthermore, Rohr et al. (2011) suggested that: "….. forecasts of climate change impacts on diseases can be improved by more interdisciplinary collaborations, better linking of data and models, addressing confounding variables and context dependencies, and applying

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metabolic theory to host-parasite systems with consideration of community-level interactions and functional traits, …" (*Sic*).

In Africa, climate change affects the geo-environmental elements that influence *health* in diverse ways. The effect of climatic perturbations on the availability of clean air, safe drinking water, and sufficient amounts of essential nutrient elements in the diet, *inter alia*, are major challenges for the health of populations in many areas of the continent. Maladies such as malaria, diarrhea, and heat stress, can be directly or indirectly linked to climate-modulating co-factors, which also still abound.

## The emergence of Candida auris in Africa: example of the climate change paradigm in characterizing fungal etiology

*Candida auris* is a human pathogenic fungus that has made a fairly recent mysterious and simultaneous appearance in Africa and four other continents (Vila et al. 2020). Its presence has been reported in countries such as Kenya (Adam et al. 2019, Heath et al. 2019) and South Africa (Magobo et al. 2014, Govender et al. 2018, Szekely et al. 2019). Where exactly *C. auris* originated from is currently unknown, and it is a matter of conjecture as to whether climate and environmental changes are contributory factors in its recent emergence as a pathogen. The fungus' precise diagnosis remains illusory and as such, logic would suggest that the interpersonal, spatial, and temporal spread of the pathogen is often underestimated (Zamith-Miranda et al. 2019).

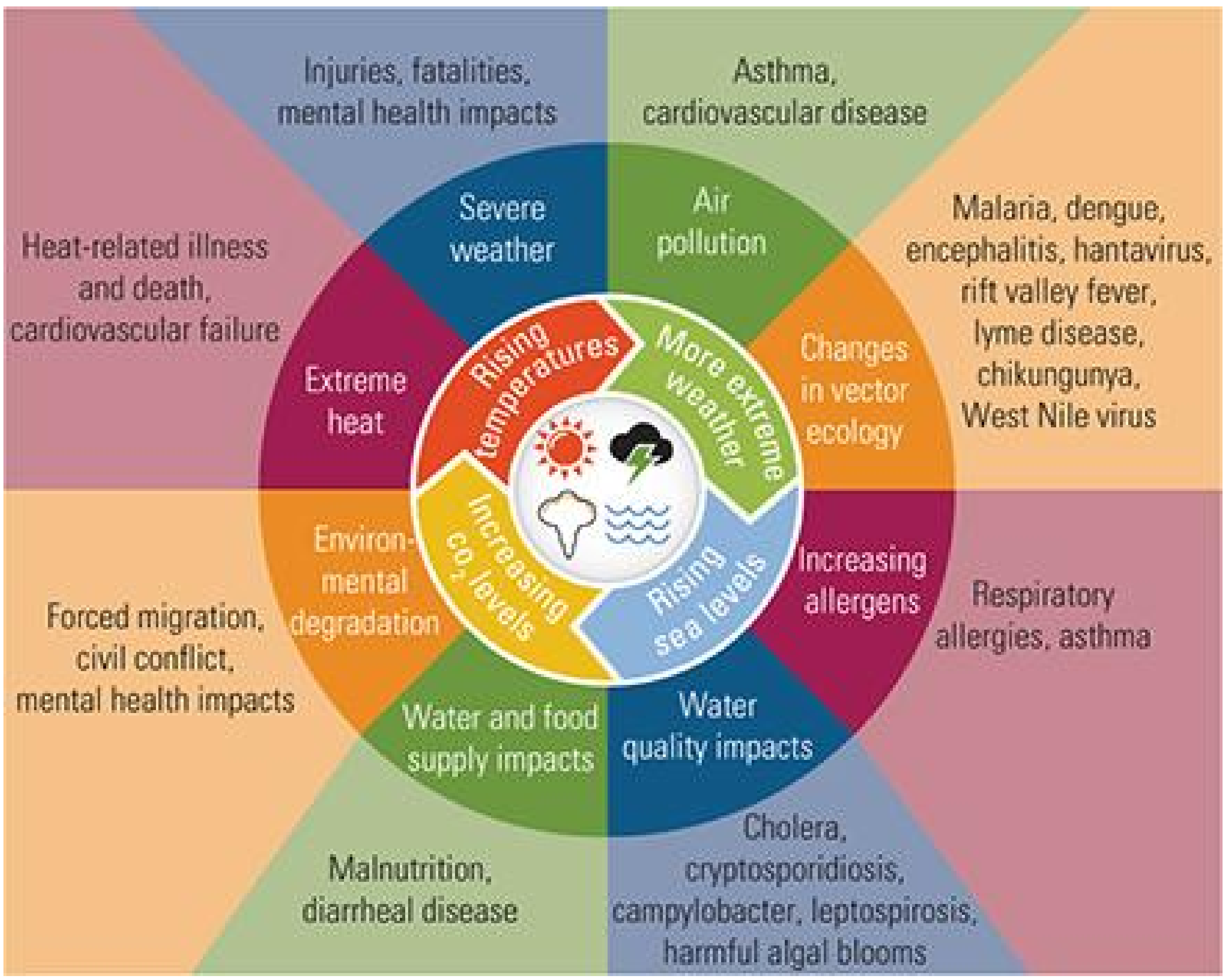


**Fig. 2. The effects of climatic changes on human health. [Credit: George Luber, CDC [Ebi et al. (2017)].**

### Origin

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Du et al. (2020) pondered the reasons why the emergence of C. auris is quite puzzling. This fungal pathogen has been shown, through genetic analyses, to have emerged in different continents at the same time, with five genetically unique clades identified in different geographical sites (Du et al. 2020). Since its emergence in 2009 (Hofer 2019), the scientific and healthcare communities have been witnessing an exponential rise in infection rates and outbreaks in hospital settings throughout the world. However, C. auris is difficult to identify and several multidrug-resistant variants have since emerged. These features, together with the evolution of infective factors, elevated patient mortality rates, and the ability to survive for extended periods on surfaces of tools, equipment, furniture, etc., make C. auris very difficult to study in a clinical setup.

## Adaptation to environmental stresses

For pathogens to effectively colonize new territories, they need an inherent ability to quickly adapt to life in different ecological niches. In the case of *C. auris*, perseverance in stressful habitats is a key distinctive feature that separates it from a host of other human fungal pathogens (Du et al. 2020). For example, while most fungi are incapable of surviving at average normal human body temperatures (36.5 - 37.5°C and up to 40°C during a fever), and therefore cannot colonize humans and cause infections (Garcia-Solache et al. 2010), *C. auris* grows well at 37 - 40°C, temperatures at which even the more genetically similar *C. haemulonii* will wax and wane (Kean et al. 2020).

Casadevall (2019) evaluated the temperature tolerance of *C. auris* in comparison to other *Candida* species and postulated that global warming had a significant impact on the evolution of *C. auris* as a human pathogen, especially with its ability to withstand high temperatures (*thermotolerance*). Furthermore, *C. auris* tolerates high salt concentrations (>10 % NaCl, wt/vol) (*osmotolerance*) compared to other *Candida* species (Welsh et al. 2017, Wang et al. 2018). This inherent ability to withstand high temperatures and salt concentrations allows the pathogen to survive on biotic and abiotic surfaces for extended periods (Sekyere 2018). Finally, Du et al. (2020) indicated that *C. auris* can thrive on human skin and environmental surfaces for several days (> 14 days) and can even withstand some commonly used disinfectants such as sodium hypochlorite and peroxyacetic acid.

## The aquatic environment as a reservoir host of pathogens

The World Health Organisation listed 'water supply' as an important environmental factor that can influence contagious disease outbreaks (WHO 2020). Other important factors include food, climate, and hygiene. This holds particularly true in the case of African cities, where improved air quality control mechanisms are most desirable (Davies 2015).

After heavy precipitation, the population of vector mosquitoes usually increases. Writing on what could be described as a surveillance paradox of communicable diseases particularly the *arboviral* disease (arthropod-borne viruses), Chikungunya virus, and West Nile virus in Africa, Chanda (2020) noted the correlation of their prevalence with heavy rainfall events wrought by global warming. Indeed, recent changes in climatic conditions, particularly fluctuations in rainfall amounts and increased ambient temperatures are widely believed to be among the major factors contributing to the endemisation process of these diseases in various locations in Africa (Nyaruaba et al. 2019, Kading et al. 2020). The concentration of reservoir hosts in stagnant water locations especially dug wells, cisterns, roof gutters, and water tanks also facilitates ease of disease transmission. Droughts, as well, can suppress mosquito predator populations, which consequently can result in post-drought increases in vector populations (Bellone et al. 2020).

Changes in rainfall patterns also contribute significantly to seasonal variations in disease outbreaks (Jofre et al. 2009). Generally, water-borne pathogens reproduce faster and are distributed (by flowing water) over larger geographical areas during rainy seasons than in drier seasons. During heavy rainfalls, sewage systems may also overflow leading to the outbreaks of both viral and bacterial infections (Olds et al. 2018). Stagnant water due to prolonged droughts or heavy rainfalls may also offer opportunities for some vectors such as mosquitoes to breed (Wu et al. 2016).

## Humidity variations and viral integrity

Some studies have also shown that some air-borne pathogens are highly sensitive to variations in ambient humidity. The influenza virus, for instance, thrives well under cold and low relative humidity (RH) conditions typical of winter seasons (Lowen et al. 2007). Recent research has indicated that enveloped viruses thrive well under low RH conditions, while unenveloped viruses survive better at higher RH (Ward et al. 2004). Growing empirical evidence suggests that sudden drops in RH induce rapid rehydration of capsids in unenveloped viruses, ultimately reducing their viability. Enveloped viruses have lipid membranes that protect capsids from changes in ambient humidity (Sobsey et al. 2003). The integrity of viral structures particularly head-tail complexes can also be disrupted by sudden fluctuations in RH. In coliphages, for example, sudden increases in RH and the resultant rehydration disrupt head-tail viral structures (Yang et al. 2012). The survival and viability of viruses on aerosols,

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however, depends on intrinsic thermodynamic and fluid mechanics a phenomenon yet to be fully elucidated.

## Temperature variations and pathogen fecundity



While floods, snow, and dry and hot weather conditions generally destroy habitats, the right combination of meteorological conditions often promotes the breeding, survival, spread, and geographical distribution of insect vectors and pathogens (Xiao et al. 2014). Like most other living organisms, the growth and reproduction of pathogens and vectors occur optimally within fairly narrow temperature (maximum-minimum) ranges. Beyond this range, several growth parameters become adversely affected (Wu et al. 2016). Exceptionally higher ambient temperatures may, for instance, result in higher pathogen and vector mortality rates, while lower temperatures stall key growth and developmental processes (Gerba 1999). According to Harvell et al. (2002), higher temperatures reduce the extrinsic incubation period of some pathogens, while lower temperatures generally have contrary effects. Ambient temperatures, therefore, modulate the length of pathogen life cycles. Logic would therefore dictate that, if all other factors remain constant, the longer the life cycle, the less frequently a given disease would occur in a given season. Higher temperatures may, however, favor the growth and reproduction of pathogenic competitors hence reducing the frequency and severity of some infectious diseases during warmer seasons (Jones 2001).

## Spread of viruses and other pathogens by air streams and wind

Another important climatic variable to consider here is wind, which mainly affects the prevalence of air-borne diseases. The dust load in the atmosphere at any given time is directly proportional to wind speed, which in turn is mainly influenced by seasonal weather patterns. Changes in weather patterns over extended periods may lead to widespread desertification which in turn increases the likelihood of dust storms (Xu et al. 2011). The incidence of influenza and avian influenza (H5N1) epidemics in the downwind areas of the Asian dust storm seems to imply that these two viruses are carried by dust particles over long distances (Chen et al. 2010). One study in Taiwan established that levels of influenza A viruses in the atmosphere significantly increase during dust storms than at other times (Chen et al. 2021). It is, however, not clear how long viruses attached to dust particles can remain viable. According to Chen et al. (2020), dehydration, natural radiation, and atmospheric pollutants could most likely diminish the viability of most viruses.

Some studies have suggested that there exists a link between different weather conditions and the spread of pathogens from one region to another (Rodo et al. 2016, Boukerche et al. 2020, WHO 2020).

Complex bio-meteorological weather analyses have shown the plausibility of distinct weather conditions having a significant influence on the occurrence of ruptured abdominal aortic aneurysms (AAA) (Schuld et al. 2013) and type A acute (Luo et al. 2020). However, several previous studies on this failed to successfully establish relationships between weather parameters (e.g. temperature and pressure) and disease outcomes such as Autoimmune Addison's disease (AAD) [ Verberkmoes et al. (2012)].

Fine particulate pollution such as black carbon (a major atmospheric-warming agent), sulphates, and nitrates readily enter the lungs and the bloodstream, rendering the immune system less effective (Genc et al. 2012). Several studies (Nurshad et al. 2020, Mostafa et al. 1997) suggest that air pollution increases the risk and virulence of COVID-19. Pozzer et al. (2020) have shown that increases in fine particulate pollution by at least 1μg $cm^{-3}$ would result in a 15 % increase in COVID-19 deaths. Therefore, massive efforts aimed at air quality improvement by reducing emissions, especially in cities, could yield substantial gains in the fight against both viral and climate risks.

## Extreme weather events

It has long been observed that communicable disease outbreaks usually occur after extreme weather conditions since pathogens, vectors, and reservoir animal hosts take advantage of unsettled social and environmental conditions emanating from harsh weather conditions events (McMichael 2015). This further strengthens calls for a deeply rooted understanding of intrinsic relationships between climatic changes, natural drivers of extreme weather events, and predicted communicable disease risks associated with this change.

## El Niño Southern Oscillation (ENSO) and disease

*El Niño Southern Oscillation* (ENSO) is mainly characterized by fluctuations in ocean surface temperatures resulting in significant shifts in atmospheric circulation systems. This unique weather phenomenon consists of cold phases (La Niña) and warm phases (El Niño), both of which contribute to the development of extreme weather events around the globe (WHO 2015). Though the effects of ENSO are felt in many parts of the world, its most intense impacts are realized in tropical regions (e.g., in Africa) that are predominantly prone to natural hazards. By significantly changing local and global weather patterns,

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ENSO can have severe impacts on several major determinants of human health (WHO 2015).

While the precise effects of global warming on the ENSO are not yet fully understood (WMO 2020a), we do now know that ENSO's characteristic heavy rainfalls and the accompanying widespread disease epidemics, such as Rift Valley fever in East Africa, changed transmission trajectories of rodent-borne, waterborne and vector-borne diseases, are induced by rising temperatures (Anyamba et al. 2019).

Some popular regional impacts of El Niño in Africa include arid conditions in the southern part of the Continent and a few areas in its Sahel region; and wet conditions in equatorial East Africa during summer (October - December) (WHO 2015).

Mosquitoes and other vectors that transmit diseases in Africa (e.g., malaria and dengue fever), with variable local impacts, generally respond swiftly to changes in humidity, rainfall, and temperature, which determine the suitability of ecosystems for vector activity, development, and reproduction (Caminade et al. 2019).

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

Other important imponderables associated with DUA are *heat waves* and *heat stress*. Heatwave refers to a period when air temperatures are excessively higher than the expected average temperatures of the area (Robinson 2001). This global phenomenon is currently increasing in frequency, duration, and magnitude; being associated with extreme weather patterns emanating from global climate changes (Smoyer-Tomic et al. 2003, WMO 2020b).

Prolonged exposure to heat waves may result in the human body failing to get rid of excess internal heat, which in turn may lead to dehydration, heat exhaustion, and heatstroke (Brody 2018). Quite often, heat waves result in either low humidity (which may lead to droughts), or high humidity, both of which intensify the effects of the related stresses on human health. Existing medical conditions may also worsen, causing disabilities or premature death. In the case of idiopathic *Harlequin* ( "Glossary of terms" ), excessive internal body temperatures can result in asymmetric sweating, and flushing of the face and upper thoracic region of the body (Hojo et al. 2011).

Heat stress often occurs when the human body fails to cool down normally through sweating, resulting in body temperatures way above the usual average body temperature (*ca*. 37 °C). Symptoms of heat stress include heat rash, heat cramps, and in extreme cases, heat exhaustion (Li et al. 2020). Heat stress has also been shown to induce the production of heat stress proteins (HSP 27, HSP 47, and HSP 90) which elicit abnormal secretion and deposition of extracellular matrix (ECM) in the lung (Zhang et al. 2021), which in turn may result in the development of DUA like idiopathic pulmonary fibrosis (Kliment et al. 2010). The increase in global temperatures caused by climate change will no doubt increase the prevalence of heat stress (Li et al. 2020).

Glaser et al. (2016) evaluated the effect of heat stress (emanating from climate change) on the incidence of chronic kidney disease (CKD) in rural communities around Central America and proposed that "… heat stress nephropathy (HSN) may be a major cause of CKD, representing an overlooked disease in neglected populations in hot communities."

## Geopathic stress and health

It has long been established that geopathic stresses (GS) impend some key morpho-physiological functions in the human body (Freshwater 1997). This is particularly true for functions linked to key energy systems (*the chakras, etheric body*, and *meridians*) (See "Glossary of Terms", this article for definitions) and electrical systems (brain, heart, and muscles) within the human body. Thankfully, though, living organisms have adapted to the natural vibrations (radiation) of the Earth which occur at a frequency of 7.83 Hz (Tătar 2016).

The word "geopathic" is a combination of two Greek terms: *geo* (of the Earth) and *pathos* (suffering/ medical disorder). During the early 1920s, researchers noted that GS was location specific, and as such industrial, residential, and recreational sites were to be located outside *geopathic stress zones* (*GSZ*), known also as geo-pathically disturbed zones, location disturbance or power zones (Dharmadhikari et al. 2011). Geopathic stress zones emanate from, among other things, weak electromagnetic field disruptions by underground deposits of coal, gas, or oil. Underground streams of water, as well as artificial structures particularly bridges, electricity lines, railway lines, and sewers, may also distort the earth's electromagnetic forces resulting in GS (Chafekar et al. 2012, Creightmore 2012). Geo-electromagnetic stress zones have been associated with the development of several medical disorders (Hacker et al. 2008). Geopathic diseases are therefore medical conditions whose onset and/ or progression are closely linked to distorted geo-electromagnetic forces (Tong et al. 2021).

How exactly geopathic stresses contribute to human ill-health is still a subject of extensive geo-medical research. Growing scientific evidence, however, suggests that geopathic stresses disrupt protein structures, offset pH balances, and moderate the electrical polarity of cell membranes (Nair 2017, Creightmore 2012, Hacker et al.

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2008). Additionally, they modify the electrical systems responsible for regulating brain, heart, muscle, and central nervous system functions (Tong et al. 2021). Prolonged exposure to geopathic stress therefore adversely affects homeostatic functions in the body thereby increasing our vulnerability to pathogenic infections, environmental pollution, and a host of other disease risk factors. Due to their adverse effects on the immune system, geopathic stresses also prolong healing and recovery from diseases (Hacker et al. 2008). Some DUA associated with geopathic stresses include myalgia encephalomyelitis, SIDS, and Parkinson's disease (Creightmore 2012).

## Environmental soil factors and diseases in the agricultural milieu

Soil can be a reservoir for a variety of disease-causing organisms for both plants and animals. Pathogens may be transmitted from the soil *via* insect vectors or by soil organisms such as nematodes.

Some recent studies support the observation that soil conditions can influence the occurrence and progression of several diseases through the activities of soil microorganisms. Factors that influence bacterial growth in the soil include: physical requirements such as oxygen availability, pH, and osmosis; sources of energy, carbon, and nitrogen; nutritional requirements; and growth determinants including amino acids, purines, pyrimidines and vitamins that a cell must have for growth but cannot synthesize its own (Rousk et al. 2011). In the case of virus survival in the soil, temperature, and virus adsorption to soil appear to be of paramount importance (Huang et al. 2005).

Below are a few classic cases of soil-borne diseases and important soil environmental conditions that favor their prevalence; a relationship that we still do not fully understand.

## The mysterious prion diseases

Prion diseases are a group of rare and deadly neuro-degenerative brain disorders common among humans and a few mammals. These fatal and progressive degenerative disorders include bovine spongiform encephalopathy (BSE) (cattle), Creutzfeldt-Jakob disease and kuru (humans), chronic wasting disease (CWD) [deer family (cervids)], scrapie (sheep and goats) and transmissible mink encephalopathy (TME) (mink), (Greenlee et al. 2015, USCDC 2018).

Less than two decades ago, the aetiological agents for TSEs had not been fully characterized, but recently available evidence, suggests that prions (protein-containing particles) are the aetiological agents of TSEs (Ma 2012, Kuznetsova et al. 2020, **Prusiner 1998**) and that a mal-folded variant of the host-encoded prion protein (PrP) comprises the major, if not the only part, of the prion (Lathe et al. 2020).

## Attachment of prions to soil particles

Several studies, including the use of laboratory experiments and epidemiological modeling, have shown that prion-induced diseases, particularly scrapie, and CWD, can easily be transmitted through secondary environmental routes (Zabel et al. 2017, Saunders et al. 2012). A few years ago, Smith et al. (2011) noted that soils act as a reservoir for scrapie and CWD agents, thus allowing their persistence in the environment for prolonged periods. We now know, for instance, that some local soil types vitally determine the incidence of prion-induced diseases by serving as potential exposure routes and/or reservoirs for prions (Kuznetsova et al. 2020, Johnson et al. 2006, Saunders et al. 2011).

Animals habitually ingest soil. Humans inadvertently, but also sometimes deliberately, ingest soil, *cf*., the phenomenon of "Geophagy" which is very common in Africa. Prions can attach to and replicate on different soil minerals (Johnson et al. 2006). Epidemiological modeling by Saunders et al. (2012) has led to the inference that soil parameters such as soil texture possibly determine the prevalence of prion disease. Observations from these epidemiological modeling are buttressed by imperial evidence that showed marked differences in prion interactions with different soil types, particularly prion-soil adsorption as well as soil-bound prion replication (Kuznetsova et al. 2020). Yuan et al. (2022) developed a new ultra-sensitive and efficient method for CWD prion recovery and quantification from various physical materials, such as glass, stainless steel, and wood, an innovation in prion detection that will be useful across many settings and applications.

## Prion research in Africa

Among the few reported researches as of 2020 on prion disease occurrence in Africa, or accounts by researchers in Africa, are those by Obi et al. (2008), who documented a narrative review of the subject; Teferedegn et al. (2019), whose work on the significance of prion-related scientific inquiries in Ethiopia also considered the management of livestock, food safety, quality, and security; Babelhadj et al. (2018), who reported the detection of novel prion disease (*Camelus dromedarius*) in Algerian dromedary camels for the first time; and WOAH (2019) who reported on the prevalence of camel prion disease (CPD) in Algeria and Tunisia.

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## Other examples of soil-related diseases in Africa, having uncertain aspects of their pathology

### (i) Rift Valley Fever



Rift Valley fever (RVF) was first observed in 1931 among sheep raised on a farm situated along the Rift Valley, Kenya (Daubney et al. 1931). The viral disease is most prevalent in sub-Saharan Africa among buffalo, cattle, goats, sheep, and camels and can be contracted through contact with infected animals, body fluids, tissues, or through bites from infected mosquitoes (Fig. 3).

Williams et al. (2016) evaluated the 2008-2011 RVF outbreaks in South Africa and noticed that continuous and widespread seasonal rainfall in the country caused soil saturation and flooding of *dambos* (seasonally flooded depressions), which in turn elicit RVF outbreaks. Integration of soil saturation and rainfall statistical data into models designed to predict RVF outbreaks resulted in the accurate identification of risk factors in approximately 90 % of cases, within roughly a month before the epidemic occurs. Findings from the study also suggested that irrigation accounted for the remaining 10 % of outbreaks.

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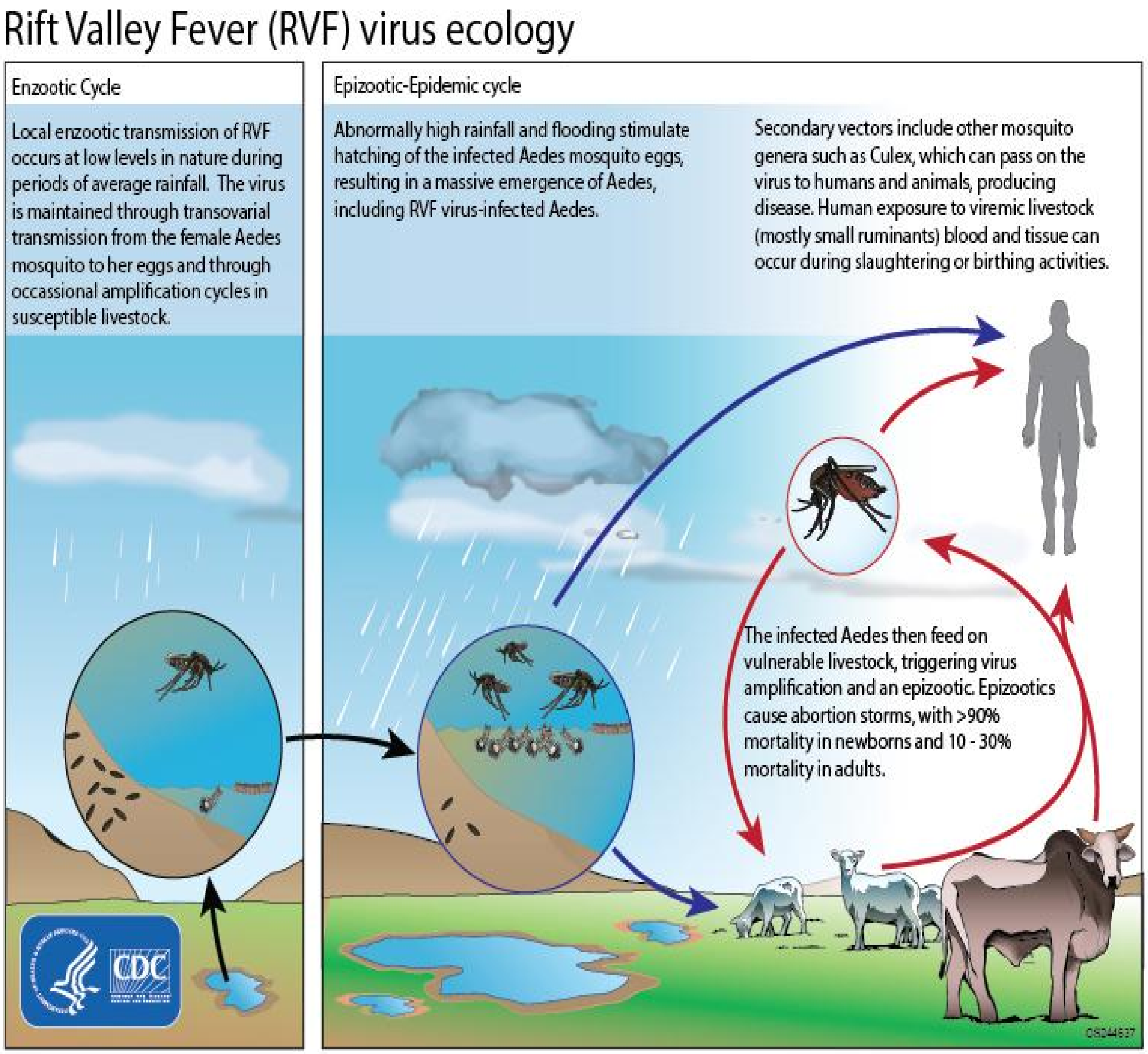


**Fig. 3. The Rift Valley Fever virus ecological cycle [Greenhalgh (2015)].**

Numerous other recent studies exist on the outbreak of RVF in Africa and its impact on animal and human health (Javelle et al. 2020, Petrova et al. 2020), but despite the magnitude of research effort exerted on the subject, not much is known about the influence of environmental factors, especially the nature of the soil (soil conditions, soil characteristics, soil parameters), have on the aestivation (state of dormancy) of the virus. The research efforts of Verster et al. (2020), for instance, were but earlier recorded attempts to pre-determine areas susceptible to RVF livestock mortality from soil properties, which only served as a basis for comprehensive research on the relationship between mosquitoes, soil, and the Rift Valley fever virus. These authors (Verster et al. 2020) appropriately recommended that: “Future research should include other environmental components such as vegetation, climate, and water properties as well as correlating soil properties with floodwater *Aedes* spp. abundance and Rift Valley fever virus prevalence.”

### (ii) Valley Fever

Valley Fever (VF) is a lung disease resulting from the inhalation of air contaminated with spores of the fungi, *Coccidioidomycosis* (*cf.* Rift Valley Fever). In some cases, individuals infected with the pathogenic fungi become asymptomatic, though the most usual clinical symptoms of the disease are akin to those of flu and/ or pneumonia. The soil-borne fungus that causes VF (*Coccidioides immitis* and *Coccidioides posadasii*) occurs in different parts of the United States, where roughly 10,000 cases are reported yearly, mostly from the states of Arizona and California (USCDC 2020b). The extent of Valley Fever prevalence in Africa is not reported in the literature, but that does not confirm its absence. This brief overview also serves to obviate any confusion with Rift Valley Fever which is most commonly found in Sub-Saharan Africa.

A significant part of the life cycle of *Coccidioidomycosis* is spent in the soil. Frank et al. (2010) studied the habitat of this fungus and developed a systematic model for identifying factors contributing to the spread and survival of the fungus, based on analyses of long-term weather data in the Tucson area (USA). The work revealed that some of the factors affecting the survival and establishment of new *Coccidioidomycosis* colonies included geology, soil (texture, moisture content, temperature), and wind (direction and intensity). These observations, together with other supporting empirical evidence, demonstrated that both environmental, soil, and geological factors control the spatial distribution of the diseases. The model developed by Frank et al. (2010) identified factors that controlled the distribution of actual infection sites and offered important information useful in mapping possible infected sites and measures needed to control the spread of infectious diseases.

### (iii) Ticks

Naicker (2011) reported soil moisture as an important factor influencing the growth of *ticks* (small blood-sucking arachnids), with high mortality rates closely linked to arid conditions and high soil evaporation rates (Valcárcel et al. 2020). *Hyalomma ticks* (vectors for *Crimean-Congo hemorrhagic fever*), generally survive better in arid conditions than other ticks species (Duygu et al. 2018). A comprehensive study of interactions between changing climatic conditions and the occurrence of Crimean-Congo Haemorrhagic fever was done by Nili et al. (2020).

### (iv) Anthrax

The distribution of *Bacillus anthracis* (the bacterium that causes anthrax) spores has also been shown to correlate with the composition of the soil. Hugh-Jones et al. (2009) noted that optimal soil conditions (high organic content, alkaline (pH > 6.1), and high calcium conditions) are necessary for the spores to successfully survive. According to Naicker (2011), susceptible vertebrate hosts and certain human factors are also requirements for disease to occur.

## Geochemical variables and disease

Several determinants influence the behavior of trace geogenic elements as they pass through biological systems. Before chemicals enter biological systems, factors such as speciation, soil pH and salinity are of paramount importance, while dosage, chemical profiles, bio-accessibility, and bio-availability become very important when the chemicals are within living organisms (Fig. 4).

In addition, numerous geochemical factors can modulate human immunity. An understanding of the geochemical involvement in human immune system development and maturation is necessary for us to be able to tackle particular aspects of diseases (*cf.*, DUA), such as understanding their aetiology and identifying effective measures needed to minimize their epidemiological impacts.

The aforementioned factors should be linked to key host factors, particularly age, gender, genetic profile, and body size, which mainly influence the adsorption, uptake, and absorption of geo-chemicals by the human body. It is therefore plausible that a deeply rooted understanding of these geo-environmental variables will, to some extent, provide a better understanding of the aetiology of some DUA. The amalgamation of all related empirical data into an interconnected vision would help illustrate how

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geochemical variables can have long-lasting impacts on the human immune system, and how this impact can, in turn, have beneficial or potentially lethal effects.

The role of geochemical variables as causal co-factors of DUA has been extensively reviewed by Davies (2022). Here, only a cursory overview is presented by way of a few selected examples



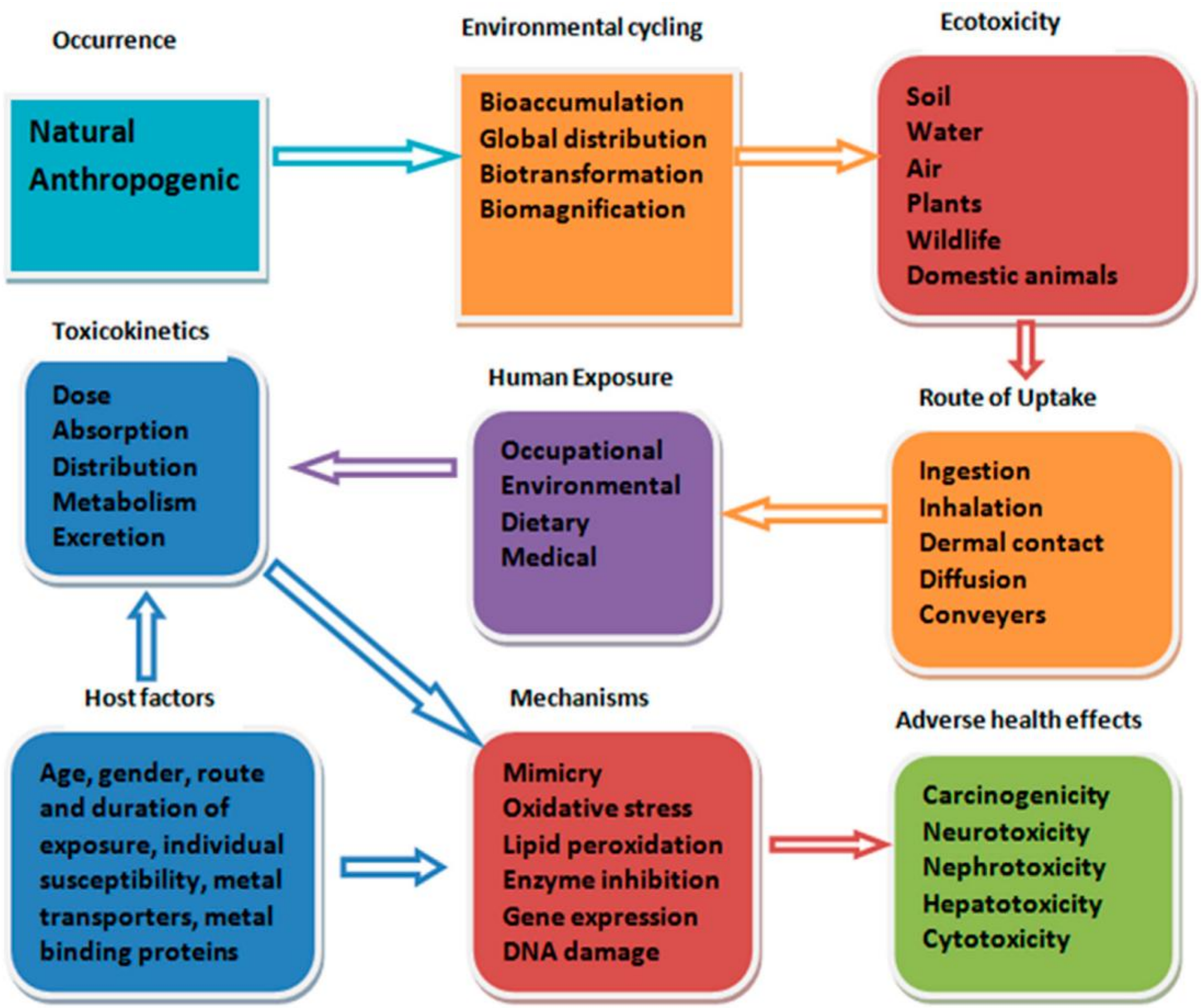


**Fig 4. Schematic of routes of exposure, from source to outcomes for metal fluxes in humans [Anyanwu et al. (2018)].**

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## Chemical aspects and toxicity of mineral dusts

Natural dust originates from several sources including dust storms, geo-climatic events (typically, volcanic eruptions), landslides, earthquakes, soil erosion, or deserts (Cook et al. 2005). Dust particles may also be liberated or re-suspended through anthropogenic activities such as farming, construction, carving, engraving, mining, and moving automobiles**.** Intra- and inter-continental travel of dust particles has been previously reported, with some reports (Moulin et al. 1997) suggesting that > 1 billion tons of dust are transported every year from African deserts to other parts of the world. The Saharan dust storm, for instance, is known to be mobilized in Australia, the Americas, the Caribbean, and southern Europe (Prospero et al. 1986). It has also been reported that dust particles can travel from Takla - Makan desert in China to the French Alps (> 20, 000 km) in just over a week (Grousset et al. 2003).

Natural dust contains a mixture of chemical entities with diverse pathological effects. Some of the common constituents of dust are silicates and iron (Cook et al. 2005). The pathophysiological effects triggered by mineral dust depend on several factors including the chemical profile, size, shape, and duration of exposure to dust particles (Derbyshire 2007). Once inhaled, minerals in dust can generate potent free radicals which can potentially cause oxidative damage to several tissues in the human body.

Volcanic dust contains an assortment of chemically diverse and biotoxic chemical entities including arsenic, copper, lead, mercury, cadmium, and zinc which could easily contaminate the air, water bodies, soils, and food chains (Cook et al. 2005).

## Ionizing radiation exposure

Uranium, which is mined in some Sub-Saharan African countries (e.g., Niger, Namibia, and South Africa), has unstable nuclei which can disintegrate to form naturally occurring radioactive isotopes such as radon-222, radium-226, thorium-230, and uranium-234 (Rajkhowa et al. 2021). Although most radiogenic minerals occur in sub-lethal concentrations in the lithosphere (earth's crust), natural and anthropogenic activities may result in the geological redistribution and increased concentration of these radioactive materials in specific geographical locations. Mao et al. (2020) demonstrated that, on a global scale, the main sources of U contamination are mining (41.1 %), groundwater (39.7 %), phosphate fertilizers (7.6 %), nuclear facilities (7.4 %) and military activities (4.4 %).

Since naturally occurring radiogenic materials are ubiquitous, we occasionally consume small sub-lethal quantities, most of which the body, thankfully, can successfully excrete (Rahman et al. 2020). However, prolonged exposure to radiogenic materials may increase the concentration of these materials in living tissues beyond sub-lethal levels. As radioactive waves pass through living tissues, they emit subatomic particles that alter the structure and functionality of molecules found within these tissues (Rajkhowa et al. 2021). Consequently, radiogenic materials have the inherent ability to induce apoptosis, autoimmunity, oxidative stress, and molecular and tissue damage. Since radioactive minerals have been shown to have toxic effects on human bones, lungs, kidneys, and reproductive system (Rahman et al. 2020), it could be inferred that these minerals possibly play a crucial role in the development of some DUA, particularly IPF, CFS, SIDS and UC. Future research should also explore the potential contribution of radiogenic minerals accumulated in organelles to the pathogenesis of DUA. Since some radioactive chemical elements (e.g. uranium) were found in umbilical cords and human semen (McDiarmid et al. 2019, Guo et al. 2020), some infant and juvenile idiopathic diseases may also be caused by pre- and/or post-birth exposure to radioactive material.

## Autoimmune diseases (ADs)

An autoimmune disease (AD) belongs to a heterogeneous group of chronic conditions involving the attack of the body's immune system by healthy body cells. Their exact aetiopathogenesis is still not well understood (Getts et al. 2020).

Several trace elements are needed for the immune system to function properly. These include Cu, Zn, and Se. It has long been known (Beck 1999) that both sufficiency and insufficiency of these elements can adversely impact several aspects of the adaptive, innate, and passive human immune system.

## Developmental immune-toxicity

The immune system is often vulnerable to toxicants during both the prenatal and perinatal phases of human life. The term *developmental immune toxicity* (DIT) is defined as environmentally-induced abnormal developments of the human immune system. This occurs as a result of exposing the immune system to toxic agents (e.g., toxic metals/metalloids) during embryonic and fetal development, resulting in adverse health outcomes.

Many changes occur in the immune system over a life span, maturing gradually from late childhood to early adulthood, and weakening slowly as old age beckons (Goenka et al. 2015, Simon et al. 2015). Each life stage is characterized by distinct immune features resulting in distinct variations in the nature, frequency, and severity of infections with age (Nicholson 2016, Rodriguez 2017).

Research on DIT has received a great deal of attention globally, not least in Africa, with the realization that a multitude of frequently occurring chronic diseases is associated with dysfunctional immune systems.

## Immune System Research in Africa

It is now well established that the immune system can be highly active in some people but much less so in others; and that there are important determinants, according to evolutionary theory, that account for these discrepancies. Such observations determine the safety of organisms against pathogens and could explain why specific groups of people might be vulnerable to diseases such as COVID-19, which was quite popular in the West than in Africa.

In Africa, perturbations in immune system function in early life have been observed in many instances to have significant short-term effects. The season in which one is born, genetic disposition, and diet for example determine humoral responses to *pertussis* (whooping cough) vaccination (Akinola et al. 2018, Zimmermann et al. 2019). Observations by Paynter et al. (2015) suggest that in West African children, cell-mediated and humoral immune responses decline significantly during rainy seasons.
Lisse et al. (1997) and Moore et al. (2008) have also shown that in West Africa, birth during the wet season increases the proportion of T-cells in the CD8+ compartment, decreasing the CD4+:CD8+ ratio. In rural Gambia, adult mortality rates have in some cases been closely related to the season in which the deceased was born and pathogenic exposure during early childhood when the immune system was still developing (Moore et al. 2008).

Recently, studies by Ayanshina et al. (2020) have focused on how changing weather patterns impact host immune response to infections by the novel COVID-19 and how humidity, sunlight, and precipitation influence host susceptibility to infectious diseases (e.g. influenza) in Nigeria and other developing countries. These researchers (Ayanshina et al. 2020) have also stressed the importance of understanding the influence of changing weather patterns on transmission rates and in improving immune response to the novel COVID-19 virus by administering vitamin supplementation to patients during the rainy seasons in Nigeria (Nigeria has two rainy seasons; the first rainy season runs from March to July; while the second one runs from early September through mid-October).

## Sudden infant death syndrome (SIDS) or crib death

There are myriads of examples of diseases aetiology that are thought to bear some links to the geochemical environment; in particular, the characteristics of geochemical migration of metals/metalloids and their isotopes (e.g., chemical form, migration pathways) before they enter the body, and the dynamics of their reactivity within the body (e.g., bioavailability and efficiency of adsorption, and transport), including their involvement in metabolic processes. Readers interested in a discussion of these links are referred to the work of Davies (2022). A brief overview of one of the more intriguing of these proffered links is given for '*sudden infant death syndrome*' or crib death.

In medicine, there are cases where extensive post-mortem investigations can fail to reveal the true cause of death (Tiemensma et al. 2012). *Sudden infant death syndrome* (SIDS) refers to the unexplainable death of infants who are a year old or younger. The syndrome seems more prevalent in developing than in developed countries. For instance, a recent study revealed that the prevalence of SIDS in South Africa was approximately 0.63 deaths/1 000 live births compared to international rates ranging from 0.05 - 0.39/1000 live births (Winterbach et al. 2021). Sudden infant death syndrome is a multifunctional syndrome, without a known aetiologic mechanism.

One of the most important functions of trace elements in the human body is to maintain the integrity and function of cells. They also assist in preventing oxidative tissue damage by acting as antioxidants or co-factors of redox enzymes. Empirical evidence suggests that deficiencies of trace elements, particularly Se can contribute to SIDS pathology (McGlashan et al. 1996). Selenium is an essential component of *glutathione peroxidase* (GSH-Px), an enzyme that plays a key role in the antioxidant defense mechanisms of the human body. The enzyme catalyzes the reduction of the metabolic product hydrogen peroxide, thereby preventing the formation of *reactive oxygen-centred radicals* (Brown et al. 2001). Ford (2000) hypothesized that a deficiency of Se and/or other trace elements that participate in redox reactions may lead to severe oxidative tissue damage, which in turn could contribute to the pathogenesis of SIDS.

Different geo-environmental factors determine the concentration of Se in the soil. High Se concentrations in soil are common in areas with predominantly phosphate rocks, organic-rich black shales, and coals (Fordyce 2013). However, the concentration of Se in plants and food chains is determined mainly by the mineral's bioavailability. Studies in Malawi, for instance, showed

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that lower soil pH results in limited soil-crop (maize) transfer of Se (Hurst et al. 2013, Ligowe et al. 2020). The soil in this regard fails to supply adequate amounts of the elements to plants, including staple crops, thus increasing the risk of dietary Se deficiency.



## Disease clusters real

In epidemiology, the word *cluster* can be used to refer to different things (Antó et al. 2001, Porta 2008, Dolk et al. 2015, Drossman 1999, PHE 2019). However, the most common thread through all popular definitions is an integration of the following aspects: (i) an extraordinarily huge combination of disease incidences (observed or predicted), in addition to the number expected by random occurrence; (ii) spatial and temporal aggregation of events or diseases. Porta (2008)'s definition encapsulates all of these features.

## Investigating Disease Clusters

Investigations of disease clusters often begin with determining whether a supposed cluster is indeed a true cluster. Allied health professionals, industrial managers, and other stakeholders can address community concerns as well as determine the appropriate level of scientific study. Epidemiologists use different systematic techniques to gather, organize, and analyze available health data. This approach allows scientists to definitively identify relevant risk factors thus revealing the underlying aetiology (*cf.*, DUA).

In recent years, modern cluster assessment techniques have been widely utilized worldwide to the extent that epidemiological and statistical analysis of clusters emerged as an important field in several international journals.

## Clusters of DUA

Rodo et al. (2016) reviewed links between environmental parameters and human ailments with poorly understood etiology. They reported numerous examples of emerging medical conditions that fall under the category and remarkably shared some similar epidemiological characteristics, "… such as their appearance in 'clusters' (grouped geographically; and temporarily progress in non-random sequences that similarly repeat every year)''. Their trends also change simultaneously within regions of a given country and among different world regions. The list by Rodo et al. (2016) included: ANCA-associated vasculitis, childhood-acquired coronary diseases, a few inflammatory diseases, Henoch-Schönlein purpura, Kawasaki disease (KD), and rheumatic diseases (vasculitides).

## Disease cluster research: Africa

Diseases of unknown aetiology clusters sporadically occur in different parts of Africa. However, the necessary scientific framework needed to investigate disease clusters in African countries barely exists, explaining why very few disease cluster investigations in the continent are reported in the literature. The few reported studies were conducted on an individual/ independent basis, each one following guidelines stipulated by the United States Centres for Disease Control and Prevention (US CDC) in 1990 (Mudau et al. 2014, Darikwa et al. 2020). Although the US CDC protocol (USCDC 1990) is quite useful, it does not, however, take into account data accessibility, data quality, and communication needs in African countries.

As Davis (2001) noted, "Frequently, vertically oriented disease surveillance programs at the national level and above in Africa often result in too much paperwork, too many different instructions, different terminologies, too many administrators, and conflicting priorities…" The lack of standardized documents for specific countries in the region has intermittently created a great deal of misperceptions, making information dissemination among stakeholders very difficult. Standardized guidelines will provide a framework for effective education, communication, and support for public health investigators and other stakeholders. These suggestions were comprehensively discussed by Mudau et al. (2014) and Darikwa et al. (2020).

A widespread increase in public awareness of environmental risk factors associated with DUA might spur investigators to vigorously follow up on reported disease clusters.
The co-clustering of DUA with trace element/metal deficiency or toxicity is observed (but not fully investigated) in many instances in Africa. The web of interactions producing such clusters and their geospatial associations are poorly understood and poorly researched at present. Regardless of being costly, multidimensional, and often inconclusive, studies of disease clusters should be encouraged, particularly for clusters prevalent in rural African populations, as they so often reveal the importance of the 'place factor' in disease causation; and potentially strong contributors to better diagnosis and therapy for DUA. Therefore, a paradigm shift in cluster response is advocated, for which new scientific tools for investigating cause-and-effect relationships in small populations need to be developed.

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## CONCLUSIONS

Biogeochemical cycles ensure a perpetual soil-human and/ or water-human flow of diverse geochemical substances. The concentration and bioavailability of these elements in nature vary from one geographical region to the other, and both factors also determine the extent to which geogenic minerals flow into the ecosystem constituting human food chains. In the present study geogenic biotoxins, radiogenic minerals, micronutrient deficiencies, and metal toxicity emerged as plausible factors responsible for the onset and progression of several IDs. Natural dust, geopathic forces, and heat stress were also implicated. The cyclicity of some IDs also suggested a pathogenic aetiology, thus linking IDs to seasonal variations in weather patterns. Based on the accessed literature, there is limited data on the effects of geo-environmental variables on the pathogenesis and progression of IDs in Africa. This could be attributed to several factors including under- and/ or misdiagnosis of these diseases. Poor documentation of IDs hinders efforts to develop novel and sustainable diagnostic, therapeutic, and preventive measures against these deadly medical disorders. This indicates an urgent need for more extensive epidemiological and pathological studies on IDs in Africa. However, for meaningful progress to be made in these investigations, healthcare professionals investigating disease clusters should, perhaps team up with Medical Geologists, a research collaboration that rarely exists in most developing countries

### Recommendations for future studies

Improving knowledge in the area of pathogen-geo-environmental interactions using advanced investigating techniques would be instrumental to the development of novel therapeutic measures (diagnostic tools) against DUA and other enigmatic disease occurrences in Africa. A comprehensive study of *non - infectious disease* clusters could help scientists develop credible and testable hypotheses. Furthermore, for diseases with poorly understood aetiology that are prevalent in specific geographical regions, more attention should be given to the geo-environmental hypotheses, and an examination made of their scientific strength. Further research is also needed to unravel geogenic materials associated with specific human pathogens and the extent to which interactions between the two influence the pathogen's virulence and survival *in vivo*. Lastly, complex humanitarian emergencies including certain DUA and communicable disease outbreaks are a common threat to public health in Africa. Extensive studies on the risk of disease epidemics in complex humanitarian emergencies are therefore urgently needed, and the composition of investigating teams reviewed, to include Medical Geologists.

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## COMPETING INTEREST

The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing the article.

## ABBREVIATIONS AND THEIR MEANINGS

**AAA:** Abdominal aortic aneurysms
**AAD:** Autoimmune Addison's disease
**AD:** Autoimmune disease
**H5N1:** Avian influenza virus
**BSE:** Bovine spongiform encephalopathy
**CKD:** Chronic kidney disease
**CWD:** Chronic wasting disease
**DIT:** Developmental immune-toxicity
**DUA:** Diseases of unknown aetiology
**ECM:** Extracellular matrix
**ENSO:** El Niño Southern Oscillation
**GS:** Geopathic stresses
**GSZ:** Geopathic stress zones
**GSH-Px:** Glutathione peroxidase
**HSN:** Heat stress nephropathy
**ID:** Idiopathic diseases
**IFP:** Idiopathic pulmonary fibrosis
**RH:** Relative humidity
**SIDS:** Sudden Infant Death Syndrome
**TME:** Transmissible mink encephalopathy
**TB:** Tuberculosis
**RVF:** Rift Valley fever (RVF)
**USCDC:** United States of America Centre for Disease Control and Prevention
**VF:** Valley Fever

### Author contribution

TD conceived the original idea, MV wrote the manuscript, KKN, TD, and RMC edited the manuscript, provided resources, and supervised the project.

### Opinion disclaimer

The views expressed in this manuscript are those of the authors and do not in any way reflect the official position of Mangosuthu University of Technology.

## GLOSSARY OF TERMS

- *Acute disease/illness* is a medical condition that develops suddenly and has severe, short-lived symptoms (often less than 1 month).
- *Bias:* A term used in statistical analysis to describe scenarios whereby statistical data are overestimated or underestimated, for one reason or the other.
- *Chakra* (pl. *chakras*), refers to various focal energy centers of the human body that are important in traditional Hinduism meditation.
- A *chronic condition* describes a medical condition whose symptoms can manifest for at least 3 months during which the patient requires constant medical attention. Classic examples of chronic diseases include asthma, cancer, diabetes, Lyme disease, acquired immunodeficiency syndrome (AIDS), and hepatitis C.
- *Communicable/infectious diseases* are those transmitted by pathogens (bacteria, fungi parasites, and viruses).
- A *confounding factor (confounding variable or confounder)* is a third variable in a scientific investigation that can influence both the dependent and independent variables.
- The etheric body (*ether-body* or æther *body)*, as used in the Hindu and Buddhist traditions, refers to the subtle energy / physical body visible to the naked eye.
- *Geo-climate*: A climate that has been affected by a geological event (typically a volcano).
- *Granulomatous disease* is a genetic disorder whereby phagocytes (white blood cells) fail to kill some pathogens e.g. bacteria, fungi, or viruses.
- *Harlequin syndrome* is a medical disorder characterized by involuntary unilateral facial flushing and sweating.
- *Health risk* is defined as the possibility that exposure to a given substance would increase the chances of someone being harmed or developing a particular disease.
- *Immuno-potentiation* represents the shifting to increased immune response.
- *Immuno-suppression* describes a state of weakened immunity.
- *Medical Geochemistry* is considered by some to represent a branch of Medical Geology. Studies in this field "… have focused on how chemical elements in rocks, soils, and sediments are transmitted *via* water or vegetation into the food chain, and how regional geochemical variations can result in 'disease clusters' either through dietary deficiency of essential elements or dietary excess of toxic elements." (Plumlee et al. 2006).
- *Metallome:* Refers to the distribution of metal ions within a cell.
- *Neurodegenerative disorders* refer to illnesses that involve the death of certain parts of the brain.
- *Non-communicable diseases* are those that are not transmitted by pathogens.
- *Melatonin* is a hormone that regulates the sleep-wake cycle in most animals.
- *Pathogenesis* refers to the onset and development of a particular disease.
- *Pathogenicity* refers to the inherent ability of an infectious agent to cause a disease.
- *Reactive oxygen species* (ROS): A highly reactive, unstable chemical containing oxygen. Accumulation of ROS in the cell may result in oxidative stress which in turn may lead to ill health.
- A *syndrome*: a group of symptoms which usually appear together and are linked to a particular medical disorder.
- *Toxicological Geochemistry*, regarded by Plumlee et al. (2006) as a somewhat narrower field of Medical Geochemistry, which focuses on deleterious interactions between geogenic materials and human body fluids, and how such interactions may trigger the development of some diseases.
- "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."

**NB**: All definitions were obtained from https://en.wikipedia.org unless otherwise stated.

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***Review Article***



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