Predicting disease onset in clinically healthy people

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ABSTRACT
Virtually all human disease is induced by oxidative stress. Oxidative stress, which is caused by toxic environmental exposure, the presence of disease, lifestyle choices, stress, chronic inflammation or combinations of these, is responsible for most disease. Oxidative stress from all sources is additive and it is the total oxidative stress from all sources that induces the onset of most disease. Oxidative stress leads to lipid peroxidation, which in turn produces Malondialdehyde. Serum malondialdehyde level is an additive parameter resulting from all sources of oxidative stress and, therefore, is a reliable indicator of total oxidative stress which can be used to predict the onset of disease in clinically asymptomatic individuals and to suggest the need for treatment that can prevent much human disease.

KEY WORDS: disease prediction; disease prevention; disease mechanism; environmental disease; infectious disease

Introduction
The incidence of disease world wide is continually increasing. Though people are living longer, we are also living sicker and with increasing numbers of multi-morbid diseases (Murray et al., 2015; Zeliger, 2014; Wallace & Salive, 2013; 2012; Pritchard & Rosenorn-Lanng, 2015). As an example of this phenomenon, in the United States, the percentage of people with multi-morbid diseases has increased from 37.2% of the population in the year 2000 to 45.3% of the population in 2010 (Freid et al., 2012).

Numerous diseases have reached epidemic and pandemic proportions in the past two generations. The dramatic increase of environmental disease prevalence with time can be seen from plots of disease percent increases versus time, from 1940s to 2010. Such plots produce hyperbolic curves as shown in Figure 1. Examples of diseases that fit this plot include autism and autism spectrum disorders (Zeliger, 2013b), type 2 diabetes (Zeliger, 2013), obesity (Wang & Beyoun, 2007) childhood cancers (Parkin et al., 1988), onset of dementia and other neurological diseases (Zeliger, 2013b), and both male and female infertility (Colborn et al., 1996). The slopes of these curves exactly correspond to those of plots for chemical production and use versus time, as exemplified by data for syntetic chemical production (Neel & Sargis, 2011), increased pesticide use (Chen & McCarl, 2001), increased world wide energy production from combustion of fossil fuel use, increases in air and water pollution (U.S. Energy Information Administration, 2014), and increases in pharmaceutical use (Kantor et al., 2015).

Free radicals are essential for homoeostasis and are generated as byproducts of normal metabolic cellular activities (Bhattarcha et al., 2014). Oxidative stress (OS) ensues when the production of free radicals, reactive oxygen species (ROS) and reactive nitrogen species (RON) occurs at a pace faster than the body’s antioxidant production. Exposures to toxins as well as the presence of disease results in increases in these free radical species and produce the oxidative imbalances in cells that produce OS. OS is, as is shown below, directly or indirectly, the cause of virtually all disease. It leads to attack on macromolecules, induction of cell death via apoptosis or necrosis and structural tissue damage, including lipid peroxidation (LP) (Lorente, 2013).

OS is directly responsible for non-communicable environmental disease (ENVD) (Davies, 1995; Zeliger & Lipinski, 2015; Bhutia et al., 2014), and indirectly responsible for the spread of infectious disease (INFD) via undermining of the immune system (Zaki et al., 2005; Valyl-Nagy & Dermody, 2005; CDC, 2015). The many causes of oxidative stress in humans include: absorption of exogenous toxic chemicals and chemical mixtures (Zeliger, 2003; Zeliger & Lipinski, 2015); exposure to...
OS causes disease via one of 4 pathways. These are: protein oxidation, DNA oxidation, lipid peroxidation and oxidative modification of sugars (Ogino & Wang, 2007). Of these, lipid peroxidation is the most indicative, as cell penetration by toxic agents initially requires the breaching lipophilic cell membranes (Zeliger, 2003; Zeliger, 2011; Zeliger & Lipinski, 2015). Such reactions produce fatty acid degradation fragments that are biomarkers for the presence of OS. Malondialdehyde (MDA) is the biomarker most reliably used to indicate the presence of disease and toxic exposure (Nielsen et al., 1997; Lorente et al., 2013; Tangvrasittichai et al., 2009; Sudha et al., 2014). Elevated levels of MDA have been shown to be present in the serum of patients with elevated OS and increased concentration of MDA accordingly is widely used as an indicator of the presence of disease in humans, with the severity of disease being a function of MDA level in a dose response relationship (Nielsen et al., 1997; Zhu et al., 2005; Romeau et al., 2008; Aflanie et al., 2015; Agarwal et al., 1987; Ayala et al., 2014).

As elevation of serum MDA can be caused by exposures as well as by disease, it is proposed here that serum MDA levels can be used to predict the onset of disease in people who are seemingly clinically healthy.

**Methods**

The hypothesis reported here is based upon a literature review of numerous published studies, both by this author and many others on oxidative stress and disease and on biomarkers for OS.

**Results**

**Causes of OS**

There are numerous causes of oxidative stress. These include: exposures to chemicals, heavy metals, particles, fibers, foods and food additives, pharmaceuticals, ionizing and non-ionizing radiation, psychological stress, physical trauma and the presence of other disease (Zeliger & Lipinski, 2015). Table 1 contains a representative list of these causes of OS.

**Chemicals**

Chemicals that cause OS include polychlorinated biphenyls (PCBs), dioxins and furans, widely distributed in the environment as a result of combustion, industrial processes and commercial applications; organochlorine pesticides such as DDT, polybrominated diphenyl ethers (PBDEs), commonly used as fire retardants in children’s clothing and upholstery; phthalates, widely used in cosmetics and other personal care products; bis-phenol A, found in plastics used as eating utensils and food containers; by products in drinking water resulting from disinfection of potable water; polynuclear aromatic hydrocarbons, resulting from fossil fuel combustion and tobacco smoke; low molecular weight hydrocarbons such...
as benzene, toluene, xylene and hexane from gasoline vaporization and incorporation into adhesives; alcohol; paints and other products; heavy metals, including mercury, cadmium, lead, chromium, copper and others arising from mining and industrial usage; and numerous other species. (Patterson et al., 2009; Zeliger, 2014; Azeez et al., Adedara et al., 2014; Lodovici & Bigagli, 2011; 2015; Pan et al., 1987; Kambia et al., 2011; Yang et al., 2009; Kaur et al., 2014; Zeliger & Lipinski, 2015; Patil et al., 2006; Li et al., 2004; Zeliger, 2003; Zeliger, 2011; Pals et al., 2013; Bhattacharyya et al., 2014; Ayala et al., 2014; Doi & Uetsuka, 2012; Lodovici & Bigagli, 2011; Gong et al., 2013; PhamHuy et al., 2008; Luongo et al., 2015; Knaapen et al., 2004; Donaldson et al., 2005); (Veraldi et al., 2006; Schneider et al., 2008; Liu et al., 2009; Banerjee et al., 1999; Jeng et al., 2011; Bagaiktar et al., 2008).

**Chemical mixtures**

Until recently, the impacts of absorption of chemical mixtures have been largely limited to considerations of additive effects. It is now known, however, that exposures to mixtures of lipophilic and hydrophilic species facilitates the absorption of hydrophilic species that would otherwise not absorb and that exposures to such mixtures induces attacks on organs not known to be attacked by the individual components of such mixtures (Zeliger, 2003; Zeliger, 2011). It has been recently been reported that aromatic lipophilic species can also transport OS inducing heavy metals through lipophilic cell membranes (Zeliger & Lipinski, 2015). It is, therefore, to be anticipated that exposures to chemical mixtures will result in increased OS and in MDA serum levels in excess of those expected from exposure to the individual species that comprise such mixtures. An example of this phenomenon is the reported finding that exposures to mixtures of pesticides result in increased OS (Fukuyama et al., 2014).

Another effect of exposure to mixtures is contributing to meeting the hallmarks necessary for the onset of disease. Multiple hallmarks of aging (Meiners et al., 2014), cancer onset (Nahta et al., 2015), type 2 diabetes (Thiering & Heinrich, 2015), asthma (Delfino et al., 2013), cardiovascular disease (Li et al., 2015) and Alzheimer’s disease (Cabezas-Opazo et al., 2015) have been identified. In these studies, the authors conclude that different chemical exposures affect different specific hallmarks and that exposures to mixtures can account for the onset of disease. All of the chemicals identified in these studies are known to induce OS. What remains to be addressed are the effects of specific chemical mixtures on individual hallmarks of disease and their effect on OS when compared to the effects of the individual components of such mixtures. Given the constant exposure of humanity worldwide to multiple chemical mixtures, the parameters of such studies require careful planning in order to produce meaningful results.

**Particles and fibers**

Particles and fibers that cause OS include asbestos, used in automobile brakes, fire-retardant materials, and

| CHEMICALS                                      |
|-----------------------------------------------|
| Polychlorinated biphenyls                     |
| Organchlorine pesticides                      |
| Polybrominated diphenyl ethers                |
| Dioxins                                       |
| Furans                                        |
| Polynuclear aromatic hydrocarbons             |
| Low molecular weight hydrocarbons             |
| Phthalates                                    |
| Bis-phenol A                                  |
| Heavy metal ions                              |
| Disinfection by products                      |
| Lipid peroxidation products                   |
| Mycotoxins                                    |
| Air pollution                                 |
| Tobacco smoke                                 |
| Textile chemicals                             |

| PARTICLES AND FIBERS                          |
|-----------------------------------------------|
| Asbestos                                      |
| Silica                                        |
| Fly ash                                       |
| Synthetic mineral fibers                      |
| Nanoparticles                                 |

| FOODS AND FOOD ADDITIVES                     |
|-----------------------------------------------|
| Animal fats                                   |
| Processed meat                                |
| Red meat                                      |
| Fructose                                      |
| Artificial colors                             |
| Artificial flavors                            |
| Extraction solvents                           |
| Preservatives                                 |

| RADIATION                                     |
|-----------------------------------------------|
| Ionizing radiation                            |
| Ultraviolet radiation                         |
| 900 MHz radio frequency radiation.            |

| PHARMACEUTICALS                               |
|-----------------------------------------------|
| Antibiotics                                   |
| Antidepressants                               |
| NSAIDs                                        |
| TNF inhibitors                                |

| PSYCHOLOGICAL STRESS                          |
|-----------------------------------------------|
| Emotional stress, anxiety and depression      |
| Sensory offenders                             |
| Circadian cycle interruption                  |
| Sleep deprivation and insomnia                |
| Excessive heat exposure                       |

| PHYSICAL TRAUMA                               |
|-----------------------------------------------|
| Chronic traumatic encephalopathy              |
Heat insulators; silica resulting from mining; concrete formulations and grinding; fly ash that emanates from combustion of coal; synthetic fibers used in clothing; and nanoparticles from industrial processes, combustion and the deliberate production for use in industrial, consumer and pharmaceutical products (Donaldson et al., 1998; Ning et al., 2003; Deshpande et al., 2002; Browne et al., 2011; Jaurand & Pairon, 2011; Steenland & Stayner, 1997).

Diet and food additives
Ingestion of some foods gives rise to OS. These include processed meats and red meat (Bovalino et al., 2016; Bouvard et al., 2015); fructose from refined sugar and high fructose corn syrup (Lustig et al., 2015; Basaranoglu et al., 2015; Park et al., 2013); synthetic chemicals used as artificial food colors and flavors including preservatives such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), calcium propionate, triclosan, and parabens (Abdel-Salam et al., 2012; El-Wahab & Moram, 2013; Stevens et al., 2013; Cemek et al., 2014); solvents such as toluene used to extract flavors and colors from natural products and to produce synthetic food additives; and chemicals such as phthalates and bisphenol A used in food packaging and which leach out into foods. (Zeliger, 2011).

Radiation
OS is caused by exposure to ionizing radiation from x-rays, exposure to radioactive isotopes, ultraviolet radiation and microwave radiation; as well as by exposure to non-ionizing radiation such as that from 900 MHz radio frequency waves commonly used for cell phone signal transmission (Esmekaya et al., 2011; Semenkov et al., 2015; Tominaga et al., 2004; Dasdag et al., 2012; Kim et al., 2011).

Drugs and pharmaceuticals
Many pharmaceuticals, examples of which are: commonly prescribed antibiotics, antipsychotics, antidepressants, drugs used to combat hypertension and NSAIDs (including widely used acetaminophen), cause OS as do alcohol and recreational drugs (Kantor et al., 2009; Bhattacharyya et al., 2014; Neustadt & Pieczenik, 2008, Csoka and Szyf, 2009).

Psychological stress
Psychological stress is a common cause of OS (Ramanathan et al., 2002), as are exposures to sensory offenders, circadian cycle interruption, sleep deprivation and insomnia and excessive exposure to heat (Chaput et al., 2013; Halonen et al., 2015; Noguti et al., 2013, McEwen, 2006). Psychological stress is associated with reduced immune system function, higher incidence and greater severity of infectious disease (Aich et al., 2009). Psychological stress and OS are bidirectional with each a cause of the other (Bouayed et al., 2009). For example, increased OS makes one more susceptible to viral disease such as the common cold and infectious illness induces psychological stress (Cohen et al., 2015). Chronic psychological stress also induces chronic inflammation which mediates chronic disease and has been linked to cancer, diabetes, cardiovascular, neurological, respiratory and other diseases. (Salzano et al., 2014; Reuter et al., 2010; Khansari et al., 2009; McEwen, 2006; Semenkov et al., 2015).

Physical stress
Physical stress in the form of exposure to excess heat (Mujahid et al., 2007; Reuter et al., 2010; Kaldur et al., 2014; Kim et al., 2015), chronic inflammation (Khansari et al., 2009; Tremellen, 2008) or chronic physical trauma, an example of which is chronic traumatic encephalopathy (CTE) (Miller & Sadeh, 2014; Faden & Loane, 2015), all cause OS.

OS and disease
Oxidative stress has been associated with chronic inflammation and numerous diseases (Reuter et al., 2010). Table 2 contains a representative list of diseases known to be caused by OS. These include non-contagious environmental diseases (ENVDs), examples of which are: metabolic (Bhutia et al., 2014; Tangsvarasittichai et al., 2009; Yang et al., 2008; Zeliger, 2013), respiratory (Alsamarai et al., 2009; Corradi et al, 2003; Stupnytska, 2014; Zeliger et al., 2012), neurological (Davies, 1995; Baipai et al., 2014; Bulut et al., 2007; Zeliger, 2013b; Zeliger, 2015), endocrine (Torun et al., 2009; Vitale et al., 2013; Colborn et al., 1996), cardiovascular, (Boaz et al., 1999; Davies, 1995; Zeliger, 2013a; Neustadt & Pieczenik, 2008; He & Zuo, 2015; Kayama et al., 2015; Griendling & Fitzgerald, 2003), gastrointestinal (Mete et al., 2013; Suzuki H et al., 2012; Kim et al., 2012), musculoskeletal, (Mete et al., 2013; Suzuki H et al., 2012; Kim et al., 2012), urinary tract (Kurutas et al., 2005; Merendino et al., 2003; Aryal et al., 2007), kidney (Forbes et al., 2008; Adedara et al., 2014; Galle, 2001), liver (Adedara et al., 2014; Cichoń-Lach & Michalak, 2014; Webb & Twedt, 2008), skin (Bickers & Athar, 2006; Trouba et al., 2002; Okayama, 2005), immunological and autoimmune (Hughes, 1991; Jeng et al., 2011; Davies, 1995; Lou et al., 2013; Lou et al., 2013; Bashir et al., 1993; Kumagai et al., 2003; Kalkan et al., 2014; Zeliger et al., 2012; Zeliger et al., 2015), eye (Williams, 2008; Kruk et al., 2015), and periodontal diseases, (Liu et al., 2014), as well as obesity (Olusi, 2002; Sankhla et al., 2012; Jain & Chaves, 2011; Zeliger, 2014; Fernandez-Sanchez et al., 2011; Mann & Jain, 2015), and numerous cancers (Federico et al., 2007; Guven et al., 1999; Brown & Bicknell, 2001; Dillilough et al., 2012; Chole et al., 2010; Taysi et al., 2003; Salzman et al., 2009; Bitla et al., 2011; Reuter et al., 2010; Khansari et al., 2009). The list also includes infectious bacterial and viral diseases (INFDs) which are indirectly caused as a result of the undermining of the immune system by OS (Hughes, 1998; Bouhafs, 1999; Cemek et al., 2005; Zaki, 2005; Rajah & Chow, 2015).

OS does not directly cause infectious diseases, but does so indirectly by undermining the functioning of the immune system via immuno-suppression (Hughes, 1999; Akaike, 2001; Xu et al., 2015; Splettstoesser & Schuff-Werner, 2002). It is to be noted that all the chemicals
listed in Table 1 are immuno-suppressants (Veraldi et al., 2006; Patterson & Gerrmolec, 2006). These include: polynuclear aromatic hydrocarbons (Jeng et al., 2011), dioxins (Schneider et al., 2008), tobacco smoke (Arcavi & Benowitz, 2004), pesticides (Banerjee et al., 1999) and heavy metals (Liu et al., 2009). Phagocytes generated when the body responds to infectious agents cause further free radical generation resulting from lipid peroxidation, thus adding to OS (Bouhafs & Jastrand, 1999; Stossel et al. 1974). It has been reported that higher levels of OS further infectious disease in critically ill patients Andresen et al., 2006).

OS also leads to infectious diseases by impacting the actions of gut microbia. The following examples illustrate this: Air pollution (Salim et al., 2013), PCBs (Choi et al., 2010) and diets chronically high in fat (Qiao et al., 2013) increase OS in the gut causing membrane damage that leads to increased permeability and translocation of gut bacteria with ensuing disease (Guarner & Soriano, 2005). Though not a disease, malnutrition is also known to lead to OS and immune system malfunction (Darmon et al., 2006).

Obesity is a chronic low-grade inflammatory disease which gives rise to OS (Vandanmagasar et al., 2011; Karbownik-Lewinska et al., 2012; Liu et al., 2014) and predisposes the onset of illness (Stokes & Preston, 2015). Obesity increases the risk for numerous diseases via impact on the immune system. For example, it is associated with increased susceptibility to infections such as the flu (Olusi, 2002; Falagas & Kompoti, 2006; Jain & Chaves, 2011) and promotes the onset of metabolic syndrome and diabetes (Furukawa et al., 2004; Vu et al., 2015). OBS is indirectly responsible for shortened life spans, with death coming from subsequent diseases. It is estimated that OBS shortens life by between 8 and 14 years (Kitahara et al., 2014; Grover et al., 2014). The world-wide obesity epidemic is a recent phenomenon that corresponds to the exponential production and wide-spread distribution of synthetic chemicals, essentially all of which are known to induce OS (Bailie-Hamilton, 2002).

Obesity plays a key role in multi-morbidity of disease. The quantity of white adipose tissue (WAT) is dramatically increased with obesity. WAT serves as a collector of absorbed exogenous lipophilic chemicals, all of which are known to cause OS, obesity and disease. Diseases such as type 2 diabetes cause the absorption of exogenous lipophiles. Obesity is known to cause ENVDs and ENVD’s have been shown to cause obesity. This sets up what has been termed the OBESITY-LIPOPHILE-DISEASE triangle (Zeliger, 2014), which is depicted in Figure 2 and reproduced with permission. The interconnection between the three parameters of this triangle is as follows: Firstly, exogenous lipophilic chemical absorption causes environmental diseases. Conversely, environmental diseases, T2D, for example, cause the absorption of exogenous lipophiles. Secondly, obesity causes environmental diseases and environmental diseases cause obesity. Thirdly, exogenous lipophiles cause obesity and obesity promotes the absorption of exogenous lipophiles.

Multi-morbiidi

It has been definitively established that the onset of disease leads to multi-morbidity (Zeliger et al., 2012; Zeliger, 2014). A preponderance of the diseases listed in Table 2 are co-morbid with each other. This is demonstrated by the co-morbidity diagram in Figure 3 (reproduced with permission) (Zeliger, 2014). The number of multi-morbidities a person can experience has been found to range between 4 and 10 in a study of multi-morbidities in chemically sensitive individuals. Figure 3 is demonstrative of this (Zeliger et al., 2012). It is to be noted that the diseases listed in Table 2 are also causes of OS and that
the onset of disease is a causative factor in the onset of co-morbidity (Zeliger, 2014).

People with ENVDs have high incidences of other ENVDs and INFDs as well. Those with INFDs have high incidences of INFDs as well as ENVDs. Thus, it has been reported that co-morbidities exist between most of the diseases in Table 2 (Zeliger, 2014) and between numerous INFDs (Andresen et al., 2006). Examples of co-morbidities between ENVDs and INFDs include: the

Table 2. Environmental and infectious diseases caused by oxidative stress.

| METABOLIC       | KIDNEY                  |
|-----------------|-------------------------|
| Type 2 diabetes | End stage renal disease |
| Metabolic syndrome | Renal vascular disease  |
| Hyperlipidemia  | Glomerulosclerosis      |

| RESPIRATORY     | LIVER                   |
|-----------------|-------------------------|
| Allergic rhinitis | Cirrhosis               |
| Chronic obstructive pulmonary disease | Hepatitis              |
| Asthma          | Fatty liver disease     |
| Chemical sensitivity |                     |

| NEUROLOGICAL    | SKIN                    |
|-----------------|-------------------------|
| Autism          | Psoriasis               |
| ADHD            | Eczema                  |
| Alzheimer’s disease | SLE (lupus)            |
| Parkinson’s disease | Dermatitis            |
| Major depression | Acne                   |
| Motor skills    |                         |
| Cognitive ability |                      |
| Learning disorders |                    |

| ENDOCRINE       | IMMUNOLOGICAL AND AUTOIMMUNE |
|-----------------|-----------------------------|
| Male infertility | ALS                        |
| Female infertility | Acute urticaria            |
| Hypothyroidism  | Chronic fatigue syndrome   |
| Birth defects   | Chemical sensitivity        |
|                 | Lupus                      |
|                 | Sjogren’s syndrome         |

| CARDIOVASCULAR  | EYE DISEASES               |
|-----------------|---------------------------|
| Heart attack    | Cataracts                 |
| Stroke          | Glaucoma                  |
| Atherosclerosis | Macular degeneration      |
| Arteriosclerosis | Corneal and conjunctive diseases |
| Ischemic heart disease |                      |
| Hypertension    |                           |

| GASTROINTESTINAL | PERIODONTAL               |
|------------------|---------------------------|
| Irritable bowel disease | Chronic periodontitis   |
| Crohn’s disease  |                           |
| Peptic ulcer     |                           |

| MUSCULOSKELETAL | OBESITY                  |
|-----------------|--------------------------|
| Rheumatoid arthritis | Metastasis             |
| Osteoarthritis  |                           |
| Osteoporosis    |                           |
| Fibromyalgia    |                           |

| URINARY TRACT   | CANCER                   |
|-----------------|--------------------------|
| Benign Prostate Hypertrophy | Virtually all cancers    |
| Urthritis       | Metastasis               |
| Urinary tract infection |                    |

| VIRAL AND BACTERIAL INFECTIOUS DISEASES | CANCER                     |
|----------------------------------------|---------------------------|
| Herpes                                 | Virtually all cancers     |
| Influenza                              | Metastasis                |
| Common cold                            |                           |
| TB                                     |                           |
| Herpes                                 |                           |
| HIV and AIDS                           |                           |
OS and aging
Though a natural consequence of living, aging is accelerated by excessive OS. A widely held theory is that OS within mitochondria damages the mitochondria, which in turn leads to the production of increased quantities of ROS which cause further damage. Once it starts, this cycle leads to further damage and corresponding aging (Romano et al., 2010). OS has been shown to shorten telomere length (Kawanishi & Oikawa, 2004; von Zglinicki, 2002). Telomeres are repetitive DNA sequences at the ends of eukaryotic chromosomes that are shortened in each somatic cell division. Reduced telomere length is associated with aging and with the onset of cancer and other age-related diseases (Epel et al., 2004; Hou et al., 2015). Lowering of OS, however, has been shown to delay the shortening of telomere length and thus prolong life and reduce cancer incidence (Crous-Bou et al., 2014).

Nine hallmarks of aging have been identified (Lopez-Otin et al., 2013; Meiners et al., 2015). These are:
- genomic instability
- telomere attrition
- epigenetic alterations
- loss of proteostasis
- deregulated nutrient-sensing
- mitochondrial dysfunction
- cellular senescence
- stem cell exhaustion
- altered cellular communication

All of these hallmarks have been shown to be negatively impacted by OS (Kawanishi & Oikawa, 2004; von Zglinicki, 2002; Lopez-Otin et al., 2013; Meiners et al., 2015). These results suggest that oxidative stress be added to the list of hallmarks of aging.

It is beyond the scope of this paper to fully explore the subject of aging. Numerous papers have been written on this subject, with the following representative of these (Junqueira et al., 2004; Andrioli-Sanchez et al., 2005).

Biomarkers of lipid peroxidation
Biomarkers of specific diseases are typically found in blood, urine, saliva and exhaled breath. These biomarkers can be single component parameters such as blood glucose as an indicator of diabetes, or complex combinations of chemical species, examples of which are: a mixture of 8 different compounds present in set concentrations in exhaled breath as an indicator of gastric cancer (Amal, 2015); or a mixture of 6 serum biomarkers that predict the risk of developing type 2 diabetes (Kolberg, 2009). Disease biomarkers can also be individual chemical species including: F2-Isoprostanes, lipid hydroxides and hydroperoxides, hydroxycholesterols, aldehydes and ketones (Ogin & Wang, 2007; Niki, 2014; Dalle-Donne et al., 2006; Milne et al., 2005; Yoshida et al., 2013). Of these, malondialdehyde (MDA) level in serum is the most commonly used biomarker of oxidative stress (Ayala et al., 2014; Aflanie et al., 2015). MDA is stable in serum and is readily and accurately analyzed (Hoving, 1992; Nielsen et al., 2007; Grotto, 2009).

MDA from disease and exogenous exposure
Both ENVDs and INFDs result in the generation of MDA (Sonerborg et al., 1988). Thus high serum MDA values are predictive of pathogenic disease. People with INFDs have high incidences of other INFDs and with ENVDs. Thus is has been reported that co-morbidities exist between most of the diseases in Table 2 (Zeliger, 2014); and between numerous INFDs (Andresen et al., 2006). Examples of co-morbidities between ENVDs and INFDs include: the flu and neurological disorders (CDC, 2015a; Blanton et al., 2012); Alzheimer’s disease and viral infections (Honjo et al., 2009; Maheshwari & Eslick, 2015; Starakis et al., 2011); HIV and type 2 diabetes (Moni & Lio, 2014); HIV tuberculosis and malaria with type 2 diabetes (Marais et al., 2013); cardiovascular disease and COPD in a bidirectional manner (Oni & Unwin, 2015); chronic infections with heart disease (Madjid et al., 2004); and type 2 diabetes with hepatitis C (Guo et al., 2013).

Elevated MDA concentrations are also associated with all of the OS inducing stimuli presented above: toxic chemicals, particles and fibers, diet and food additives, radiation, pharmaceuticals, psychological stress and physical stress.

Table 3 lists the association of diseases and other stimuli with increased MDA serum levels. The data show the elevation of serum MDA as a function of disease or exposure to other OS increasing parameters. As can be seen from the data in Table 3, the presence of disease or exposure to other OS increasing stimuli elevates MDA levels. Though most commonly reported in micrograms per liter (mcg/L) other units are also reported. For purposes of comparison of affected individuals with healthy or unexposed individuals, all the data in Table 3 have been normalized to 1.0 for control, in each instance.

Discussion
Historically, most people who became ill with a single disease perished from it. With the progress made in modern medicine, however, this is no longer the case. Mankind has progressed to where many, if not most, diseases can be treated to prolong life. As a consequence of life prolongation, people are now more likely to have multi-morbidities and more likely to die as a result of a disease other than the first one to ail them (Murray et al., 2015).

As can be seen from above, OS and subsequent disease onset as well as aging, is induced by multiple causes. These include environmental exposures, life style choices and requirements as well as the prior presence of disease. OS is directly responsible for the onset of both environmental and infectious diseases, which generate OS and lead to further disease. All of the chemicals in Table 1 cause OS and all of the diseases in Table 2. All of the diseases in Table 2 give rise to OS which triggers the onset of additional disease which, in turn, leads to more OS and multi-morbidities.
It is hypothesized here that the increase in disease incidence is not due to any one cause, but to all causes that increase OS and that OS from multiple causes is additive. Thus the slope of the curve in Figure 1 for the increase of the incidence of disease with time is directly related to the increases in environmental prevalence of numerous OS-inducing chemicals and the fact that people are living with increased numbers of multi-morbidities that are OS inducing (see below). People have tried to ascribe the increased prevalence of specific diseases to specific environmental causes – including increased exposure to mercury, PCBs, heavy metals, acetaminophen use, etc. – but this cannot be done – as it is the sum of OS from all causes that causes disease, and each OS causative agent increases the likelihood of disease onset.

It is further hypothesized that total serum MDA is a valid indicator of the level of oxidative stress in a body and a predictor of disease onset. Credence for these hypotheses comes from the following eight considerations:

1. Disease - exposure - MDA relationships
The data in Table 3 clearly show that all causes of OS-related disease induction result in increases in serum MDA levels. These causes include toxic environmental exposures as well as environmental and infectious diseases. As can be seen from the data in Table 3, serum MDA levels increase with disease as well as with other OS inducing exposures.

2. Additive serum MDA levels
The data in Table 3 show that those with multiple MDA increasing sources have higher serum MDA levels and that serum MDA levels are additive. The multiple sources can be 2 or more diseases (for example, type 2 diabetes and cardiovascular disease (Bhutia et al., 2011) or myocardial infarction (Mahareen et al., 2010); in 2 or more environmental exposures as in (for example, cigarette smoking and road tar (Bhutia et al., 2011); or a disease and a toxic exposure (for example, type 2 diabetes and cigarette smoking (Bhutia et al., 2011)).

Serum MDA data show that controls for different studies of the same disease may have a range of MDA values for “healthy” individuals. For example, the values for healthy subjects being compared to those with diabetes range from 0.9 to 1.9 mcg/L. This is so because the “healthy” people in the different studies most certainly had different exogenous exposures as well as different diets that would account for the range in MDA levels. Nielsen, for example, reported that the serum MDA levels for a healthy individual was found to vary up and down by as much as 19% over a six day period (Nielsen et al., 1997).

3. Treatment lowers serum MDA
Lowering OS by administering antioxidants (Kontush et al., 2001; Jain et al., 2000; Coskun et al., 2006); disease treatment (for example, treating asthma (Bartoli et al., 2011) and diabetes (Wang et al., 2014)) and avoidance of environmental OS inducing agents all lower serum MDA levels.
4. Dose response relationship
There is a dose response relationship (DRR) between exposure levels of OS-inducing chemical toxins and/or the presence of disease and serum MDA levels. This is illustrated by the following examples: There are DRRs between serum MDA levels and: the number of hours of smoking cigarettes (Nielsen et al., 1997); exposures to trichloroethyene and perchloroethyene (Zhu et al., 2005); exposure to air pollution (Romeau et al., 2008); exposures to arsenic, cadmium and mercury (Aflanie et al., 2015); and exposure to ultra violet radiation (Agarwal et al., 1987).

5. Multi-morbidity
The multiple causes of OS predict disease multi-morbidity. Since each disease or toxic exposure raises the level OS, additional morbidity is to be anticipated since the incidence of all the diseases in Table 2 and all the chemicals and other exposures in Table 1 are known to be associated with higher OS. Accordingly, one ill with virtually any disease or continually exposed to an OS-inducing agent is at increased risk for additional disease.

Multi-morbidities are associated with stress as one of the co-contributors (Aich et al., 2009). Psychological stress significantly increases infectious disease susceptibility via impact on immune function (Jemmott & Locke, 1984). Individuals under psychological stress have been shown to have a higher incidence and a greater severity of upper respiratory disease that those with lower stress levels (Aich et al., 2009).

Multi-morbidities of ENVDs are bi-directional. The following examples are illustrative. In those ill with both hypertension and type 2 diabetes, the first illness incidence was equally split between the two diseases (Sowers & Epstein, 1995). Diabetes was also found to be bi-directional with depression (Mayo, 2015), and data from multiple studies showed that depression was bi-directional with myocardial infarction (Chi et al., 2014). A wide range of neurological diseases (including Alzheimer’s disease and Parkinson’s disease) are co-morbid and bi-directional with epilepsy, as are stroke, cardiac, gastrointestinal and respiratory diseases (Gaitatzis et al., 2012). Asthma and anxiety are bi-directional (Lee et al., 2016), as are metabolic syndrome and mental health disorders (including schizophrenia, bipolar disorder, depression, anxiety, attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorders (Nousen et al., 2013). All of the diseases just mentioned are known to be caused by OS, indicating a common mechanism of induction.

It follows from the above that a chemical that “causes” a disease may only be part of the cause, since it may be only one of several OS contributors. It also follows that the disease that kills need not be the first disease, since an ensuing disease may be a more aggressive killer. For example, chemical sensitivity, which is rarely lethal but is a source of OS, may be followed by T2D, which can cause death. Another example of a primary disease that is generally not lethal is chronic fatigue syndrome.

Though high serum MDA is predictive of the onset of additional morbidity, it is not generally possible to predict a specific disease than can ensue based on serum MDA alone. This is so because there are thousands of different lipophilic cell membranes in the human body, all of which produce MDA upon lipid peroxidation. The disease that ensues depends upon which particular membrane type is attacked (Zeliger & Lipinski, 2015).

6. Chronic inflammation
Chronic inflammation can be caused by chronic disease, continual exposure to exogenous toxins, a regular regimen of some pharmaceuticals, smoking tobacco, living in an area of high air pollution and/or a western style diet. Oxidative stress induces inflammation and inflammation leads to OS, setting up a vicious cycle of chronic inflammation (Reuter et al., 2010). Chronic inflammation increases cancer risk by impacting every step of tumorigenesis from initiation to tumor promotion and ultimately to metastatic progression (Ikemura et al., 2013; Grivennikov et al., 2009; Hanahan & Weinberg, 2011; Milara & Cortijo, 2012) and is considered a hallmark of cancer (Diakos et al., 2014; Melnik, 2015; Liu et al., 2014). This connection underscores the importance of limiting the factors that induce oxidative stress and inflammation in preventing the onset of further disease.

7. Late onset
Environmental diseases are accumulation disorders that strike as a result of significant contributory factors. These include: genetic predispositions; sequential absorption of OS-producing agents until toxic levels are reached and/or until all components of toxic mixtures are absorbed in sufficient levels to induce disease; the ability of the body to repair damage is exceeded and its defenses are compromised; or all hallmarks of disease onset are attained (Ayala et al., 2014; Zeliger & Lipinski, 2015).

8. Disease prediction
Actual serum MDA levels are indicative of the presence of disease or disease promoting oxidative stress. A review of the data in Table 3 shows that serum MDA levels are elevated versus controls in those with illness of toxic exposures. Based on the data in Table 3 and numerous other studies, the following scale for serum MDA values in mcg/L as predictors of disease is proposed:

| MDA Level | Description                           |
|-----------|---------------------------------------|
| Less than 1.20 | Indicative of a healthy state         |
| 1.20–1.40  | Disease predicted                     |
| 1.40–3.00  | Disease onset probable                |
| Greater than 3.00 | Severe disease likely                 |

These values suggest that asymptomatic individuals with serum MDA levels of 1.20 or greater be evaluated further for disease.

Though MDA predicts disease onset, it alone, cannot predict which disease will come because of the varying exposures, states of disease and the particular one of thousands of different lipophilic membranes in the body which can be attacked by free radicals, each of which may attack a different organ or system.
Disease prevention
The discussion above strongly suggests that the key to disease prevention is to eliminate as many of the causes of OS as is possible, for it is the total OS from whatever source(s) that causes disease onset. Such sources can include toxic chemical exposure, chronic inflammation from existing environmental and/or infectious disease and lifestyle choices such as diet and tobacco use. This, prevention can be accomplished by aggressively treating all diseases, by treating symptoms from conditions with intermittent or occasional manifestations such as allergic reactions and by limiting exposures via what are termed here as micro- and macro-preventative measures and the treatment of disease, be it environmental or infectious where possible. It is important that treatment include attention to all morbidities present as well as to all sources of exposures that contribute to OS. It should be noted that the body can recover from occasional high-dose acute levels of OS, but is subject to the onset of disease from chronic elevated levels of OS. Asymptomatic Patients who present with elevated serum MDA levels should be further evaluated to determine the source(s) of their high MDA levels and precautions taken to reduce such sources before the onset of disease, as disease onset will provide additional OS and can lead to further disease.

Micro-preventative measures include exposure-limiting steps that can be undertaken by the individual. These include: lifestyle actions such as adherence to a Mediterranean type diet that is high in antioxidant phytochemicals; carbon-filtering tap water; limiting intake of processed and red meats; avoidance of foods and personal care products that contain preservatives such as triclosan, butylated hydroxy anisole (BHA), butylated hydroxy toluene (BHT) and parabens; limiting exposures to exogenous toxins such as tobacco smoke and pesticides; exercising in times of high air pollution levels; avoiding packaging foods in plastics that exude phthalates and bisphenol A; limiting pharmaceutical use to those medically deemed essential; combating obesity; and seeking prompt medical help when disease strikes.

Macro-preventative measures are societal actions that lead to healthier living. These include: educational programs to produce awareness of environmental hazards to good health; regulatory control of hazardous chemical release, tobacco products, pesticides and chemical-containing products; encouragement of the production of organic foods; mandating strict warnings for hazardous materials; and stimulation of green energy production to reduce global warming, which enhances the volatilization of toxic chemicals, increases the rates of environmental chemical reactions which lead to higher levels of ozone and other air pollutants, as well as the increased risk of wildfires which spew large quantities of pollutants into the air.

It has been recently reported that the deleterious effects of obesity linger long after significant weight loss (Stokes & Preston, 2015). White adipose tissue (WAT) serves as a collector and bio-concentrator of exogenous lipophilic chemicals such as PCBs, chlorinated hydrocarbon pesticides, polynuclear aromatic hydrocarbons, other persistent organic pollutants (POPs) and chemicals that are found in air, water, food and everyday products (Arrebola et al., 2013; Brown et al., 2016). These chemicals partition from WAT to blood serum and serve as a constant supplier of OS-inducing toxins to the blood (Yu et al., 2011; Lind et al., 2013). Rapid weight loss, involving drastic reduction in WAT, results in the release of large quantities of toxic lipophiles with resultant significant systemic OS increase, an event that can lead to the onset of diabetes, cardiovascular, renal, liver and other diseases (Lind et al., 2013; Olusi, 2002; Zeliger, 2013; Zeliger, 2013a; Zeliger, 2013b). Accordingly, gradual weight reduction is preferable to rapid weight loss, to allow for the metabolism and elimination of toxic lipophilic chemicals. It is to noted, however, that many POPs (such as PCBs, dioxins, furans and chlorinated pesticides such as DDT and its metabolite DDE) have very long half lives in the body and may linger up to 30 years or more (Gallo et al., 2011; Yu et al., 2011). This consideration offers an explanation of why the effects of initial obesity linger throughout one’s life and the need to prevent obesity throughout life, particularly during childhood and early adulthood.

There are limitations to disease prevention for several reasons and it is not implied here that all disease can be eliminated for three reasons. First, there are genetic differences which protect some and put others at risk for the onset of disease. Second, ignorance, socio-economic status, lifestyle, peer pressure and economic interests of chemical manufacturers, mining operations and intentional polluters act counteractively to prevent chemical exposures. Third, there are conflicting situations where well meaning people on both sides of an issue can reasonably disagree. Two examples of such situations serve as illustrations of this point and the often difficult choices that need to be made. DDT and its metabolite DDE are persistent organic pollutants that are causative agents of OS and disease (Zeliger, 2011). DDT, however, is still in use in parts of the world to control malaria causing mosquitoes. Drinking water is routinely disinfected with chlorine to remove water-borne pathogens. Disinfection byproducts of chlorine treatment, however, are known human toxins that have associated with adverse reproductive effects and diseases including cancer (Tardiff et al., 2006; Bove et al., 2007).

Conclusions
Virtually all human disease is induced by oxidative stress. Total oxidative stress, from whatever source, be it toxic environmental exposure, the presence of disease, lifestyle choices or combinations of these, increases the incidence of OS. OS leads to lipid peroxidation of lipophilic cell membranes, which in turn produces MDA. Serum MDA level is an additive parameter resulting from all sources of OS and, therefore, is a reliable indicator of total oxidative stress that can be used to predict the onset of disease in clinically asymptomatic individuals and to suggest the
need for further clinical evaluation and treatment that can prevent much human disease. Routine MDA screening is recommended for addition to annual medical checkup blood work.

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