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CARDIOVASCULAR DISEASE COULD BE CONTAINED BASED ON CURRENTLY AVAILABLE DATA!

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□ Largely due to better control of infectious diseases and significant advances in biomedical research, life expectancy worldwide has increased dramatically in the last three decades. However, as the average age of the population has risen, the incidence of chronic age-related diseases such as arthritis, Alzheimer's, Parkinson's, cardiovascular disease, cancer, osteoporosis, benign prostatic hyperplasia, and late-onset diabetes have increased and have become serious public health problem, as well. The etiology of these disorders is still incompletely understood, therefore, neither preventive strategies nor long-term effective treatment modalities are available for these disorders. In keeping with the aforementioned, the ultimate goal in cardiovascular research is to prevent the onset of cardiovascular episodes and thereby allow successful ageing without morbidity and cognitive decline. Herein, I argue that cardiovascular episodes could be contained with relatively simple approaches. Cardiovascular disorder is characterized by cellular and molecular changes that are commonplace in age-related diseases in other organ system, such alterations include increased level of oxidative stress, perturbed energy metabolism, and "horror autotoxicus" largely brought about by the perturbation of ubiquitin -proteasome system, and excessive oxidative stress damage to the cardiac muscle cells and tissues, and cross-reactions of specific antibodies against human heat shock protein 60 with that of mycobacterial heat shock protein 65." Horror autotoxicus", a Latin expression, is a term coined by Paul Ehrlich at the turn of the last century to describe autoimmunity to self, or the attack of "self" by immune system, which ultimately results to autoimmune condition. Based on the currently available data, the risk of cardiovascular episodes and several other age-related disorders, including cancer, Alzheimer's disease and diabetes, is known to be influenced by the nature and level of food intake. Now, a wealth of scientific data from studies of rodents and monkeys has documented the significant beneficial effects of calorie restriction (CR) or dietary restriction (DR), and multiple antioxidant agents in extending life span and reducing the incidence of progeroid-related diseases. Reduced levels of cellular oxidative stress, protection of genome from deleterious damage, detoxification of toxic molecules, and enhancement of energy homeostasis, contribute to the beneficial effects of dietary restriction and multiple antioxidant agents. Recent findings suggest that employment of DR and multiple antioxidant agents (including, catalase, gluthatione peroxidase, CuZn superoxide dismutase, and Mn superoxide dismutase = enzymes forming the primary defense against oxygen toxicity), and ozone therapy may mount an effective resistance to pathogenic factors relevant to the pathogenesis of cardiovascular episodes. Hence, while further studies will be needed to establish the extent to which CR and multiple antioxidant agents will reduce incidence of cardiovascular episodes in humans, it would seem prudent to recommend CR and multiple antioxidant agents as widely applicable preventive approach for cardiovascular disorders and other progeroid-related disorders.

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INTRODUCTION

It is now well-established, based on a plethora of scientific data, that strong link exists between the way a person or population lives and their risk for developing or dying from cardiovascular diseases (CVD). Despite the fact, that heredity has impacting role to play in events with regards development of cardiovascular cases, for some people however, their personal health habits and environmental and/or cultural exposure are highly important factors, that in most cases, surpass hereditary susceptibility. For instance, adapting to a heart healthy diet, being physically active and staying appropriately lean (Scranton et al., 2004), not smoking, avoiding major stress (Black, 2002, 2003) and depression can directly lead to accelerated prevention of cardiovascular episodes. Cardiovascular disease, including heart attack, stroke and heart failure, is believed to be the leading cause of disease and death in the USA and Europe and is poised to become the most significant health problem worldwide. Atherosclerosis, presently accepted as an inflammatory disease (Rose, 1999: Libby, 2002) and an autoimmune reaction highly associated disease (Wick and Xu, 1999; Pockley et al., 2000; Wick et al., 2001; Pankuweit et al., 2002; Bason et al., 2003), constitutes the single most important contributor to the growing burden of cardiovascular disease.

PATHOPHYSIOLOGY OF CARDIOVASCULAR DISEASE

Atherosclerosis, an underlying cause of myocardial infarction, stroke resulting in premature death, is a progressive disease consisting of focal plaques characterized by cholesterol deposition, fibrosis, and inflammation in the large arteries. The first visible atherosclerotic lesion demonstrates macrophage foam cells “fatty streak” and lipid droplets within intimal smooth muscle cells (SMC) and heterogeneous droplets of extracellular lipid followed by intimal thickenings (progressive-prone locations) in young adults (Stary HC et al., 1994; Lusis,2000; Scott, 2004).

Complement activation

Activation and over-reactivity of the complement system belongs to important factors intimately implicated in driving cardiovascular disease. Complement, a double-edged sword, is a sophiscated essential component of the innate immune system that largely contributes to the recognition and destruction of pathogens and other invaders,and to assist in the phogocytosis of waste materials. However, under certain conditions, as it can be the case in most pathological conditions, inappropriate activation of the complement system could result to severe damage to the

host. The major components of the complement system execute four major functions: 1) recognition, 2) opsonization, 3) inflammatory stimulation through anaphylatoxins, and 4) mediate killing through the membrane attack complex (MAC). Membrane attack complex (MAC) is the dimer of a fusion product of complement proteins C5b, C6, C7, C8, and C9. MAC is directly responsible for complement-dependent membrane damage and catalysis (see Methods for detailed discussion of complement system; Quigg, 2002, Webster et al., 1997).

There is now substantial evidence that circulating levels of the acute phase reactant C-reactive protein (CRP) constitute a cardiovascular risk factor. Concentration levels in healthy persons or patients with stable or unstable angina pectoris are associated with stable or unstable angina pectoris are associated with an increased incidence of cardiovascular events (Haverkate. et al. 1997; Ferreiros et al., 1999; Ridker et al., 1998). Ventricular rupture occurs only in patients with peak serum CRP levels higher than 200 mg/liter (Ueda et al., 1996), and high CRP levels predict mortality over the next 6 months from all causes related to myocardial infarction (Pietilä et al., 1996). Human CRP, after aggregation or ligand binding, has been reprted to possess the potentials to activate complement via the classical complement pathway, thereby implying that CRP may strongly enhance inflammation by activating complement (Volanakis et al., 1974; Wolbink et al., 1996; Wolbink et al., 1998; Torzewski et al., 1998).

Apoptosis

Apoptosis, a prominent event in the pathogenesis of cardiovascular diseases, is a factor intimately associated with the orchestrated network of inflammatory events in cardiovascular disease (Gustafsson and Gottlieb, 2003; Calkosinski et al., 2004; Scott, 2004) . Apoptosis is an active type of cell death. It differs from necrosis in its programmed manner, complex regulatory mechanisms, distintive morphological changes and lack of inflammation (Wyllie AH et al., 1981, Graham and Chen, 2001). The injurious stimuli as direct consequence of the actions of the aforementioned patho-biological processes seems to be aggravation of endogenous oxidative stress, leading to excessive oxidative modification of lipids, proteins, and DNA, and thereby the structural and functional alterations within the vascular wall (Cai H and Harrison, 2000; Ames BN, et al., 1993).

Oxidative Stress

Oxidative stress is caused by the presence of free radicals or radical-generating agents in concentrations that overwhelm natural radical-blocking or -scavenging mechanisms. Sources of oxidative stress include exogenous factors, such as cigarette smoke, and endogenous factors, such as oxidative burst from activated macrophages. Oxidative stress can cause oxidative damage to DNA, proteins, and lipids, and many clinical conditions includ-

ing cardiovascular disease are associated with increased indices of oxidant stress; thereby suggesting that overwhelming the antioxidant defense system initiates and propagates processes involved in the pathogenesis of many diseases (Halliwell and Gutteridge, 1990). Hence, in line with the aforementioned, oxidative stress, although largely a secondary event, has been shown by a huge body of data as the major driving force in the pathogenic cascade of events responsible for sustaining and exacerbation of the disease process in atherosclerotic vascular disease, and therefore, strongly suggests that the development and progression of atherosclerosis can be inhibited by antioxidants (Berliner and Heinecke, 1996; Diaz et al., 1997), and other measures such as calorie restriction (CR), and appropriate employment of chemopreventive agents, such as cucurmin.

Ubiquitin-Proteasome System (UPS)

Dysfunction of the ubiquitin-proteasome system (UPS) has been implicated in driving cardiovasculatr disease by a huge body of scientific data (Igarashi et al., 1994; Bulteau et al., 2001; Herrmann et al., 2003). An important factor, which largely contributes to maintenance of the homeostasis of the cells is the process of ubiquitin-proteasome catalytic pathway. Normal cellular functioning requires processing of proteins regulating cells cycle, growth, and apoptosis. The UPS or the ubiquitin-proteasome pathway (UBP) is the principal mechanism for proteolysis in the mammalian cytosol and nucleus. The UPS modulates intracellular protein degradation. To this end, UPS fullfils important function in cell defense : 1) removal of damaged proteins generated by adduct formation and oxidatative stress, 2) regulates cell-cycle progression and apoptosis by modulation of proteasomal p 53 degradation (Yang and Yu, 2003), 3) regulation of nucleocytoplasmic transport and gene transcription (Schwartz and Hochstrasser, 2003). Hence, dysfunction or blokade of the proteasomal degradation pathways results in accumulation of unwanted protein and cell death. A total perturbation of the cellular homeostasis.

Importantly, recently accumulating data, consistent with the aforementioned notion, strongly suggest that albeit that cardiovascular diseases and neurodegenerative disorders such as Alzheimer's disease (AD) display different pathological outcome, they, however, sufficiently share common pathogenic features, such as inflammation, over-reactivity of the complement system, ubiquitin-proteasome dysfunction and significant oxidative stress-associated damage to the cells and viable tissues (Aliev et al., 2002; Aliev et al., 2003; Aliev, 2002; Arlt et al., 2001; Miyakawa, 2002; Skoog and Gustafson,2002; de La Tore, 2002; Rodin and Thomas, 2001; Zekry et al., 2002; Berliner and Heinecke, 1996; Mayer et al.,1991;Layfield et al., 2001; Yasojima et al., 2001; Lagrand et al., 1997; Li et al., 1995; Torzewski et al., 1998; McGerr and McGerr, 2000; 2001: Igarashi et al., 1994; Bulteau et al., 2001; Herrmann et al., 2003). Support for this notion explains the puzzle

posed by seemingly unrelated drugs (drugs primarily produced for the management of cardiovascular diseases that confer protection against neurodegenerative pathological conditions (Jones et al., 1999; Tsuschida et al., 1990; Feleszko et al., 1999; Stuve et al., 2003; Teunissen et al., 2003; Zamrini et al., 2004). Furthermore, in agreement with this notion, a large body of evidence implicates free radical toxicity, radical induced perturbation of the ubiquitin-proteasome catalytic pathway (Mayer et al., 1991; Layfieldet al., 2001;Herrmann J et al., 2003), radical induced mutations and oxidative enzyme impairment and mitochondrial dysfunction, and perturbation of the homeostasis of calcium in the brain (Marin-Garcia et al., 2002; Sheehan et al., 1997; Calabrese et al., 2001; Golden and Melov, 2001; Nicholls, 2002; Aliev et al., 2003) in the clinical manifestation of neurodegenerative and cardiovascular diseases. Unregulated accumulation of oxidative damage in neurons and in the cardiac muscles either primarily or secondarily may account for the increased incidence of a variety of neurodegenerative diseases and cardiovascular pathological conditions. Hence, consistent with the above observations, accumulating data favors antioxidants agents and dietary calorie restriction (CR or DR) as potential measures in the management of cardiovascular and neurodegenerative diseases in humans. This strongly indicates that therapeutic strategies worked out for effective management of cardiovascular disease may equally find efficacy in the management of some neurodegenerative disorders, such as Alzheimer's disease (AD). Hence, in agreement with the above data, it is conceivable that appropriate employment of dietary calorie restriction and multiple antioxidant agents may strongly impact an effective resistance to the pathogenic factors relevant to cardiovascular pathology. While further investigations will be needed to establish to which extent DR and antioxidant agents will attenuate the disease development and progression in CVD, it would be prudent to recommend the employment of dietary calorie restriction and antioxidant agents as widely applicable intervention, in form of potential adjuncts, for the management of cardiovascular diseases. It is, thus, the subject of this article to discuss the potential free radical scavenger, antioxidant actions, the promising beneficial cardioprotective effects of DR and the need for the use of these agents as potential adjuncts to the standard therapy in the management of cardiovascular diseases, and alongside briefly treat the effect of the same agents on neurodegenerative disease, such as Alzheimer's disease.

ANTIOXIDANT AGENTS

It is now well established that during the course of normal metabolism, reactive oxygen species (ROS) are produced from within the respiratory chain of the mitochondria. These ROS have the ability to oxidize and damage a variety of cellular constituents including lipids, carbohydrates, DNA, and proteins. Oxygen, although essential for aerobic life, can be converted

to highly reactive species, including superoxide ion, hydrogen peroxide, and hydroxyl radical, as aforementioned, known collectively as reactive oxygen species. Increased ROS formation, in particular, under pathological conditions is believed to cause damage to the cells and tissues through chemical interactions with proteins, lipids, carbohydrates and DNA. The heart is supposed to be the most susceptible of all the organs to premature aging and free radical-mediated oxidative stress. In agreement with this, a large body of scientific evidence indicated that oxidative stress induced by reactive oxygen species (ROS) play pivotal role in the etiology of several chronic degenerative diseases, including cardiovascular disease (Berliner and Heinecke, 1996; Sevanian and Hochstein, 1985; Aliev et al., 2002, Nunomura et al., 2001; Sayre et al. 2001). Conversely, the brain and the nervous system are considered to be highly susceptible to peroxide damage than most organs and tissues due to their high content of iron, catecholamine, excitatory amino acids, polyunsaturated lipid-rich neural parenchyma, high oxygen utilization accounting for one fifth of the total system consumption, low anti-oxidative enzymes, such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSHPX) (Rouach et al., 1987; Patole and Ramasara, 1988; Haliwell B,1989; Juurlink and Sweeney,1997). Oxidation of the circulating low-density lipoprotein (LDL) that carry cholesterol into the blood stream to oxidized LDL (LDLox) is believed to play a pivotal role in the pathogenesis of atherosclerosis, which, as previously described, is the underlying disorder (Berliner and Heinecke, 1996). Therefore, the antioxidant potential should be very important in the development and management of cardiovascular disorders. (Sies, 1993; Finkel and Holkrook, 2000; Halliwell, 1996; Diaz et al., 1997; Diplock et al., 1998). Hence, a large number of anti-oxidant agents have been shown to exhibit neuroprotective and cardioprotective effects in the cell culture and animal models relevant to age-associated disorders. These include estrogen, caratenoids, uric acids, N-acetylcysteine, Coenzyme Q10, lipoic acid, and Ginko biloba extract (Shepherd et al., 2001; Karev et al., 1993; Pereira et al., 1999; McCarty, 2001; Prasad et al., 1999; Mayne, 2003; Sole and Jeejeebhoy 2002; Jeejeebhoy et al., 2002; Hu, 2003; Diaz et al. 1997; Van der Loo et al., 2002). Nevertheless, extending on each of every antioxidant agent will be beyond the scope of this articule, however, it is wished in this articule to extend on vitamin E and Gluthatione (GSH), and few other antioxidant agents that have major pivotal play in cardioprotection and neuroprotection, as well.

Vitamin E

Epidemiological experimental studies have provided evidence for an inverse relation between cardiovascular disease and antioxidant intake, particularly, vitamin E supplementation (Gaziano and Hennekens, 1992; Stampfer et al., 1993; Rimm et al., 1993).Vitamin E (alpha/gamma-toco-

pherol) is a lipid soluble antioxidant that is very effective in suppressing membrane lipid per-oxidation. Vitamin E cannot be produced in the body of animals and humans. Foodstuffs, such as vegetables oils, nuts and cod roe, are good sources of Vitamin E (Azzi and Stocker, 2000). The term "Vitamin E" was introduced in the year 1922 (Evans and Bishop, 1922) when a new dietary factor in animal nutrition considered important for reproduction was described. Isolation of two components with vitamin E characteristics, designated as alpha- and beta-tocopherol, was performed in the year 1936 from wheat oil. However, presently, a total of about eight isomers are known to occur in nature. The nutritional importance of vitamin E was confirmed in the year 1968 by the American Food Nutrition Board, and right from that time, a plethora of studies has confirmed its role in protecting the integrity of tissues by acting as chain breaking antioxidant (Esterbauer et al., 1987; Butterfield et al.2002). Vitamin E may counteract the effects of aging and neurodegenerative disorders by suppressing membrane lipid per-oxidation and thereby preserving membrane transporter function and stabilizing cellular ion homeostasis (Goodman Y., Mattson MP, 1995; Mark et al., 1995; Butterfield et al., 2002) and in cardiovascular disorder, by directly scavenging reactive oxygen species, as well (Carr et al., 2000). Vitamin E has recently been shown to attenuate inflammatory damages in association with vitamins A and C, after burn trauma, by markedly inhibiting the translokation of the cardiac NF-kB (nuclear factor-kappa B), resulting in decreased cardiac synthesis of inflammatory cytokines, and, thereby conferring protection against burn-trauma mediated cardiac injury (Horton et al., 2001). Consistent with the notion of involvement of common pathogenic features in AD pathology and in cardiovascular diseases, high dose of vitamin E has earlier been reported to slow the progression of Alzheimer's disease (Sano et al., 1997). A randomized study by Chapell and associates (Chapell et al., 1999) that combined supplementation of vitamin E and C conferred protection against the frequency or reoccurrence of the pre-eclampsia syndrome. It should be very recommendable, to employ vitamin E, in high levels, in combination with other antioxidants, in order to counteract the occasional pro-oxidant reaction of vitamin E, which can occur when vitamin E is administered alone. Consistent with this notion, Bowry and Stocker (Bowry and Stocker, 1993; Bowry et al., 1995) and Neuzil and associates (Neuzil et al., 1997) reported that alpha-tocopherol can act as a pro-oxidant in LDL via alpha-tocopheroxyl radical-mediated formation of lipid radicals. Hence, together, the above observations strongly suggest that in absense, or rather in association, with other efficient free radical scavengers, vitamin E will continue to be one therapeutic strategy in CVD and neurodegenerative pathological conditions characterized by oxidative stress and inflammatory processes such as Alzheimer's disease.

Glutathione (GSH)

When cells are exposed to oxidative stress, GSH synthesis is increased through up-regulation of glutamate-cysteine ligase (GCL) gene expression, providing a protective/adaptive mechanism against oxidative stress (Meister A and Anderson ME, 1983; Moinova and Mulcahy, 1998; Rahman and MacNee, 1999). Glutathione (GSH), ubiquitous tripeptide thiols, is a major and naturally occurring antioxidant involved in many cellular functions. GSH is, however, predominantly involved in the regulation of intracellular redox state and protects cells from oxidative injury (Meister A and Anderson ME, 1983). These includes protein and DNA synthesis; enzyme activation; amino acid transport; and the protection from the negative effects of radiation, oxygen radicals, and other reactive oxygen intermediates (Bogden et al., 1994), such as glutathione peroxidase catalyzed inactivation of hydrogen peroxide. Flohe et al. (Flohe et al., 1999) recently revealed that survival and virulence of various parasites depend on endogenous antioxidant defense systems, and GSH activity was suggested to be implicated in this event. Furthermore, GSH in its virtue as a major antioxidant in the brain has been shown to protect neurons against a variety of oxidative insults in experimental models relevant to the pathogenesis of AD, PD, ALS, and stoke (Keller et al., 1998; Mark et al., 1997; Pederson et al., 1999). Now, as demonstrated in vitro studies, GSH depletion inhibits nitric oxide (NO) production in endothelial cells. In agreement with this, a plethora of data concludes that supplementation of GSH or its precursor improved endothelial vasomotor dysfunction in patients with coronary risk factors in which oxidative stress has a pathogenic role (Kugiyama et al., 1998; Vita et al., 1998). Additionally, in commensurate to this, "GSH stability" in the red blood cells (RBCs) both in gestational hypertension and, in pre-eclampsia syndrome, a pathological condition characterized by an increased blood pressure, proteinuria, and edema (Roberts JM et al., 1989: Roberts JM and Redman C, 1993; ACOG, 1996) and excessive inflammatory responses and endothelial dysfunction (Redman CW et al., 1999), is thought to be highly perturbed (Knapen M et al., 1998). Consistent with this notion, the rate of GSH oxidation has been shown by Spickert and colleagues (Spickert et al., 1998) to strongly correlate to the severity of the illness and the susceptibility, as well. Hence, the above data suggest a pivotal role for GSH as an antioxidant, and further support the notion that appropriate administration of GSH may significantly contribute to the prevention and management of cardiovascular events.

Curcumin: a potent cytoprotector

Based on the notion of oxygen-stress theory of aging and age-associated chronic degenerative diseases (Harman, 1956), diet supplementa-

tion with a number of phenolic or thiolic antioxidants have been able to increase the life span of laboratory animals, protect against senescent immune decline, repair damaged DNA molecules, and preserve the function of aged mitochondria (Miquel and Weber, 1990; Henning and Chow, 1988; Miquel et al., 1995; De la Fuente et al., 1998). Curcumin and other antioxidant products from the dried rhizome of Curcuma longa are believed to be useful for the prevention and/or treatment of a variety of age-related degenerative processes (Ammon and Wahl, 1991). In keeping with this notion, many lines of scientific evidence (Srimal and Dhawan., 1973; Huang et al., 1988; Reddy and Lokesh, 1994; Mukhopadhyay et al. 1982; Ruby et al., 1995; Ramirez-Tortosa et al., 1999; Araujo and Leon, 2001; Balasubramayam et al., 2003; Calabrese et al., 2003) suggest that that the main anti-oxidant from Curcuma (i.e. Curcumin) or 1.7-bis-(-4-hydroxy-3-methoxiphenyl)-1,6-heptadiene-2,5-dione) as well as hydro-alcoholic extract of dry Curcuma rhizome posses potential anti-inflammatory, immunomodulating, tumoricidal, antiprotozoal, antioxidant and antiatherogenic properties. In vivo model studies carried out by Ramirez-Tortosa and associate (Ramirez-Tortosa et al., 1999) demonstrated significant reduction of oxidation of serum LDL-cholesterol in a model of atherosclerotic rabbits after intake of 1.6 mg/kg curcumin extract in the diet. Additionally, in commensurate to this, administration of hydro-alchoholic extract of curcuma to rabbits strongly decreased the plasma level of cholesterol and the susceptibility of LDL to oxidation (Ramirez-Tortosa et al., 1999). A plethora of clinical studies with humans further substantiated the protective effects of curcumin and related products of the dry rhizome of the spice plant C. longa against lipid peroxidation-associated damages and other related cases (Ramirez-Bosca et al., 1995; 1997; Cheng et al., 2001). Now, most importantly, it is believed that pharmacologically, there is no side effects by appropriate administration of curcumin (Aggarwal et al., 2003), thereby, strongly indicative that using of curcumin is not connected with any toxicity or negative side effects (Cheng et al., 2001). Furthermore, most recent evidence, suggests that high intake of curcumin of up to 800mg-2500mg daily was devoid of every negative side effects (Chainami-Wu, 2003). Curcumin and related products have been shown to mediate their protective effects (antioxidant, free radical scavenging, and anti-inflammatory, and anti-parasitic activity) through a variety of pathways or mechanisms: 1) inhibition of Ca2+ influx and protein kinase C (PKC) activity (Balasubramayam et al., 2003), 2) Curcumin has also been shown to beneficial effects due to its ability to strongly activate the haem oxygenase pathway (Scapagnini et al., 2002). Haem oxygenase-1 (HO-1), a ubiquitous and redox-sensitive inducible stress protein that degrades haem to CO, iron and biliverdin, is a ~32-kDa microsomal enzyme that catalyzes the rate-limiting step in haem degradation. Induction of HO-1 occurs as an adaptive and protective response

to a variety of inflammatory stimuli (Maines, 1997). It has been revealed that under severe hypoxic condition s the potency of curcumin to increase endothelial Heam oxygenase-1 (HO-1) expression and, thereby, consequently protect cells against oxidative stress is highly enhanced (Motterlini et al., 2000), 3) by induction of the heat shock response (Dunsmore et al., 2001), 4) suppression of the superoxide anion production directly or indirectly through inhibition of xanthine dehydrogenase/xanthine oxidase (XD/XO) conversion (Kunchandry and Rao, 1990; Asser I et al., 2002), 5) through buffering of impaired oxidant/antioxidant unbalance, thereby attaining the levels of thiobarbituric acid-reactive substances (TBARS) similar to baseline levels and to less reduced coenzyme Q10 levels thiobarbituric acid-reactive substances (Quiles et al., 2002), 6) Curcumin ability to confer anti-inflammatory effect (Chuang et al., 2000) and this effect is apparently due to the fact that can influence the metabolisms of arachidonic acid blocking the phosphorylation of cytosolic phospholipase A2 (cPLA2), decreasing the expression of cyclooxygenase 2 (COX-2), and inhibiting the catalytic activity of the inflammatory factor 5-lipoxygenase (5-LOX) (Skrzypezac-Jankun et al., 2000; Hong et al., 2004), 7) recent study revealed that curcumin can confer protection against lead-and cadmium induced oxidative stress-damage to neuronal cells in an in vivo by effectively binding to the metals to build a compound, thus, by chaleting mechanism (Daniel et al., 2004). This indicates that curcumin also represents a potent pharmacological target by metal poisoning, for it has got the property of chaleting toxic metals, and finally, curcumin has been shown to enhance the activities of detoxifying enzymes such as glutathione-S-transferase via dose-dependent induction of increased activity of g-glutamyl cystein synthetase (g-GCS), which catalyzes the rate-limiting step in GSH biosynthesis (Piper et al., 1998). This action, which involves the detoxification of the electrophilic toxic products lipid peroxidation is suggested to equally contribute to the anti-inflammatory and antioxidant properties of curcumin. The molecular underpinnings responsible for the beneficial effects observed by Curcumin has been suggested to be largely due to modulation of pools of transcription factors that compose EpRE and AP-1 complexes, which results in influencing gene expression of the glutamate-cystein ligase (GCL) and other phase II enzymes (Dickinson DA et al., 2003). Additionally, in commensurate to this, the antioxidant activity of curcumin and its derivatives could be attributed to the 1,3-diketone conjugated diene system, essential for scavenging of the oxygen radicals than the phenolic and methoxy groups (Sreejayan and Rao,1994; Kuchandy and Rao, 1990) and the ability of tetrahydrocurcumin via beta-diketone moity to exhibit antioxidant activity by cleavage of the C-C bond at the active methylene carbon between the two carbonyls (Pan et al., 1999). Conversely, the anti-inflammatory activitiy of curcumin and its

derivatives has been suggested to be due to the presence of hydroxyl and phenol groups in the molecule, which are essential for the inhibition of prostaglandins (PG synthetase) and leucotrienes (LT), and also due to the presence of the beta-dicarbonylic system, equipped with the double bonds(dienes).The presence of the a-dicarbonylic system, with its conjugated double bonds (dienes) is also believed to be responsible for antiparasitic activity of curcumin and its derivatives (Araujo and Leon, 2001). Substantially, the above observations strongly indicate that curcumin and its derivatives may be especially beneficial as potential antiatherogenic agents in the processes associated with a marked increase in blood lipid peroxidation such as diabetes (Suresh Babu and Srinivasan, 1997), myocardial infarction and dislipemias in women, which mostly accompany biochemical alterations after menopause (Miquel et al., 1998). Therefore, curcumin and related products of the dry rhizome of the spice plant C. longa could be employed both as preventive by patients with peripheral vascular disease and equally in the management of the concerned diseases, as well.

Ozone therapy and Cardioprotection

Controlled administration of ozone is thought to influence oxidative stress, preventing the damage induced by reactive oxygen species and, thereby, protecting against cases associated with ischaemia reperfusion injury. Thus, appropriate administration of ozone in form of endovenous ozone monotherapy to patents with myocardial infarction, where, as well-established, decrease in glutathione peroxidation and superoxide dismutase activities is commonplace (Loeper J et al., 1991), has been reported to be beneficial. Ozone hemotherapy has been reported to induce the stimulation of glutathione peroxidase activity (Hernandez F., et al. 1995) and also to reduce the blood cholesterol level (Rilling, 1985), thereby linking ozone therapy to peroxide and cholesterol metabolism. Support for this notion is evidenced by studies carried out by Frank Hernandez and associates (Hernandez et al., 1995). These investigators demonstrated the antioxidant beneficial effect of ozone autohemotherapy in human subjects. After 15th session of ozone treatment, cholesterol (CHO) level was shown to be significantly diminished and glutathione peroxidase (GPx) activity significantly elevated. Despite the fact that the molecular underpinnings responsible for the biochemical alterations associated with ozone therapy have yet to be fully determined, ozone scavenger enzyme stimulation is largely believed to have a role in this process. Additionally, in commensurate to this, ozone treatment has been recently shown to considerably reduce markers of oxidative stress-associated endothelial damage in vivo model of rats associated with diabetes (AL-Dalain et al., 2001). Ozone therapy, when appropriately employed, is an efficient approach in a position to confer adequate protection against

lipid peroxidation which is thought as an important risk factor for atherosclerotic-related cardiovascular disease (Lusis, 2000). LDL is modified by free radical-mediated reactions, both in their lipid and protein moieties, resulting to the alterations that are the starting point for the first event in the outcome and development of atherogenetic process (Lusis, 2000). Ozone therapy is relatively inexpensive and simpler than a variety of surgical interventions. Therefore, in spite of the possible toxic effects associated with ozone therapy, which is presently being proactively addressed (Tylicki L et al., 2003), decreasing scavenger enzyme activity in individuals with cardiovascular cases can be addressed or restored by appropriate application of ozone autohemotherapy.In agreement with the fact that cardiovascular disease share major pathogenic factors with neurodegenerative disorders such as Alzheimer's disease (Aliev et al., 2002; Aliev et al., 2003; Aliev, 2002; Arlt et al., 2001; Miyakawa, 2002; Skoog and Gustafson, 2002; de La Tore, 2002, 2004; Berliner and Heinecke, 1996; Mattson and Kroemer, 2003; Sparks, 1997; Newman et al., 2001; Hofman et al., 1997; Bulteau et al., 2001), it is thus conceivable that appropriate application of ozone therapy be ameliorative, under certain conditions, in individuals with Alzheimer's disease, as well.

Lycopene: evolving importance in chronic degenerative diseases

Data on the antioxidant potentials of Lycopene, a naturally present carotenoid, and the exploitation of this potential in the management of neurodegenerative diseases, cardiovascular disorders, and other chronic degenerative conditions are increasingly accumulating. Agarwal and associate recently reviewed the possible importance of lycopene in prevention and management of various diseases (Agarwal et al, 2000). Lycopene, an acylic isomer of beta-carotine with no provitamin A activity (Stahl et al., 1996), is a carotinoid present in tomatoes, tomato products, watermelons, pink grapefruits, apricots and pink guavas. Dimascio and associates described lycopene as highly potent antioxidants, which possesses a singlet oxygen quenching ability twice that of beta-carotene and ten times than that of alpha-tocopherol (Dimascio et al., 1989). Earlier studies by Agarwal and associate, reported that leocopene from tomato products is absorbed readily, increasing serum levels and lowering the oxidative damage to lipids, lipoproteins, proteins and DNA (Agarwal et al. 1988). Support for this notion is strongly evidenced by more recent study, which showed 50% loss of serum lycopene with a 25% increase in the in vivo lipid oxidation following the ingestion of lycopene free diet for two weeks in healthy human subjects (Rao et al., 1998). This is strongly indicative of the potent antioxidant ability of lycopene. In keeping with this, lycopene has been shown to significantly exert beneficial effects in subjects associated with diverse neurodegenerative conditions such as PD, AD and vascular dementia (Foy et al., 1999). Longnecker and associates reported as

a result of a case-control study that dietary administration of lycopene was protective against cases of ALS (Longnecker et al., 2000). Earlier, Snowdon and associates reported a corresponding correlation between high blood lycopene level and a positive influence on the functional capacity of the elderly, such as the capacity to perform self-care tasks (Snowdon et al., 1996). Consistent with this notion, studies by Sinclair and colleagues (1998) and by Clinton (1998) revealed that antioxidants such as lycopene may act directly on neurons and by an in- direct manner affecting peripheral markers of oxidative stress, and also strongly suggested that lycopene may be capable of crossing the blood-brain barrier (Sinclair et al., 1998; Clinton, S.K. 1998). Mechanisms underlying the beneficial effects of lycopene have been recently briefly reviewed by Heber and associate (Heber and Lu, 2002). Now, consistent with the fact that Alzheimer's disease share important key pathogenic factors with cardiovascular disease (Aliev et al., 2002; Aliev et al., 2003; Aliev, 2002; Arlt et al., 2001; Miyakawa, 2002; Skoog and Gustafson, 2002; de La Tore, 2002, 2004; Berliner and Heinecke, 1996; Mattson and Kroemer, 2003;, Sparks, 1997; Newman et al., 2001; Hofman et al., 1997; Bulteau et al., 2001; Herrmann et al., 2003), we are led to believe that appropriate employment of lycopene as an antioxidant adjunct may equally be beneficial in the management cardiovascular diseases. Support for this notion is evidenced by relentlessly accumulating data attributing significant cardioproctive properties to lycopene (Rissanen et al., 2002; Sesso et al., 2003; 2004). Furthermore, Arab and associate (Arab and Steck, 2000) reported that the thickness of the innermost wall of blood vessels and the risk of myocardial infarction are reduced in persons with higher adipose tissue concentrations of lycopene. Thus, further studies on lycopene and its properties may even lead to development of novel therapeutic strategies through which cardiovascular conditions could be more effectively contained.

Salen Manganese Complexes

As briefly discussed above, antioxidant therapies have been employed for a wide range of disorders in which oxidative stress is considered to play a significant role. However, administration of single antioxidants such as Vitamin E (Lipman et al., 1998) and endogenous SOD in various clinical indications have produced extremely little or limited success. In the attempt to improve this condition, Cerchiari and associates (Cerchiari et al., 1987) demonstrated that the employment of combined superoxide dismutase succeeded to regain cerebral blood flow and function after cardiac arrest in mammal. This apparently encouraged the development of very strong antioxidant agents in this direction, and eventually led the investigators working at Eukarion, Inc, Susan R. Doctrow and associates (Doctrow et al., 1997; Baker et al., 1998; Doctrow et al., 2002; Liu et al.,

2003) to develop synthetic antioxidant mimetics, equipped with both SOD and catalase activities (properties). These products have been shown to be potentially efficative against reactive oxygen species-associated pathological conditions, and aging-associated alterations (Doctrow et al., 1997; Baker et al., 1998; Doctrow et al., 2002; Liu et al., 2003; Melov et al., 2000). Salen Manganese complexes are low molecular weight synthetic compounds that have both superoxide dismutase and catalase activities, thereby mimicking two endogenous enzymes involved in the first-line of antioxidant defence against ROS. The prototypes of these synthetic Salen Manganese Complexes are: EUK-8, EUK-108, EUK-122, EUK-121, EUK-15, EUK-123, EUK-113, EUK- 13, EUK-124, EUK-115, EUK- 114, EUK-160, and EUK-189 Doctrow, SR. (Doctrow et al., 2002). This article will, however, concentrate on the antioxidant effects of the two prototypes, EUK-8 and EUK-134. Salen-Manganese complexes have the ability to catalytically scavenge multiple ROS, including superoxide ion and hydrogen peroxide. This depicts salen manganese complexes as potentially valuable agents for combating a wide range of conditions in which oxidative stress is implicated.

Cytoprotective effects of Salen-Manganese Complexes

Salen-Manganese Complexes have been shown to be highly efficacious as potential cytoprotective agents in experiments where they were tested for protection in human dermal fibroblasts (HF cells) against glucose and glucose oxidase, a hydrogen peroxide-generating system. EUK-8, EUK-134 and EUK-189 have been demonstrated to be highly effective in protecting primary neurons and PC12 cells from toxicity by the peroxide-generating agent sin-1, Anderson and associates (Anderson et al, 2002). They have also been shown to be very effective in inhibiting apoptosis in primary neurons and highly efficacious as antioxidant agents in a mouse model for mitochondrial oxidative stress (Melov et al., 2001).

Salen-Manganese Complexes may be Beneficial in Extension of Lifespan in Mammals

Studies on nematode Caenorhabditis elegance (C. elegans), which is widely used as a model for research in aging, by Melov and associates (Melov et al. 2000) demonstrated the an increase in mean lifespan averaging about 40% of life span by administration of either EUK-8 nor EUK-134. The EUK compounds extended lifespan without affects on growth or reproduction. This finding was further extended and buttressed by the studies of Ishii et al. (Ischii, et al., 1998). These investigators, utilizing the mev-1 (Kn1) nematode in their experiments reported that treatment of EUK-134 resulted in extension of Lifespan by over 60%, thereby lending support to the hypothesis that therapeutic employment of EUK-134 causes a decrease in chronic oxidative stress in mev-1 mutant, effectively, normalizing its lifespan to approximate that of the wild type. Thus, the above

described points imply: 1) that age-associated loss of neurological functions in mammals can (could) be partially reversed through the supplementation of antioxidants, 2) apparently age-related decline in cognitive function in humans could be reduced by consuming diets rich in antioxidants or through supplementing diet with appropriate antioxidants, 3) since cardiovascular disease share major pathogenic factors with some aging-associated neurodegenerative disorders such as Alzheimer's disease (Aliev et al., 2002; Aliev et al., 2003; Aliev, 2002; Arlt et al., 2001; Miyakawa, 2002; Skoog and Gustafson,2002; de La Tore, 2002, 2004; Berliner and Heinecke, 1996; Mattson and Kroemer, 2003; Sparks, 1997; Newman et al., 2001; Hofman et al., 1997; Bulteau et al., 2001), appropriate employment of salen-manganese complexes in the management of cardiovascular disease may be of enormous benefit.

Essentially, the data above collectively suggested that: 1) These two catalytic antioxidants, Euk-8 and Euk-134, strongly mimic the catalytic activities of both superoxide dismutase and catalase, and are convincingly more effective than non-catalytic antioxidants such as vitamin C or E, 2) Salen-manganese complexes (SOD-mimetics with catalase activity, such as EUK-8 and EUK-134) may represent novel therapeutic approach, in their properties as potential antioxidant agents, for preventing and treating oxidative-stress related conditions, and 3) that multiple functional catalytic antioxidant may serve as a very effective therapeutic approach, which will be applicable to a broad range of chronic degenerative pathological conditions and possibly to the enhancement of health during the aging process. Hence, a combination of appropriate multiple micronutrients (including antioxidants) with dietary calorie restricting measures may be more effective, than a single agent, in the management, and as an adjunct to standard therapy in the management of cardiovascular disease than the individual agent.

DIETARY RESTRICTION (DR)

There is now credible and overwhelming evidence that dietary restriction (DR) is the only effective experimental manipulation known to extend lifespan and retard aging in mammals, and it has been shown to retard a variety of processes that change with age. (Weindruch and Walfort, 1988; Yu et al., 1985; Blackwell et al., 1995). Despite the fact that most studies conducted on dietary restriction have been in rodents and lower animals, a large body of accumulating data from studies on rhesus monkeys strongly suggests that the beneficial effects of DR may also be extrapolated to primates, including humans (Zainal et al., 2000; Roth et al., 2001; Ingram et al., 2004; Lane et al., 2004; Hursting SD et al., 2003; Knight, 1999). Dietary Restriction, which means reduced calorie intake, maintained at 60 % of ad libitum intake, thus represents a well-established means of prolonging the life span in mammals and increase their resist-

ance to cancer, cardiovascular diseases, diabetes, and other age-related diseases (Knight,1999; Yu, 1994; Sohal and Weindruch 1996; Yu et al., 2002). On the other hand, the term, calorie restriction literally and commonly refers to a reduction in calorie intake without a reduction in essential nutrients or malnutrition (Yu, 1994). Thus, dietary restriction, indeed, differs from severe fasting or starvation in that it reduces total caloric or energy intake without causing deficiencies of any specific nutrients. It was reported for the first time in 1930s that food restriction significantly extends the life span of rodents (McCay et al. 1935). It, thus, also exerts beneficial effects on the brain including enhanced learning and memory and increased neuronal resistance to excitotoxic, oxidative and metabolic insults. There are numerous nutritional factors and other measures that have been reported to affect the brain and heart physiologically in a way that could, at least, in theory beneficially influence brain and cardiovascular ageing in non-pathological and as well as in pathological states. However, it is wished to focus here mainly on the factor of dietary restriction (DR; reduced calorie intake: maintained on 60% of ad libitum feeding). Dietary restriction is also known as calorie restriction (CR).

Despite the fact that CR benefits have been known for many years, the mechanism(s) of its action are still incompletely resolved. Its complexity seemingly lies in multiple cascade of events that involves a broad spectrum of physiological, biochemical, endocrinological, and metabolic effects, which may vary in intensity and exhibit striking differences among specific organ systems A variety of mechanisms have been suggested to underlie the beneficial effect of calorie restriction, including reduction in oxidative stress (Sohal and Weinruch, 1996; Kristal and Yu,1994), “membrane peroxidation cycle 2 concept” a novel phenomenon by which dietary restriction (maintained on 60% of ad libitum feeding) suppresses age-related oxidative damage by modulation the amount of fatty acid composition and also that of fatty acid composition of tissue phospholipids (Yu et al., 2002), by increasing the expression of apoptosis repressor with a caspase recruitment domain (ARC) (Shelke and Leeuwenburgh, 2003), by upregulation of heat shock protein 70, glucose-regulator protein and brain-derived neurotrophic factor (BDNF) (Duan and Mattson,1999; Yu and Mattson, 1999; Guo et al., 2000), by enhancing the fidelity of DNA replication, thereby promoting DNA stability (Srivastava et al, 1998; Horton et al. 2000; Cabelof et al. 2003), positively modulating (suppressing the increase of COX-2 in the brain) the activity cyclooxygenase 2 (COX-2) (Baek et al., 2001), by increased expression of immunosuppressive TFG-beta 1, positively modulating the balance between Th-2 and Th-1 cytokine, and blocking the expression of interleukin 10 (IL-10) and some other immunoactive pro-inflammatory cytokines, thereby conferring enormous protection against excessive immune reactions such as autoimmune reaction (Abe et al., 2001;

Chandrasekar et al., 1995; Jolly et al., 1999; Sun et al., 2004), and responsible for detoxification of a variety of toxic substances in the body (Hart et al., 1992, 1995). In keeping with the aforementioned, recent studies have shown that DR can stabilize mitochondrial function and reduce oxidative stress in brain cells of rodents (Guo et al, 2000), and thus may increase the resistance of neurons to many different types of genetic and enviromental features. CR also upregulates several antioxidants including catalase, glutathione reductase, glutathione S-transferase, and superoxide dismutase (Koizumi et al., 1987; Langaniere, and Yu, 1989). A wealth of scientific data demonstrates, in a number of genotypes and species that CR can also inhibit chronic toxicity induced by physical, chemical, and microbial agents (Turturro and Hart, 1992; Hart and Turturro, 1993; Chou et al., 1993).

CR has also been reported to reduce age-associated neuronal loss in most mouse models of neurodegenerative disorders such as Parkinson's disease (Duan and Mattson 1999) or Alzheimer's disease (Zhu et al. 1999). CR also improves the brain's plasticity and ability for self-repair (Mattson, 2000). Now, conversely, CR has been shown by a wealth of scientific data to confer beneficial effects on a variety of cardiovascular pathological conditions. Blood pressure is decreased by CR in the obese and in chronically undernourished laborers (Apfelbaum, 1978; Shetty and Kurpad, 1990). Landsberg and associate (Landsberg and Young, 1981; 1983) demonstrated that calorie CR is implicated in a decrease in plasma norepinephrine concentration, decreased excretion of catocholamines, and, perhaps in diminished sympathetic activity. This, therefore, indicates that the decrease in blood pressure during CR may be mediated by decrease in insulin concentration and sympathetic nervous activity (Velthuis-te Wierik et al., 1994). CR has also been reported to positively impact on endothelial dysfunction such as endothelial-dependent vasodilatation in obese hypertensive subjects (Sasaki et al., 2002). CR also reduces markers for inflammation including C-reactive protein, interleukin 6, and plasminogen activator inhibitor type 1 in obese and nonobese subjects (Heilbronn et al., 2001; Bastard et al., 2000; Marvri et al., 2001; Velthuis-te Wierik et al., 1995). This notion is further evidenced by Chandrasekar and associates (Chandrasekar et al., 2001) reporting that CR significantly reduced myocardial oxidative stress and the postischemic inflammatory response to myocardial ischemia-reperfusion injury in Male Fisher rats. This observation has been further strengthened by the works of other research groups (Roberts et al., 2002; Abete et al., 2002). Additionally, Taffet and colleagues earlier disclosed that CR is intimately associated with the prevention of age-related impairments in the late diastolic function (Taffet et al., 1997). Moreover, recent report by Mattson and co-workers (Wan et al., 2004) robustly indicated that CR should be beneficial for the management of both cardiovascular and neu-

rodegenerative diseases. Taken together, the aforementioned observations strongly buttress the concept that moderately restricting dietary calories is potentially cytoprotective, and, thus, should have pivotal role in both prevention and management of cardiovascular disease.

Molecular underpinnings responsible for the beneficial effects of calorie restriction

A variety of pathways and phenomena have been suggested to underlie the molecular underpinnings responsible for the biochemical alterations registered in the actions of calorie restricting measures, nevertheless, the phenomenological process of hormesis appears to be pivotal in this event (Masoro EJ, 1999; Masoro EJ, 2000a, 2000b; Rattan SL, 2004).

Hormesis: evolving importance in dietary caloric restriction

The term hormesis by definition describes the beneficial, biological effect at low levels, as seen in reduced calorie intake, which at higher levels would cause deleterious effects (Calabrese and Baldwin, 1998, 2002). As previously described, a plethora of studies on CR have established its efficacy as the most robust and effective life-prolonging intervention, extending both average and maximum life span. Studies of Parson P.A. (Parson, 1996) and that of Holliday R. (Holliday, 1989), coupled with a plethora of more recent other studies on extended longevity, have led us to also believe that CR's resistive action against stress is an evolutionary, adapted measure, which is largely characteristic of a hormetic response. Thus, the phenomenological process or the concept of hormesis may offer a biological basis for such a phenomenon by CR (Neafsey, 1990). This strongly indicates, as suggested by Weindruch R. and co-workers (Lee et al., 1999; Weindruch et al., 2002) that an organism's adaptive response to CR was acquired through evolution by its turning on proper genes essential for a high metabolically efficient state for the survival of the species. Thus, elucidating the cellular and molecular underpinnings responsible for the phenomenological process of hormesis may bear relevance to effective management of ageing-associated alterations, and ageing-associated pathological alterations, and other chronic degenerative conditions in humans and animals.

Thus, essentially, all the experimental evidence suggests that dietary restriction may be an important approach for mitigating of processes that leads to diseases where oxidative stress and inflammation play pivotal role such as neurodegenerative diseases, cancer, rheumatoid arthritis and cardiovascular diseases, as well. Therefore, since this measure takes advantage of components involved in simple nutrition, the application of caloric restriction measures to improve public health may be highly welcomed and easy to establish. Hence, whatever the reason for the evolu-

tion of CR, however, because of its potent anti-oxidant and neuroprotective and cardioprotective actions and its apparent extrapolation to humans, elucidation of its mechanism(s) may add more tools to the standard therapy used to combat cardiovascular disease, neurodegenerative disorders, and other chronic diseases. It is, thus, conceivable, based on the above data, that appropriate employment of DR should be equally beneficial in the prevention and management of cardiovascular disease

CONCLUSIONS

Cardiovascular disease, including heart attack, stroke and heart failure, is believed to be the leading cause of disease and death in the USA and Europe and is poised to become the most significant health problem worldwide. As a result the societal cost attributed to cardiovascular disorder is immense and is poised to get worse. This clearly underscores the urgent need for the medical community to seek new therapies that can reduce the frequency of cardiovascular disorder and impact. Despite the fact that cardiovascular disorder is multifactorial in its etiology, nevertheless, there remain some potential for disease prevention and more effective management by employment of various antioxidant agents, and dietary caloric restriction measures, because these measures may play important role in modulating blood lipids and their propensity for oxidation. Cardiovascular disease share various important pathogenic factors with some chronic diseases, which are characterized by dysfunction of ubiquitin-proteasome system, oxidative stress and accelerated inflammatory processes, ranging from neurodegenerative disorder such as Alzheimer's disease (Aliev et al., 2002; Aliev et al., 2003; Aliev, 2002; Arlt et al., 2001; Miyakawa, 2002; Skoog and Gustafson,2002; de La Tore, 2002; Rodin and Thomas, 2001; Zekry et al., 2002; Berliner and Heinecke, 1996; Mayer et al.,1991;Layfield et al., 2001; Torzewski et al., 1998; Igarashi et al., 1994; Bulteau et al., 2001; Herrmann et al., 2003) to diabetes mellitus and rheumatoid arthritis (Sevanian and Hochstein, 1985; Halliwell et al., 1986; Onorato et al., 1998; Brod, 2000). This broadly implies, that, appropriate employment of agents to effectively manage rheumatoid arthritis, for instance, may confer some protection against cardiovascular disease and also neurodegenerative pathological conditions, such as Alzheimer's disease and multiple sclerosis, as well (McGeer et al., 1996; Ossandon et al., 2002; Greig et al., 2004; Ofodile: Rheumatoid Arthritis, a Double-faced Syndrome: relevance to neurodegenerative disorder. In prep). Conversely, this type of link appears to be very strong between cardiovascular disease and Alzheimer's disease, as previously described (Jones et al., 1999; Tsuschida et al., 1990; Feleszko et al., 1999; Stuve et al., 2003; Teunissen et al., 2003; Zamrini et al., 2004). Therefore, this work further strengthens the concept that therapeutic

strategies worked out for the management of cardiovascular disease may equally find significant efficacy in the management of some other chronic pathological states characterized by oxidative stress and inflammatory processes, in particular, Alzheimer's disease. Hence, appropriate and consequent incorporation of dietary calorie restriction (CA) measures and antioxidant agents, as potential adjuncts, into the armamentarium of the standard therapy for cardiovascular disease, should be, therefore, an ideal approach for prevention strategies and more effective disease management that are simple and comparatively inexpensive.

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