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Review Article

Translating The New Perspect of Homocysteine Metabolism and Mitochondrial Dysfunction Towards New Therapeutic Insights of Aging, Atherogenesis and Cancer

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Review

Reviewing annual world health organization statistics on mortality and morbidity in the last few decades reveals an astonishing persistence of heart disease as the number one killer in all world nations and races. The substantial scientific advances in the last eight decades contradict this disappointing fact. This means with no time for hesitation or comprehensive thinking, that the road map is wrong. Medical protocols and guidelines have improved longevity, but also increased the incidence of chronic diseases, and created new psychophysiological problems. Much of this is due to the influence of powerful pharmaceutical companies.

The historical background of the hypothesis of a causal relationship between the level of serum cholesterol and the development of atherosclerosis began with *Rudolf Virchow´s* (1821-1902) description in 1856 of the atherosclerotic plaque with its cholesterol deposits [1]. *Nikolai Anitschkov's* (1885-1964) experiments with rabbits in St Petersburg first demonstrated what was thought to be the role of cholesterol in the development of atherosclerosis [1]. He fed rabbits cholesterol from egg yolks and found that they developed atherosclerotic plaques containing cholesterol. When he tried with other animals that were carnivores, it was not possible to reproduce the results. They didn't get atherosclerosis. In 1915 *Anitschkov* moved to Freiburg to work under *Dr Aschoff*, who at that time was considered the most accomplished of all German pathologists. This provided indirect support to his atherosclerosis theory.

A century has passed since the word "atherosclerosis" was introduced. It seems timely to revisit the early work of *Anitschkov* and his colleagues and to review their contribution to the total sum of our present understanding of one of the most dreadful human diseases. As reviewed by *Kilmer McCully*, *Lewis Harry Newburgh* (1883-1956) investigated the pioneering studies of cholesterol feeding to rabbits by *Anitschkov* during the period from 1915-1925. Newburgh and his team repeated the experiments of *M. A. Ignatowsky* (1875-1955), the investigator who first fed meat, milk and eggs to rabbits to produce arteriosclerotic plaques [2]. Although *Anitschkov* attributed *Ignatowsky's* results to the cholesterol of the experimental diet, Newburgh's studies showed that removal of all fats and cholesterol from the experimental diet by extraction by organic solvents produced a protein powder that induced the same arteriosclerotic plaques observed by *Ignatowsky*. Newburgh's team injected pure amino acids intravenously in dogs and rabbits to determine which amino acid of the protein powder produced experimental arteriosclerotic plaques. No arterial plaques were demonstrated, but the animals developed chronic nephritis and albuminuria after injection of cysteine, tyrosine or tryptophan, confirming *Ignatowsky's* observations of nephritis in rabbits consuming a diet of meat, milk and eggs. Newburgh and his team failed to produce arterial plaques in his experiment, because the chemical structure of methionine and its presence in proteins were not determined until 1928. Moreover, the methionine derivative, homocysteine, was not discovered until 1932 by *L. H. Butz* and *Vincent DuVigneaud* (1901-1978) by demethylation of methionine by sulfuric acid. If Newburgh had

been able to use methionine and homocysteine in his experiments in 1925, he undoubtedly would have discovered their ability to produce experimental arteriosclerotic plaques.

In 1953, *Ancel Keys* (1904-2004) reported that the dietary intake of fat was significantly correlated to the serum cholesterol level and the incidence of cardiovascular death in six countries. It appeared very convincing, but the problem was that 6 countries were selected from 22 that were available. There was no correlation when all the countries were included, and had he selected six others, he would have come to the opposite conclusion. The study was obviously falsified, and the hypothesis based on it is false and should be buried [3]. Another striking challenge of the claimed causality of cholesterol in atherosclerosis came from studies of familial hypercholesterolemia population. *Harlan, et al.,* in 1966, and later *Mundal, et al.,* in 2014, reported that individuals with two to three times the normal level of LDL, have an overall normal rate of survival into their sixth, seventh, and even eighth decades of life. Indeed, *Mundal. et al.,* showed that individuals with FH from 70-79 years of age have a significantly lower rate of death than non-FH individuals with normal cholesterols. An elevated level of LDL does not cause Coronary Heart Disease (CHD) or premature death. David Diamond and colleagues, who made an extensive review of FH literature, clearly pointed out the necessity of screening coagulation markers in those individuals, based on well-established evidence that a subset of FH individuals exhibit abnormal markers related to hypercoagulation. Given their higher risk of developing CHD, these FH individuals should be prioritized for interventions to optimize treatment that targets coagulopathy [4]. It became very clear that the true road map to fight against the number one world killer needed revolutionary thinking. A landmark publication in the field was published in 1969 by Kilmer McCully, who is often called the father of homocysteine theory in medicine, describing a new pathological mechanism leading to atherosclerosis called "Protein Intoxication due to high homocysteine in the blood" [5,6].

Homocysteine was named as an amino acid containing one extra carbon atom, in comparison with the similar chemical structure of cysteine, the amino acid which had previously first isolated from urinary bladder stones. Around the same time an eight-year-old boy of Irish American ancestry admitted to Massachusetts General Hospital was evaluated for four days for headache, vomiting and drowsiness with signs of poor mental development in addition to dislocation of lenses in both eyes. Severe deterioration in the boy's condition with signs of stroke and weakness with abnormal reflexes on the left side were also reported. Furthermore, although there were no signs of infection, there was a rise in blood pressure and temperature; the boy succumbed to the illness within a few days. The cause of death was reported as arteriosclerosis of the carotid artery with cerebral infarct; published as case 19,471 in the *New England Journal of Medicine* in 1933 [7]. It was found later that homocysteine is a Sulphur containing amino acid derived from the essential amino acid methionine, present in large amounts in protein from animal sources like meat, eggs and milk. If there are adequate levels of vitamins B6, B12 and folic acid in the body, the homocysteine is broken down into harmless waste products or protein building blocks [8]. But if there's a deficiency of those vitamins, the homocysteine begins its ravages on the blood vessels. In retrospect, it seems clear that *McCully* was a man ahead of his time when everything focused on cholesterol. ''*Kilmer McCully's hypothesis seemed to challenge the cholesterol-heart hypothesis, which was riding high*,'' says *Irwin Rosenberg*, director of the U.S.D.A. Human Nutrition Research Center on Aging at Tufts University. His glorious discovery started when he became intrigued by two different cases of children with homocystinuria, a rare genetic disease in which the levels of homocysteine in the blood are unnaturally high. In both cases, the cause of death was severe arteriosclerosis, a narrowing and loss of elasticity in arteries that is normally seen only in the elderly. By re-examining the autopsy tissues of both children and drawing on previous animal research, *McCully* emerged with two linked and provocative suggestions: perhaps homocysteine directly damages the cells and tissues of the arteries, in much the way that cholesterol is thought to do, and perhaps that damage occurs not just in these rare genetic cases, but in the population at large, in anyone with an elevated homocysteine. He soon expanded his theory to include a probable cause of elevated levels of homocysteine: a deficiency of vitamins B6, B12 and folic acid. When these vitamins were administered to animals with high homocysteine levels, those levels plummeted, often within hours. Once McCully started extrapolating from his cellular- tissue and animal studies to the human situation, and said, ''*it all began to fit together.*'' It is very clear now that high homocysteine is a pathological cause involved in a large spectrum of degenerative disorders. Numerous studies have demonstrated an association of high homocysteine with vascular disease, cancer and several age- related pathologies and neurodegenerative diseases, including *Alzheimer's* disease, Parkinson's disease, and dementia. Diabetes, Down syndrome, and megaloblastic anemia have also been linked to high levels of homocysteine. Additionally, there are studies showing an association between high homocysteine and osteoporosis, eye lens dislocation, end stage renal disease, insulin resistance, aneurysms, hypothyroidism, gastrointestinal and many other disorders.

The role of high homocysteine level in vascular injury and endothelial dysfunction is now clearer and has been attributed to impaired bioavailability of Nitric Oxide [NO]. One likely mechanism for reduced bioavailability of NO is mediated by Asymmetric Dimethylarginine (ADMA). This endogenous inhibitor of Endothelial Nitric Oxide Synthase (eNOS) competes with the natural substrate, L-arginine thus limiting the formation of NO. Elevated plasma levels of ADMA have been associated with hyper homocysteinemia and endothelial dysfunction in both animals and humans. Apart from inhibiting the production of NO, ADMA may also promote the "uncoupling" of eNOS, thereby increasing the production of superoxide and other Reactive Oxygen Species(ROS) which in turn may further decrease NO bioavailability. Recent advances have proven that there is a close link between hyper homocystinuria and cancer. First, higher levels of plasma homocysteine have been observed in cancer patients, and Venous Thromboembolism (VTE) is the sec-

ond most common cause of death in cancer patients. Second, several polymorphisms in the enzymes involved in the homocysteine detoxification pathways (the trans- sulfuration and remethylation) have close clinical ties to several types of cancer. Third, folate, which is pivotal for cell proliferation, has an inverse relation with homocysteine. Fourth, homocysteine has also been proposed as a potential tumor biomarker for a variety of cancers. The hyper homocysteinemia of aging and dementia is attributed to decreased synthesis of adenosyl methionine by thioretinaco ozonide and ATP, causing decreased allosteric activation of cystathionine synthase and decreased allosteric inhibition of methylenetetrahydrofolate reductase and resulting in dysregulation of methionine metabolism [9]. This new understanding is opening new era for cancer therapeutics. Mitochondria are the primary energy-producing organelles within human cells. Progressive mitochondrial dysfunction occurs in aging because of loss of the thioretinaco ozonide oxygen ATP complex from mitochondrial membranes by opening of the Mitochondrial Permeability Transition Pore (mPTP). Melatonin, a neuro- hormone, and cycloastragenol, a telomerase activator, both prevent mitochondrial dysfunction by inhibition of mPTP opening [10]. The carcinogenic effects of radiofrequency radiation and mycotoxins are attributed to loss of thioretinaco ozonide from opening of the mPTP and decomposition of the active site of oxidative phosphorylation. The anti-aging effects of retinoids, the decreased concentration of cerebral cobalamin coenzymes in aging, and the diminished concentration of NAD+ from sirtuin activation, as observed in aging, all support the concept of loss of the thioretinaco ozonide oxygen ATP active site from mitochondria as the cause of decreased oxidative phosphorylation and mitochondrial dysfunction in aging [10,11]. In neurons, mitochondria are required for oxidative phosphorylation, intracellular calcium homeostasis, and regulation of cellular pH. Dysfunction of these organelles leads to cellular apoptosis through mechanisms such as intracellular reactive oxygen species generation and induction of the intrinsic apoptotic pathway. Mitochondrial dysfunction is implicated in the pathogenesis of many neurodegenerative disorders, including glaucoma, Alzheimer's disease, and Parkinson's disease. Interestingly, these diseases have been associated with elevated levels of plasma homocysteine. Homocysteine is thought to perturb the balance of mitochondrial fusion and fission in vivo. In retinal ganglion cells, this result in excessive mitochondrial fission and cellular apoptosis. Homocysteine appears to exert its actions by altering mitochondrial gene expression, function and structure [12]. A better understanding of the complex mechanisms through which homocystein affects mitochondrial functions could contribute to the development of more specific therapeutic strategies targeted at hyperhomocysteinemia associated disorders [13].

Another recent molecular correlation was established between increased homocysteine levels in the blood and Pulmonary Embolism (PE) [14,15]. A Group of researchers examined the effects of homocysteine on PE pathogenesis and the molecular mechanisms underlying these effects. The results of the investigation demonstrated that 1 millimole of homocysteine significantly decreased Cyclooxygenase (COX) activity and downregulated the expression of COX 17 in human umbilical vein endothelial cells. Decreased COX activity levels may lead to the elevation of intracellular Reactive Oxygen Species (ROS) levels, further inducing apoptosis. It was seen that 1 millimole of homocysteine significantly increased the intracellular hydrogen peroxide (H2O2) level and the apoptosis rate in endothelial cells [16]. Homocysteine acts synergistically with H2O2 to exert some of its noxious effects and may modulate the cytotoxic effects of Tumor Necrosis Factor (TNF). Cytokines such as TNF alpha may exert their cytotoxic effects by opening the permeability transition pore on the mitochondrial membrane thus uncoupling oxidative phosphorylation by dissipating the protonmotive force upon which ATP resynthesis depends.

In the quinquagenarian celebration of what Kilmer McCully described as" protein Intoxication" and the accumulated explosive scientific evidence-since then-of the causal relationship of abnormal homocysteine blood levels and the widespread human pathologies combined with the unequivocal cellular pathways derangements associated with hyper homocysteinemia, we are facing historical obligations and responsibilities. This emerging level of evidence contradicts the faulty, scrawny and meager scientific evidence for the cholesterol theory of atherosclerosis. It is coming after a decade of my first meeting with *Kilmer McCully* in the Third King of Organs International Conference for Advanced Cardiac Sciences 2010. The King of Organs series of conferences was founded and chaired by myself in the years 2006, 2008, 2010, 2012 and 2019. Turning points in the journey of human sciences emerged from King of Organ Conferences. One of those turning points was **The Saudi Arabian Homocysteine Atherosclerosis and Cancer Clinical Trial (SAHACT)**. The father of homocysteine theory in modern medicine, *Kilmer McCully* is again the father of SAHACT. *Abdullah Alabdulgader* is the principal Investigator of SAHACT. The later, *Paul Rosch* (1927-2020) is our honorary consultant and teacher in the field. Considering his magnificent input to the homocysteine science and this paper we are honored to add him as co-author of this paper after his death. The objective of SAHACT is to utilize a nutritional-metabolic multicenter clinical interventional trial to demonstrate how therapeutic strategies for controlling homocysteine metabolism are effective in prevention and treatment of degenerative diseases associated with aging.

New understanding of the importance of retinol (vitamin A), ascorbate (vitamin C), and homocysteine thiolactone in the biosynthesis of thioretinamide and thioretinaco by cystathionine synthase suggests a promising new dawn in therapeutics of subjects with arteriosclerosis and cancer utilizing strategies to control the abnormal metabolism of homocysteine in human species. The recent advances and knowledge of mitochondrial functions and dysfunctions were incorporated intelligently in SAHACT protocols. The efficacy of pancreatic enzyme therapy of cancer is interpreted as a promising method for promoting catabolism of macromolecules, specifically proteins, nucleic acids, and glycosaminoglycans that contain excess homocysteine groups resulting from abnormal ac-

cumulation of homocysteine thiolactone in aging, atherogenesis and carcinogenesis [17]. Dietary deficiencies of nitriloside (vitamin B17), folate (vitamin B9), pyridoxal (vitamin B6), and cobalamin (vitamin B12) contribute to abnormal homocysteine metabolism in degenerative diseases. Dietary deficiency of proteins containing sulfur amino acids down-regulates cystathionine synthase, causing abnormal homocysteine metabolism and increased risk of cardiovascular disease. Infections by a variety of micro-organisms promote abnormal homocysteine metabolism in atherogenesis and carcinogenesis, leading to creation of vulnerable plaques of arteries and dysplastic transformation of susceptible cells of various organs.

The protocol of the SAHACT trial consists of retinol, thioretinamide, and cobalamin as precursors of thioretinaco, combined with pancreatic enzyme extracts, nutritional modification to eliminate processed foods and to enhance dietary consumption of nitrilosides and other vitamins, and combined with vitamin supplements, essential amino acids, beneficial dietary fats, beneficial dietary protein, and antibiotics to combat chronic infections. Groups of subjects with vascular disease will be randomized into treatment with the nutritional-metabolic protocol versus usual therapy, and outcome will be followed for prevention of adverse vascular events, including acute coronary syndrome, stroke and amputation. Groups of subjects with recurrent prostate cancer or breast cancer will be randomized into treatment with the nutritional-metabolic protocol versus usual therapy, and outcome will be followed for prevention of mortality and complications of cancer. The SAHACT trial is designed to demonstrate the efficacy of a novel nutritional-metabolic approach to prevention and therapy of the important degenerative diseases of aging, arteriosclerosis and cancer. This approach will be compared with current methods of therapy for these diseases in a randomized, prospective, multicenter clinical interventional trial. The advantage of this novel approach is the non- toxic nature of the methods, utilizing vitamins, vitamin derivatives, amino acids, beneficial fats and proteins, essential amino acids, and antibiotics to achieve prevention and therapy. The design of the trial permits direct comparison of outcomes of the SAHACT protocols with the outcomes of conventional therapy with cholesterol-lowering drugs and other measures for prevention of vascular disease, and outcomes of chemotherapy, hormone therapy, radiation therapy and surgery for malignant disease.

Successful completion of the SAHACT trial will for the first time allow consideration of this innovative protocol for prevention and treatment of degenerative diseases of aging in susceptible populations in humankind worldwide. The nutritional-metabolic concept of SAHCT is based on the understanding of the function of thioretinamide, thioretinaco, and thioretinaco ozonide in the metabolic origin of degenerative diseases, including arteriosclerosis, stroke, acute coronary syndrome, cancer, dementia and other neurodegenerative diseases, autoimmune diseases such as ulcerative colitis, lupus erythematosus, thyroiditis, rheumatoid arthritis and pernicious anaemia, osteoporosis and fracture, venous thrombosis and embolism, retinal vein thrombosis, macular degeneration, hypothyroidism, accelerated aging, renal failure and uremia, diabetes mellitus, metabolic syndrome, severe psoriasis, organ transplantation with therapeutic immune suppression, protein energy malnutrition, familial or spontaneous amyloidosis, dietary deficiencies of folate, pyridoxal, and cobalamin, complications of pregnancy such as placenta previa and pre-eclampsia, and congenital birth defects including neural tube defects, cleft palate, and congenital heart disease.

In each of these degenerative diseases and conditions, abnormal homocysteine metabolism has been demonstrated by an increased level of homocysteine bound to plasma proteins by disulphide bonds. ***SAHACT is adopting intelligent scientific directions incorporating the human cellular pathways in health and disease to combat the pathological process of degenerative disorders, most importantly atherosclerosis and cancer. The role of mitochondrial dysfunction in aging and degenerative diseases is key to our understanding of the SAHACT protocol***. *Elucidation of trophoblastic origin of malignant cells was utilized in SAHACT intelligently*. In 1902, in an article in The Lancet, John Beard proposed that the answer to questions about the origin of cancer could be found in his own field, embryology [17,18]. The trophoblastic origin of malignant cells, as described by Beard was incorporated in the therapeutic goals of SAHACT. This is based on the premise that trophoblastic cells of the embryo, which invade the uterine endometrium and myometrium during implantation of the fertilized embryo, are related to the asexual cycle of cellular organisms and are converted to placental cytotrophoblastic and syncytiotrophoblastic cells by the action of enzymes produced by the pancreas of the developing fetus. Based on the concept that trophoblastic cells, which are distributed within developing tissues of the fetus, are similar in their cellular behavior to malignant cells, Beard introduced the enzyme therapy of cancer [19]. This treatment consists of injecting enzymes and pro- enzymes extracted from porcine pancreas into patients with various forms of primary or metastatic cancer. The trophoblastic theory of the origin of cancer is based on the assumption that adult stem cells are related to the trophoblastic cells which migrate from the yolk sac of the developing embryo into somatic tissues, as described by Beard [18].

Human fetal and malignant cells produce small quantities of chorionic gonadotrophin. This hormone is produced in large quantities by the highly malignant tumor of placenta, choriocarcinoma. These observations provide additional evidence for the trophoblastic origin of malignant cells. Although the origin of adult stem cells in normal human tissues is currently not well understood, the sensitivity of trophoblastic cells to oncolysis by pancreatic enzymes and pro- enzymes forms the theoretical basis for this therapeutic approach. This sensitivity is related to the accumulation of homocysteinylated enzymes, plasma proteins, and cellular proteins, ribonucleic acid, deoxyribonucleic acid, and glycosaminoglycans by reaction with excess homocysteine thiolactone that accumulates during aging, atherogenesis, carcinogenesis, and autoimmune diseases. Pancreatic extracts contain active trypsin, chymotrypsin, elastase, amylase, lipase, ribonuclease, and deoxyribonuclease, as well as proenzyme precursors of these digestive enzymes. These

enzymes are capable of hydrolyzing the homocysteinated proteins, nucleic acids and glycosaminoglycans that accumulate in malignant tissues and in the tissues of aging persons. *The discovery of thioretinamide, thioretinaco and thioretinaco ozonide and its antineoplastic properties was incorporated in the SAHACT protocol*. Homocysteine thiolactone reacts with retinoic acid to form N-Homocysteine Thiolactonyl Retinamide (NHTR), known as thioretinamide, in organic synthesis. Thioretinamide reacts with cobalamin to form N-Homocysteine Thiolactonyl Retinamido Cobalamin((NHTR)2Cbl), known as thioretinaco. Both thioretinamide and thioretinaco have anti-carcinogenic and anti-neoplastic activities in mice treated with a carcinogen and in mice with transplanted neoplasms.

The accumulated knowledge on ascorbate, homocysteine thiolactone oxidation, and growth hormone properties as anticancer factors was added to strengthen the SAHACT protocol. In the 1930s, ascorbic acid was found to influence the growth of cancer in animals, mainly acting to extend longevity. Moreover, the amount of ascorbic acid in the tissues of animals with cancer is decreased, further suggesting the possibility of a therapeutic action in cancer patients. Otto Warburg discovered the role of cytochrome enzymes in cellular respiration. He later demonstrated that cancer cells and embryonic cells have a characteristic mode of cellular respiration known as aerobic glycolysis in which glucose is converted to lactic acid instead of conversion to carbon dioxide, as seen in normal cells [20]. Ascorbic acid inhibits cellular respiration and glycolysis of cancer cells. Early and controversial studies claimed that massive doses of ascorbic acid cause regression of some advanced human cancers and extended the life span of patients with terminal malignancies, compared with controls. Subsequent controlled studies showed that massive doses of ascorbic acid have minor effects on side effects of chemotherapy and radiation and produce a slight increase in survival times of cancer patients. *The advances in understanding the pathways of glycolysis, nitrilosides, and hydrogen sulfide role in malignant cells is integral to the SAHACT protocol*.

In the early 20th century Warburg discovered that embryonic tissues and malignant cells are unable to utilize oxygen for cellular metabolism but instead metabolize glucose to lactate as a source of cellular energy. In other studies, Warburg showed that carcinogenic chemicals decrease normal cellular respiration by irreversible inhibition of oxygenases and by irreversible inhibition of transport of electrons by cytochrome enzyme systems [21]. These findings are supported by the demonstration of deficient succinic dehydrogenase and cytochrome oxidase activities within malignant tissues. Taken together these early observations can be interpreted as examples of the clonal selection of malignant cells from trophoblastic stem cells that are deficient in the heme oxidase activity of cystathionine synthase. The resulting failure of oxidation of retinol to retinoic acid and failure of reaction of retinoic acid with homocysteine thiolactone to produce thioretinamide by these malignant cells will lead to deficient formation of thioretinaco and failure of oxidative phosphorylation, catalyzed by thioretinaco ozonide. The failure of oxidative phosphorylation by malignant cell clones that are deficient in the heme oxygenase function of cystathionine synthase, resulting from decreased production of thioretinaco ozonide from cobalamin and thioretinamide, will lead to an embryonic form of metabolism in which ATP synthesis is dependent upon production of lactate from glucose, otherwise known as aerobic glycolysis.

Nitrilosides are substances containing nitrile groups produced by plants. The most important plant nitriloside is amygdalin (mandelonitrile β-diglucoside), and other nitrilosides are dhurrin (hydroxy mandelonitrile β-glucoside), lotaustralin (methylethylketone-cyanohydrin β-glucoside), and linamarin (acetone-cyanohydrin β-glucoside). Malignant cells contain glucosidase, the enzyme that metabolizes amygdalin and other nitrilosides to cyanide. Normal cells contain rhodanese, a sulfotransferase enzyme that catalyzes thiocyanate synthesis from cyanide and hydrogen sulfide. Malignant cells contain insufficient rhodanese to prevent accumulation of cyanide. Therefore, the prevention and control of growth of malignant cells and tissues by dietary nitrilosides are attributable to the consequent accumulation of cyanide within malignant cells. The reaction of cyanide with the cobalt atom of thioretinaco inactivates thioretinaco ozonide, thereby preventing oxidative phosphorylation. This system of chemical surveillance against the growth of trophoblastic malignant cell clones is promoted by dietary or supplemental consumption of amygdalin and other plant nitrilosides. Hydrogen sulphide is generated from homocysteine by cystathionine synthase and cystathionase, and low levels of hydrogen sulphide decrease oxidative stress and ameliorate pathological conditions such as ischemia-reperfusion injury, hypertension, and renal failure. Hydrogen sulphide is a key gasotransmitter in sensing oxygen availability in tissues. The reducing properties of hydrogen sulphide are responsible for scavenging the reactive oxygen species production induced by increased blood levels of homocysteine, inhibiting myocardial injury. Increased production of hydrogen sulphide from homocysteine, metabolized from homocysteinylated proteins, nucleic acids, and glycosaminoglycans of apoptotic cells by pancreatic enzymes will promote catabolism of homocysteine and conversion of the sulfur atom of homocysteine to thiocyanate by reaction of hydrogen sulphide with the cyanide generated from dietary nitrilosides [22].

The role of homocysteine, thioretinamide, and thioretinaco in degenerative diseases is the cornerstone of the SAHACT scientific protocol. The etiology of many of these degenerative diseases and conditions is incompletely understood. However, many of these chronic degenerative diseases are strongly correlated with the aging process. The importance of deficiencies of thioretinaco ozonide in cells of aging tissues is related to accumulation of homocysteine thiolactone and homocysteinylation of macromolecules. Regardless of etiology, however, elevation of plasma homocysteine levels and homocysteinylation of macromolecules in chronic degenerative diseases are susceptible to therapeutic intervention by preservation of cellular oxidative metabolism through increased production of thioretinaco ozonide and by enhanced catabolism of homocysteine produced by enzymatic degradation of homocysteinylated macromolecules. Moreover, preservation of cellular thioretinaco ozonide by membranergic proteins and by the liposomal complex

of ATP and oxygen with thioretinaco prolongs survival and counteracts the aging process.

The role of infectious organisms in the pathogenesis of arteriosclerotic plaques was considered carefully in the SAHACT protocol. Vulnerable plaques of arteries in atherosclerosis originate from obstruction of vasa vasorum of arterial wall by aggregates formed from lipoproteins complexed with microbial remnants, homocysteinylated lipoproteins, and lipoprotein autoantibodies in areas of high tissue pressure, causing ischemia, degeneration of arterial wall cells and rupture into arterial intima to form a micro-abscess [23]. The evidence that human arteriosclerotic plaques contain ozone supports the theoretical role of ozone in activation of thioretinaco to form thioretinaco ozonide as the active site for oxidative phosphorylation. As a matter of fact, SAHACT represents a promising innovative approach to control degenerative diseases of aging that has never been studied in human trials. The work of Kilmer McCully over the past five decades has focused on understanding the underlying abnormalities of homocysteine metabolism in degenerative diseases by studies of pathological anatomy of arteries in human and experimental hyperhomocysteinemia, by studies of homocysteine metabolism in cell cultures, in physiological animal experiments, and by studies of experimental atherogenesis and carcinogenesis in animal models. SAHACT trial is testing for the first time this approach in human disease.

The clarity of the cellular pathways of homocysteine metabolism in health and disease and the ability of the researchers in the last half decade to establish unequivocally the pathogenic role of what was described in 1969 as "Protein Intoxication" are compulsive historical messages to the international community to find pathways that will cure or at least ameliorate the devastating effects of degenerative diseases. This is in contrast to the fallacious cholesterol hypothesis, which has no proven scientific support of a causal role. It is merely an epidemiological created correlation contaminated by cherry picking, selective data management, skewed with statistical deception [1]. It is no surprise that efforts to treat this false assumption have resulted in massive epidemics of cardiac and non-cardiovascular diseases. Translating the new perspective of homocysteine metabolism and mitochondrial dysfunction towards new therapeutic Insights of aging, atherogenesis and cancer is a critical measure that we must undertake. We, human species are in critical demand to introduce intelligent alternative therapeutic approaches based on nature and natural products, to replace the highly toxic and poisonous chemicals and radiation therapies to treat degenerative diseases. Raising planetary global consciousness is our duty.

Acknowledgments

None.

Conflicts of Interest

None.

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