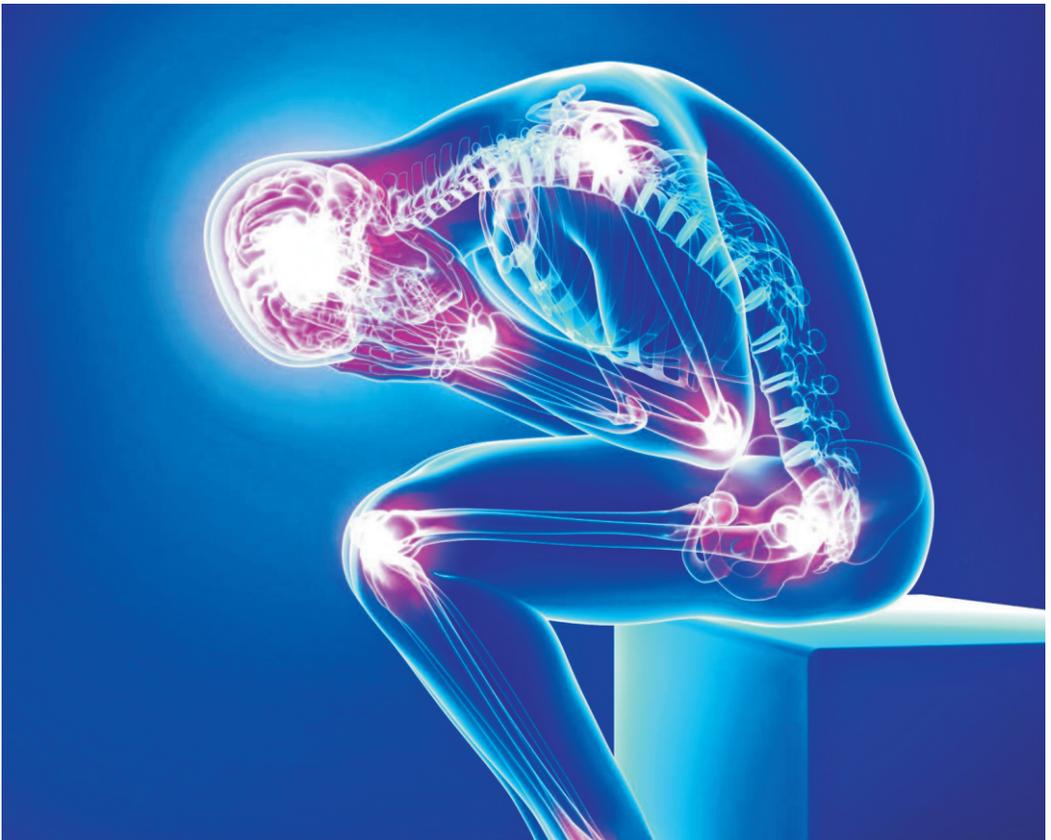
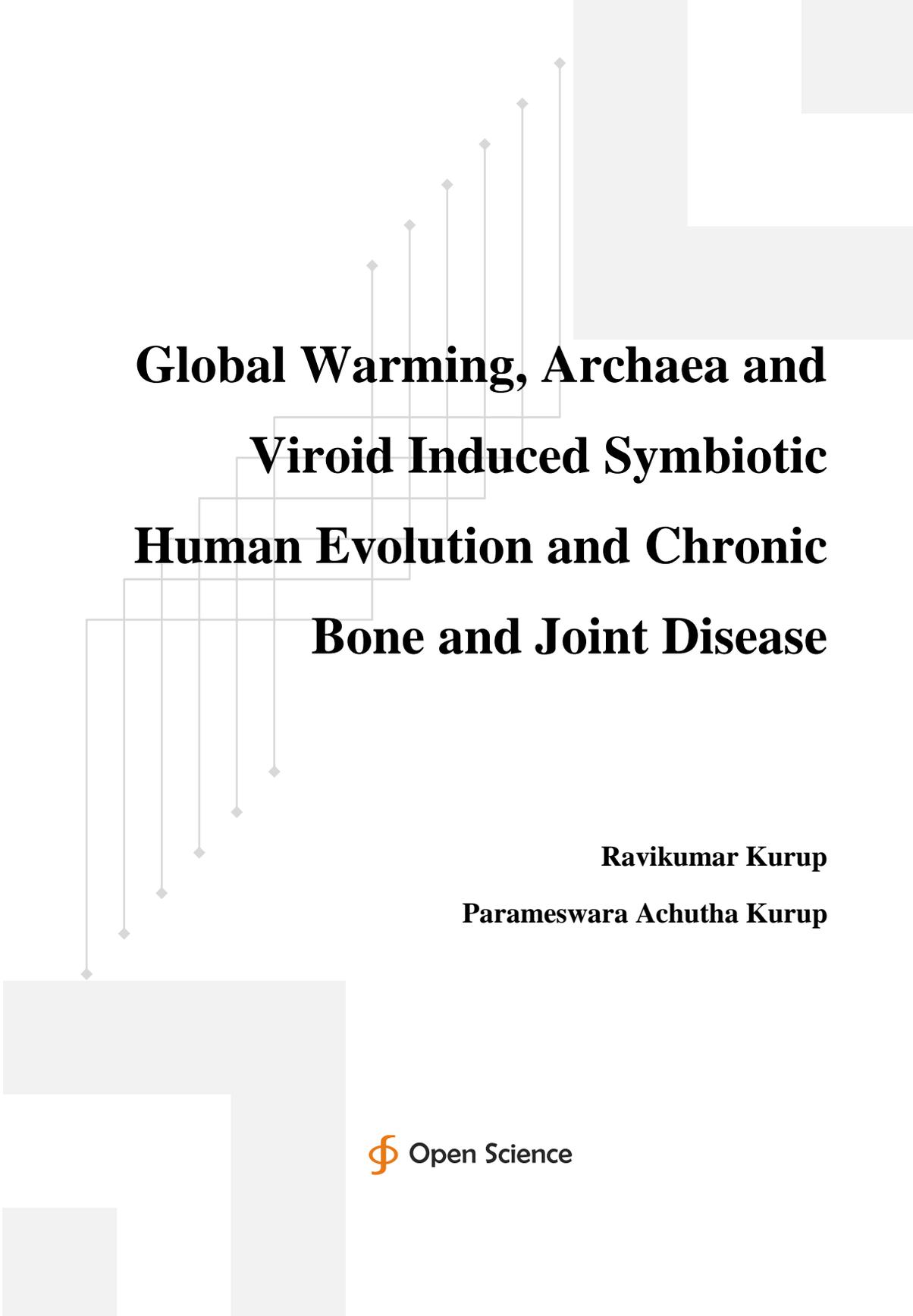


Ravikumar Kurup & Parameswara Achutha Kurup

# **Global Warming, Archaea and Viroid Induced Symbiotic Human Evolution and Chronic Bone and Joint Disease**





An abstract graphic consisting of a series of vertical lines of varying heights, each ending in a small diamond shape. These lines are connected by horizontal lines, creating a stepped, staircase-like effect. The lines and diamonds are light gray. The background features large, light gray geometric shapes in the corners.

# **Global Warming, Archaea and Viroid Induced Symbiotic Human Evolution and Chronic Bone and Joint Disease**

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# 1

## The Endosymbiotic Archaea, Fructose Disease, Chronic Bone and Joint Disease and Global Warming

Global warming induces endosymbiotic archaeal and RNA viroidal growth. The porphyrins form a template for the formation of RNA viroids, DNA viroids, prions, isoprenoids and polysaccharides. They can symbiose together to form primitive archaea. The archaea can further induce HIF alpha, aldose reductase and fructolysis resulting in further porphyrinogenesis and archaeal self replication. The primitive archaeal DNA is integrated along with RNA viroids which are converted to their corresponding DNA by the action of redox stress induced HERV reverse transcriptase into the human genome by the redox stress induced HERV integrase. The archaeal DNA sequences that are integrated into the human genome forms endogenous archaeal human genomic sequences akin to HERV sequences and can function as jumping genes regulating genomic DNA flexibility. The integrated endogenous genomic archaeal sequences can get expressed in the presence of redox stress forming endosymbiotic archaeal particles which can function as a new organelle called the archaeons. The archaeon can express the fructolytic pathway constituting an organelle called the fructosome, cholesterol catabolic pathway and digoxin synthetic forming an organelle called the steroidelle, the shikimic acid pathway forming an organelle called the neurotransminoid, antioxidant vitamin E and vitamin C synthetic organelle called the vitaminocyte as well as the glycosaminoglycan synthetic organelle called glycosaminoglycoid. The archaea can secrete capsulated RNA viroidal particles which can function as blocking RNAs modulating cell metabolism and such archaeon organelle are called viroidelle. The archaea suppresses pyruvate dehydrogenase and promotes fructolysis resulting in accumulation of pyruvate which enters the GABA shunt pathway producing succinyl CoA and glycine, the substrates for porphyrin synthesis. Porphyrin forms a template for the formation of RNA viroids, DNA viroids, prions and isoprenoids which can symbiose together to form an archaea. Thus endosymbiotic archaea have an abiogenic replication. The archaeon concerned

with GABA shunt pathway and porphyrinogenesis are called porphyrinoids. The archaeon colony forms a network with different areas showing differential specialization of function - fructosoids, steroidelle, vitaminocyte, viroidelle, neurotransminoid, porphyrinoids and glycosaminoglycoids. This forms a living organized structure within human cells and tissues regulating their function and reducing the human body to zombie working under the directions of the organized archaeal colony. The organized archaeal colony has abiogenetic replication and is eternal.

The endosymbiotic actinidic archaea forms the basis of life and can be considered as the third element in the cell. It regulates the cell, the neuro-immune-endocrine system and the conscious / unconscious brain. The endosymbiotic actinidic archaea can be called as the elixir of life. A definite population of endosymbiotic actinidic archaea is required for the existence and survival of life. A higher density of endosymbiotic actinidic archaeal population can lead to human disease. Thus actinidic archaea are important for survival of human life and can be considered as crucial to it. Symbiosis by actinidic archaea is the basis of evolution of humans and primates. The increase in endosymbiotic archaeal growth can lead to the induction of homo neanderthalis. This endosymbiotic archaea induced neanderthalisation of the species leads to human disease like metabolic syndrome X, neurodegenerations, schizophrenia and autism, autoimmune disease and cancer. The reduction in endosymbiotic archaeal growth by a high fibre, high medium chain triglyceride and legume protein ketogenic diet, antibiotics from higher plants like *Curcuma longa*, *Embllica officianalis*, *Allium sativum*, *Withania somnifera*, *Moringa pterygosperma* and *Zingiber officianalis* and transplantation of colonic microflora from normal homo sapien population can lead to deneanderthalisation of species and treatment of the above mentioned diseased states. The colonic microflora of neanderthalised diseased states like metabolic

syndrome X, neurodegenerations, schizophrenia and autism, autoimmune disease and cancer when transferred to the normal homo sapien species leads to generation and induction of homo neanderthalis. Thus primate and human evolution is symbiotic event which can be induced the modulating symbiotic archaeal growth. Human populations can be divided into matrilineal Neanderthal population in South Indian Dravidians, Celts, Basques, Jews and Berbers and the cro-magnon population seen in Africa and Europe. The symbiotic archaeal colonization decides which species - Neanderthal or Cro-magnon to which the society belongs to. It is tempting to postulate symbiotic microflora and archaea determining the family behavior and traits as well as societal and caste behavior and traits. The cell has been postulated by Margulis to be a symbiotic association of bacteria and viruses. Similarly, the family, the caste, the community, nationalities and the species itself is determined by archaeal and other bacterial symbiosis.

Symbiosis by microorganisms especially archaea drives the evolution of the species. In such a case symbiosis can be induced by transfer of microflora symbionts and evolution induced. Endosymbiosis by archaea as well as archaeal symbionts in the gut can modulate the genotype, the phenotype, the social class and the racial group of the individual. The symbiotic archaea can have horizontal and vertical transmission. Endosymbiotic archaeal growth leads to neanderthalisation of the species. The neanderthalised species is matrilineal society and includes the Dravidians, the Celts, the Basques and the Berbers. The inhibition of the endosymbiotic archaeal growth leads to evolution of the homo sapiens. This includes the Africans, Aryan invaders of North India and the Aryan derived European population. Symbiosis mediated evolution depends on the gut flora and the diet. This has been demonstrated in the drosophila pseudoobscura. The drosophila mates only with other individuals eating the same diet. When the drosophila gut microflora is altered by feeding antibiotics

they mate with other individuals eating different diets. The diet consumed by the drosophila regulates its gut microflora and mating habits. The combination of the human genome and the symbiotic microbial genome is called the hologenome. The hologenome especially its symbiotic microbial component drives human evolution as well as animal evolution. The evolutionary distance between species of wasp depends on the gut microflora. The human gut microflora regulates the endocrine, genetic and neuronal systems. Humans and primate evolution depends on endosymbiotic archaea and gut microflora. The endosymbiotic archaeal growth determines the racial differences between the matrilineal Harappan / Dravidian societies and the patriarchal Aryan society. The matrilineal Harappan / Dravidian society was neanderthalic and had increased endosymbiotic archaeal growth. Endosymbiotic archaeal growth and neanderthalisation can lead to autoimmune disease, metabolic syndrome X, neurodegeneration, cancer, autism and schizophrenia. The Neanderthal gut flora and endosymbiotic archaea was determined by the non vegetarian ketogenic high fat high protein diet consumed by them in the Eurasian steppes. The homo sapiens including the classical Aryan tribes and African ate a high fibre diet and had lower archaeal growth both endosymbiotic and gut. The dietary fibre intake determines the microbial diversity of the gut. The high fibre intake is associated with increased generation of short chain fatty acids - butyric acid by the gut flora. Butyrate is a HDAC inhibitor and leads to increased generation and incorporation of endogenous retroviral sequences. The high dietary fibre intake related increased HERV sequences leads to increased synaptic connectivity and a dominant frontal cortex as seen in homo sapien species. The neanderthalic species consume a ketogenic non vegetarian high fat high protein low fibre diet. This leads to decreased generation of endogenous HERV sequences and reduced genomic flexibility in neanderthalic species. This produces smaller cerebral cortex and a dominant cerebellar cortex in the neanderthalic brain. The

homo neanderthalic species by the low dietary fibre intake starve their microbial self. This leads to increased endosymbiotic and gut archaeal growth. The mucous membrane lining the gut becomes thinned out as the gut bacteria eats up the mucous lining of the gut. This results in leakage of endotoxin and archaea from the gut to the blood breaching the barrier and produces a chronic immunostimulatory inflammatory state which forms the basis of autoimmune disease, metabolic syndrome, neurodegeneration, oncogenic and psychiatric disorders. The Neanderthal species eat a low fibre diet and have a deficiency of microbiota accessed carbohydrate generating short chain fatty acid. There is a deficiency of butyrate generated in the gut from the dietary fibre which can produce suppression of the chronic inflammatory process. The Neanderthals have got the fermentation by-product deficiency syndrome. The induction of neanderthalic species depends on the low fibre intake induced high archaeal density endosymbiotic and the gut microflora. The homo sapiens species consume a high fibre diet generating large amounts of short chain fatty acid butyrate which inhibits endosymbiotic and gut archaeal growth. The microbial self of the homo sapien species is more diverse than that of the neanderthalic species and the archaeal population density is less. This results in a protection against chronic inflammation and the induction of diseases like autoimmune disease, metabolic syndrome, neurodegeneration, oncogenic and psychiatric disorders. The homo sapien species have a higher intake of dietary fibre contributing to around 40 g/day and a diverse microbial gut flora with less of archaeal population density. The butyrate generated from dietary fibre produces an immunosuppressive state. Thus the symbiotic microflora with less of archaeal density induces a homo sapien species. This can be demonstrated by experimental induction of evolution. A high fibre high MCT diet as well as antibiotics derived from higher plants and fecal microbiota transfer from sapien species can inhibit the Neanderthal metabolonomics and phenotype and induce

the evolution of homo sapiens. A low fibre high fat high protein diet as well as fecal microbiota transfer from the Neanderthal species can produce Neanderthal metabolonomics and phenotype inducing the evolution of homo neanderthalis. Transfer of colonic microflora predominantly archaea and modulation of endosymbiotic archaea by a paleo diet and antibiotics from higher plants can lead to interconversion of human species between homo neanderthalis and homo sapiens. The hologenome especially the microbial flora endosymbiotic/gut drives human and animal evolution and can be experimentally induced. Symbiotic microflora drives evolution. Every animal, every human species, different communities, different races and different caste have their signature endosymbiotic and gut microflora which can be transmitted vertically and horizontally. Thus symbiosis drives human and animal evolution.

This can be interpreted on the basis of Villarreal hypothesis of group identity and cooperativity of RNA collectives. Archaeal symbiosis in the gut and in the tissue spaces determines speciation of human beings as homo sapiens and homo neanderthalis. The endosymbiotic archaea can secrete RNA viroids and viruses and there is a viroid-archaeal host relationship between the two. A dynamic state of virus lysis and persistence can occur in archaea suggesting that viral addiction can occur in archaea. The RNA viroids in the archaea coordinate their behavior by information exchange, modulation and innovation generating new sequence based content. This occurs due to a phenomenon of symbiosis in contrast to the concept of survival of the fittest. The generation of new RNA viroidal sequences is a result of practical competence of living agents to generate new sequences by symbiosis and sharing. This represents highly productive RNA viroidal quasi-species consortia for the evolution, conservation and plasticity of genomic environments. The behavioural motives of the RNA are single stem loop structures. They have self folding and group building capabilities depending upon functional needs. The evolution process depends

upon what Villareal calls RNA stem loop consortia. The whole entity can function only if participatory groups of RNA viroids can get their function coordinated. There is competent denovo generation of new sequences by cooperative action and not by competition. These RNA viroidal group consortia can contribute to the host identity, group identity and group immunity. The term used for this is RNA viroidal sociological behavior. The RNA viroids can build groups that invade the archaea and compete as a group for limited resources such host genomes. A key behavioural motif is able to integrate a persistent life style into the archaeal colony with the addiction module forming competing viroidal groups that are counter balancing each other together with the archaeal/host immune system. This leads to creation of an identity for the archaeal colony and the homo neanderthalis host. Viroids can kill their host and also colonize their host without disease and protect the host from similar viruses and viroids. Together with lysis and protection we see a viroid colonized host that is both symbiotic and innovative acquiring new competent codes. Thus the viroid-host relationship is a pervasive, ancient force in the origin and evolution of life. Cumulative evolution at the level of RNA viroids is like a ratchet effect used for transmission of cultural memes. This learning accumulates so that every new generation must not repeat all innovative thoughts and techniques. Quasi-species of RNA viroids are cooperative and exclusive of other quasi-species. They have group recognition differentiating self-groups and non-self-groups allowing for quasi-species to promote the emergence of group identity. With group identity via counter related addiction modules two opposing components must be present and work coherently and define the group as a whole. Biological identity is constituted by dynamic interaction of cooperative groups. Virus addiction module is an essential strategy for existence of life in the virosphere. Viruses are transmissible and can persist in specific host population leading to a form of group immunity / identity since identical

but uncolonized host population remains susceptible to a killing action of lytic viruses. In this way we see that viruses are necessary providing opposing functions for addiction (persistence/protection and lytic/killing). Viroids can function as consortia, an essential interacting group and provide a mechanism from which consortial function could emerge in the origin of protobiotic life. Genetic parasites can act as a group (qs-c). But for this group to be coherent they must attain group identity and this is typically via an addiction strategy. Antiviral and proviral system in the archaea will themselves emerge in the host from virus derived information. The archaeal viruses themselves provide the critical function required for antiviral defence. The opposing functions are the basis of addiction modules. Thus the emergence of group identity becomes an essential and early event in the emergence of life. This is coherent to the basically group behavior of RNA viroids in archaea. This group selection and group identity are needed to create information coherence and network formation and to establish a system of communication - code competent interactions. This identity serves as information also for the ones that do not share this identity. This is the beginning of self/non-self differentiating capability. In this way viroids promote the emergence of group identity in archaeal colonies and host humans. The archaeal colony identity depends upon the colonizing set of RNA viroids producing a coherent network that is inclusive opposing functions and favours the persistence of parasite derived new information. On the basis of population-based functions of RNA DNA can be considered as a habitat for consortia RNA. Thus RNA viroids of the archaea are involved in complex multicellular identity. This is called as the Gangen hypothesis by Villarreal. The Gangen describes the emergence of commonly shared code use, group membership and collective living function of RNA viroids. Communication is a code depended interaction and transmission of infectious code defines the origin of the virosphere. This issue refers to the idea

of collective of RNA viroids with inherent toxic and antitoxic features should be able to transmit or communicate these agents and their features to a nearby competing population. It strongly favours the survival of RNA viroidal population with compatible addiction modules that will inhibit agent toxicity and allow persistence of new agents. This is thus the survival of the persistently colonized set which is an inherently symbiotic and consortial process. It also promotes increasing complexity and identity/immunity of the host collective via a new agent colonization, and stable addition. Thus the transmission of RNA agents attains both communication and recognition of group membership. In this way the emergence of the virosphere must had been an early event in the origin of life and group identity. Viruses and viroids are genetic parasites and the most abundant living entities on earth. The virosphere is a network of infectious genetic agents. Evolution, conservation and plasticity of genetic identities are the result of cooperative consortia of RNA viroids that are competent to communicate. Thus the archaeal viroidal consortia can symbiotically share and communicate producing new sequences and give an identity to the archaeal colony. The low fibre diet and extreme temperatures of the Eurasian steppes leads to archaeal multiplication and induction of the homo neanderthalis species. The archaeal colony's characteristics are determined by the cooperative consortia of RNA viroids in the archaea and the archaeal colony identity determines the homo neanderthalis identity. Thus the archaeal colonies with their quasi-species consortia of RNA viroids determine the homo neanderthalis identity. The new sequence generation by the RNA viroidal consortia's symbiotic sharing character contributes to the diversity in the behavior and creativity of the homo neanderthalis population. The archaeal RNA viruses and viroids and the archaeal colonies themselves protect the homo neanderthalis population from retroviral infections. Thus the homo neanderthalis population is retroviral resistant and the quasi-species consortia of

archaea and archaeal viroids gives them a group identity as retroviral resistant. Thus the quasi-species consortia of archaea and RNA viroids give homo neanderthalis colonies their identity and idea of self. The homo neanderthalis is resistant to retroviral infection like the Australian aboriginals and the endogenous retroviral sequences in the Neanderthal genome are limited. This leads to lack of plasticity and dynamicity of the human genome and the cerebral cortex is ill-developed with a dominant impulsive cerebellar cortex in the homo neanderthalis population. This produces the impulsive creative surrealistic spiritual neanderthalic brain. As the extreme of temperature goes off and the ice age ends the archaeal population density also comes down. This also can result from the consumption of a high fibre diet in the African continent. The high fibre diet digested by clostridial clusters in the colon promotes butyrate synthesis and butyrate will induce HDAC inhibition and expression of retroviral sequences in the primate genome. This leads to increase in endogenous retroviral sequences in the human genome, increasing genomic dynamicity and the evolution of complicated cerebral cortex dominant brain with its complex synaptic connectivity in the homo sapiens. This leads onto a logical, commonsensical, pragmatic and practical homo sapiens brain. The homo sapiens due to lack of archaea and the RNA viroids are susceptible retroviral infection. Thus the archaeal colonies and RNA viroidal quasi-species consortia determine the evolution of the human species and the brain networks. Thus extremes of temperature, fibre intake, archaeal colony density, RNA viroidal quasi-species, group identity and retroviral resistance decides on the evolution of homo sapiens and homo neanderthalis as well as the brain networks. The present extremes of temperature and low fibre intake in civilized society can lead to increase in archaeal population densities and quasi-species RNA viroidal networks generating a new homo neanderthalis in a new neanderthalic anthropocene age as opposed to the present homo sapiens anthropocene age. The

archaeal population densities and quasi-species RNA viroidal networks determine homo sapien / homo neanderthalis species, racial, caste, community, national, sexual, metabolic, phenotypic, immune, genotypic and individual identity. The archaea secretes the trephone digoxin which can edit the RNA viroids and generate new sequences. Archaeal dipolar magnetite and porphyrins in the setting of digoxin induced membrane sodium potassium ATPas inhibition can produce a pumped phonon system mediated quantal perceptive state and quantal communication in the RNA viroidal symbiotic system generating new sequences by steroidal digoxin enzymatic editing action. This gives rise to archaeal RNA viroidal quasi-species symbiotic diversity and identity to species, race, caste, sex, culture, individual and national identity.

The roots of Western civilisational disease can be related to the starvation of the colonic microflora. The colonic microflora depends upon complex carbohydrates derived from dietary fibre. The processed food of high protein, fat and sugars is digested and absorbed in the stomach and small intestine. A very little of it reaches the colon and widespread use of antibiotics in medicine has produced mass extinction of the colonic microflora. The colonic microflora is extremely diverse and the diversity is lost. There are 100 trillion bacteria in the colon belonging to 1200 species. They regulate the immune system by inducing the T-regulatory cells. A high fibre diet contributes to colonic microbiota diversity. Interaction with farm animals like cows and dogs also contributes to the colonic microflora diversity. The typical Western diet of high fat, high protein and sugars decreases the colonic microbiota diversity and increase colonic/endosymbiotic archaea producing methanogenesis. The colonic archaea feed upon the mucous lining of the colon and produces leakage of archaea into the blood and tissue system producing endosymbiotic archaea. This results in a chronic inflammatory state. The high fibre diet of Africans, South Americans and Indians produces increased colonic microbiota diversity and

increase in clostridial clusters generating SCFA in the gut. High fibre diet is protective against metabolic syndrome and diabetes mellitus. Metabolic syndrome is related to degeneration, cancer, neuropsychiatric illness and autoimmune disease. A high fibre diet of upto 40 g/day can be called as a gut diet. The colonic microflora especially the clostridial cluster digests the fibre generating short chain fatty acids which regulates immunity and metabolism. High fibre diet increases the colonic mucus secretion and the thickness of the mucus lining. A high fibre diet produces increase in clostridial clusters and mucous secretion. This produces a strong gut blood barrier and prevents metabolic endotoxemia which produces a chronic inflammatory response. High dietary fibre intake and the diversity of the colonic microflora with prominent SCFA producing clostridial clusters are interrelated. The clostridial clusters metabolise the complex carbohydrate in dietary fibre to short chain fatty acids butyrate, propionate and acetate. They increase the T-regulatory function. A high fibre diet increases the bacteroides and reduces the firmecutes of the colonic microflora. A high fibre diet is associated with a low body-mass index. A low fibre diet produces increase in colonic archaeal growth as well as endosymbiotic tissue and blood archaea. This produces more of methanogenesis rather than short chain fatty acid synthesis contributing to immune activation. A low fibre diet is associated a high body-mass index and chronic systemic inflammation. Germ-free mice show cardiac, pulmonary and liver atrophy. Gut microflora is required for the generation of organ systems. The gut microflora is also required for generation of T-regulatory cells. High fibre intake produces more colonic microbiota diversity and increase in clostridial clusters and fermentation by products like butyrate which suppresses inflammation and increases T-regulatory cells. A low fibre diet produces increase in archaeal growth, methanogenesis, destruction of the mucus lining and leakage of the colonic archaea producing endosymbiotic tissue and blood archaea. This

produces an immune hyperreactivity contributing to the modern plagues of civilisation - metabolic syndrome, schizophrenia, autism, cancer, autoimmunity and degenerations. The gut microbiota drives human evolution. The humans don't host the gut microbiota but the gut microbiota host us. The human system forms an elaborate culture laboratory for the propagation and survival of the microbiota. The human system is induced by the microbiota for their survival and growth. The human system exists for the microbiota and not the other way round. The same mechanism holds good in plant systems. Plant started the colonized earth as they started symbiosing with bacteria in the roots systems which can derive nutrients from the soil. Human beings form a mobile culture laboratory for the more effective propagation and survival of the microbiota. The microbiota induces the formation of specialized immune cells called innate lymphoid cells. The innate lymphoid cells will direct the lymphocytes not to attack the beneficial bacteria. Thus the endosymbiotic archaea and the gut archaea induce human, primate and animal evolution to generate structures for them to survive and propagate. The source of endosymbiotic archaea, the third element of life is the colonic archaea that leaks into the tissue spaces and blood systems due to breach in the gut blood barrier. The increase in colonic archaea is due to the starvation of the gut microbiota consequent to a low fibre diet. This results in increase in colonic archaeal growth and destruction of clostridial clusters and bacteroides. The increase colonic archaeal growth in the presence of gut starvation due to low fibre diet eats up the mucus lining and produces breakages in the gut blood barrier. The colonic archaea enters the blood stream and produces endosymbiosis generating endosymbiotic archaea and various new organelle - fructosoids, steroidelle, vitaminocyte, viroidelle, neurotransminoid, porphyrinoids and glycosaminoglycoids.

The increase in endogenous EDLF, a potent inhibitor of membrane  $\text{Na}^+\text{-K}^+$  ATPase, can decrease this enzyme activity. The results showed increased

endogenous EDLF synthesis as evidenced by increased HMG CoA reductase activity, which functions as the rate limiting step of the isoprenoid pathway. Studies in our laboratory have demonstrated that EDLF is synthesized by the isoprenoid pathway. The endosymbiotic archaeal sequences in the human genome get expressed by redox stress and osmotic stress of global warming. This results in induction of HIF alpha which will upregulate fructolysis and glycolysis. In the setting of redox stress all glucose gets converted to fructose by the induction of enzymes aldose reductase and sorbitol dehydrogenase. Aldose reductase converts glucose to sorbitol and sorbitol dehydrogenase converts sorbitol to fructose. Since fructose is preferentially phosphorylated by ketohexokinases the cell is depleted of ATP and glucose phosphorylation comes to a halt. Fructose becomes the dominant sugar that is metabolized by fructolysis in expressed archaeal particles in the cell functioning as organelle called fructosoids. The fructose is phosphorylated to fructose 1-phosphate which is acted upon by aldolase B which converts it into glyceraldehyde 3-phosphate and dihydroxy acetone phosphate. Glyceraldehyde 3-phosphate is converted to D 1,3-biphosphoglycerate which is then converted to 3-phosphoglycerate. The 3-phosphoglycerate is converted to 2-phosphoglycerate. 2-phosphoglycerate is converted to phosphoenol pyruvate by the enzyme enolase. Phosphoenol pyruvate is converted to pyruvate by the enzyme pyruvic kinase. The archaeaon induces HIF alpha which upregulates fructolysis and glycolysis but inhibits pyruvate dehydrogenase. The forward metabolism of pyruvate is stopped. The dephosphorylation of phosphoenol pyruvate is inhibited in the setting of pyruvic kinase inhibition. Phosphoenol pyruvate enters the shikimic acid pathway where it is converted to chorismate. The shikimic acid is synthesized by a pathway starting from glyceraldehyde 3-phosphate. Glyceraldehyde 3-phosphate combines with the pentose phosphate pathway metabolite sedoheptulose 7-phosphate which is converted to erythrose

4-phosphate. The pentose phosphate pathway is upregulated in the presence of the suppression of glycolytic pathway. Erythrose 4-phosphate combines with phosphoenol pyruvate to generate shikimic acid. Shikimic acid combines with another molecule of phosphoenol pyruvate to generate chorismate. The chorismate is converted to prephenic acid and then to parahydroxy phenyl pyruvic acid. Parahydroxy phenyl pyruvic acid is converted to tyrosine and tryptophan as well as neuroactive alkaloids. The shikimic acid pathway is structured in expressed archaeon organelle called the neurotransminoid. The fructolytic intermediates glyceraldehydes 3-phosphate and pyruvate are the starting points of the DXP pathway of cholesterol synthesis. Glyceraldehyde 3-phosphate combines with pyruvate to form 1-deoxy D-xylulose phosphate (DOXP) which is then converted to 2-C methyl erythritol phosphate. 2-C methyl erythritol phosphate can be synthesized from erythrose 4-phosphate a metabolite of the shikimic acid pathway. DXP combines with MEP to form isopentenyl pyrophosphate which is converted to cholesterol. Cholesterol is catabolised by archaeal cholesterol oxidases to generate digoxin. The digoxin sugars digitoxose and rhamnose are synthesized by the upregulated pentose phosphate pathway. Glycolytic suppression leads to upregulation of the pentose phosphate pathway. The expressed archaeon organelle concerned with cholesterol catabolism and digoxin synthesis is called the steroidelle. The suppression of glycolysis and stimulation of fructolysis results in upregulation of the hexosamine pathway. Fructose is converted to fructose 6-phosphate by ketohexokinases. The fructose 6-phosphate is converted to glucosamine 6-phosphate by the action of glutamine fructose 6-phosphate amidotransferase (GFAT). Glucosamine 6-phosphate is converted to UDP N-acetyl glucosamine which is then converted to N-acetyl glucosamine and various amino sugars. UDP glucose is converted to UDP D-glucuronic acid. UDP D-glucuronic acid is converted to glucuronic acid. This forms the uronic acid synthetic pathway.

Uronic acids and hexosamines form repeating units of glycosaminoglycans. In the setting of glycolytic suppression and fructolytic metabolism fructolysis leads to increase synthesis of hexosamines and GAG synthesis. The GAG synthesizing archaeon particles are called the glycosaminoglycoids. The expressed archaeon particles are capable of synthesizing antioxidant vitamin C and E. The UDP D-glucose is converted to UDP D-glucuronic acid. UDP D-glucuronic acid is converted to D-glucuronic acid. D-glucuronic acid is converted to L-gulonate by enzyme aldoketoreductases. L-gulonate is converted to L-gulonolactone by lactonase. L-gulonolactone is converted to ascorbic acid by the action of archaeal L-gulo oxidase. The vitamin E is synthesized from shikimate which is converted to tyrosine and then to parahydroxy phenyl pyruvic acid. Parahydroxy phenyl pyruvic acid is converted to homogentisate. Homogentisate is converted to 2-methyl 6-phytyl benzoquinone which is converted to alpha tocopherol. 2-methyl 6-phytyl benzoquinone is converted to 2,3-methyl 6-phytyl benzoquinone and gamma tocopherol. Vitamin E can also be synthesized by the DXP pathway. Glyceraldehyde 3-phosphate and pyruvate combined to form 1-deoxy D-xylulose 5-phosphate which is converted to 3-isopentenyl pyrophosphate. 3-isopentenyl pyrophosphate and dimethyl allyl pyrophosphate combined to form 2-methyl 6-phytyl benzoquinone which is converted to tocopherols. The ubiquinone another important membrane antioxidant and part of the mitochondrial electron transport chain is synthesized by the shikimic acid pathway and DXP pathway. The isoprenoid moiety of ubiquinone is contributed from the DXP pathway and the rest of it by tyrosine catabolism. The tyrosine is generated by the shikimic acid pathway. The archaeon particles concerned with the synthesis of vitamin C, vitamin E and ubiquinone which are all antioxidants are called the vitaminocyte.

Global warming can lead to osmotic stress consequent to dehydration. The increase in actinidic archaeal growth leads to cholesterol catabolism and digoxin

synthesis. Digoxin produces membrane sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial dysfunction. This results in oxidative stress. The oxidative stress and osmotic stress can induce the enzyme aldose reductase which converts glucose to fructose. Fructose has got a low  $K_m$  value for ketokinase as compared to glucose. Therefore fructose gets phosphorylated more to fructose phosphate and the cell is depleted of ATP. The cell depletion of ATP leads to oxidative stress and chronic inflammation consequent to induction of NF $\kappa$ B. Oxidative stress can open the mitochondrial PT pore producing release of cyto C and activation of the caspase cascade of cell death. The fructose phosphate can enter the pentose phosphate pathway synthesizing ribose and nucleic acid. The depletion of cellular ATP results in generation of AMP and ADP which are acted upon by deaminases causing hyperuricemia. Uric acid can produce endothelial dysfunction and vascular disease. Uric acid can also produce mitochondrial dysfunction. The fructose phosphate can enter the glucosamine pathway synthesizing GAG and producing mucopolysaccharide accumulation. Fructose can fructosylate proteins making them antigenic and producing an autoimmune response. This can lead to global warming related bone and joint disease.

Global warming induces endosymbiotic archaeal and RNA viroidal growth. The endosymbiotic archaea and the generated RNA viroids induce aldose reductase which converts glucose to sorbitol. The archaeal polysaccharides and lipopolysaccharides as well as viroids and viruses can induce aldose reductase. Sorbitol is acted upon by sorbitol dehydrogenase to generate fructose which enters fructolytic pathway. Aldose reductase is also induced by the osmotic stress of global warming and redox stress. Aldose reductase is induced by inflammatory and immune stimulation. Archaeal synthesized endogenous digoxin can produce intracellular redox stress and activate NF $\kappa$ B which produces immune activation. Both redox stress and immune activation can

activate aldose reductase which converts glucose to fructose. Hypoxic stress or anaerobic conditions induces HIF alpha which activates ketohexokinase C which phosphorylates fructose. Fructose is acted upon by fructokinase which converts fructose to fructose 1-phosphate. Fructose 1-phosphate is converted to dihydroxy acetone phosphate and glyceraldehydes 3-phosphate which is converted to pyruvate, acetyl CoA and citrate. Citrate is used for lipid synthesis. Fat deposition occurs in the visceral organs like the liver, heart and kidney. There is no subcutaneous fat deposit. Fructose metabolism bypasses phosphofructokinase which is inhibited by citrate and ATP. Fructose metabolism is therefore not under the regulatory control of the enzyme phosphofructokinase. Fructose transport and metabolism is not regulated by insulin. Fructose is transported by GLUT-5 receptor. Fructose does not increase insulin secretion and therefore does not activate lipoprotein lipase. This results in visceral adipogenesis. Fructose induces ChREBP and SREBP elements. This results in increased hepatic lipogenesis by the induction of the enzyme fatty acid synthase, acetyl CoA carboxylase and stearoyl CoA desaturase. This increases fatty acids and cholesterol synthesis. Fructose is a lipophilic carbohydrate. Fructose can be converted to glycerol 3-phosphate and fatty acids involved in triglyceride synthesis. Fructose administration leads to increase in triglycerides and VLDL. Fructose consumption leads to insulin resistance, fat accumulation in visceral organs like liver, heart and kidney, insulin resistance, dyslipidemia with increased triglycerides, VLDL and LDL as well as the metabolic syndrome. The metabolic syndrome X can be considered as a fructolytic syndrome. Fructose will increase lipid storage and promote insulin resistance. Fructose can fructosylate proteins producing dysfunction. Fructose has no effect upon ghrelin and leptin in the brain and can lead to increased feeding behaviour. Glucose decreases ghrelin and increases leptin levels. This leads to suppression of appetite. Thus fructose can modulate eating behaviour leading onto obesity.

Fructose results in NF $\kappa$ B activation and TNF alpha secretion. TNF alpha can modulate the insulin receptor producing insulin resistance and metabolic syndrome X. Fructose can also lead to leptin resistance and obesity. There is an epidemic of metabolic syndrome X in relation to global warming.

Fructose can activate the sympathetic nervous system. This leads to hypertension and increase in heart rate. Fructose is involved in left ventricular hypertrophy, increase in left ventricular mass and decrease in left ventricular ejection fraction in hypertension. Fructose suppresses the parasympathetic nervous system. Fructose acts as a key inducer for uncontrolled proliferation and hypertrophy of the cardiac musculature consequent to hypertension. The heart uses beta oxidation of fatty acids to generate energy. In the setting of anaerobic glycolysis consequent to myocardial infarction and hypertensive hypertrophy of the heart, there is induction of HIF alpha. This produces increase in ketohexokinase C in the heart which phosphorylates fructose. Ketohexokinase C is a predominant liver enzyme as fructose metabolism is primarily focused in the liver. In the setting of anaerobic glycolysis ketohexokinase C is also produced in the brain and the heart. Ketohexokinase A is the predominant enzyme in the heart and brain. In the setting of anaerobic glycolysis ketohexokinase A which preferentially metabolizes glucose is converted to ketohexokinase C metabolizing fructose by the mechanism of RNA splicing. Anaerobic conditions can induce HIF alpha which activates the splicing factor SF3B1. Thus HIF alpha induced by glycolysis induces SF3B1 which induces ketohexokinase C producing fructolysis in the heart. The fructose is converted to lipids, glycogen and glycosaminoglycans in the heart producing cardiac hypertrophy. Fructose metabolism is not under regulatory control of the key enzyme phosphofructokinase by citrate and ATP. The fructolytic pathway functions as a rogue pathway not under any regulatory control. Fructose is a key contributor. The sympathetic overactivity and parasympathetic blockade consequent to fructose can produce immune activation.

The sympathetic overactivity and parasympathetic blockade can lead to dysregulation of the nervous system.

Fructose can activate NF $\kappa$ B and tumour necrosis factor alpha. The vagal blockade produced by fructose also leads to increase in immune activation. Fructose can inhibit neutrophilic phagocytosis. Increased fructose ingestion can lead to immune activation and respiratory diseases like chronic bronchitis, COPD and bronchial asthma as well as interstitial lung disease. This immune activation induced by fructose is called as fructositis. Fructosylated proteins can serve as autoantigens. Fructosylated proteins can bind to RAGE receptors producing immune activation. Global warming induced fructose disease is the basis of the epidemic of autoimmune disease rising with the global warming.

Fructose increases flux through the pentose phosphate pathway. This increases the availability of hexose sugars like ribose for nucleic acid synthesis. This increases DNA synthesis. There is also consequent increase in protein synthesis. The tumour cells can slurp up fructose. Tumour cells utilise fructose for proliferation. The fetal cells like tumour cells also utilize fructose for proliferation. Fructose can promote metastatic deposits. The tumour cells use fructose differently from glucose. Cancer cells utilize fructose to support proliferation and metastasis. Fructose increases nucleic acid synthesis. Fructose can help the cancer cells to grow fast by inducing the transketolase enzyme and the pentose phosphate pathway. Fructose administration increases redox stress, DNA damage and cell inflammation all contributing to oncogenesis. Fructose is the most abundant sugar in the fetal tissues and is important in the development of fetus by promoting cell proliferation. Fructose is 20-times more concentrated in the fetal blood than glucose. Sperm cells and ova also use fructose for metabolism and energy. Thus all rapidly proliferating cells - cancer cells, fetal cells and reproductive cells depends upon fructolysis. Fructose is the principal diet of the cancer cells. Global warming and archaeal growth results in HIF

alpha induction. HIF alpha induces tumour growth. HIF alpha also increases glycolysis. But archaeal induced HIF alpha also induces aldose reductase which converts glucose to fructose and metabolism proceeds along the fructolytic pathway. Fructosylation of glycolytic enzymes brings glycolysis to a halt. Fructosylation of mitochondrial PT pore hexokinase can result in PT pore dysfunction and cell proliferation. The fructolytic pathway is the principal energetic pathway for rapidly proliferating cancer cells, fetal cells and stem cells. The global warming will induce the Warburg phenotype of the fructolytic variety. This leads to an epidemic of cancer. There is an epidemic of cancer in relation to global warming. The fructolytic pathway can lead to increased DNA synthesis and RNA synthesis due to flux via the pentose phosphate pathway. The fructolytic pathway can be directed to the GABA shunt generating succinyl CoA and glycine. These are substrates for porphyrin templates to form RNA viroids. The archaeal induced redox stress can induce endogenous HERV expression and reverse transcriptase expression. The RNA viroids are converted by HERV reverse transcriptase to corresponding DNA and integrated into the genome by HERV integrase. The integrated RNA viroid related DNA can function as jumping genes producing genomic plasticity and genomic change.

Fructose as said before induces the thiamine dependent transketolase flux. It increases both the oxidative and non oxidative pentose phosphate pathway. This increases nucleic acids and glycosaminoglycan synthesis. Fructose is converted to fructose 1-phosphate which is acted upon by aldolase B converting it into glyceraldehyde and dihydroxy acetone phosphate. Glyceraldehyde is converted glyceraldehyde 3-phosphate by triokinase. DHAP can be converted to glyceraldehyde 3-phosphate by the enzyme triose phosphate isomerase. Glyceraldehyde 3-phosphate can be converted to pyruvate. This pyruvate can be channeled to gluconeogenesis and glycogen storage by the action of the enzyme pyruvate carboxylase. This results in the conversion of glyceraldehyde

3-phosphate to pyruvate and via pyruvate carboxylase to glucose 1-phosphate. Glucose 1-phosphate is converted to glycogen polymers. Thus fructolysis results in glycogen storage. The pyruvate that is generated by fructolysis is converted to glutamate which can enter the GABA shunt pathway. The GABA shunt pathway generates glycine and succinyl CoA which are substrates for ALA synthesis. Thus fructolysis stimulates porphyrin synthesis. The porphyrins can self organize to form supramolecular arrays called porphyrions. Porphyrions can self replicate by using other porphyrions as templates. Porphyrions can have energetic and ATP synthesis by electron or photon transport. Porphyrions are dipolar molecules and in the setting of digoxin induced membrane sodium potassium ATPase inhibition can generate a pumped phonon system induced quantal state and quantal perception. They can function as quantal computers with information storage. The porphyrions are basic self replicating living structures. The porphyrins can act as a template for the formation RNA, DNA and proteins. The RNA viroids, the DNA viroids and proteins generated by abiogenesis on porphyrin templates can self organize to form primitive archaea. The archaea are thus capable of abiogenic replication on porphyrin templates. The archaea can induce HIF alpha and further aldose reductase induction promoting fructolysis.

Fructose is an addictive substance. Fructose affects the hedonic centres in the brain concerned with pleasure and reward. In the addiction scale fructose is more addictive than cocaine and cannabis. Fructose decreases BDNF. Low BDNF produces changes in the brain resulting in schizophrenia and depression. Fructose can also produce chronic inflammation involved in schizophrenia. The fructolytic pathway is important in the genesis of psychiatric disorders. The increased fructolysis can lead to fructosylation of lipoproteins especially apoprotein E and apoprotein B. Apo B can undergo lysine fructosylation leading to defective LDL and cholesterol uptake by the brain. This results in

autism and schizophrenia. Fructolysis leads to cholesterol depletion of the brain. Cholesterol is required for the formation of synaptic connections and cerebral cortex. This leads to cerebral cortical atrophy and cerebellar dominance in the presence of cholesterol depletion. This can contribute to the genesis of the cerebellar cognitive affective syndrome, the basis of schizophrenia and autism. There is an epidemic of schizophrenia and autism correlating with global warming. Fructosylation of LDL and brain cholesterol depletion can lead to dysfunction in synaptic transport. There is more release of glutamate into the synaptic from the presynaptic neuron consequent to a presynaptic neuron membrane dysfunction as a result of cholesterol depletion. This contributes to glutamate excitotoxicity. Glutamate excitotoxicity can contribute to neuronal degeneration. Fructose can also produce zinc deficiency. Increased fructose intake produces zinc depletion leading to defective formation of metallothionines leading to defective heavy metal excretion. This leads to mercury, cadmium and aluminium toxicity in the brain leading to psychiatric disorders like autism and degenerations like Alzheimer's disease. Zinc deficiency consequent to fructose excess can lead to copper excess. The zinc containing neurons in the cerebral cortex are called the gluzineric neurons. The cerebral cortex especially the prefrontal cortex will atrophy producing cerebellar and brain stem dominance. Copper is required for the dominance of subcortical cognitive structures. Fructose ingestion can also lead to calcium deficiency which can produce defective calcium signaling. Fructose ingestion leads to fructolysis and the generation of reactive species 3-deoxyglucosone important in mallard reaction and fructosylation of neuronal proteins leading to their defective function. Neuropsychiatric disorders and neurodegenerative disorders can be described as fructose diseases. Topiramate a fructose analogue is used to treat motor neuron disease. Fructose biphosphate aldolase B mutation has been seen in schizophrenia, bipolar disorders and depression.

6-phosphofructo 2-kinase and fructose 2,6-biphosphotase abnormalities have been seen in schizophrenia. Fructose metabolism abnormalities have been noted in schizophrenia, manic depressive psychosis and autism. Fructose inhibits brain plasticity. Fructose inhibits the ability of neurons to communicate with each other. The wiring and re-wiring of neurons is inhibited. Fructose leads to a neuronal disconnection syndrome.

Fructose can increase flux via the pentose phosphate pathway and hexosamine pathway leading to glycosaminoglycan synthesis. Glycosaminoglycan accumulation in the tissues can produce mucopolysaccharidosis and fibrosis. Increased heparan sulphate accumulation in the brain leads to formation of amyloids plaques and Alzheimer's disease. Connective tissue accumulation in the lung leads to interstitial lung disease, in the kidneys it produces tubular atrophy and a chronic renal failure similar to meso-American nephropathy. Connective tissue accumulation in the heart can lead to a restrictive cardiomyopathy. Accumulation of GAG especially hyaluronic acid in bones and joints leads to osteoarthritis and spondylosis. GAG accumulation in the endocrine organs can produce thyroid dysfunction resulting in MNG and thyroiditis, pancreatic dysfunction producing chronic calcific pancreatitis and adrenal dysfunction producing hypoadrenalism. Accumulation of GAG in the vascular tissues can result in mucoid angiopathy contributing to coronary artery disease and stroke. The accumulation of lipids due to the fructolytic pathway along with glycosaminoglycans can lead to fatty liver. This can later lead onto cirrhosis of the liver. Fructose is the principal culprit for fatty liver and cirrhosis. The glycine synthesized from the fructolytic intermediate phosphoglycerate can play a role inhibiting fatty liver. There is an epidemic of chronic renal failure due to tubular fibrosis, mucoid angiopathic vascular diseases, cardiomyopathy, multiple endocrine failures, cirrhosis of the liver, interstitial lung disease, degenerative

bone and joint diseases and degenerative brain disease like Alzheimer's disease and Parkinson's disease as a consequence of global warming.

The increasing growth of archaea results in increased secretion of archaeal RNA viroids. They can interrupt mRNA function and dysregulate cell metabolism. This is by the mechanism of mRNA blockade. The viroidal RNA can combine with proteins generating prion proteins. This produces a protein conformation defect. This produces a prion protein disease. Abnormal protein conformation of beta amyloid, alpha synuclein, ribonucleoproteins, islet associated amyloid polypeptide and tumour suppressor protein can lead to an epidemic of Alzheimer's disease due to beta amyloid accumulation, alpha synuclein accumulation producing Parkinson's disease, prion like ribonucleoproteins producing motor neuron disease, metabolic syndrome X due to defective insulin secretion as a result of IAPP and abnormal prion like tumour suppressor protein producing tumours. These prion diseases induced by archaeal RNA viroids are also transmissible. Thus global warming related fructolysis leads to archaeal induced RNA viroidal mediated prion disease and amyloidosis. This raises the spectre of a Cassandra syndrome of human extinction.

Fructose is phosphorylated to fructose 1-phosphate by ketohexokinase C or fructokinase. Fructose 1-phosphate is converted to glyceraldehyde which is then converted to glyceraldehyde 3-phosphate and dihydroxy acetone phosphate (DHAP). Fructose 1-phosphate is cleaved to DHAP and glyceraldehyde 3-phosphate. DHAP can enter the glycolytic pathway or can go to gluconeogenic pathway. DHAP generated from fructose 1-phosphate by the action of aldolase B is acted upon by triose phosphate isomerase converting it into glyceraldehyde 3-phosphate. Glyceraldehyde 3-phosphate can be fructolysed to pyruvate and acetyl CoA. Acetyl CoA can be used for cholesterol synthesis for storage. The pyruvate generated from glyceraldehyde 3-phosphate can be converted to the citrate which can be used for fatty acid

synthesis by the action of enzymes acetyl CoA carboxylase, fatty acid synthase and malonate dehydrogenase. Glyceraldehyde is acted upon by alcohol dehydrogenase which converts it into glycerol. Glycerol is acted upon by glycerolkinase converting it into glycerol phosphate used for phosphoglyceride and triglyceride synthesis. Glyceraldehyde can also be acted upon by triokinase converting it into glyceraldehydes 3-phosphate which is then converted to DHAP by triose phosphate isomerase. Glycerol phosphate and dihydroxy acetone phosphate are interconvertible by the action of the enzyme glycerol phosphate dehydrogenase. Glycerol and fatty acids generated by fructolysis contribute to lipid synthesis and fat is stored. Fructose does not increase insulin secretion and doesn't need insulin for transport into the cell. Fructose is transported by the fructose transporter GLUT-5. Ketohexokinase C is exclusively seen in the liver which is the principal site of fructose metabolism. In the presence of hypoxia and anerobic states, there is induction of HIF alpha which can induce ketohexokinase C or fructokinase in the liver, kidney, gastrointestinal tract, brain and heart. Fructose 1-phosphate by-passes the enzyme phosphofructokinase which is the key regulatory enzyme the glycolytic pathway. Phosphofructokinase is inhibited by ATP and citrate. Thus stress induced fructolysis is an unregulated pathway not amenable to metabolic switches. Fructose does not depend upon insulin for its transport and fructolysis. Therefore fructolysis is not under insulin or endocrine control. It is an unregulated pathway.

The phosphorylation of fructose depletes the cell of ATP. Ketohexokinases preferentially phosphorylate fructose over glucose if it is available. In the presence of redox stress, osmotic stress and archaea / viroids aldose reductase is induced converting all the glucose to fructose. Glycolytic pathway comes to a halt as no ATP is available for phosphorylation of glucose and glucose as such gets converted to fructose. The fructose phosphorylation depletes the cell of

ATP. ATP is converted to ADP and AMP which is deaminated to produce uric acid. Fructose increases flux in the pentose phosphate pathway increasing nucleic acid synthesis. Purine degradation results in hyperuricemia. Thus fructolysis results in increase in uric acid accumulation in the body. Uric acid will suppress the mitochondrial oxidative phosphorylation as well as produce endothelial dysfunction. The depletion of ATP by fructose phosphorylation results in membrane sodium potassium ATPase inhibition. This results in reduced energy needs of the cell as 80 percent of the ATP generated by metabolism is used for maintaining the sodium potassium pump. This results in membrane ATPase inhibition generated hibernatory state. The glyceraldehydes 3-phosphate generated by fructolysis can be converted to the pyruvate and acetyl CoA used for cholesterol synthesis. The cholesterol that is synthesized is used for digoxin synthesis. Digoxin also has got aglycone part which contains sugars like digitoxose and rhamnose. Digitoxose and rhamnose are generated by the fructose induced flux and upgradation of the pentose phosphate pathway. Thus fructolysis results in a hyperdigoxinemic state and membrane sodium potassium ATPase inhibition. This results in cell protection and hibernation.

Fructose produces flux along the pentose phosphate pathway and hexosamine pathway. This results in GAG and nucleic acid synthesis. Fructose is converted to fructose 1-phosphate which is then converted to ribulose 5-phosphate. Ribulose 5-phosphate is acted upon by an isomerase converting it into xylulose 5-phosphate and ribose 5-phosphate. Xylulose 5-phosphate and ribose 5-phosphate interact to produce glyceraldehydes 3-phosphate and sedoheptulose 7-phosphate which is then converted to fructose 6-phosphate and erythrose 4-phosphate. The pentose phosphate pathway generates ribose for nucleic acid synthesis. The pathway also generates hexosamines for GAG synthesis. The pentose phosphate pathway also produces digitoxose and rhamnose for digoxin synthesis.

The global warming results in endosymbiotic archaeal growth. Archaea can induce aldose reductase which converts glucose to fructose. Fructolysis promotes flux along the pentose phosphate pathway generating nucleic acids and glycosaminoglycans. Fructolysis also generates glyceraldehydes 3-phosphate and further pyruvate. The pyruvate can enter the pyruvate carboxylase scheme generating gluconeogenesis and glycogen synthesis. Thus fructolysis can produce glycogen storage. Pyruvate can be converted to citrate for lipid synthesis. Pyruvate can also be converted to acetyl CoA for cholesterol synthesis. The flux along the pentose phosphate pathway generates the digoxin sugars, digitoxose and rhamnose. Cholesterol can be converted to digoxin producing a hyperdigoxinemic state. Digoxin produces membrane sodium potassium ATPase inhibition. The selective phosphorylation of fructose by fructokinase depletes the cell of ATP producing membrane sodium potassium ATPase inhibition. This results in the generation of a hibernatory state. The fructolysis generated pyruvate can get converted to glutamate which can enter the GABA shunt pathway producing succinyl CoA and glycine for porphyrin synthesis. Porphyrins can form self replicating porphyrions or act as a template for the formation of RNA viroids, DNA viroids and prions which can symbiose to form archaea. Thus the archaea are capable of self replicating on porphyrin templates. The fructolysis thus produces a hibernatory syndrome with fat, glycogen and nucleic acid synthesis and storage. Fructolysis results in the generation of a hibernatory species, the homo neanderthalis. The fructolysis generated membrane sodium potassium ATPase inhibition results in cell hibernation and ATP sparing. The lack of ATP and digoxin induced membrane sodium potassium ATPase inhibition results in cortical inhibition and cerebellar dominance. This produces a somnolent state and a cerebellar cognitive affective disorder. The porphyrions generated by fructolysis produces quantal perception and cerebellar dominance. The storage of glycogen, fat and GAG results in

obesity. The cerebellar cognitive affective syndrome results in a hypersexual state. The fructolysis and fructose can activate NFkB producing immune activation. The fructosylation of glycolytic and mitochondrial proteins suppresses the body's normal energetic which depends upon glycolysis and mitochondrial oxidative phosphorylation. Fructosylation of proteins results in blockade of glycolysis and mitochondrial oxidative phosphorylation. The body's energy needs are produced by fructolysis, porphyrin array mediated electron transport chain and ATP synthesis as well as membrane sodium potassium ATPase inhibition relation ATP synthesis. This produces a new species by archaeal symbiosis consequent to global warming - the homo neanderthalis. This can be called as the tropical hibernatory syndrome consequent to global warming.

This can be called also as a fructose disease. Endosymbiotic archaea and viroids induce aldose reductase and converts body glucose to fructose leading to preferential fructose phosphorylation by ketohexokinase C. Fructolysis results in fructose 1-phosphate being acted upon by aldolase B resulting in the formation of glyceraldehyde and dihydroxy acetone phosphate. Glyceraldehyde can be converted to glyceraldehyde 3-phosphate and this contributes to pyruvate formation. Pyruvate enters the GABA shunt resulting in the formation of succinyl CoA and glycine. They are substrates for porphyrin synthesis and porphyrion formation. The porphyrins form a template for the formation of RNA viroids, DNA viroids, prions, isoprenoids and polysaccharides. They can symbiose together to form primitive archaea. The archaea can further induce HIF alpha, aldose reductose and fructolysis resulting in further porphyrinogenesis and archaeal self replication. The archaea by methanogenesis contributes to global warming which leads to further archaeal growth and a vicious cycle with no regulatory switches. The fructolytic pathway induced by archaea by-passes regulatory enzyme phosphofructokinase and is practically

unregulated. Fructolytic pathway contributes to glycogen, lipids, cholesterol, hexose sugars and mucopolysaccharides synthesis and storage. This leads onto a hibernatory state and archaeal symbiosis induced species change resulting in neanderthalisation of the homo sapien species. The digoxin and fructose phosphorylation induced ATP depletion leads to membrane sodium potassium ATPase inhibition, sparing of ATP and tissue hibernation as most of the energy needs of the body are for the working of the sodium potassium pump. The cholesterol that is synthesized by fructolysis is catabolized cholesterol oxidases for archaeal energetics. Archaea also derives its energy from a primitive form of electron transport chain functioning in self replicating porphyrin arrays. The archaeal digoxin induced sodium potassium ATPase inhibition can lead to membrane ATP synthesis. The archaea and the new human species phenotype derive its energy from the above mentioned mechanism. The glycolytic enzymes and the mitochondrial PT pore hexokinase are fructosylated making them dysfunction. The fructosylated glycolytic enzymes lead to generation of antiglycolytic enzyme antibodies and disease states. The human body's principal method of energetics tissue glycolysis and oxidative phosphorylation comes to a grinding halt. The human body is taken over by the overgrowth of endosymbiotic archaea and assumes hibernatory state with accumulation of glycogen, lipids, mucopolysaccharides and nucleic acids. The catabolic pathways for energy generation related to glucose, glycolysis and oxphos scheme stops. The human body can depend upon ketogenesis from fat and proteins. The upregulated fructolytic pathway generates phosphoglycerate which converted to phosphoserine and glycine. They can be converted to other amino acids and used for ketogenesis. The body assumes a high BMI index and obesity with visceral fat storage and adiposity akin to the Neanderthal metabolic phenotype. Digoxin induced membrane sodium potassium ATPase inhibition results in cortical dysfunction. The brain porphyrins can form a quantal pumped

phonon system resulting in quantal perception and low level EMF absorption. This leads to prefrontal cortex atrophy and cerebellar dominance. Fructose itself leads to sympathetic hyperactivity and parasympathetic blockade. This leads onto a functional form of cerebellar cognition and quantal perception resulting in a new brain phenotype. The cerebellar cognitive syndrome leads to a robotic human phenotype. The phenotype is impulsive, has extrasensory perception and has less of speech production. Communication is by symbolic acts. The cerebellar phenotype doesn't have a cortical control and contributes to surrealistic behavior patterns. This produces impulsive behavior and an epidemic of surrealism where the rational prefrontal cortex becomes extinct. This leads to extremes of spirituality, violent and terroristic behavior and hypersexual states contributing to a state of transcendence underlined and reinforced by quantal perception. Cerebellar phenotype owing to its quantal perception behaves as a community and not as an individual. This creates new social and psychological phenotypes. Fructose induces NF $\kappa$ B and immune activation. This results in an immune activatory phenotype. Cultured T-reg cells on high fructose diet have 62% less IL-40 secretion than controls. This results in a hyperimmune state with fructosylated proteins acting as antigens. The fructolytic pathway can lead to increased DNA synthesis and RNA synthesis due to flux via the pentose phosphate pathway. The fructolytic pathway can be directed to the GABA shunt generating succinyl CoA and glycine. These are substrates for porphyrin templates to form RNA viroids. The archaeal induced redox stress can induce endogenous HERV expression and reverse transcriptase expression. The RNA viroids are converted by HERV reverse transcriptase to corresponding DNA and integrated into the genome by HERV integrase. The integrated RNA viroid related DNA can function as jumping genes producing genomic plasticity and genomic change. This produces a new genotype. Fructosylation of body proteins and enzymes results in a protein processing

defect resulting in loss of protein function. The human cell function due to protein fructosylation, protein processing defects and protein conformational defects comes to a grinding halt. Fructolytic pathway generates porphyrin arrays induced ATP production, membrane sodium potassium ATPase inhibition induced ATP synthesis and fructolysis induced ATP generation. This provides energy for porphyrin template induced archaeal replication. The digoxin and fructose phosphorylation induced ATP depletion produces cell membrane sodium potassium ATPase inhibition and a hibernatory state. This leads onto a somnolent sleepy state. The cholesterol catabolism by cholesterol oxidases for archaeal energetics leads to defective sex hormone synthesis. This leads onto an asexual androgynous state. The cerebellar cognitive syndrome due to prefrontal cortical atrophy consequent to porphyrion induced low level EMF perception produces a hypersexual state. This results in male-female equidominance and changes in sexual behavior of the population. Thus the fructose disease consequent to global warming results in a new neuronal, immune, metabolic, sexual, social phenotype. The human body is converted to a zombie for the global warming related endosymbiotic archaea to thrive. The neuronal, metabolic, sexual and social phenotype creates the necessary environment endosymbiotic archaeal multiplication and the human body is converted to a zombie phenotype. This can be called as a hibernatory zombie syndrome. Due to the new sexual and social phenotype with asexuality and hypersexuality and female-male equidominance the human population falls. The global warming and archaeal induction of HIF alpha resulting in the Warburg phenotype leads to changes in the metabolic scheme of the cells producing body cell transformation to stem cells. The stem cells depend upon glycolysis or fructolysis for energy needs. The Warburg phenotype produces an acidic pH which can result in conversion of body cells to stem cells. The stem cells conversion results in loss of tissue function. The cerebral cortex synaptic connectivity is lost and becomes

dysfunction leading to subcortical cerebellar dominance. The immune stem cells proliferate producing an autoimmune disease. The various tissue cells the specialized function like neuron, nephron and muscle cell all because of stem cell conversion becomes dysfunctional. This produces a stem cell syndrome with human somatic cells being converted to stem cells with loss of function and uncontrolled proliferation. The fructosylation of proteins results in protein function defects. The fructosylation of LDL results in defective cholesterol transport to the cells. This results in steroidal hormone synthesis defects. Cholesterol is required for formation of synaptic connectivity and this leads to cerebral cortical dysfunction. The hemoglobin becomes fructosylated and oxygen transport is affected. This leads to hypoxia and anerobic states. The hypoxia and anerobic states induces HIF alpha and the Warburg fructolytic phenotype. The HIF alpha also induces aldose reductase converting glucose to fructose and inducing the fructolytic scheme. The fructolysis induced GABA shunt pathway and porphyrin synthesis results in further archaeal porphyrin template related replication. This results in further archaeal induced fructolysis and the vicious irreversible cycle proceeds. The uncontrolled growth of archaea leads to still further global warming. The world of endosymbiotic eternal archaea takes over and persists during the extremophilic climatic changes of global warming. The human beings exist as neanderthalic zombies serving archaeal multiplication. The homo sapiens gets converted to a new phenotype, genotype, immunotype, metabolonomic type and brain type. This is called as hibernatory zombie related to global warming - homo neoneanderthalis.

**Table 1**

	Serum fructose		Serum fructokinase		Aldolase B		Total GAG	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
Normal	2.50	0.195	8.50	0.405	3.50	1.304	3.50	0.707
DBJD	33.06	5.970	22.42	3.714	11.21	1.660	17.76	3.556
Spondylosis	32.70	4.430	21.92	1.840	14.10	2.423	26.80	3.679
F value	17.373		13.973		13.903		21.081	
p value	< 0.01		< 0.01		< 0.01		< 0.01	

**Table 2**

	Total TG		Serum ATP levels		Uric acid		Anti-aldolase	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
Normal	124.00	3.688	2.50	0.405	5.70	0.369	7.50	1.704
DBJD	282.60	27.573	0.79	0.136	8.28	0.978	1.89	0.315
Spondylosis	295.30	16.600	0.72	0.108	10.21	1.310	1.54	0.377
F value	16.378		59.169		14.166		55.173	
p value	< 0.01		< 0.01		< 0.01		< 0.01	

**Table 3**

	Anti-enolase		Anti-pyruvatekinase		Anti-GAPDH	
	Mean	±SD	Mean	±SD	Mean	±SD
Normal	1.50	0.358	50.40	5.960	5.20	0.363
DBJD	0.54	0.211	22.48	4.638	1.33	0.302
Spondylosis	0.40	0.134	19.91	5.099	1.49	0.282
F value	14.091		21.073		58.769	
p value	< 0.01		< 0.01		< 0.01	

## References

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# 2

## Global Warming and Actinide Dependent Shadow Biosphere of Archaea and Viroids in Chronic Bone and Joint Disease

## Introduction

Endomyocardial Fibrosis along with the root wilt disease of coconut is endemic to Kerala with its radioactive actinide beach sands. Actinides like rutile, endogenous digoxin as well as organisms like phytoplasmas and viroids have been implicated in the etiology of these diseases.<sup>1-4</sup> Endogenous digoxin has been related to the pathogenesis of degenerative bone and joint disease like spondylosis and osteoarthritis as well as postmenopausal osteoporosis.<sup>4</sup> The possibility of endogenous digoxin synthesis by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered.<sup>5-8</sup> An actinide dependent shadow biosphere of archaea and viroids in the above mentioned disease states is described.<sup>7,9</sup> Metal actinides in beach sands have been postulated to play a role in abiogenesis.<sup>7</sup> A hypothesis of cholesterol as the primal prebiotic molecule synthesized on actinide surfaces with all other biomolecules arising from it and a self replicating cholesterol lipid organism as the initial life form is presented.

Global warming can lead to osmotic stress consequent to dehydration. The increase in actinidic archaeal growth leads to cholesterol catabolism and digoxin synthesis. Digoxin produces membrane sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial dysfunction. This results in oxidative stress. The oxidative stress and osmotic stress can induce the enzyme aldose reductase which converts glucose to fructose. Fructose has got a low  $K_m$  value for ketokinase as compared to glucose. Therefore fructose gets phosphorylated more to fructose phosphate and the cell is depleted of ATP. The cell depletion of ATP leads to oxidative stress and chronic inflammation consequent to induction of NF $\kappa$ B. Oxidative stress can open the mitochondrial PT pore producing release of cyto C and activation of the caspase cascade of cell death. The fructose phosphate can enter the pentose phosphate pathway

synthesizing ribose and nucleic acid. The depletion of cellular ATP results in generation of AMP and ADP which are acted upon by deaminases causing hyperuricemia. Uric acid can produce endothelial dysfunction and vascular disease. Uric acid can also produce mitochondrial dysfunction. The fructose phosphate can enter the glucosamine pathway synthesizing GAG and producing mucopolysaccharide accumulation. Fructose can fructosylate proteins making them antigenic and producing an autoimmune response. This can lead to global warming related bone and joint disease.

## Materials and Methods

The following groups were included in the study:- Degenerative bone and joint disease like spondylosis and osteoarthritis as well as postmenopausal osteoporosis. The study also included normal population with right hemispheric dominance and left hemispheric dominance. There were 10 patients in each group and each patient had an age and sex matched healthy control selected randomly from the general population. The blood samples were drawn in the fasting state before treatment was initiated. Plasma from fasting heparinised blood was used and the experimental protocol was as follows (I) Plasma+phosphate buffered saline, (II) same as I+cholesterol substrate, (III) same as II+rutile 0.1 mg/ml, (IV) same as II+ciprofloxacin and doxycycline each in a concentration of 1 mg/ml. Cholesterol substrate was prepared as described by Richmond.<sup>10</sup> Aliquots were withdrawn at zero time immediately after mixing and after incubation at 37 °C for 1 hour. The following estimations were carried out: Cytochrome F420, free RNA, free DNA, polycyclic aromatic hydrocarbon, hydrogen peroxide, dopamine, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids.<sup>11-13</sup> Cytochrome F420 was estimated fluorimetrically (excitation wavelength 420 nm and emission

wavelength 520 nm). Polycyclic aromatic hydrocarbon was estimated by measuring hydrogen peroxide liberated by using glucose reagent. Informed consent of the subjects and the approval of the ethics committee were obtained for the study. The statistical analysis was done by ANOVA.

## Results

Plasma of control subjects showed increased levels of the above mentioned parameters with after incubation for 1 hour and addition of cholesterol substrate resulted in still further significant increase in these parameters. The plasma of patients showed similar results but the extent of increase was more. The addition of antibiotics to the control plasma caused a decrease in all the parameters while addition of rutil increased their levels. The addition of antibiotics to the patient's plasma caused a decrease in all the parameters while addition of rutil increased their levels but the extent of change was more in patient's sera as compared to controls. The results are expressed in tables 1-7 as percentage change in the parameters after 1 hour incubation as compared to the values at zero time. The archaeal cholesterol catabolites and various parameters were upregulated in right hemispheric dominance, osteoarthritis and spondylosis. The archaeal cholesterol catabolites and various parameters were downregulated in left hemispheric dominance and osteoporosis.

**Table 1.** Effect of rutile and antibiotics on free DNA and RNA.

Group	DNA % change (Increase with Rutile)		DNA % change (Decrease with antibiotics)		RNA % change (Increase with Rutile)		RNA % change (Decrease with antibiotics)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
LHD	4.37	0.15	18.39	0.38	4.37	0.13	18.38	0.48
RHD	22.99	1.56	65.19	4.10	23.27	1.36	65.66	3.93
Osteoporosis	2.26	0.25	7.45	0.40	2.30	0.12	7.62	0.30
Osteoarthritis	22.56	2.46	62.70	4.53	23.32	1.74	65.67	4.16
Spondylosis	23.30	1.42	65.07	4.95	23.11	1.52	66.68	3.97
F value	337.577		356.621		427.828		654.453	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

**Table 2.** Effect of rutile and antibiotics on *cyt F 420* and muramic acid.

Group	CYT F420 % change (Increase with Rutile)		CYT F420 % change (Decrease with antibiotics)		Muramic acid % change (Increase with Rutile)		Muramic acid % change (Decrease with antibiotics)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
LHD	4.48	0.15	18.24	0.66	4.34	0.15	18.24	0.37
RHD	11.35	0.64	60.49	6.22	22.68	1.99	63.29	5.93
Osteoporosis	2.13	0.13	5.37	1.47	2.26	0.25	7.45	0.40
Osteoarthritis	22.29	1.66	59.02	7.50	23.23	1.97	65.89	5.05
Spondylosis	22.06	1.61	57.81	6.04	23.46	1.91	61.56	4.61
F value	306.749		130.054		348.867		364.999	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

**Table 3.** Effect of rutile and antibiotics on HMG CoA reductase and PAH.

Group	HMG CoA R % change (Increase with Rutile)		HMG CoA R % change (Decrease with antibiotics)		PAH % change (Increase with Rutile)		PAH % change (Decrease with antibiotics)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
LHD	4.30	0.20	18.35	0.35	4.45	0.14	18.25	0.72
RHD	21.06	2.32	63.87	6.22	21.00	2.54	57.42	7.07
Osteoporosis	2.33	0.17	7.24	0.59	2.25	0.17	7.01	0.65
Osteoarthritis	22.86	2.58	66.53	5.59	23.15	1.62	66.48	4.17
Spondylosis	22.38	2.38	60.65	5.27	23.00	1.64	66.67	4.21
F value	319.332		199.553		391.318		257.996	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

**Table 4.** Effect of rutile and antibiotics on digoxin and bile acids.

Group	Digoxin (ng/ml) (Increase with Rutile)		Digoxin (ng/ml) (Decrease with antibiotics)		Bile Acids % change (Increase with Rutile)		Bile Acids % change (Decrease with antibiotics)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
LHD	0.11	0.00	0.054	0.003	4.29	0.18	18.15	0.58
RHD	0.55	0.10	0.248	0.058	21.10	2.43	54.82	8.28
Osteoporosis	0.07	0.01	0.026	0.004	2.25	0.19	7.25	0.66
Osteoarthritis	0.56	0.05	0.220	0.052	22.29	1.47	64.35	5.58
Spondylosis	0.53	0.06	0.212	0.045	23.30	1.88	62.49	7.26
F value	135.116		71.706		290.441		203.651	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

**Table 5.** Effect of rutile and antibiotics on pyruvate and hexokinase.

Group	Pyruvate % change (Increase with Rutile)		Pyruvate % change (Decrease with antibiotics)		Hexokinase % change (Increase with Rutile)		Hexokinase % change (Decrease with antibiotics)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
LHD	4.34	0.21	18.43	0.82	4.21	0.16	18.56	0.76
RHD	11.12	0.66	59.68	6.24	23.27	1.68	67.35	3.77
Osteoporosis	2.16	0.18	5.91	1.38	2.24	0.17	6.29	1.06
Osteoarthritis	21.21	2.36	58.73	8.10	21.11	2.25	64.20	5.38
Spondylosis	21.07	1.79	63.90	7.13	22.47	2.17	65.97	4.62
F value	321.255		115.242		292.065		317.966	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

**Table 6.** Effect of rutile and antibiotics on ATP synthase and hydrogen peroxide.

Group	ATP synthase % change (Increase with Rutile)		ATP synthase % change (Decrease with antibiotics)		H <sub>2</sub> O <sub>2</sub> % change (Increase with Rutile)		H <sub>2</sub> O <sub>2</sub> % change (Decrease with antibiotics)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
LHD	4.40	0.11	18.78	0.11	4.43	0.19	18.13	0.63
RHD	11.99	0.38	66.34	3.39	17.60	3.53	54.68	5.09
Osteoporosis	2.30	0.12	7.62	0.30	2.24	0.23	5.36	0.99
Osteoarthritis	23.45	1.79	66.32	3.63	23.32	1.71	63.15	7.62
Spondylosis	23.17	1.88	68.53	2.65	22.86	1.91	63.66	6.88
F value	449.503		673.081		380.721		171.228	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

**Table 7.** Effect of rutile and antibiotics on delta amino levulinic acid and dopamine.

Group	ALA % (Increase with Rutile)		ALA % (Decrease with antibiotics)		DOPAMINE % change (Increase with Rutile)		DOPAMINE % change (Decrease with antibiotics)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
LHD	4.40	0.10	18.48	0.39	4.41	0.15	18.63	0.12
RHD	22.98	2.06	66.10	4.03	11.36	0.58	65.41	4.83
Osteoporosis	2.13	0.11	7.62	0.32	2.13	0.11	7.62	0.32
Osteoarthritis	23.45	1.79	66.32	3.63	23.43	1.57	66.30	3.57
Spondylosis	23.17	1.88	68.53	2.65	23.70	1.75	68.06	3.52
F value	372.716		556.411		403.394		680.284	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

## Abbreviation

BHD: Bihemispheric dominance

RHD: Right hemispheric dominance

LHD: Left hemispheric dominance

## Discussion

There was increase in cytochrome F420 indicating archaeal growth in spondylosis and osteoarthritis as well as a decrease in growth in osteoporosis. The archaea can synthesize and use cholesterol as a carbon and energy source.<sup>6, 14</sup> The archaeal origin of the enzyme activities was indicated by antibiotic induced suppression. The study indicates the presence of actinide based archaea with an alternate actinide based enzymes or metalloenzymes in the system as indicated by rutile induced increase in enzyme activities.<sup>15</sup> There was also an increase in archaeal HMG CoA reductase activity indicating increased cholesterol synthesis by the archaeal mevalonate pathway. The archaeal beta hydroxyl steroid dehydrogenase activity indicating digoxin synthesis and archaeal cholesterol hydroxylase activity indicating bile acid synthesis were increased.<sup>8</sup> The archaeal cholesterol oxidase activity was increased resulting in generation of pyruvate

and hydrogen peroxide.<sup>14</sup> The pyruvate gets converted to glutamate and ammonia by the GABA shunt pathway. The archaeal aromatization of cholesterol generating PAH, serotonin and dopamine was also detected.<sup>16</sup> The archaeal glycolytic hexokinase activity and archaeal extracellular ATP synthase activity were increased. The archaea can undergo magnetite and calcium carbonate mineralization and can exist as calcified nanoforms.<sup>17</sup> There was an increase in free RNA indicating self replicating RNA viroids and free DNA indicating generation of viroid complementary DNA strands by archaeal reverse transcriptase activity. The actinides modulate RNA folding and catalyse its ribozymal action. Digoxin can cut and paste the viroidal strands by modulating RNA splicing generating RNA viroidal diversity. The viroids are evolutionarily escaped archaeal group I introns which have retrotransposition and self splicing qualities.<sup>18</sup> Archaeal pyruvate can produce histone deacetylase inhibition resulting in endogenous retroviral (HERV) reverse transcriptase and integrase expression. This can integrate the RNA viroidal complementary DNA into the noncoding region of eukaryotic noncoding DNA using HERV integrase as has been described for borna and ebola viruses.<sup>19</sup> The noncoding DNA is lengthened by integrating RNA viroidal complementary DNA with the integration going on as a continuing event. The archaea genome can also get integrated into human genome using integrase as has been described for trypanosomes.<sup>20</sup> The integrated viroids and archaea can undergo vertical transmission and can exist as genomic parasites.<sup>19, 20</sup> This increases the length and alters the grammar of the noncoding region producing memes or memory of acquired characters as well as eukaryotic speciation and individuality.<sup>21</sup> The viroidal complementary DNA can function as jumping genes producing a dynamic genome important in storage of synaptic information, HLA gene expression and developmental gene expression. The RNA viroids can regulate mRNA function by RNA interference.<sup>18</sup> The phenomena of RNA interference

can modulate T-cell and B-cell function, insulin signaling lipid metabolism, cell growth and differentiation, apoptosis, neuronal transmission and euchromatin / heterochromatin expression. More of extensive archaeal integration into the human genome consequent to global warming can lead to spondylosis and osteoarthritis. Less of archaeal integration into the genome can lead to osteoporosis.

The archaea and viroids can regulate the nervous system including the NMDA / GABA thalamo-cortico-thalamic pathway mediating conscious perception.<sup>4,22</sup> NMDA / GABA receptors can be modulated by digoxin induced calcium oscillations resulting NMDA / GAD activity induction, PAH increasing NMDA activity and inducing GAD as well as viroid induced RNA interference.<sup>4</sup> The cholesterol ring oxidase generated pyruvate can be converted by the GABA shunt pathway to glutamate and GABA. The dipolar PAH and archaeal magnetite in the setting of digoxin induced sodium potassium ATPase inhibition can produce a pumped phonon system mediated Frohlich model superconducting state<sup>22</sup> inducing quantal perception with nanoarchaeal sensed gravity producing the orchestrated reduction of the quantal possibilities to the macroscopic world.<sup>4,22</sup> The archaea can regulate limbic lobe transmission with archaeal cholesterol aromatase / ring oxidase generated norepinephrine, dopamine, serotonin and acetyl choline.<sup>16</sup> The higher degree of integration of the archaea into the genome produces increased digoxin synthesis producing right hemispheric dominance and lesser degree producing left hemispheric dominance.<sup>4</sup> The increased integration of archaea into the neuronal genome can produce increased cholesterol oxidase and aromatase mediated monoamine and NMDA transmission producing right hemispheric dominant state. The left hemispheric dominant state is produced by less of archaeal integration into the genome. Right hemispheric dominance leads to osteoarthritis and spondylosis. Left hemispheric dominance leads to osteoporosis.<sup>29-36</sup>

Archaea and RNA viroid can bind the TLR receptor induce NF $\kappa$ B producing immune activation and cytokine TNF alpha secretion. The archaeal DXP and mevalonate pathway metabolites can bind  $\gamma\delta$  TCR and digoxin induced calcium signaling can activate NF $\kappa$ B producing chronic immune activation.<sup>4, 23</sup> The archaea and viroid induced chronic immune activation and generation of superantigens can lead on to spondylosis and osteoarthritis. Archaea, viroids and digoxin can induce the host AKT PI3K, AMPK, HIF alpha and NF $\kappa$ B producing the Warburg phenotype.<sup>24</sup> The increased glycolytic hexokinase activity, decrease in blood ATP, leakage of cytochrome C, increase in serum pyruvate and decrease in acetyl CoA indicates the generation of the Warburg phenotype. There is induction of glycolysis, inhibition of PDH activity and mitochondrial dysfunction. The archaea and viroid generated cytokines can lead to TNF alpha induced immune activation. The accumulated pyruvate enters the GABA shunt pathway and is converted to citrate which is acted upon by citrate lyase and converted to acetyl CoA, used for cholesterol synthesis.<sup>24</sup> The pyruvate can be converted to glutamate and ammonia which is oxidised by archaea for energy needs. The increased cholesterol substrate leads to increased archaeal growth and digoxin synthesis leading to metabolic channeling to the mevalonate pathway. The archaeal bile acids are steroidal hormones which can bind GPCR and modulate D2 regulating the conversion of T<sub>4</sub> to T<sub>3</sub> which activates uncoupling proteins, can activate NRF $\frac{1}{2}$  inducing NQO1, GST, HOI reducing redox stress, can bind FXR regulating insulin receptor sensitivity and bind PXR inducing the bile acid shunt pathway of cholesterol detoxification.<sup>25</sup> This can lead to osteoarthritis and spondylosis. The archaea and viroid induced monocyte activation and Warburg phenotype induced osteoarthritis and spondylosis. A decrease in endosymbiotic archaeal density can lead to osteoporosis. The Warburg phenotype induced increased mitochondrial PT pore hexokinase, archaeal PAH and viroid induced RNA interference can lead on to

oncogene activation important in spondylosis and osteoarthritis. The digoxin and PAH induced increased intracellular calcium can lead to PT pore dysfunction, cell death important in degenerative bone and joint disease.<sup>4</sup> The archaeal cholesterol catabolism can deplete the cell membranes of cholesterol resulting in organelle dysfunction and degenerative bone and joint disease. The RNA viroids can recombine with HERV sequences and get encapsulated in microvesicles contributing to the retroviral induction. The prion protein conformation is modulated by RNA viroid binding producing prions. Endogenous retrovirus and prionopathies can contribute to osteoarthritis and spondylosis.<sup>4</sup> Less of endosymbiotic archaeal integration into the genome can produce osteoporosis by the opposite metabolonomic, genomic and immune changes.

The metal actinides provide radiolytic energy, catalysis for oligomer formation and provide a coordinating ion for metalloenzymes all important in abiogenesis.<sup>7</sup> The metal actinide surfaces would by surface metabolism generate acetate which could get converted to acetyl CoA and then to cholesterol which functions as the primal prebiotic molecule self organizing into self replicating supramolecular systems, the lipid organism.<sup>9, 26, 27</sup> Cholesterol by radiolysis by actinides would have formed PAH generating PAH aromatic organism.<sup>9</sup> Cholesterol radiolysis would generate pyruvate which would get converted to amino acids, sugars, nucleotides, porphyrins, fatty acids and TCA acids. Anastase and rutile surfaces can produce polymerization of amino acids, isoprenyl residues, PAH and nucleotides to generate the initial lipid organism, PAH organism, prions and RNA viroids which would have symbiosed to generate the archaeal protocell. The archaea evolved into gram negative and gram positive bacteria with a mevalonate pathway which had a evolutionary advantage and the symbiosis of archaea with gram negative organism generated the eukaryotic cell.<sup>28</sup> The data supports the persistence of an actinide and cholesterol based shadow biosphere which throws light on the actinide based origin of life and cholesterol as the premier prebiotic

molecule. Thus the global warming related extent of genomic integration of archaeal DNA contributes to hemispheric dominance and predilection to osteoarthritis, spondylosis and osteoporosis.<sup>29-36</sup>

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# 3

## Archaeal Digoxin and Bone Pathophysiology

## Introduction

Global warming induces a genomic change in humans. Global warming induces endosymbiotic archaeal and RNA viroidal growth. The porphyrins form a template for the formation of RNA viroids, DNA viroids, prions, isoprenoids and polysaccharides. They can symbiose together to form primitive archaea. The archaea can further induce HIF alpha, aldose reductase and fructolysis resulting in further porphyrinogenesis and archaeal self replication. The primitive archaeal DNA is integrated along with RNA viroids which are converted to their corresponding DNA by the action of redox stress induced HERV reverse transcriptase into the human genome by the redox stress induced HERV integrase. The archaeal DNA sequences that are integrated into the human genome forms endogenous archaeal human genomic sequences akin to HERV sequences and can function as jumping genes regulating genomic DNA flexibility. The integrated endogenous genomic archaeal sequences can get expressed in the presence of redox stress forming endosymbiotic archaeal particles which can function as a new organelle called the archaeaons. The archaeaon can express the fructolytic pathway constituting an organelle called the fructosome, cholesterol catabolic pathway and digoxin synthetic forming an organelle called the steroidelle, the shikimic acid pathway forming an organelle called the neurotransminoid, antioxidant vitamin E and vitamin C synthetic organelle called the vitaminocyte as well as the glycosaminoglycan synthetic organelle called glycosaminoglycoid. The archaeaon secreting RNA viroids is called the viroidelle.

Global warming can lead to osmotic stress consequent to dehydration. The increase in actinidic archaeal growth leads to cholesterol catabolism and digoxin synthesis. Digoxin produces membrane sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial dysfunction. This results in oxidative stress. The oxidative stress and osmotic stress can induce the

enzyme aldose reductase which converts glucose to fructose. Fructose has got a low  $K_m$  value for ketokinase as compared to glucose. Therefore fructose gets phosphorylated more to fructose phosphate and the cell is depleted of ATP. The cell depletion of ATP leads to oxidative stress and chronic inflammation consequent to induction of NF $\kappa$ B. Oxidative stress can open the mitochondrial PT pore producing release of cyto C and activation of the caspase cascade of cell death. The fructose phosphate can enter the pentose phosphate pathway synthesizing ribose and nucleic acid. The depletion of cellular ATP results in generation of AMP and ADP which are acted upon by deaminases causing hyperuricemia. Uric acid can produce endothelial dysfunction and vascular disease. Uric acid can also produce mitochondrial dysfunction. The fructose phosphate can enter the glucosamine pathway synthesizing GAG and producing mucopolysaccharide accumulation. Fructose can fructosylate proteins making them antigenic and producing an autoimmune response. This can lead to global warming related bone and joint disease.

The increase in endogenous EDLF, a potent inhibitor of membrane Na<sup>+</sup>-K<sup>+</sup> ATPase, can decrease this enzyme activity. The results showed increased endogenous EDLF synthesis as evidenced by increased HMG CoA reductase activity, which functions as the rate limiting step of the isoprenoid pathway. Studies in our laboratory have demonstrated that EDLF is synthesized by the isoprenoid pathway. The endosymbiotic archaeal sequences in the human genome get expressed by redox stress and osmotic stress of global warming. This results in induction of HIF alpha which will upregulate fructolysis and glycolysis. In the setting of redox stress all glucose gets converted to fructose by the induction of enzymes aldose reductase and sorbitol dehydrogenase. Aldose reductase converts glucose to sorbitol and sorbitol dehydrogenase converts sorbitol to fructose. Since fructose is preferentially phosphorylated by ketohexokinases the cell is depleted of ATP and glucose phosphorylation comes

to a halt. Fructose becomes the dominant sugar that is metabolized by fructolysis in expressed archaeal particles in the cell functioning as organelle called fructosoids. The fructose is phosphorylated to fructose 1-phosphate which is acted upon by aldolase B which converts it into glyceraldehyde 3-phosphate and dihydroxy acetone phosphate. Glyceraldehyde 3-phosphate is converted to D 1, 3-biphosphoglycerate which is then converted to 3-phosphoglycerate. The 3-phosphoglycerate is converted to 2-phosphoglycerate. 2-phosphoglycerate is converted to phosphoenol pyruvate by the enzyme enolase. Phosphoenol pyruvate is converted to pyruvate by the enzyme pyruvic kinase. The archaeon induces HIF alpha which upregulates fructolysis and glycolysis but inhibits pyruvate dehydrogenase. The forward metabolism of pyruvate is stopped. The dephosphorylation of phosphoenol pyruvate is inhibited in the setting of pyruvic kinase inhibition. Phosphoenol pyruvate enters the shikimic acid pathway where it is converted to chorismate. The shikimic acid is synthesized by a pathway starting from glyceraldehyde 3-phosphate. Glyceraldehyde 3-phosphate combines with the pentose phosphate pathway metabolite sedoheptulose 7-phosphate which is converted to erythrose 4-phosphate. The pentose phosphate pathway is upregulated in the presence of the suppression of glycolytic pathway. Erythrose 4-phosphate combines with phosphoenol pyruvate to generate shikimic acid. Shikimic acid combines with another molecule of phosphoenol pyruvate to generate chorismate. The chorismate is converted to prephenic acid and then to parahydroxy phenyl pyruvic acid. Parahydroxy phenyl pyruvic acid is converted to tyrosine and tryptophan as well as neuroactive alkaloids. The shikimic acid pathway is structured in expressed archaeon organelle called the neurotransminoid. The fructolytic intermediates glyceraldehydes 3-phosphate and pyruvate are the starting points of the DXP pathway of cholesterol synthesis. Glyceraldehyde 3-phosphate combines with pyruvate to form 1-deoxy D-xylulose phosphate

(DOXP) which is then converted to 2-C methyl erythritol phosphate. 2-C methyl erythritol phosphate can be synthesized from erythrose 4-phosphate a metabolite of the shikimic acid pathway. DXP combines with MEP to form isopentenyl pyrophosphate which is converted to cholesterol. Cholesterol is catabolised by archaeal cholesterol oxidases to generate digoxin. The digoxin sugars digitoxose and rhamnose are synthesized by the upregulated pentose phosphate pathway. Glycolytic suppression leads to upregulation of the pentose phosphate pathway. The expressed archaeon organelle concerned with cholesterol catabolism and digoxin synthesis is called the steroidelle. The suppression of glycolysis and stimulation of fructolysis results in upregulation of the hexosamine pathway. Fructose is converted to fructose 6-phosphate by ketohexokinases. The fructose 6-phosphate is converted to glucosamine 6-phosphate by the action of glutamine fructose 6-phosphate amidotransferase (GFAT). Glucosamine 6-phosphate is converted to UDP N-acetyl glucosamine which is then converted to N-acetyl glucosamine and various amino sugars. UDP glucose is converted to UDP D-glucuronic acid. UDP D-glucuronic acid is converted to glucuronic acid. This forms the uronic acid synthetic pathway. Uronic acids and hexosamines form repeating units of glycosaminoglycans. In the setting of glycolytic suppression and fructolytic metabolism fructolysis leads to increase synthesis of hexosamines and GAG synthesis. The GAG synthesizing archaeon particles are called the glycosaminoglycoids. The expressed archaeon particles are capable of synthesizing antioxidant vitamin C and E. The UDP D-glucose is converted to UDP D-glucuronic acid. UDP D-glucuronic acid is converted to D-glucuronic acid. D-glucuronic acid is converted to L-gulonate by enzyme aldoketoreductases. L-gulonate is converted to L-gulonolactone by lactonase. L-gulonolactone is converted to ascorbic acid by the action of archaeal L-gulo oxidase. The vitamin E is synthesized from shikimate which is converted to tyrosine and then to parahydroxy phenyl

pyruvic acid. Parahydroxy phenyl pyruvic acid is converted to homogentisate. Homogentisate is converted to 2-methyl 6-phytyl benzoquinone which is converted to alpha tocopherol. 2-methyl 6-phytyl benzoquinone is converted to 2, 3-methyl 6-phytyl benzoquinone and gamma tocopherol. Vitamin E can also be synthesized by the DXP pathway. Glyceraldehyde 3-phosphate and pyruvate combined to form 1-deoxy D-xylulose 5-phosphate which is converted to 3-isopentenyl pyrophosphate. 3-isopentenyl pyrophosphate and dimethyl allyl pyrophosphate combined to form 2-methyl 6-phytyl benzoquinone which is converted to tocopherols. The ubiquinone another important membrane antioxidant and part of the mitochondrial electron transport chain is synthesized by the shikimic acid pathway and DXP pathway. The isoprenoid moiety of ubiquinone is contributed from the DXP pathway and the rest of it by tyrosine catabolism. The tyrosine is generated by the shikimic acid pathway. The archaeon particles concerned with the synthesis of vitamin C, vitamin E and ubiquinone which are all antioxidants are called the vitaminocyte.

The human hypothalamus also produces an endogenous membrane  $\text{Na}^+\text{-K}^+$  ATPase inhibitor called digoxin. Digoxin increases the intracellular calcium load and also leads on to intracellular magnesium depletion. An increase in the intracellular calcium load consequent to digoxin can affect the bone histopathology. The intracellular magnesium depletion consequent to digoxin can affect glycoconjugate metabolism. Hypomagnesemia has been reported to upregulate glycosaminoglycan metabolism. Digoxin can also function as an immunomodulator. Lithium, an exogenous membrane  $\text{Na}^+\text{-K}^+$  ATPase inhibitor that can produce immune activation. Immunological mechanisms as well as alterations in the bone connective tissue matrix have been postulated to play an important role in the pathogenesis of degenerative osteoarthritis.

Articular cartilage is composed of two major macromolecular species: proteoglycans (PG) and collagen. The cartilage contains matrix

metalloproteinases (MMPs) which can degrade the proteoglycans. Lysosomal cathepsin present in the chondrocyte also plays a role in proteoglycan catabolism. The turnover of normal cartilage is effected through a degradative cascade for which the driving force is interleukin - 1 (IL-1) produced by mononuclear cells (including synovial lining cells) and synthesized by chondrocytes. IL 1 stimulates the synthesis and secretion of the latent MMPs and of the tissue plasminogen activator. Plasminogen can activate MMPs. IL-1 suppresses PG synthesis. Lysosomal enzymes and MMPs account for much of the loss of the cartilage matrix in OA.

It was therefore considered pertinent to study digoxin synthesis and related alterations in glycoconjugate and free radical metabolism in the following degenerative bone and joint disease (cervical and lumbar spondylosis, degenerative osteoarthritis and postmenopausal osteoporosis). The patterns were compared to those obtained in right hemispheric and left hemispheric dominance to find out whether hemispheric dominance has any correlation with these disease states.<sup>1-8</sup>

## Results

- (1) The results showed that HMG CoA reductase activity, serum digoxin and dolichol were increased and serum ubiquinone, RBC membrane  $\text{Na}^+\text{-K}^+$  ATPase activity and serum magnesium were reduced in degenerative bone disease (osteoarthritis and spondylosis). The results also showed that HMG CoA reductase activity, serum digoxin and dolichol were decreased and serum ubiquinone, RBC membrane  $\text{Na}^+\text{-K}^+$  ATPase and serum magnesium increased in senile osteoporosis.
- (2) There was an increase in lipid peroxidation as evidenced from the increase in the concentration of MDA, conjugated dienes, hydroperoxides and NO with decreased antioxidant protection as indicated by a decrease in

ubiquinone and reduced glutathione in degenerative bone disease (spondylosis and osteoarthritis).

- (3) The activity of enzymes involved in free radical scavenging like superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and catalase is decreased in degenerative bone disease (spondylosis and osteoarthritis). There was a decrease in lipid peroxidation as evidenced by the decrease in the concentration of MDA, conjugated dienes, hydroperoxides and NO with increased antioxidant protection as indicated by an increase in ubiquinone and reduced glutathione in senile osteoporosis. The activity of enzymes involved in free radical scavenging like superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and catalase is increased in postmenopausal senile osteoporosis.
- (4) The results show an increase in the concentration of serum total GAG and carbohydrate components of glycoproteins (hexose, fucose and sialic acid) in degenerative bone disease (spondylosis and osteoarthritis). The increase in the carbohydrate components (total hexose, fucose and sialic acid) in the degenerative bone disease was not to the same extent in all cases suggesting qualitative change in glycoprotein structure. The pattern of change in individual GAG in the serum was different, though heparan sulphates (HS) and chondroitin sulphates (ChS) increased in degenerative bone disease (osteoarthritis and spondylosis). The activity of GAG degrading enzymes (beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D) and that of glycohydrolases (beta galactosidase, beta fucosidase and beta glucosidase) showed significant increase in the serum in degenerative bone disease (osteoarthritis and spondylosis). The results show a decrease in the concentration of the serum total GAG and carbohydrate components of glycoproteins (hexose, fucose and sialic acid) in postmenopausal senile osteoporosis. The

decrease in the carbohydrate components (total hexose, fucose and sialic acid) in the disorders studied was not to the same extent in senile osteoporosis also suggesting qualitative change in glycoprotein structure. The pattern of change in the individual GAG in the serum was different, however heparan sulphate (HS) chondroitin sulphates (ChS) decreased in postmenopausal senile osteoporosis. The activity of GAG degrading enzymes (beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D) and that of glycohydrolases (beta galactosidase, beta fucosidase and beta glucosidase) showed a significant decrease in the serum in postmenopausal senile osteoporosis.

(5) The cholesterol: phospholipid ratio of the RBC membrane is decreased in osteoporosis and increased in spondylosis and osteoarthritis. The concentration of total GAG, hexose and fucose content of glycoproteins increased in the serum and decreased in the RBC membrane in spondylosis and osteoarthritis. The concentration of total GAG, hexose and fucose content of glycoproteins decreased in the serum and increased in the RBC membrane in osteoporosis.

(6) The results showed that HMG CoA reductase activity serum digoxin and dolichol were increased and ubiquinone, reduced, in left handed / right hemispheric dominant individuals. The results also showed that HMG CoA reductase activity serum digoxin and dolichol were decreased and ubiquinone increased in right - handed/left hemispheric dominant individuals.

## Discussion

### Archaeal Digoxin and Membrane $\text{Na}^+\text{-K}^+$ ATPase Inhibition in Relation to Bone and Joint Disease

The archaeon steroidelle contributes to lipid synthesis and metabolism. The archaeon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The decrease in the activity of HMG CoA reductase in postmenopausal senile osteoporosis suggests a downregulation of the isoprenoid pathway. There is a marked decrease in plasma digoxin and dolichol and this decrease may be a consequence of a decreased channeling of intermediates of the isoprenoid pathway for their biosynthesis. In this connection, incorporation of  $^{14}\text{C}$ -acetate into digoxin in rat brain was shown, indicating that acetyl CoA is the precursor for digoxin biosynthesis in mammals also. The decrease in endogenous digoxin, a potent inhibitor of membrane  $\text{Na}^+\text{-K}^+$  ATPase, can increase this enzyme activity. In postmenopausal senile osteoporosis there was significant stimulation of the RBC membrane  $\text{Na}^+\text{-K}^+$  ATPase. The stimulation of  $\text{Na}^+\text{-K}^+$  ATPase by digoxin is known to cause a decrease in intracellular calcium by decreased sodium - calcium exchange, decreased entry of calcium via the voltage gated calcium channel and decreased release of calcium from intracellular endoplasmic reticulum calcium stores. This decrease in intracellular calcium can cause an increase in the functional availability of intracellular magnesium because both these ions have an adversarial relationship. This increase in the availability of magnesium can cause increased mitochondrial ATP synthesis and further stimulation of  $\text{Na}^+\text{-K}^+$  ATPase, since the ATP-magnesium complex is the actual substrate for this reaction. Cytosolic free calcium is normally buffered by two mechanisms: ATP dependent calcium extrusion from the cell and ATP dependent sequestration of calcium within the endoplasmic reticulum. The increased intracellular magnesium related upregulated mitochondrial ATP

synthesis results in increased calcium extrusion from the cell. There is thus, a progressive stimulation of  $\text{Na}^+\text{-K}^+$  ATPase activity by digoxin. High intracellular magnesium and low intracellular calcium consequent to  $\text{Na}^+\text{-K}^+$  ATPase stimulation appear to be crucial to the pathophysiology of postmenopausal senile osteoporosis. The intracellular negative calcium signal and positive magnesium signal can regulate diverse cellular processes. Serum magnesium was assessed in postmenopausal osteoporosis and was found to be increased. Decrease in bone calcium load can lead to osteoporosis.

The increase in endogenous digoxin, a potent inhibitor of membrane  $\text{Na}^+\text{-K}^+$  ATPase, can decrease this enzyme activity in degenerative bone disease. In degenerative bone and joint disease (osteoarthritis and spondylosis), there was significant inhibition of the RBC membrane  $\text{Na}^+\text{-K}^+$  ATPase. The inhibition of  $\text{Na}^+\text{-K}^+$  ATPase by digoxin is known to cause an increase in intracellular calcium resulting from increased  $\text{Na}^+\text{-Ca}^{++}$  exchange, increased entry of calcium via the voltage gated calcium channel and increased release of calcium from intracellular endoplasmic reticulum calcium stores. This increase in intracellular calcium by displacing magnesium from its binding sites causes a decrease in the functional availability of magnesium. The decrease in the availability of magnesium can cause decreased mitochondrial ATP formation which along with low magnesium can cause further inhibition of  $\text{Na}^+\text{-K}^+$  ATPase. The intracellular magnesium depletion related mitochondrial dysfunction results in defective calcium extrusion from the cell. There is thus, a progressive inhibition of  $\text{Na}^+\text{-K}^+$  ATPase activity first triggered by digoxin. Low intracellular magnesium and high intracellular calcium consequent to  $\text{Na}^+\text{-K}^+$  ATPase inhibition appear to be crucial to the pathophysiology of degenerative bone disease. The intracellular positive calcium signal and negative magnesium signal can regulate diverse cellular processes. Serum magnesium was assessed in degenerative bone and joint disease (osteoarthritis and spondylosis) and was found to be reduced. Increased

intracellular calcium can lead to calcification that is noted in articular and ligamentous structures in cervical and lumbar spondylosis.<sup>1-8</sup>

### **Archaeal Digoxin and Regulation of Golgi Body / Lysosomal Function in Relation to Bone and Joint Disease**

The archaeon glycosaminoglycoid and fructosoid contributes to glycoconjugate synthesis and catabolism by the process of fructolysis. The elevation in the level of dolichol in degenerative bone disease (spondylosis and osteoarthritis) may suggest its increased availability of the N-glycosylation of proteins. In magnesium deficiency found in osteoarthritis and spondylosis; the glycolysis, citric acid cycle and oxidative phosphorylation are blocked and more glucose 6-phosphate is channelled for the synthesis of glycosaminoglycans (GAG). Intracellular magnesium deficiency also results in defective ubiquitin-dependent proteolytic processing of glycoconjugates as it requires magnesium for its function. The increase in the activity of glycohydrolases and GAG degrading enzymes could be due to reduced lysosomal stability and a consequent leakage of lysosomal enzymes into the serum. The increase in the concentration of carbohydrate components of glycoproteins and GAG in spite of increased activity of glycohydrolases suggests a qualitative change in their structure. Proteoglycan complexes formed in the presence of altered calcium:magnesium ratios intracellularly, may be structurally abnormal and contribute to altered bone structure in osteoarthritis. Lysosomal stability is reduced and there is increased release of lysosomal enzymes, especially cathepsin-D contributing to bone and joint destruction. The protein processing defect can result in defective glycosylation of endogenous bone glycoprotein antigens with a consequent defective formation of MHC antigen complex. The MHC linked peptide transporter; a P-glycoprotein which transports MHC-antigen complex to the antigen presenting cell surface; has an ATP binding site. The peptide

transporter is dysfunctional in the presence of magnesium deficiency. This results in defective transport of MHC class-1 bone glycoprotein antigen complex to the antigen presenting cell surface for recognition by CD<sub>4</sub> or CD<sub>8</sub> cells. Defective presentation of endogenous bone glycoprotein antigen can explain the immune dysregulation contributing to osteoarthritis. A number of fucose and sialic acids containing natural ligands are involved in the trafficking of leukocytes, and similar breaches in the blood brain barrier and adhesion of the lymphocyte producing leukocyte trafficking and extravasation into the perivascular space have been described in osteoarthritis.

In postmenopausal senile osteoporosis, the hypodigoxinemia and resultant membrane Na<sup>+</sup>-K<sup>+</sup> ATPase stimulation-related increased intracellular magnesium levels can affect the metabolism of glycosaminoglycans and glycoproteins. The decrease in the level of dolichol may suggest its decreased availability for the N-glycosylation of proteins. In intracellular magnesium excesses noted in osteoporosis, the glycolysis, citric acid cycle and oxidative phosphorylation are activated and less glucose 6-phosphate is channelled for the synthesis of glycosaminoglycans (GAG). The results show a decrease in the concentration of serum total GAG, and carbohydrate components of glycoproteins (hexose, fucose and sialic acid) in postmenopausal senile osteoporosis. The individual's GAG fractions in the serum-heparan sulphate (HS), chondroitin sulphates (ChS), heparin (H), hyaluronic acid (HA) and dermatan sulphate (DS) decreased in postmenopausal senile osteoporosis. The activity of GAG degrading enzymes (beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D) and that of glycohydrolases (beta galactosidase, beta fucosidase and beta glucosidase) showed a significant decrease in serum in postmenopausal senile osteoporosis. Intracellular magnesium excess also results in increased ubiquitin-dependent proteolytic processing of glycoconjugates as it requires magnesium for its function. The

decrease in the activity of glycohydrolases and GAG degrading enzymes could be due to increased lysosomal stability. Increased lysosomal stability and defective degradation of glycoprotein - GAG complexes could lead to postmenopausal senile osteoporosis as it leads to defective bone remodelling. Reduction in the level of bone glycosaminoglycans can also affect the structural integrity of bone, leading to osteoporosis. The sulphated glycosaminoglycans have a negative charge and can be complex with calcium ions. This helps to retain the calcium ions in the bone matrix and contributes to the bone's structural integrity. The reduction in the level of sulphated glycosaminoglycans can thus, contribute to osteoporosis.<sup>1-8</sup>

### **Archaeal Digoxin and Alteration in Membrane Structure and Membrane Formation in Relation to Bone and Joint Disease**

The archaeon steroidelle, glycosaminoglycoid and fructosoid contribute to cell membrane formation synthesizing cholesterol by the DXP pathway and glycosaminoglycans by fructolysis. The alteration in the isoprenoid pathway specifically, cholesterol, as well as changes in glycoproteins and GAG can affect cellular membranes. The upregulation of the isoprenoid pathway in osteoarthritis and spondylosis can lead to increased cholesterol synthesis and magnesium deficiency can inhibit phospholipid synthesis. Phospholipid degradation is increased owing to an increase in the intracellular calcium activating phospholipases A<sub>2</sub> and D. The cholesterol: phospholipid ratio of the RBC membrane was increased in spondylosis and osteoarthritis. The concentration of total GAG, hexose and fucose of glycoprotein decreased in the RBC membrane and increased in the serum, suggesting their reduced incorporation into the membrane and defective membrane formation. The glycoproteins, GAG and glycolipids of cellular membrane are formed in the endoplasmic reticulum, which is then budded of as a vesicle, which fuses with

the golgi complex. The glycoconjugates are then transported via the golgi channel and the golgi vesicle fuses with the cell membrane. This trafficking depends upon GTPases and lipid kinases, which are crucially dependent on magnesium and are defective in magnesium deficiency. The change in membrane structure produced by alteration in glycoconjugates and the cholesterol: phospholipid ratio can produce changes in the conformation  $\text{Na}^+\text{-K}^+$  ATPase, resulting in further membrane  $\text{Na}^+\text{-K}^+$  ATPase inhibition. The same changes can affect the structure of the organelle membrane. This results in defective lysosomal stability and leakage of glycohydrolases and GAG degrading enzymes into the serum. Defective peroxisomal membranes lead to catalase dysfunction, which has been documented in these disorders.

The downregulation of the isoprenoid pathway in senile osteoporosis can lead to decreased cholesterol synthesis and magnesium excess can stimulate phospholipid synthesis. Phospholipid degradation is decreased owing to a decrease in intracellular calcium inhibiting phospholipase  $\text{A}_2$  and D. The cholesterol: phospholipid ratio of the RC membrane was decreased in hypodigoxinemia. The concentration of total GAG, hexose and fucose of glycoprotein increased in the RBC membrane and decreased in the serum suggesting their increased incorporation into the membrane and defective membrane formation. The membrane trafficking depends upon GTPases and lipid kinases, which are crucially dependent on magnesium and are activated in magnesium excess. The change in membrane structure produced by an alteration in glycoconjugates and the cholesterol: phospholipid ratio can produce changes in the conformation of  $\text{Na}^+\text{-K}^+$  ATPase resulting in further membrane  $\text{Na}^+\text{-K}^+$  ATPase stimulation. The same changes can affect the structure of the organelle membrane. This results in increased lysosomal stability. Altered peroxisomal membranes could lead to a catalase hyperactivity noticed in hypodigoxinemic states.<sup>1-8</sup>

## Archaeal Digoxin and Mitochondrial Dysfunction in Relation to Bone and Joint Disease

The archaeon vitaminocyte contributes to the synthesis of ubiquinone and mitochondrial electron transport chain function. The mitochondrial function related free radical generation is regulated by the archaeon vitaminocyte synthesized tocopherol and ascorbic acid. The concentration of ubiquinone decreased significantly in osteoarthritis and spondylosis which may be the result of low tyrosine levels, reported in degenerative bone and joint disease (spondylosis and osteoarthritis) consequent to digoxin's effect in preferentially promoting tryptophan transport over tyrosine. The aromatic ring portion of ubiquinone is derived from tyrosine. Ubiquinone, which is an important component of the mitochondrial electron transport chain, is a membrane antioxidant and contributes to free radical scavenging. The increase in intracellular calcium can open the mitochondrial PT pore, causing a collapse of the hydrogen gradient across the inner membrane and an uncoupling of the respiratory chain. Intracellular magnesium deficiency can lead to a defect in the function of ATP synthase. All this leads to defects in mitochondrial oxidative phosphorylation, incomplete reduction of oxygen and generation of a superoxide ion, which produces lipid peroxidation. Ubiquinone deficiency also leads to reduced free radical scavenging. The increase in intracellular calcium may lead to an increased generation of NO by inducing the enzyme nitric oxide synthase, which combines with a superoxide radical to form peroxynitrite. Increased calcium can also activate phospholipase A<sub>2</sub>, resulting in an increased generation of arachidonic acid which can undergo increased lipid peroxidation. Increased generation of free radicals like the superoxide ion and hydroxyl radical can produce lipid peroxidation and cell membrane damage, which can further inactivate Na<sup>+</sup>-K<sup>+</sup> ATPase, triggering the cycle of free radical generation once again. Magnesium deficiency can affect the glutathione synthase and

glutathione reductase functions. The mitochondrial superoxide dismutase leaks out and becomes dysfunctional with a calcium related opening of the mitochondrial PT pore and outer membrane rupture. The peroxisomal membrane is defective owing to a membrane  $\text{Na}^+\text{-K}^+$  ATPase inhibition-related defect in membrane formation and leads to reduced catalase activity. Mitochondrial dysfunction-related free radical generation has been implicated in the pathogenesis of immune-mediated dysfunctions described in degenerative bone and joint disease (osteoarthritis).

The increased intracellular calcium-related opening of the mitochondrial PT pore also leads to a volume dysregulation of the mitochondria causing hyperosmolality of the matrix and expansion of the matrix space. The outer membrane of the mitochondria ruptures and releases an apoptosis-inducing factor and cytochrome C into the cytoplasm. This results in activation of caspase-9 and caspase-3. Caspase-9 can produce apoptosis of the cell. Apoptosis has been implicated in cell death. Increased apoptosis of osteoblast can contribute to degenerative bone and joint disease (osteoarthritis and cervical spondylosis).

The concentration of ubiquinone increased significantly in postmenopausal senile osteoporosis, which may be the result of increased tyrosine levels, consequent to digoxin deficiency promoting tyrosine transport over tryptophan. The decrease in intracellular calcium can stabilise the mitochondrial PT pore and improve mitochondrial function. Intracellular magnesium excess can lead to an increase in the activity of ATP synthase. All this leads to improved efficiency in mitochondrial oxidative phosphorylation and reduced free radical generation. Ubiquinone excess also leads to increased free radical scavenging. The decrease in intracellular calcium may lead to decreased generation of NO by inhibiting the enzyme nitric oxide synthase and reduced peroxynitrite formation. Decreased calcium can also inhibit phospholipase  $\text{A}_2$  resulting in decreased generation of arachidonic acid and free radical formation. Decreased

generation of free radicals like the superoxide ion and hydroxyl radical can stabilise the cell membrane and stimulate membrane  $\text{Na}^+\text{-K}^+$  ATPase. There was a decrease in lipid peroxidation as evidenced from the decrease in the concentration of MDA, conjugated dienes and hydroperoxides and the increase in free radical scavengers like ubiquinone and reduced glutathione in senile osteoporosis. The activity of enzymes involved in free radical scavenging like superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase is increased in postmenopausal senile osteoporosis suggesting increased free radical scavenging. The peroxisomal membrane is stabilised owing to membrane  $\text{Na}^+\text{-K}^+$  ATPase stimulation-related alteration in membrane formation and leads to increased catalase activity. Glutathione is synthesized by the enzyme glutathione synthetase, which needs magnesium and ATP. The high intracellular magnesium consequent to  $\text{Na}^+\text{-K}^+$  ATPase stimulation and the resulting increased ATP synthesis can result in increased synthesis of glutathione. Glutathione peroxidase, a selenium containing enzyme, oxidises reduced glutathione (GSH) to oxidised glutathione (GSSG) which is then rapidly reduced to GSH by glutathione reductase. There is also a concomitant conversion of  $\text{H}_2\text{O}_2$  to  $\text{H}_2\text{O}$ . The activity of glutathione reductase needs NADPH for the regeneration of GSH. This NADPH comes mostly from the pentose phosphate pathway. Intracellular magnesium excess due to membrane  $\text{Na}^+\text{-K}^+$  ATPase stimulation leads to increased formation of glucose 6-phosphate and upregulation of the pentose phosphate pathway with consequent increased generation of NADPH. The glutathione system of free radical scavenging is activated in the presence of membrane  $\text{Na}^+\text{-K}^+$  ATPase stimulation. Superoxide dismutase exists in a mitochondrial and cytoplasmic form. The stabilisation of the mitochondrial PT pore consequent to reduced intracellular calcium produces increased superoxide dismutase activity. Free radicals are required for osteoclastic activity and bone remodelling. The reduced generation of free

radicals owing to an increased efficiency of mitochondria leads to defective osteoclast related bone remodelling and postmenopausal senile osteoporosis. The decreased intracellular calcium related stabilisation of the mitochondrial PT pore also leads to downregulation of the apoptotic program and reduced apoptosis. The stabilisation of the mitochondrial PT pore leads to reduced release of the apoptosis inducing factor and cytochrome C into the cytoplasm. This results in inactivation of caspase-9 which produces cellular apoptosis. Apoptosis is an important component of bone remodelling. Defective apoptosis leads to defective bone remodelling and senile postmenopausal osteoporosis.<sup>1-8</sup>

### **Archaeal Digoxin and Immunoregulation in Relation to Bone and Joint Disease**

The archaeon fructosoid contributes to fructolysis and immune activation. Fructose can contribute to induction of NF $\kappa$ B and immune activation. The archaeon steroidelle synthesized digoxin induces NF $\kappa$ B producing immune activation. In hyperdigoxinemia related degenerative bone disease (spondylosis and osteoarthritis) increased intracellular calcium activates the calcium dependent calcineurin signal transduction pathway which can produce T-cell activation and secretion of interleukin-1. This can also explain the immune activation leading to joint destruction in degenerative bone disease (osteoarthritis). Membrane Na<sup>+</sup>-K<sup>+</sup> ATPase inhibition can produce immune activation and is reported to increase CD<sub>4</sub>/CD<sub>8</sub> ratios as exemplified by the action of lithium.<sup>1-8</sup>

### **Archaeal Digoxin, Oncogene Activation and Bone and Joint Disease**

The archaeon secreting RNA viroids is called the viroidelle. The primitive archaeal DNA is integrated along with RNA viroids which are converted to their corresponding DNA by the action of redox stress induced HERV reverse

transcriptase into the human genome by the redox stress induced HERV integrase. The archaeal DNA sequences that are integrated into the human genome forms endogenous archaeal human genomic sequences akin to HERV sequences and can function as jumping genes regulating genomic DNA flexibility. The integrated endogenous genomic archaeal sequences can get expressed in the presence of redox stress forming endosymbiotic archaeal particles which can function as a new organelle called the archaeons. In hyperdigoxinemic degenerative bone and joint disease, increased intracellular calcium activates phospholipase C beta which results in increased production of diacylglycerol (DAG) with resultant activation of protein kinase C. The protein kinase C (PKC) activates the MAP kinase cascade resulting in cellular osteoblastic proliferation. The decreased intracellular magnesium can produce dysfunction of the GTPase activity of the alpha-subunit of G-protein. This results in ras oncogene activation, as more of the ras is bound to GTP rather than GDP, Upregulation of the isoprenoid pathway can result in increased production of farnesyl phosphate, which can farnesylate the ras oncogene, producing its activation. Thus in the hyperdigoxinemic state-related degenerative bone and joint disease (spondylosis and osteoarthritis), there is increased growth potential of the osteoblast which leads to an increase in bone density and spondylosis. In the hypodigoxinemic postmenopausal senile osteoporosis, high intracellular magnesium and low intracellular calcium consequent to  $\text{Na}^+\text{-K}^+$  ATPase stimulation appears to reduce the growth potential of the osteoblast. Decreased intracellular calcium inactivates phospholipase C beta which results in decreased production of diacylglycerol (DAG) with resultant inactivation of protein kinase C The protein kinase C (PKC) activation of the MAP kinase cascade is inhibited, resulting in a blockade of cellular proliferation. The increased intracellular magnesium can produce an increase in the GTPase activity of the alpha-subunit of G protein.

This results in ras oncogene inactivation, as more of the ras is bound to GDP rather than GTP and a reduction in osteoblastic growth potential. The downregulation of the isoprenoid pathway can result in decreased production of farnesyl phosphate which is required for ras oncogene activation. Therefore the ras oncogene is inactivated. In the hypodigoxinemic postmenopausal senile osteoporosis there is a reduction in the growth potential of the osteoblast. This contributes to the pathogenesis of senile postmenopausal osteoporosis.<sup>1-8</sup>

### **Archaeal Induced Hyperdigoxinemic State and Hemispheric Dominance in Relation to Bone and Joint Disease**

The archaeon related organelle - steroidelle, neurotransminoid and vitaminocyte contribute to hemispheric dominance. Thus, the degenerative bone and joint disease (spondylosis and osteoarthritis) represents the hyperdigoxinemic state. This leads to (1) increased free radical production and reduced scavenging leading to increased osteoclastic activity, (2) increased glycoconjugate synthesis and defective lysosomal stability, (3) immune activation. (4) membrane  $\text{Na}^+\text{-K}^+$  ATPase inhibition related increased calcium load in the bone, (5) digoxin related increased apoptosis and (6) hyperdigoxinemia related increased osteoblastic proliferation potential. The hyperdigoxinemic state occurs in right hemispheric dominant individuals.

The postmenopausal senile osteoporosis is a hypodigoxinemic state. This leads to (1) reduced free radical production, (2) reduced glycoconjugate synthesis, (3) stable lysosomes which can contribute to defective osteoclastic activity and bone remodeling, (4) membrane  $\text{Na}^+\text{-K}^+$  ATPase inhibition-related reduced intracellular calcium load, (5) hypodigoxinemia related immune inactivation, (6) hypodigoxinemia related reduced apoptosis and bone remodeling and (7) hypodigoxinemia related blockade of osteoblastic

proliferation. The pattern in postmenopausal senile osteoporosis is similar to the left hemispheric dominant state.

The hyperdigoxinemia related patterns seen in spondylosis and osteoarthritis correlates with right hemispheric dominance. Similarly the hypodigoxinemia related pattern in senile osteoporosis correlates with left hemispheric dominance. Hemispheric dominance and archaeal digoxin decide the predisposition to these disease states.<sup>1-8</sup>

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