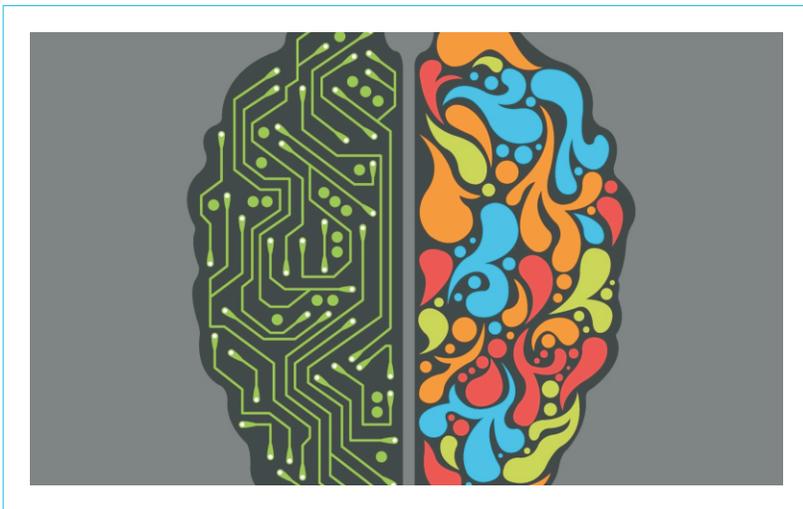


GLOBAL WARMING

Archaea and Viroid Induced Symbiotic Human Evolution and Hemispheric Dominance

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Global Warming, Archaea and Viroid Induced Symbiotic Human Evolution and Hemispheric Dominance

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ISBN: 978-1-941926-85-7

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Published in 2016 by Open Science Publishers

228 Park Ave., S#45956, New York, NY 10003, U.S.A.

<http://www.openscienceonline.com>

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Chapter 1

The Endosymbiotic Archaea, Fructose Disease and
Global Warming - Relation to
Hemispheric Dominance

Hemispheric dominance is a reflection of endosymbiotic and colonic archaeal symbiosis. A higher density of archaeal symbiosis produces right hemispheric dominance and a lower density of archaeal symbiosis produces left hemispheric dominance. 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 archaea can secrete capsulated RNA viroidal particles which can function as blocking RNAs modulating cell metabolism and such archaeaon 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. Human 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 sapiens* 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. 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. The colonic and endosymbiotic archaea and other microbes like clostridial clusters determine the species, race, caste, community and personal identity of the individual. The identity of the individual - personal, community, caste, race, nationality and species is determined by the colonic and endosymbiotic archaeal and clostridial clusters. Predominant archaeal symbiosis produces homo neanderthalis and less prominent archaeal symbiosis and dominant clostridial clusters in the gut produces the homo sapien species. Each individual, race, nationality, caste, creed and community have the endosymbiotic and colonic microbiota signature. This colonic and endosymbiotic microbiota signature is

transferable by the change of endosymbiotic and colonic microbiota from one group to another. Thus the evolution and identity based on individuality, race, nationality, caste and creed can be induced.

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 Villarreal 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 in 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 sapien 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 sapien anthropocene age. The archaeal population densities and quasi-species RNA viroidal networks determine homo sapien, homo neanderthalis, racial, caste, community, national, sexual and individual 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 civilization - 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 D1,3-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.

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 κ B which produces immune activation. Both redox stress and immune activation can activate aldose reductase which converts glucose to fructose. Hypoxic stress or anerobic 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 steroyl 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 NFKB 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 anerobic 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 anerobic 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 anerobic glycolysis ketohexokinase A which preferentially metabolizes glucose is converted to ketohexokinase C metabolizing fructose by the mechanism of RNA splicing. Anerobic 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 NFKB 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 metallothioneins 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 glutamatergic 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 Maillard 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 dysregulates 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 spectacle 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 glyceraldehydes 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 glyceraldehydes 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% 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 reductase 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 trance 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 NFkB 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 porphyria 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 and 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
LHCD	2.50	0.195	8.50	0.405	3.50	1.304	3.50	0.707
RHCD	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
LHCD	124.00	3.688	2.50	0.405	5.70	0.369	7.50	1.704
RHCD	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
LHCD	1.50	0.358	50.40	5.960	5.20	0.363
RHCD	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	

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Chapter 2

Neanderthalic Actinide Dependent Shadow Biosphere
of Archaea and Viroids and Hemispheric Dominance

Introduction

The human brain synthesizes an endogenous membrane sodium-potassium ATPase inhibitor digoxin which plays a role in neuro-immuno-endocrine integration and pathogenesis of several neuropsychiatric and systemic diseases. Endomyocardial fibrosis (EMF) along with the root wilt disease of coconut is endemic to Kerala with its radioactive actinide beach sands. Actinides like rutile producing intracellular magnesium deficiency due to rutile-magnesium exchange sites in the cell membrane have been implicated in the etiology of EMF.¹ Endogenous digoxin, a steroidal glycoside which functions as a membrane sodium-potassium ATPase inhibitor has also been related to its etiology due to the intracellular magnesium deficiency it produces.² Organisms like phytoplasmas and viroids have also been demonstrated to play a role in the etiology of these diseases.^{3, 4} Endogenous digoxin has been related to hemispheric dominance.² Right hemispheric dominant individuals were hyperdigoxinemic, left hemispheric dominant individuals were hypodigoxinemic and bihemispheric dominant individuals were normodigoxinemic. The possibility of endogenous digoxin synthesis by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered.⁵⁻⁷ Davies has put forward the concept of a shadow biosphere of organisms with alternate biochemistry present in earth itself.⁸ An actinide dependent shadow biosphere of archaea and viroids in the above mentioned disease states is described.⁶ The intracellular endosymbionts archaea and their intron derived viroids constitute the third element regulating the human body. Hemispheric dominance is a reflection of endosymbiotic and colonic archaeal symbiosis. A higher density of archaeal symbiosis produces right hemispheric dominance and a lower density of archaeal symbiosis produces left hemispheric dominance.

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 endotoxins 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.

The human brain can be considered as a modified archaeon colony network. The archaeon are eternal and can last for billions of years. The human brain is basically an information storage system. The archaeon has got dipolar magnetite and porphyrins and can function as quantal computer. The archaeal colony with its dipolar magnetite and porphyrin in the setting of archaeal digoxin induced membrane sodium potassium ATPase inhibition can function as a pumped phonon system mediating quantal perception. The archaeon in the brain is capable of information storage at a point in time and space. The experiences and information stored in the archaeon is immortal and eternal. The archaeon can have a wave particle existence and can exist in multiple quantal possible states and can inhabit multiple quantal multiverses. The interaction between information stored in quantal computers in multiple different archaeon systems all over the universe by the quantal interactions results in eternal existence of information in quantal multiverses. The information in the quantal multiverses can have a particulate existence creating a newer mode by quantal interactions between information stored at multiple points of time. This creates the particulate mythic world of human existence. These are what are called as Samsaras. The mind is uploaded into information in the neuronal archaeal colony network and its quantal computers. The information stored in the archaeal colony network mediated quantal state is eternal and can be considered as a digital version of the brain, a mind downloading technique or whole brain emulation. The archaeal colony network stores the human experiences in an eternal manner and can contribute to biological reincarnation.

Materials and Methods

Informed consent of the subjects and the approval of the ethics committee were obtained for the study. The following groups were included in the study: - (I) right handed and left hemispheric dominant group, (II) left handed and right hemispheric dominant group and (III) ambidextrous and bihemispheric dominant individuals. Hemispheric dominance was assessed by methods described in previous reports.² There were 10 healthy normal individuals in the age range between 20 and 30 years in each group. They were selected randomly from the general population. The blood samples were drawn in the fasting state. 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.⁹ 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, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, dopamine, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids.¹⁰⁻¹³ 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. The statistical analysis was done by ANOVA.

Results

The parameters checked as indicated above were: - cytochrome F420, free RNA, free DNA, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase,

ATP synthase, HMG CoA reductase, digoxin and bile acids. The plasma of the bihemispheric dominant group showed detectable levels of the above mentioned parameters after incubation for 1 hour and addition of cholesterol substrate resulted in still further increase in these parameters. The addition of antibiotics to the bihemispheric dominant group caused a decrease in all the parameters while addition of rutiline increased their levels. The plasma of right hemispheric dominant group showed a significant increase in the above mentioned parameters as compared to bihemispheric dominance group. The addition of antibiotics to the right hemispheric dominant group caused a decrease in all the parameters while addition of rutiline increased their levels but the extent of change was more in right hemispheric dominant group as compared to bihemispheric dominant group. The plasma of left hemispheric dominant group showed a significant decrease in the above mentioned parameters as compared to the bihemispheric dominant group. The addition of antibiotics to the left hemispheric dominant group caused a decrease in all the parameters while addition of rutiline increased their levels but the extent of change was less in left hemispheric dominant group as compared to bihemispheric dominant group. 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.

Table 1. Effect of rutiline and antibiotics on free DNA and RNA.

Group	DNA % change (Increase with Rutiline)		DNA % change (Decrease with antibiotics)		RNA % change (Increase with Rutiline)		RNA % change (Decrease with antibiotics)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
BHD	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
LHD	2.26	0.25	7.45	0.40	2.30	0.12	7.62	0.30
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
BHD	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
LHD	2.13	0.13	5.37	1.47	2.26	0.25	7.45	0.40
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
BHD	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
LHD	2.33	0.17	7.24	0.59	2.25	0.17	7.01	0.65
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
BHD	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
LHD	0.07	0.01	0.026	0.004	2.25	0.19	7.25	0.66
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
BHD	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
LHD	2.16	0.18	5.91	1.38	2.24	0.17	6.29	1.06
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 ₂ O ₂ % change (Increase with Rutile)		H ₂ O ₂ % change (Decrease with antibiotics)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
BHD	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
LHD	2.30	0.12	7.62	0.30	2.24	0.23	5.36	0.99
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
BHD	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
LHD	2.13	0.11	7.62	0.32	2.13	0.11	7.62	0.32
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. The archaea can synthesize and use cholesterol as a carbon and energy source.^{14, 15} 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.¹⁶ 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.⁷ The archaeal cholesterol oxidase activity was increased resulting in generation of pyruvate and hydrogen peroxide.¹⁵ 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.¹⁷ 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.¹⁸ 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.¹⁹ The decrease in free self replicating RNA and DNA with the addition of antibiotics indicates that the RNA viroids are derived from archaeal introns. 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.²⁰ 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.²¹ The integrated viroids and archaea can undergo vertical transmission and can exist as genomic parasites.^{20, 21} This increases the length and alters the grammar of the noncoding region producing memes or memory of acquired characters.²² The viroidal complementary DNA can function as jumping genes producing a dynamic genome important in storage of synaptic information, HLA gene expression and neurodevelopmental gene expression. The alteration in DNA sequences produced by viroidal complementary DNA jumping genes can lead onto schizophrenia and primary seizure disorder. The RNA viroids can regulate mRNA function by RNA interference.¹⁹ The phenomena of RNA interference can modulate T-cell and B-cell function, neuronal transmission and euchromatin/heterochromatin expression. The RNA viroid induced mRNA interference can modulate dopaminergic, glutamatergic and serotonergic synaptic transmission. The archaea and viroidal density is high in right hemispheric dominance, intermediate in bihemispheric dominance and low in left hemispheric dominance.

The presence of muramic acid, HMG CoA reductase and cholesterol oxidase activity inhibited by antibiotics indicates the presence of bacteria with mevalonate pathway. The density of the mevalonate pathway bacterial is high in right hemispheric dominance, low in left hemispheric dominance and intermediate in bihemispheric dominance. The bacterial with mevalonate pathway include streptococcus, staphylococcus, actinomycetes, listeria, coxiella and borrelia.²³ The bacteria and archaea with mevalonate pathway and cholesterol catabolism had a evolutionarily advantage and constitutes the isoprenoidal clade organism with the archaea evolving into mevalonate pathway gram positive and gram negative organism through horizontal gene transfer of viroidal and virus genes.²⁴ The isoprenoidal clade prokaryotes develop into other groups of prokaryotes via viroidal/virus as well as eukaryotic horizontal gene transfer producing bacterial speciation.²⁵ The RNA viroids and its complementary DNA developed into cholesterol enveloped RNA and DNA viruses like herpes, retrovirus, influenza virus, borna virus, cytomegalo virus and ebstein barr virus by recombining with eukaryotic and human genes resulting in viral speciation. Bacterial and viral species are ill defined and fuzzy with all of them forming one common genetic pool with frequent horizontal gene transfer and recombination. Thus the multi and unicellular eukaryote with its genes serves the purpose of prokaryotic and viral speciation. The multicellular eukaryote developed so that their endosymbiotic archaeal colonies could survive and forage better. The multicellular eukaryotes are like bacterial biofilms. The archaea and bacteria with a mevalonate pathway uses the extracellular RNA viroids and DNA viroids for quorum sensing and in the generation of symbiotic biofilm like structures which develop into multicellular eukaryotes.^{26, 27} The endosymbiotic archaea and bacteria with mevalonate pathway still uses the RNA viroids and DNA viroids for the regulation of multicellular eukaryote. Pollution is induced by the primitive nanoarchaea and

mevalonate pathway bacteria synthesized PAH and methane leading on to redox stress. Redox stress leads to sodium potassium ATPase inhibition, inward movement of plasma membrane cholesterol, defective SREBP sensing, increased cholesterol synthesis and nanoarchaeal / mevalonate pathway bacterial growth.²⁸ Redox stress leads on to viroidal and archaeal multiplication. Redox stress can also lead to HERV reverse transcriptase and integrase expression. The noncoding DNA is formed of integrating RNA viroidal complementary DNA and archaea with the integration going on as a continuing event. The archaeal pox like dsDNA virus forms evolutionarily the nucleus. The integrated viroidal, archaeal and mevalonate pathway bacterial sequences can undergo vertical transmission and can exist as genomic parasites. The genomic integrated archaea, mevalonate pathway bacteria and viroids form a genomic reserve of bacteria and viruses which can recombine with human and eukaryotic genes producing bacterial and viral speciation. Bacteria and viruses can contribute to the regulation of hemispheric dominance as exemplified by schizophrenia, a disorder of consciousness. *Borrelia*, *Toxoplasma*, *Chlamydia*, *Mycoplasma*, retroviruses, herpes virus, influenza virus and borna virus contribute to the neuropathogenesis of schizophrenia.²⁹⁻³¹ The change in the length and grammar of the noncoding region produces eukaryotic speciation and individuality.³² Changes in the length of noncoding region can lead onto modulation of hemispheric dominance and conscious perception as exemplified in schizophrenia.³³ The human endogenous retroviruses and change in the length and grammar of the noncoding region has been described in schizophrenia. The integration of nanoarchaea, mevalonate pathway prokaryotes and viroids in to the eukaryotic and human genome produces a chimera which can multiply producing biofilm like multicellular structures having a mixed archaeal, viroidal, prokaryotic and eukaryotic characters which is a regression from the multicellular eukaryotic tissue. This results in a new

neuronal, metabolic, immune and tissue phenotype producing microchimeras. Microchimeras can also generate tissue and neuronal polyploidy. The higher degree of integration of archaea, mevalonate pathway bacteria and viroids into the genome produces right hemispheric dominance, intermediate degree of integration produces bihemispheric dominance and lower degree of integration left hemispheric dominance.

The archaea and viroids can regulate the nervous system including the NMDA / GABA thalamo-cortico-thalamic pathway mediating conscious perception.^{2, 34} NMDA / GABA receptors can be modulated by digoxin induced calcium oscillations resulting in NMDA / glutamic acid decarboxylase (GAD) activity induction, PAH increasing NMDA activity and inducing GAD as well as viroid induced RNA interference modulating NMDA / GABA receptors.² The cholesterol ring oxidase generated pyruvate can be converted by the GABA shunt pathway to glutamate and GABA. Increased NMDA transmission has been described in schizophrenia and primary seizure disorder. 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 inducing quantal perception with nanoarchaeal sensed gravity producing the orchestrated reduction of the quantal possibilities to the macroscopic world.^{2, 34} The archaea can regulate limbic lobe transmission with archaeal cholesterol aromatase / ring oxidase generated norepinephrine, dopamine, serotonin and acetyl choline.¹⁷ Thus the shadow biosphere of archaea and viroids can regulate conscious and quantal perception. The archaea and viroids can also modulate multiple neurotransmitter systems. Schizophrenia is described as a disorder of consciousness and increased integration of archaea and viroids into the genome can contribute to its neuropathogenesis. Increased dopaminergic, serotonergic and NMDA transmission is important in the pathogenesis of schizophrenia. 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.² Bihemispheric dominance is intermediate with normal digoxin synthesis. Right hemispheric dominance has been described in schizophrenia. The increased integration of archaea into the neuronal genome can produce increased cholesterol oxidase and aromatase mediated monoamine and NMDA transmission producing schizophrenia. The archaeal bile acids are chemically diverse and structurally different from human bile acids. The archaeal bile acids can bind olfactory GPCR receptors and stimulate the limbic lobe producing a sense of social identity. The dominance of archaeal bile acids over human bile acids in stimulating the olfactory GPCR - limbic lobe pathway leads to loss of social identity leading to schizophrenia and autism³⁵.

Archaea and RNA viroid can bind the TLR receptor induce NF κ 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 signalling can activate NF κ B producing chronic immune activation.^{2, 36} The archaea and viroid induced chronic immune activation and generation of superantigens can lead on to autoimmune disease. This produces a state of chronic immune activation in right hemispheric dominance producing increased predisposition to autoimmune diseases. The left hemispheric dominant group is immunosuppressed and the bihemispheric dominant group has normal immune function.

Archaea, viroids and digoxin can induce the host AKT PI3K, AMPK, HIF alpha and NF κ B producing the Warburg metabolic phenotype.³⁷ 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 resulting in inefficient energetics. The

immune activation mediated increased levels of TNF alpha can produce insulin resistance acting at the level of insulin receptor. Thus a state similar to metabolic syndrome X exists in right hemispheric dominance. Left hemispheric dominance can have a pattern of insulin sensitivity while bihemispheric dominance will be metabolically intermediate. Cholesterol oxidase activity, increased glycolysis related NADPH oxidase activity and mitochondrial dysfunction generates free radicals. Free radical production and mitochondrial dysfunction can increase NMDA transmission important in conscious perception. 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.³⁷ The increased cholesterol substrate leads to increased archaeal growth and digoxin synthesis leading to metabolic channelling to the mevalonate pathway. Hyperdigoxinemia is important in the regulation of hemispheric dominance.² The right hemispheric dominant group is hyperdigoxinemic, left hemispheric dominant group is hypodigoxinemic and bihemispheric dominant group is normodigoxinemic. The pyruvate can be converted to glutamate and ammonia which is oxidised by archaea for energy needs. Ammonia can regulate both NMDA and GABA transmission depending on its levels. The Warburg phenotype can contribute to the hemispheric dominance by augmenting the bacterial shikimic acid pathway. The upregulated glycolysis consequent to the Warburg phenotype produces phosphoenolpyruvate, a basic substrate for the bacterial shikimic acid pathway which can synthesize monoamines and neuroactive alkaloids. The shikimic acid pathway can generate dopamine and serotonin producing increased monoaminergic transmission. The shikimic acid pathway can also synthesise the neuroactive alkaloids strychnine, nicotine, morphine, mescaline and LSD important in regulating neural transmission.² The upregulated glycolysis can also contribute to increased NMDA and GABA transmission in the

thalamo-cortico-thalamic pathway. The glycolytic pathway produces phosphoglycerate which is converted to phosphoserine and then serine which activates the NMDA receptor. The glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase is a GABA receptor kinase and activates GABA transmission. Thus the archaea and viroid induced Warburg phenotype can contribute to the modulation of hemispheric dominance by regulating the multiple neurotransmitter systems. The archaeal cholesterol catabolism can deplete the cell membranes of cholesterol resulting in alteration in lipid microdomains and their related neurotransmitter receptor contributing to the regulation of NMDA, serotonergic and dopaminergic transmission. Thus the archaeal cholesterol catabolism and viroids can regulate brain function and hemispheric dominance. The archaea and viroids have axonal and transynaptic transport functioning as biological neurotransmitters. The brain can be visualized evolutionarily as a modified mevalonate pathway bacteria and archaeal colony functioning by mechanisms of quorum sensing using RNA viroids with its bacterial flagellar system forming axo-axonic and axo-dendritic connections. The third element of archaea and their derived viroids can also regulate the immune, genetic, metabolic and neural systems producing its integration.

The third element formed of intracellular archaea and viroidal symbiosis determines hemispheric dominance. Archaeal cholesterol synthesis and catabolism determines hemispheric dominance.

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Chapter 3

Archaeal Digoxin - Central Role in Conscious
Perception, Neuro-Immuno-Endocrine Integration and
Coordination of Cellular Function - Relation to
Hemispheric Dominance

Introduction

Hemispheric dominance is a reflection of endosymbiotic and colonic archaeal symbiosis. A higher density of archaeal symbiosis produces right hemispheric dominance and a lower density of archaeal symbiosis produces left hemispheric dominance. 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 archaea can secrete capsulated RNA viroidal particles which can function as blocking RNAs modulating cell metabolism and such archaeaon 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. Human 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 endotoxins 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.

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 D1,3-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 archaeaon 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 aldoketo reductases. 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 archaea particles concerned with the synthesis of vitamin C, vitamin E and ubiquinone which are all antioxidants are called the vitaminocyte.

Isoprenoid pathway produces various metabolites that are essential for diverse cellular functions such as cholesterol involved in membrane structure, dolichol involved in protein glycosylation, and ubiquinone, which participates in mitochondrial electron transport. It is also a membrane antioxidant and digoxin, and an inhibitor of $\text{Na}^+\text{-K}^+$ ATPase produced by the hypothalamus. A deficiency of ubiquinone has been documented in Parkinson's disease, epilepsy, schizophrenia and multiple sclerosis. Increased levels of EDLA (endogenous digoxin-like activity) have been reported in epilepsy, bipolar mood disorder, vasculitis and syndrome X. Altered levels of dolichol have been observed in Alzheimer's disease.

The coexistence of four pathophysiological phenomena - oncogene activation and malignant transformation, neuronal degeneration, psychiatric manifestation and immune activation has been described in motor neuron disease, systemic malignancy, multiple sclerosis and schizophrenia. Autoantibodies have been demonstrated in multiple sclerosis, motor neuron disease, Alzheimer's disease, Down syndrome, paraneoplastic syndromes and acquired immunodeficiency syndrome. Psychosis has been documented in multiple sclerosis, Alzheimer's disease, Parkinson's disease, neoplasms and AIDS dementia. Lymphoma has been shown to coexist with multiple sclerosis, motor neuron disease, vasculitis and the acquired immunodeficiency syndrome. Viral persistence as an etiological factor has been documented in multiple sclerosis, Parkinson's disease, neoplasms and schizophrenia. Insulin resistance has been reported in Alzheimer's disease. Immune mediated neuropathies and neoplasms are described in syndrome X. This interrelationship between these disorders suggests the possibility that a central dysfunction may exist which could play a part in the pathophysiology of these disorders. The isoprenoid pathway may be a candidate in this respect in view of many reports on the changes in the concentration of many products of this pathway in many neurological and psychiatric disorders and therefore this pathway was assessed in these disorders. The disorders included in the study are multiple sclerosis, schizophrenia, Parkinson's disease, CNS glioma, syndrome X with multiple lacunar state, Down's syndrome and acquired immunodeficiency syndrome. The isoprenoid pathway was assessed by plasma HMG CoA reductase activity, serum digoxin, ubiquinone and dolichol levels. The digoxin induced membrane $\text{Na}^+\text{-K}^+$ ATPase can produce magnesium depletion and therefore serum magnesium was assessed in all these disorders. Digoxin, apart from affecting cation transport is also reported to influence the transport of various metabolites across cellular membranes, including amino acids and various neurotransmitters. Two of the

amino acids in this respect are important, tryptophan, a precursor for strychnine and nicotine and tyrosine a precursor for morphine. Ongoing studies in our laboratory have shown the presence of endogenous morphine in the brains of rats loaded with tyrosine and endogenous strychnine, and nicotine in the brains of rats loaded with tryptophan. In view of thus the levels of the following substances were assessed in the serum of the patients of the disorders studied: concentration of tryptophan and its metabolites (serotonin, quinolic acid, strychnine and nicotine), and the concentration of tyrosine and its metabolites (dopamine, norepinephrine and morphine). The Mg^{++} depletion produced by digoxin and membrane Na^+-K^+ ATPase inhibition can affect the metabolism of glycosaminoglycans, glycoproteins and glycolipids. The elevation in the level of dolichol may suggest its increased availability of N-glycosylation of proteins. The concentration of glycosaminoglycans, carbohydrate components of glycoprotein, glycolipids and glycohydrolases was studied in the serum in all these disorders. Alteration in ubiquinone levels and altered intracellular calcium/magnesium ratios can affect free radical metabolism. The free radical metabolism was studied in all these orders. The isoprenoid metabolites ubiquinone, dolichol and digoxin can affect membrane structure and function. Therefore RBC membrane composition was studied in all these disorders. A family with coexistence of schizophrenia, Parkinson's disease, neoplasms, rheumatoid arthritis, syndrome X and increased incidence of left handedness with hyperdigoxinemia has been described previously. The isoprenoid pathway related biochemical cascade was also assessed in the family members. The isoprenoid pathway was also assessed in left handed and right handed individuals to find out whether cerebral dominance can affect the operation of the isoprenoid pathway. The results are presented in this paper and a hypothesis discussing the central role of endosymbiotic archaeal digoxin in conscious perception, neuro-immuno-endocrine integration and coordination of cellular

functions is presented. The relationship between digoxin status and cerebral dominance is also discussed. The role of these factors in the pathogenesis of these disorders is also highlighted.

Materials and Methods

Freshly diagnosed cases of CNS glioma, multiple sclerosis, primary generalised epilepsy, schizophrenia, Parkinson's disease, Down's syndrome, AIDS dementia with neuropsychiatric features, and syndrome X with multiple lacunar state were included in the study. Fifteen cases were included in each group. Fifteen members of the indexed family were also included in the study. Each patient had an age and sex matched healthy control. Fifteen cases of healthy right and left-handed individuals between the ages of 20 and 30 years were also chosen for the study. None of the subjects studied were under medication at the time of blood removal. Fasting blood was removed in citrate tubes from each of the number of patients mentioned above. RBCs were separated within one hour of the collection of blood for the estimation of membrane $\text{Na}^+\text{-K}^+$ ATPase. Plasma was used for the analysis of various parameters.

The methodology used in the study was as follows: All biochemicals used in this study were obtained from M/s Sigma Chemicals, USA. Activity of HMG CoA reductase of the plasma was determined by the method of Rao and Ramakrishnan by determine the ratio of HMG CoA to mevalonate. For the determination of the RBC $\text{Na}^+\text{-K}^+$ ATPase activity of the erythrocyte membrane, the procedure described by Wallach and Kamat was used. The procedure described by Palmer et al. was used to determine the digoxin in the plasma. For an estimation of ubiquinone and dolichol in the plasma, a procedure described by Palmer et al. was used: Magnesium in the plasma was estimated by atomic absorption spectrophotometry. Tryptophan was estimated by the method of David and William and tyrosine by the method of Wong et al. Serotonin was

estimated by the method of Curzon et al. and catecholamines by the method of Well-Malherbe et al. The quinolinic acid content of plasma was estimated by the HPLC (C₁₈ column micro Bondapak™ 4.6 x 140 mm), solvent system 0.01 M acetate buffer (pH 3.0) and methanol (6:4), flow rate 1.0 ml/minute and detection UV 250 nm). Morphine, strychnine and nicotine were estimated by the method described by Arun et al. Details of the procedures used for the estimation of the total and individual GAG, carbohydrate components of glycoproteins, activity of enzymes involved in the degradation of GAG (beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D), activity of glycohydrolases (beta galactosidase, beta fucosidase and beta glucosidase) are described before. Serum glycolipids (gangliosides, glycosyl diglycerides, cerebrosides and sulphatides) were estimated as described in methods in enzymology. Cholesterol was estimated by using commercial kits supplied by M/s Sigma chemicals, USA. SOD was assayed by the method of Nishikini et al. as modified by Kakkar et al. Catalase activity was estimated by the method of Maehly and Chance, glutathione peroxidase by the method of Paglia and Valentine as modified by Lawrence and Burk and glutathione reductase by the method of Horn and Burns. MDA was estimated by the method of Wills et al. and conjugated dienes and hydroperoxides by the procedure of Brien et al. Reduced glutathione was estimated by the method of Beutler et al. Nitric oxide was estimated in the plasma by the method of Gabor and Allon. Statistical analysis was done by student's 't' test.

Results

(1) The results showed that HMG CoA reductase activity serum digoxin and dolichol were increased in all these disorders and in the family described indicating upregulation of the isoprenoid pathway, but serum ubiquinone was reduced in all these disorders and in the indexed family.

(2) The results showed that the concentration of tryptophan, quinolinic acid and serotonin was found to be higher in the plasma of patients with all these disorders and in the family described while that of tyrosine, dopamine and norepinephrine was lower. Serum of patients with multiple sclerosis showed the presence of morphine. Serum of patients with epilepsy, PD, schizophrenia, multiple sclerosis, syndrome X with multiple lacunar state and the indexed family showed the presence of strychnine. Serum of patients with epilepsy, Parkinson's disease, syndrome X, schizophrenia CNS glioma patients and the indexed family contained detectable amounts of nicotine.

(3) 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 most of the disorders and the indexed family studied. The activity of enzymes involved in free radical scavenging like superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and catalase is decreased in the above disorders and the indexed family studied suggesting reduced free radical scavenging.

(4) The results show an increase in the concentration of serum total GAG, glycolipids (ganglioside, glycosyl-diglyceride, cerebroside and sulphatides) and carbohydrate components of glycoproteins (hexose, fucose and sialic acid) in all the disorders and in the indexed family studied. The increase in the carbohydrate components - total hexose, fucose and sialic acid - in the disorders studied was not to the same extent in all cases suggesting qualitative change in glycoprotein structure. For example in epilepsy, the percentage change in total hexose, fucose and sialic acid when compared to control is 54.3%, 20% and 33% respectively. The pattern of change in individual GAG in the serum was different, however heparan sulphate (HS) and chondroitin sulphates (ChS) increased in most of the disorders and in the indexed family studied. 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 increase in the serum in most cases and in the indexed family.

(5) The cholesterol: phospholipid ratio of the RBC membrane was increased in glioma, indexed family and schizophrenia, decreased in MS and PD and not significantly altered in epilepsy. 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 in these disorders and in the indexed family.

(6) The left-handed individuals compared to right handed individuals had elevated HMG CoA reductase activity, with increased serum digoxin and dolichol levels. The serum ubiquinone, serum magnesium and RBC $\text{Na}^+\text{-K}^+$ ATPase activity were reduced in left handed individuals. The left handed individuals compared to right handed individuals had elevated levels of serum tryptophan, quinolinic acid, serotonin, nicotine and strychnine in the serum. The levels of tyrosine, dopamine, noradrenaline and morphine were lower in the left handed individuals.

(7) It showed a high prevalence of Parkinson's disease (8%), schizophrenia (23%), neoplasms (20%), syndrome X (33%), rheumatoid arthritis (16%) and epilepsy (6.6%). The psychological behavioural patterns of the family were as follows - Creativity and high IQ (60%), hypersexual behaviour (60%), reduced appetite and eating behaviour (60%), insomnia and reduced sleep patterns (60%), increased tendency for spirituality (80%), increased tendency for addiction (50%) and less of bonding and affectionate behaviour (75%). 30% of the family members were left handed.

Discussion

Archaeal Digoxin and Membrane $\text{Na}^+\text{-K}^+$ ATPase Inhibition

The archaeon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The increase in endogenous digoxin, a potent inhibitor of membrane $\text{Na}^+\text{-K}^+$ ATPase, can decrease this enzyme activity. In all the disorders studied, there was significant inhibition of the RBC membrane $\text{Na}^+\text{-K}^+$ ATPase and this inhibition appears to be a common feature for neuropsychiatric disorders. 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 Ca^{++} via the voltage gated calcium channel and increased release of Ca^{++} from intracellular endoplasmic reticulum Ca^{++} stores. This increase in intracellular Ca^{++} by displacing Mg^{++} from its binding sites causes a decrease in the functional availability of Mg^{++} . This decrease in the availability of Mg^{++} can cause decreased mitochondrial ATP formation, which along with low Mg^{++} can cause further inhibition of $\text{Na}^+\text{-K}^+$ ATPase, since ATP-Mg^{++} complex is the actual substrate for this reaction. Cytosolic free calcium is normally buffered by two mechanisms, ATP dependent calcium extrusion from cell and ATP dependent sequestration of calcium within the endoplasmic reticulum. The Mg^{++} 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 Mg^{++} and high intracellular Ca^{++} consequent to $\text{Na}^+\text{-K}^+$ ATPase inhibition appear to be crucial to the pathophysiology of these disorders. The intracellular positive Ca^{++} signal and negative Mg^{++} signal can regulate diverse cellular processes. Ca^{++} on entry into the cell is used to charge up the internal endoplasmic reticulum stores which then release a burst of signal calcium responsible for activating a large variety of calcium dependent cellular processes. The information processing capability of the calcium signalling

system is enhanced by amplitude and frequency modulation. The Ca^{++} is released from channels on internal ER individually or in small groups (blip/quark and puffs/sparks). Further diversity of calcium signalling is produced by compartmentalization as cytosolic calcium signal and nuclear calcium signal. Serum Mg^{++} was assessed in all these disorders and was found to be reduced. Increased intracellular calcium can lead on to basal ganglia calcification noticed in the family members.

Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function

The archaeon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. There is an increase in tryptophan and its catabolites and a reduction in tyrosine and its catabolites in the serum of patients with all these disorders. This could be due to the fact that digoxin can regulate neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine. The decrease in membrane $\text{Na}^+\text{-K}^+$ ATPase activity in all the disorders studied could be due to the fact that the hyperpolarising neurotransmitters (dopamine, morphine and noradrenaline) are reduced and the depolarising neuroactive compounds (serotonin, strychnine, nicotine and quinolinic acid) are increased.

The schizoid neurotransmitter pattern of reduced dopamine, noradrenaline and morphine and increased serotonin, strychnine and nicotine is common to all the disorders studied and could predispose to their development. Quinolinic acid, an NMDA agonist can contribute to NMDA excitotoxicity reported in schizophrenia. Strychnine by blocking the glycinergic transmission can contribute to the decreased inhibitory transmission in schizophrenia. Recent data suggest that the initial abnormality in schizophrenia involves a

hypodopaminergic state and the low dopamine levels now observed agrees with this. Nicotine by interacting with nicotine receptors can facilitate the release of dopamine, promoting the dopaminergic transmission in the brain. This can explain the increased dopaminergic transmission in the presence of decreased dopamine levels. The increase serotonergic activity and reduced noradrenergic outflow from locus coeruleus reported earlier in schizophrenia agrees with our finding of elevated serotonin and reduced noradrenaline levels.

In the presence of hypomagnesemia, the Mg^{++} block on the NMDA receptor is removed leading to NMDA excitotoxicity. The increased presynaptic neuronal Ca^{++} can produce cyclic AMP dependent phosphorylation of synapsins resulting in increased neurotransmitter release into the synaptic junction and vesicular recycling. Increased intracellular Ca^{++} in the post synaptic neuron can also activate the Ca^{++} dependent NMDA signal transduction. The plasma membrane neurotransmitter transporter (on the surface of the glial cell and presynaptic neuron) is coupled to a Na^+ gradient which is disrupted by the inhibition of Na^+-K^+ ATPase, resulting in decreased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, inhibition Na^+-K^+ ATPase can promote glutamatergic transmission. The elevated levels of quinolinic acid, strychnine and serotonin can also contribute to NMDA excitotoxicity. Strychnine displaces glycine from its binding sites and inhibits glycinergic inhibitory transmission in the brain. The glycine is free to bind to the strychnine insensitive site of the NMDA receptor and promote excitatory NMDA transmission. Quinolinic acid and serotonin are also positive modulators of the NMDA receptor. Increased glutamatergic transmission resulting in excitotoxicity has been implicated in neuronal degeneration observed in Parkinson's disease, primary generalised epilepsy, schizophrenia and AIDS dementia. Inhibition of Na^+-K^+ ATPase can also result in defective

neuronal membrane repolarisation and a paroxysmal depolarization shift resulting in epileptogenesis.

Thus in the right hemisphere dominant hyperdigoxinemic state there is upregulated serotonergic, cholinergic and glutamatergic transmission and downregulated dopaminergic, glycinergic and noradrenergic transmission.

Endosymbiotic Archaea, Hyperdigoxinemic State and Hemispheric Dominance

In left handed individuals there was a derangement of the isoprenoid pathway. They had upregulated HMG CoA reductase activity with increased digoxin and dolichol levels and reduced ubiquinone levels. In the RBC membrane $\text{Na}^+\text{-K}^+$ ATPase activity was reduced and serum magnesium depleted. The isoprenoid pathway metabolites - digoxin, dolichol and ubiquinone, membrane $\text{Na}^+\text{-K}^+$ ATPase and serum magnesium levels were normal in right handed individuals. The left handed individuals had increased levels of tryptophan, serotonin, quinolinic acid, strychnine and nicotine while the levels of tyrosine, dopamine, noradrenaline and morphine were lower. Thus an upregulated isoprenoid pathway, increased level of tryptophan and its catabolites and hyperdigoxinemia is suggestive of right hemispheric dominance. Altered right hemispheric function has been described in several of these disorders. In infantile schizophrenia or autism, right hemispheric dysfunction is noticed. In Lewy body variant of Parkinson's disease right hemispheric dysfunction is documented. In immune mediated disorders increased left handedness and right hemispheric dominance has also been described. Epileptic individuals have a heightened sense of creativity and dominant right hemispheric function. The disorders described - schizophrenia, neoplasms, degeneration, epilepsy, multiple sclerosis, acquired immunodeficiency syndrome and syndrome X may have right hemispheric chemical dominance contributing to their pathogenesis. The

hyperdigoxinemic state is seen in normal left handed individuals and may indicate right hemispheric dominance. We had earlier reported about a family with hyperdigoxinemia and coexistence of schizophrenia, epilepsy, Parkinson's disease, rheumatoid arthritis, syndrome X, neoplasms and left handedness. The analysis of the members of the family also showed the following behavioural pattern. There was an increased tendency for spirituality in 75% of the family members. Temporal lobe epileptic phenomenon has been described in spiritual individuals. There was an increase in creativity and intelligence and the family members had a very high IQ. Increased glutamatergic transmission is associated with memory and intelligence. They had a tendency towards reduced appetite and eating behaviour. Increased serotonergic transmission can lead on to reduced appetite. There was also hypersexual behaviour in the majority of family members. This could be related to increased production of nitric oxide in hyperdigoxinemic individuals. Nitric oxide has been related to erectile function. There was an increased tendency to addictive behaviour in family members. Endogenous morphine deficiency has been related to addiction. Morphine synthesis was low in members of the indexed family because of low tyrosine levels. There was a tendency toward insomnia and reduced sleep. This could be related to reduce levels of morphine. There was less bonding and affectionate behaviour. Bonding and affectionate behaviour has been related to dopamine and dopamine deficiency in hyperdigoxinemic individuals could contribute to less bonding and affectionate behaviour.

Archaeal Digoxin and Conscious Perception

The increase in serum digoxin levels in schizophrenia is significant. It has been postulated that there is an underlying generalised disorder of consciousness or self awareness that impairs the ability of thought with meta-representations in schizophrenia. Digoxin a membrane $\text{Na}^+\text{-K}^+$ ATPase

inhibitor may regulate conscious perception. The elements of conscious perception include perceptual binding, focussed attention and short-term memory. The evidence of increased endosymbiotic archaeal digoxin points to the hypothalamus. The hypothalamus is connected to the thalamus by the mamillothalamic tract and digoxin may play a role in regulating these synapses. There are two way connections between the cerebral cortex and the thalamic nucleus. There are also two way connections between the cerebral cortex and hypothalamus and digoxin may possibly regulate these synapses also. The hypothalamus-thalamus-cerebral cortex circuit would play a role in mediating conscious perception. Perceptual binding, important in consciousness, occurs when all the neurons associated with any one object's perceptual map in the fifth layer of cerebral cortex fire in bursts and in a synchronised pattern but out of synchrony with those representing other objects. When an object is perceived there is a simultaneous activation of the cerebral cortex hypothalamic two-way connections and liberation of digoxin from the hypothalamus to stimulate the widely dispersed cerebral cortical neurons receiving the incoming perception and their resultant synchronised burst firing. Digoxin, by the $\text{Na}^+\text{-K}^+$ ATPase inhibition it produces can lead to a paroxysmal depolarisation shift resulting in sustained synchronised burst firing of cerebral cortical neurons. Short-term memory important in conscious perception depends on the hypothalamic-thalamic-cerebral cortex reverberatory circuit as well as the phenomena of sustained synchronised burst firing of neurons in layer five of the cerebral cortex. Sustained synchronised burst firing produced by digoxin can temporarily strengthen the relevant synapses so that this particular pattern of firing is recalled quickly - a type of short-term memory. Transient synaptic changes of this type are due to the alteration in the presynaptic neuronal calcium produced by digoxin. The thalamic-cerebral cortex reverberatory circuit mediating short-term memory is glutamatergic and digoxin could amplify the

Circuit by its inhibitory effect on glial uptake of glutamate and increasing synaptic glutamate content.

All axons that pass either way between the cerebral cortex and thalamic nuclei must go through the thalamic reticular nucleus and all give off collateral excitatory glutamatergic branches that innervate the reticular nucleus. The reticular nucleus in turn provides an inhibitory GABAergic innervation back to the thalamic nucleus that provides the input. The reticular nucleus is involved in mediating selective attention by intensifying or detaching a particular active thalamic input into the cortex. The amplification (or focussing) and detachment of attention occurs due to digoxin's effect in promoting glutamatergic transmission in the collaterals to the reticular nucleus by inhibiting the glial uptake of the glutamate and increasing its synaptic content. The back projections from the cerebral cortical perceptual map of external world to hypothalamus decides whether endosymbiotic archaeal digoxin should act on the glutamatergic collaterals to reticular nucleus and thus focus or detach attention. In schizophrenia, hypersensitivity to perceptual stimulae is noticed as a deficit and patients find it difficult to screen out various stimuli and focus on one piece of information. The defective stimulus barrier causes difficulty throughout every phase of development. The increased secretion of digoxin produces a hyperconscious state with increased focussed attention, perceptual binding and short-term memory. The altered glycoconjugates in schizophrenia lead to disordered synaptic connectivity in the hypothalamic-thalamo-cerebral cortical circuit leading to disordered conscious perception. Cortical cytoarchitectural disorganization of the temporolimbic cortex has been reported in schizophrenia. Elevated levels of serum digoxin and schizoid neurochemical pathology are common to all the disorders studied and could predispose to their development. In the hyperdigoxinemic right hemisphere overdominant state conscious perceptive

mechanisms are disrupted leading on to a schizoid state. Endosymbiotic archaeal digoxin and regulation of golgi body / lysosomal function.

Archaeal Digoxin and Regulation of Golgi Body / Lysosomal Function - Relation to Cerebral Dominance

The archaeon glycosaminoglycoid and fructosoid contributes to glycoconjugate synthesis and catabolism by the process of fructolysis. The elevation in the level of dolichol may suggest the increased availability of N-glycosylation of proteins. Magnesium deficiency can lead to defective metabolism of sphinganine producing its accumulation, which may lead to increased cerebroside and ganglioside synthesis. In Mg^{++} deficiency the glycolysis, citric acid cycle and oxidative phosphorylation are blocked and more glucose 6-phosphate is channelled for the synthesis of glycosaminoglycans (GAG). Intracellular Mg^{++} deficiency also results in defective ubiquitin dependent proteolytic processing of glycoconjugates as it requires Mg^{++} for its function. The increase in the activity of glycohydrolases and GAG degrading enzymes could be due to reduced lysosomal stability and the 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 many glycohydrolases may be due to their possible resistance to cleavage by glycohydrolases consequent to qualitative change in their structure. Proteoglycan complexes formed in the presence of altered $Ca^{++}: Mg^{++}$ ratios intracellularly may be structurally abnormal and resistant to lysosomal enzymes and may accumulate.

Previous reports of an alteration in glycoproteins in this connection include alterations in alpha acid glycoprotein (AAG) and beta amyloid precursor protein in epilepsy and Alzheimer's disease and alpha synuclein in Parkinson's disease. Structurally abnormal glycoproteins resist catabolism by lysosomal enzymes

and accumulate in neuronal degeneration. Interaction between HS-proteoglycan and ChS-proteoglycan with proteins like beta amyloid, tau protein, parkin and alpha synuclein and reduced proteolytic digestion of these complexes leading to their accumulation in the neurons have been reported in neurodegenerative diseases like Alzheimer's disease and Parkinson's disease. Alterations in sulphated proteoglycan matrix of the synaptic vesicles can alter the neurotransmitter release into the synapse and produce a functional disorder like schizophrenia and epilepsy. Membrane $\text{Na}^+\text{-K}^+$ ATPase inhibition can lead to defective notch signalling. Notch is a transmembrane protein that acts as a signal receptor and is important in neurogenesis. Neuronal growth by extending neurites and forming connections is regulated by the notch signalling pathway. The notch signalling inhibits the extension of neurites and keeps them stable in the mature brain. A notch ligand known as delta regulates neurogenesis by binding to notch in the membranes of embryonal cells and prevents them from developing along the neuronal pathway. Notch activation by the ligand causes notch to be cleaved releasing the notch intracellular domain. This then passes into the nucleus and activates a transcription as part of DNA binding complex with CSL protein. Intracellular cleavage of the notch is regulated by presenilin and also depends upon the lysosomal protease. In the presence of a lysosomal instability consequent to defective lysosomal membranes notch cleavage by protease is defective leading to functional disorders consequent to defective synaptic connectivity. A defective notch signalling pathway can lead to neuronal degeneration. Altered glycoproteins, glycolipids and GAG of neuronal membrane can also contribute to schizophrenia and epilepsy by producing disordered synaptic connectivity.

The protein processing defect can result in defective glycosylation of endogenous myelin glycoprotein antigens and exogenous viral glycoproteins antigens with 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 ATP binding site. The peptide transporter is dysfunctional in the presence of Mg^{++} deficiency. This results in defective transport of MHC class-1 glycoprotein antigen complex to the antigen presenting cell surface for recognition by CD_4 or CD_8 cell. Defective presentation of endogenous myelin glycoprotein antigen can explain the immune dysregulation in MS. A CD_8 MHC class-1 restricted immune dysregulatory defect has been described in MS. Defective presentation of exogenous viral antigens can produce immune evasion by the virus as in AIDS dementia. Viral persistence has been implicated in the development of tumours (ebstein barr virus and lymphoma), degenerations (Parkinson's disease and corona virus) and schizophrenia (borna virus disease). A number of fucose and sialic acids containing natural ligands are involved in trafficking of leukocytes and similar breaches in the blood brain barrier. The adhesion of the lymphocyte producing leukocyte trafficking and extravasation into the perivascular space have been described in MS. Altered myelin glycoprotein, due to defective glycosylation and an alteration in GAG of proteoglycans of myelin can affect the structural integrity of myelin leading on to demyelination. Abnormal glycosylated tumour antigens can lead to a defective tumour antigen presentation and loss of immunosurveillance by the natural killer cells. Altered cell surface glycoproteins, glycolipids, and GAG can lead to defective contact inhibition and oncogenesis. A number of fucose and sialic acids containing natural ligands have been implicated in neoplastic transformation and metastasis. The MHC glycoproteins are involved in the formation of synaptic connectivity during neuronal development. The defective formation and presentation of MHC - neuronal glycoprotein complex can lead on to disordered synaptic connectivity and functional disorders like schizophrenia and epilepsy. Thus in the hyperdigoxinemic right hemisphere dominant state there is reduced

lysosomal stability, defective ubiquitin dependent proteolytic processing of proteins and an alteration in the glycoconjugate structure leading to their defective catabolism and accumulation. There is also a defect in the MHC antigen-presenting pathway leading on to immunodysregulation and viral persistence.

Archaeal Digoxin and Alteration in Membrane Structure and Membrane Formation - Relation to Cerebral Dominance

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 can lead to increased cholesterol synthesis and Mg^{++} deficiency can inhibit phospholipid synthesis. Phospholipid degradation is increased due to an increase in intracellular calcium activating phospholipase A_1 and D. The cholesterol: phospholipid ratio of the RBC membrane was increased in glioma, indexed family and schizophrenia, decreased in MS and PD and not significantly altered in epilepsy. 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 the cellular membrane are formed in the endoplasmic reticulum, which is then budded 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 Mg^{++} deficiency. The change in membrane structure produced by alteration in glycoconjugates and cholesterol:

phospholipid ratio can produce changes in the conformation of $\text{Na}^+\text{-K}^+$ 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.

Thus in the hyperdigoxinemic right hemisphere dominant state there is defective membrane formation, membrane structure and function.

Archaeal Digoxin and Mitochondrial Dysfunction - Relation to Cerebral Dominance

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 most of the cases which may be the result of low tyrosine levels, reported in most of the disorders, 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 Ca^{++} can open the mitochondrial PT pore causing a collapse of the H^+ gradient across the inner membrane and uncoupling of the respiratory chain. Intracellular Mg^{++} 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 superoxide ion, which produces lipid peroxidation. Ubiquinone deficiency also leads to reduced free radical scavenging. The increase in intracellular calcium may lead to increased

generation of NO by inducing the enzyme nitric oxide synthase, which combines with superoxide radical to form peroxynitrite. Increased calcium also can activate phospholipase A₂ resulting in 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⁺-K⁺ ATPase, triggering the cycle of free radical generation once again. Mg⁺⁺ deficiency can affect glutathione synthetase and glutathione reductase function. The mitochondrial superoxide dismutase leaks out and becomes dysfunctional with calcium related opening of the mitochondrial PT pore and outer membrane rupture. The peroxisomal membrane is defective due to a membrane Na⁺-K⁺ ATPase inhibition related defect in the membrane formation and leads to reduced catalase activity. Mitochondrial dysfunction related free radical generation has been implicated in the pathogenesis of the neuronal degeneration oncogenesis and immune mediated disorders.

The increased intracellular calcium and ceramide related opening of the mitochondrial PT pore also leads to 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 apoptosis inducing factor and cytochrome C into the cytoplasm. This results in the activation of caspase-9 and caspase-3. Caspase-9 can produce apoptosis of the cell. Apoptosis has been implicated in neuronal degeneration. Apoptosis can produce defective synaptogenesis and synaptic connectivity contributing to functional disorders like schizophrenia and epilepsy. Apoptosis of the CD₄ cell can contribute to CD₄ depletion in the acquired immunodeficiency syndrome. Oligodendrocyte (the myelin forming cell) apoptosis is crucial to the pathogenesis of MS. Caspase-3 activation can cleave P₂₁ involved in linking DNA duplication to cell division resulting in a polyploid cell and oncogenesis.

We have been able to demonstrate neuronal degeneration and apoptosis in digoxin injected rat brain.

Thus in the hyperdigoxinemic right hemisphere dominant state there is a defect in the mitochondrial function and increased free radical generation and reduced scavenging. There is also increased apoptosis.

Archaeal Digoxin and Immune Activation - Relation to Cerebral Dominance

The archaeon fructosoid contributes to fructolysis and immune activation. Fructose can contribute to induction of NF κ B and immune activation. The archaeon steroidelle synthesized digoxin induces NF κ B producing immune activation. Increased intracellular calcium activates the calcium dependent calcineurin signal transduction pathway, which can produce T-cell activation and secretion of interleukin - 3, 4, 5, 6 and tumour necrosis factor alpha. TNF alpha binds to its receptor TNFR1 and activates the transcription factors NF κ B and AP-1 leading to the induction of proinflammatory and immunomodulatory genes. This can also explain the immune activation in MS. TNF alpha can also bring about apoptosis of the cell. It binds to its receptor and activates caspase-9, an ICE protease which converts IL-1 beta precursor to IL-1 beta. IL-1 beta produces apoptosis of the neurons (in Alzheimer's disease and AIDS dementia), oligodendrocyte - the myelin forming cell in MS and the CD₄ cell in HIV infection. IL-1 beta and TNF alpha induce HIV protein expression by transcription related mechanism and contributes to the pathogenesis of AIDS dementia. Membrane Na⁺-K⁺ ATPase inhibition can produce immune activation and is reported to increase CD₄/CD₈ ratios as exemplified by the action of lithium. The hyperdigoxinemic right hemisphere dominant state results in immune activation.

Archaeal Digoxin and Regulation of Cell Division, Cell Proliferation and Neoplastic Transformation - Relation to Cerebral Dominance

Intracellular magnesium depletion can produce defective phosphorylation of microtubule associated proteins (MAP). This results in defective microtubule related spindle fibre dysfunction and chromosomal non-dysjunction probably contributing to trisomy 21.

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 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. Phosphorylation mechanisms are required for the activation of the tumours suppressor gene P₅₃. The activation of P₅₃ is impaired due to intracellular magnesium deficiency producing a phosphorylation defect. Upregulation of the isoprenoid pathway can result in increased production of farnesyl phosphate, which can farnesylate the ras oncogene producing its activation. The ubiquitin system of catabolic processing for the processing of proteins is important in DNA repair mechanism. In the presence of intracellular magnesium deficiency the ubiquitin protein catabolic processing and DNA repair mechanisms are defective and this could contribute to oncogenesis. In the hyperdigoxinemic right hemisphere dominant state there is oncogene activation and increased cell proliferation.

Archaeal Digoxin and Metabolism - Relation to Cerebral Dominance

The archaeon steroidelle contributes to lipid synthesis and metabolism. Inhibition of Na⁺-K⁺ ATPase can also explain the pathogenesis of syndrome X. Increased TNF alpha as mentioned above consequent to Na⁺-K⁺ ATPase

inhibition related T-cell activation can contribute to insulin resistance in syndrome X at the receptor level. A decrease in intracellular magnesium can block the phosphorylation reactions involved in protein tyrosine kinase receptor activity leading to insulin resistance. An increase in beta cell calcium can contribute to increased insulin release from beta cells and hyperinsulinemia. Increased intracellular calcium can activate the G-protein coupled signal transduction of the contra insulin hormones (growth hormone and glucagon) leading to hyperglycemia. A decrease in intracellular magnesium can lead on to inhibition of glycolysis. Decreased intracellular magnesium can lead on to a mitochondrial ATP synthase defect. Increased intracellular calcium can open up the mitochondrial PT pore, disrupt the H^+ gradient across the inner membrane and block mitochondrial oxidative phosphorylation. All these lead to defective glucose utilisation and hyperglycemia. Increase in intracellular calcium can activate G-protein coupled angiotensin receptor producing hypertension and G-protein coupled thrombin receptor and platelet activating factor producing thrombosis observed in syndrome X. Na^+-K^+ ATPase inhibition related increased smooth muscle calcium and decreased magnesium can contribute to vasospasm and ischaemia observed in stroke and CAD. Na^+-K^+ ATPase inhibition related altered glycoprotein can contribute to the microangiopathy and macroangiopathy observed in syndrome X. Metabolic syndrome X could be visualised as due to endosymbiotic archaeal digoxin hypersecretion. In the hyperdigoxinemic right hemisphere dominant state glucose metabolism and utilisation is impaired consequent to insulin resistance as also a tendency for vasospasm and thrombosis.

Archaeal Digoxin and Regulation of the Immune Response to Viral Infection

The same biochemical $\text{Na}^+ - \text{K}^+$ ATPase related cascade described above could contribute to the acquired immunodeficiency syndrome. There is increased incidence of neoplasms like non-Hodgkin's lymphomas and vasculitis in the acquired immunodeficiency syndrome. Neuronal degenerations like AIDS dementia has been related to glutamate excitotoxicity. An AIDS related schizophreniform psychosis has been described. Polyclonal B-cell proliferation and lymphadenopathy have been described in AIDS. Digoxin induced calcineurin signal transduction mediated T-cell activation and polyclonal B-cell proliferation can contribute to HIV-1 replication. This is because chief among the inducible cellular proteins that promote the growth of HIV-1 is transcription factor NF- κ B. HIV-1 has incorporated two such NF- κ B binding-enhancer elements into its own genome, which allows the triggering of HIV-1 transcription in the presence of nuclear NF- κ B. Digoxin induced protein glycosylation defects can also lead to defective glycosylation of HIV glycoprotein antigens leading on to defective formation of HIV glycoprotein antigen-MHC complex for presentation to CD_4 cell. This results in immune evasion by the virus and could also contribute to the persistence of herpes virus and Epstein Barr virus producing Kaposi's sarcoma and non-Hodgkin's lymphoma respectively. Hypothalamic structural abnormalities have been described in homosexuals predisposed to the development of acquired immunodeficiency syndrome. In the hyperdigoxinemic right hemisphere dominant state there is a tendency for viral persistence consequent to defective processing of viral proteins and defective immune response to the virus.

Archaeal Digoxin and Neuro-Immuno-Endocrine Integration

Archaeal digoxin can thus integrate multiple brain functions. Digoxin can regulate neuronal transmission and conscious perception in the brain by its effect on neutral amino acid and neurotransmitter transport. Digoxin can also play a role in endocrine integration. The hypothalamic hormone secretion is regulated by the biogenic amines noradrenaline, dopamine and serotonin. Digoxin by regulating the release and uptake of these neurotransmitters can control hypothalamic hormone secretion. Digoxin, by its lithium like action in modulating G-protein function and by facilitating calcium induced signal transduction by increasing sodium-calcium exchange, can regulate the function of these hormones. Digoxin can act as an immuno-modulator owing to its effect on calcineurin signal transduction in the lymphocyte and subsequent immune activation.

Archaeal Digoxin and Integration of Cellular Function

Digoxin can regulate multiple cellular functions. Digoxin can regulate plasma membrane transport as well as membrane structure and fluidity. It can also regulate the fluidity of organelle membranes. Digoxin by its effects of calcium mediated opening of mitochondrial PT pore and ubiquinone synthesis can regulate mitochondrial function. The dolichol pathway can regulate protein glycosylation and golgi body function. Digoxin induced hypomagnesemia can regulate the ubiquitin dependent protein catabolic pathway. Digoxin induced change in intracellular magnesium can regulate nuclear function as DNA polymerase, DNA ligase and ribosomes require magnesium for their function. Digoxin by producing magnesium depletion can regulate GAG metabolism and the structure of the cell matrix. Digoxin can regulate cell death or apoptosis by opening up the mitochondrial PT pore consequent to a rise in the intracellular calcium it produces. Digoxin by its effect upon ras oncogene can modulate cell proliferation. Digoxin induced hypomagnesemia by producing changes in cell

surface glycoproteins and GAG can regulate contact inhibition and cell proliferation. Digoxin can regulate the function of heat-shock protein which coordinates the trafficking and regulation of diverse signalling proteins, and which also functions as a molecular chaperone involved in protein folding and maturation. The heat-shock protein has an ATP/ADP switch domain that regulates hsp conformation and digoxin induced hypomagnesemia can modulate its function. Intracellular magnesium deficiency can regulate phosphorylation of microtubule associated proteins (MAP) and regulate cytoskeletal structure / function.

Digoxin can thus produce conscious perception, neuro-immuno-endocrine integration and integrate the function of multiple cellular organelles. The hyperdigoxinemic state is a right hemisphere dominant state.

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GLOBAL WARMING

and Symbiotic Evolution of Species

Archaea and Viroid Induced Symbiotic Human Evolution and the Fructosoid Organelle

Archaea and Viroid Induced Symbiotic Human Evolution and Hemispheric Dominance

Archaea and Viroid Induced Symbiotic Human Evolution - Vitaminocycle Organelle and Brain Evolution

Archaea and Viroid Induced Symbiotic Human Evolution and the Steroidelle - The Isoprenoid Cholesterol Organism

Archaea and Viroid Induced Symbiotic Human Evolution - Retrovirus, Prions and Viroids - Porphyrinoids and Viroidelle

Archaea and Viroid Induced Symbiotic Human Evolution and Shikimate Pathway - The Neuronal Neurotransminoids

Archaea and Viroid Induced Symbiotic Human Evolution - Human Family and Social Bonding - Archaeal RNA Viroidal Quasi-Species Consortia and Human Social Identity

Archaea and Viroid Induced Symbiotic Human Evolution - Human Creativity and Autistic Psychopath Syndrome

Archaea and Viroid Induced Symbiotic Evolution of Homo Sapiens and Homo Neanderthalis - Archaeal RNA Viroidal Quasi-Species Consortia and Human Species Identity - The Neoneanderthal Age and Kali Yuga

Archaea and Viroid Induced Symbiotic Human Evolution - Atavistic Neoneanderthalisation and Archaeal Life Elixir - Archaeal RNA Viroidal Quasi-Species Consortia and Human Species Identity

Archaea and Viroid Induced Symbiotic Human Evolution - The Philosopher's Stone and Transmutoid - Nuclear Energetics in Brain

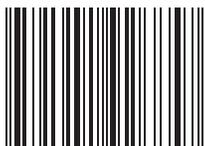
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