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Disclosure of Causes of Human-specific Intractable Immune Diseases

- Mitochondrial Deterioration Due to Intracellular Infections -

Katsunari Nishihara

NISHIHARA INSTITUTE

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Disclosure of causes of human-specific intractable immune diseases

Mitochondrial deterioration due to intracellular infections

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1. INTRODUCTION

Human-specific intractable immune diseases are now commonplace as they essentially exhibit a close correlation with today's modern lifestyles. However, to disclose what human specific intractable immune diseases are, it is necessary not only to strictly define life but also to read the three riddles of the vertebrates to disclose the mechanisms of the mammalian life system. Even in the 21st century, life has still not been strictly defined. Schrödinger had proposed to establish biology at the molecular level. However, he did not define life, but noticed inheritance to be a key characteristic of life. Therefore, he proposed to solve the phenomena of inheritance by using the simplest prokaryote bacteria and their parasites, viruses of bacteriophage, without defining life (Schrödinger, 1906). Vertebrates have three kinds of riddles. The first is multicellular interaction or multiple organ correlation in systemic behavior as a synthetic creature like a single-cell protozoa; this is known as Cuvier's principle (Cuvier, 1812). The second is the mechanism of evolution under Lamark's Theory (Lamarck, 1809). The third is Haeckel's biogenetic law of correlation of ontogeny and phylogeny (Haechel, 1896). Riddles of development in bone marrow hemopoiesis and the immune system are both included in evolutionary phenomena.

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Life has not yet been scientifically defined even in the 21st century. The author defines life as follows: life is a hydrocolloid matter of organic substances with various kinds of minerals encapsulated by phospholipid membranes in which a part or the whole structure remodels itself by means of energy metabolism. Consequently, this organic system can overcome aging by remodeling, namely the renewal of tissues or cells. Therefore, remodeling concomitant with energy metabolism is essential for life (Nishihara, 2004). Life of higher animals like vertebrates is the circulating system of energy metabolism under sunlight energy, just like waterwheel or windmill, as well as earth and moon gravity energy streams, which enable energy metabolism conjugated with remodeling in the animal body by the energy of metabolized nutrition absorbed from digested food. By this remodeling, animal cells can overcome aging, i.e., decrease entropy (Nishihara, 2006). This circulating system of energy metabolism necessitates both energy from the cosmos (sunlight) and energy from nutrition (food). The life of higher animals has both acceptors of energy and substance with mass of food. The former are sensory organs and the latter are visceral organs.

2. TWO MAJOR LIFE SYSTEMS

To realize the life system of multicellular vertebrates two major life systems are compared.

A) Prokaryote and eukaryote.

There are two major life systems at the cellular level, namely prokaryote and eukaryote. The former are bacteria with a haploid DNA helix and the latter are protozoa, yeast, mold and multicellular organisms, namely the so-called animals. Only Eukaryote evolves into a multicellular animal. In its cells there is a diploid DNA helix having various kinds of organelle, i.e., mitochondria, a Golgi apparatus and an endoplasmic reticulum. Mitochondria have a haploid DNA helix. Therefore, they are kinds of prokaryote parasiting in eukaryote 10^{-18} years ago. As mitochondria are living prokaryote in live animal cells, to disclose life system of multicellular vertebrates, an investigation correlating the dependency of the life system between protein synthesis of cytoplasmic nuclear and that of mitochondria is essential. Mitochondria in animal and plant cells and chloroplast in plant cells are a symbiosis of prokaryote parasiting in eukaryote. Considering mitochondria as parasiting bacteria in living animal cells, various kinds of bacteria, microplasma and virus can be alive in animal cells. These are an infected condition of bacteria into cells, namely an intracellular infection (Nishihara, 2004). Conventionally, intracellular infection is well

known only in viruses. However, we have to consider intracellular infection into leukocytes of non-pathogenic enterobacteria and enterovirus from M-cell in Peyerpatch. Infected leukocytes disseminate into tissue cells or organ cells. Now, we have to investigate what happens in intracellularly infected cells.

B) Protozoa, namely monocellular creatures and multicellular animals

There are two major animals on earth, namely monocellular animals of protozoa and multicellular animals. In the latter, the most progressively evolved are the vertebrates. The basic construction of protozoa and a cell of a multicellular animal are quite similar. However, all the apparatus essentially required for protozoa are organelle in cells and those of the multicellular animal are organs constructed with numerous cells. Development of the more highly evolved animals of the vertebrates in the cosmos required essential and necessary conditions: sound substances with mass, i.e., water, oxygen, and other elements, and nutrition under sunlight energy as well as moderate gravity energy of the earth and moon (Nishihara, 2004).

C) The vertebrates and plants

The origin of the vertebrates is ascidia, which is also the origin of higher plants. Ascidia have gills and muscle as well as roots made of cellulose. Special ascidia, losing gut respiration and digestion, had to respirate with skin epithelial and subcutaneous cells and to absorb nutrition directly by means of roots, thus becoming plants. Plant leaf cells have mitochondria and chloroplasts. The differences at the cellular level between plants and animals are only chloroplasts and cellulose cell walls; other nuclei, organelle and cytoplasm are the same.

The characteristic difference between plants and animals is movement. Animals, namely the vertebrates, are the vehicle of the gut respiratory and digestive system. The locomotive system is essentially skeletal muscles, which develop concomitant with the neural brain system. In creatures without muscles, no neural-cerebral and sensory system develops (Nishihara 2004).

3. BASIC CONSTRUCTION OF EUKARYOTE CELLS.

The correlation between cytoplasmic nucleic function and mitochondrial activity.

Mitochondria are believed to be aerobic bacteria parasiting into eukaryote cells ca. 1.8×10^9 years ago. The basic function of mitochondria in eukary-

ote cells is oxidative phosphorylation conjugated with cellular respiration obtaining the energy substance, ATP. Mitochondria are small spherical to rod-shaped components (organelles) found in the cytoplasm of cells, enclosed in a double membrane, with an internal membrane space between the two units, the inner one infolded into the interior of the organelle as a series of projections (cristae). They are the principal sites of the generation of energy in the form of ion gradients and adenosine triphosphate (ATP) synthesis resulting from the oxidation of foodstuffs, and they contain the enzymes of the Krebs and fatty acid cycles and the respiratory pathway. Mitochondria also contain RNA and DNA, by means of which they can independently replicate and code for the synthesis of some of their proteins. Mitochondria in special functioning cells synthesize characteristic cytokine for the organ (Nishihara, 2006).

It had been well known that in cancer cells glycolysis increases and cellular respiration decreases in conjugation with mitochondrial deformity and decreased numbers. The author carried out using yeast (Sacharomyces Cerevisiae) studies on biogenesis and differentiation of mitochondria observing development of petite mutants namely respiration deficient mutants with deteriorated mitochondria about 40 years ago. Applying three kinds of antibiotics to a yeast culture medium, namely chloramphenicol, which disturbs mitochondrial DNA protein synthesis, cycloheximide, which disturbs cytoplasmic nuclear DNA protein synthesis, and streptovalicine, which disturbs bacterial (mitochondrial) DNA-dependent RNA polymerase. Only cycloheximide induced petite mutants at a 10 times higher rate than the control. Applying these antibiotics, mitochondrial DNA polymerase as well as RNA polymerase activities were measured. Also cycloheximide application in a culture medium decreased mitochondrial DNA and RNA polymerase. However, by cycloheximide no respiration depression nor loss of ATPase activity of mitochondria was observed. By chloramphenicol or streptovalicine no petite mutations but a depression of respiration was observed (Nishihara, 1970, 1971). For this research the author was granted a doctoral degree from the university of Tokyo.

From this experiment the author concluded that disturbance of cytoplasmic nuclear protein synthesis by cycloheximide, namely antinotices for hindering eukaryotic protein synthesis, induce deterioration of DNA polymerase of mitochondria resulting in the mutation of mitochondrial DNA. Consequently, degradation of mitochondria occurs. Therefore, the proliferation of mitochondria, i.e., replication of mitochondrial DNA is dependent on healthy cytological protein synthesis (Nishihara, 1970, 1971). Not only by eukaryotic antibiotics

like cycloheximide, but also by intracellular bacterial or viral or toxic contamination mitochondrial deterioration occurs. Mitochondrial function is wholly dependent on the cytological physiologic condition (Nishihara, 2006).

4. READING THE RIDDLES OF THE VERTEBRATES

The definition of a vertebrate is a chordate having a bony backbone, with differing degrees of ossification. The structures and organs defined as being characteristic of vertebrates are the spine, and the gut respiratory system, (the gill and lung system). The definitive structures and organs are the bone and respiratory apparatus of the gut. Moreover, all organisms have the cellular respiration system of mitochondria. What is the structure of the organ system between the outer (gut) respiration of gills and lungs and inner (cellular) respiration of mitochondria? It is the hemopoietic system in bone marrow, blood cells and the cardiovascular system. Therefore, if the definitive substance of bones is synthesized, then, using them, the riddles of the evolution of the vertebrates can be solved by developing artificial bone marrow chambers and inducing the hemopoietic system (Nishihara, 1993, 1999).

The author has successfully developed hybrid artificial bone marrow by applying biomechanical stimuli to sintered apatite (Nishihara, 1992, 1994). This took on the characteristics of bone marrow hemopoiesis peculiar to higher vertebrates after migrating to land.

The author has also developed a hybrid-type artificial dental root that took on the characteristics of the gompholic tooth peculiar to mammals (Nishihara, 1987, 2003). In this way, the author has clarified that evolution occurs according to the mechanical functions of the animal in response to gravitational forces. In order to elucidate the law of evolution, the author has developed trilateral research that integrates morphology, including embryology and phylogeny, the functional study of molecular biology, and molecular genetics concerning remodeling with biomechanics (Nishihara, 1998). The author has also devised an experimental evolutionary study method that applies trilateral research to work of every phylogenetic stage representing phylogeny (Nishihara et al., 1996). From these studies the author has tried to reinterpret Wolff's Law (1870), Lamarck's Use and Disuse Theory (1809) and Haeckel's Biogenetic Law (Alberch, 1994) with the current level of science using biomechanics and molecular biology. The author used artificial bone marrow organs made of synthetic apatite and Ti-electrodes as well as using an artificial dental root inducing the cementum (fibrous bone) and hemopoietic nest by biomechanics. The author, moreover, verified Lamarck's Use and Disuse Theory. Following

that, the author carried out research on the basic construction of mammalia from the viewpoint of the Gravity Influencing Evolutionary Theory (Gravity Evolutionary Theory, Nishihara, 2003).

5. WHAT ARE THE CHARACTERISTICS OF VERTEBRAL ANIMALS?

Common characteristics of animals are somatic locomotive as well as visceral gut movement carried out with the neuromuscular system. Animals are quintessentially vehicles of the visceral gut system, which move to seek places of eating, resting, and genital reproduction. Cuvier (1769–1832) established paleontology and the principle of comparative anatomy. Based on his research, he proposed empirically the following two principles: 1) the principle of subordination and 2) the principle of correlation. From these principles Cuvier stated that "Animals move and live with united order (unity) and have each the complete system. Animals can move with objective behavior, with harmony, because of many organs can move with a chain reaction and react with each other (Cuvier 1812).

What is the mechanism of animal movement in united order? There are five major correlating systems among organs in animals. The first is the biomechanics of animal movement under earth gravity, all of which is converted into hydrodynamic energy in the animal body which triggers gene expression of mesenchymal cells. The second is the somatic locomotive neuromuscular system with sensory organs. The third is the visceral gut movement of the neuromuscular system with the digestive absorbing system. The forth is the cardiovascular as well as lymphovascular system with the erythrocyte blood system and with the leukocyte remodeling system of MHC (major histocompatibility antigen complex or HLA, i.e., human leukocyte antigen) (Nishihara, 2004). The fifth is the direct controlling system of energy metabolism of whole cells in animals by means of the hypophysis-suprarenal hormone (Nishihara, 2006).

Vertebral animals with the visceral gut muscular system as well as the somato-muscular system have sensory organs and, using them, the animal controls the gut peristaltic system of mastication, respiration, eating, digesting, vermiculating, and absorbing as well as somato muscle movement and reproduction. The neuro-muscular system can be divided into two systems, namely the somatomuscular-sensory organ-cerebral system and the visceral-limbic system. This is the anatomical, morphological system, which has functions biomechanically, related to animal movement and morphology influenced by gravity action. By these systems, animals can systemically move, live, and

change form physiologically. By the cardiovascular system, not only oxygen and nutrition as well as toxins and parasitic microbes absorbed from the gut, but also hormones and cytokines secreted from hormonal organ cells, can be delivered to all cells in body. By the lymphovascular system, nutrient supply as well as parasitic microbes in the central nervous system, and the remodeling system of aged cells as well as tumor cells and intracellularly infected cells in the mammalian body by HLA are carried out. Through these five mammalian characteristic systems, animals can live, utilizing both the energy of the cosmos without mass (sunlight and earth gravity) and nutrient foods of substance with mass by means of the somatomuscular-sensory organ system as well as the visceromuscular system. Through the gut incorporation system of oxygen and nutrients into circulating body fluid, as well as through the hypophysis-suprarenal hormonal system, the direct control system of energy metabolism in all cells, including the organ and tissue correlation system, is carried out (Nishihara, 2006).

6. BASIC CONSTRUCTION OF MAMMALIA AND THE FUNCTION OF MITOCHONDRIA

All life phenomena, including morphology, and function, remodeling, and the genito-urinary system of protozoa, completely depend upon the energy metabolism of their mitochondria and the genome function of their nucleus. Adult Eutheria, multicellular mammalia, have circa 60×10^{12} cells, and many specialized organs and structures. As they have complicated correlated functions they can move as if constructed from a single cell, like protozoa. The fertilized oosperm cell divides into multiple cells, develops into complicated gastulura, branchilura, neurura, and embryos. In the 21st century, no scientist has considered in medicine or the life sciences how human ontogeny, i.e., development, takes place and how the multicellular human body is constructed from a newborn baby with 3×10^{12} cells to an adult with 6×10^{13} cells with a close correlation, systemically, and a cooperating system among tissue cells and organs, which are constructed from enormous numbers of cells. We have to recognize initially that the multicellular human body acts as a whole, systemically, as if it was a single-cellular organism of protozoa. Second, prokaryote bacteria cannot form a multicellular organism; only eukaryote with mitochondria can develop into a multicellular creature. Therefore, mitochondria have the essentially important function to develop a multicellular animal (Nishihara, 2006).

Let us consider the evolution from protozoa to a multi-cellular organism. What are the most different structural parts of cells between them? The most remarkable different parts are the innumerable organelle mitochondria and

the structure of the cell membrane, which is controlled by both nuclear and mitochondrial genes. In the human body, there are various cells in several different evolutionary stages. Leukocytes correspond to the stage of protozoa. Therefore, they can penetrate through small pit holes of blood or lymphovessels with amoeboid movement. They can invade even cerebral liquor and a fetus through placenta. Now, consider the differences between the membrane of leukocytes and other organ cells. Leukocytes have MHC (major histocompatibility antigen, namely HLA) in its membrane. All cells in the human body, except matured erythrocytes, have MHC genes. However, genes of MHC in cells, except leukocytes, are dormant (Nishihara, 2004).

Mitochondria are living organisms in living cells and control all 6×10^{13} cells as a whole, in adult mammals systemically, and correlate all cells as one creature as a united system. Comparing the human body to a nation, various organs are states or prefectures, cities or towns, or large communities. Each cell, having eight hundred to three thousand mitochondria, are like a union of a community, factory, or large, well-run department store. Then what are the enumerous mitochondria? Mitochondria are just like citizens in a nation-state. Only citizens can support the nation. Likewise, only vivid mitochondria can sustain the human body. Without mitochondrial functions, humans could never maintain their health. Complexion, color, looks and expression of the face, vigor and vitality, fatigue, tiredness, and exhaustion, all of these body states indicate mitochondrial conditions (Nishihara, 2006).

We will know the deterioration of their mitochondria, if some important organs loose their function, e.g., a heart attack is a dysfunction of mitochondria in cardiac muscles, dementia is a dysfunction of mitochondria in neurons in the cortex of the cerebrum, and nephritis is a bacterial infection resulting in a dysfunction of mitochondria in the glomerulus and mesangium. These dysfunctions of mitochondria occur as a result of improper energy metabolism, chronic fatigue, and intracellular infection by enterobacteria or viruses.

Various kinds of environmental energies, e.g., heat and cold, light and sound, atmospheric pressure, gravity and moisture, including the bio-energy of emotion, religion, spirit, fear and death of intimate life, and thought and ideology, influence directly all mitochondria in 6×10^{13} cells. In addition, energy metabolism of animals, namely movement and behavior, and emotion, are supported and influenced reciprocally by mitochondria. By these energies, mitochondria in all body cells become lively or exhausted. Not only energy but also toxic substances, intracellular parasitic microbes, and malnutrition influence mitochondria (Nishihara, 2004).

7. ANIMAL MOVEMENT AND MORPHOLOGY AND THEIR CORRELATION WITH GRAVITY

Locomotive movement is the most characteristic property of animals in comparison to plants, both of which are originally derived from ascidia. Animal movement under gravity requires enormous energy for muscle contraction. Energy substances are synthesized in mitochondria as ATP (adenosine-triphosphate). The development of muscle inevitably induced the nervous system concomitant with the cardiovascular system and the cardiovascular system inevitably derived the gut respiration and digestive absorptive system. Also the muscle-neural system was derived concomitant with the sensor system against external circumstances and these sensors are constructed along with the epithelium and mesenchyme. All of these derivations are supported by energy substances and are generated by mitochondria.

Common sensors are for muscle movement. Representative sensors are the cerebrum, the neural system, the eye, the ear, the nose, sensus tactilis in cutaneous tissue, and the tooth. The neuromuscular system requires sensors for space and time and movement energy. For the cardiovascular system, sensors for gravity and pressure are necessary. Animals are a vehicle of the visceral gut system moving toward food and reproduction. In the animal body there are multiple sensors for movement against environmental energy: sensors of the eye to light, the ear to sound, the semicircular duct to sense of balance to gravity, the sense of touch to pressure, the tooth to mastication, namely, the collision of food and pressure, and the spindle in muscle to movement (Nishihara, 2006).

Let us go back to the question of the influence of gravity. It has to be remarked that all organisms are constructed with water-soluble colloids of organic substances, even skeletal osseous tissue. Looking attentively, gravitational force acts in an important way on the shape of substances in a liquid state. This is more pronounced with water soluble, high molecular colloids, like those that compose living body tissues. Mammals have three kinds of sensors against gravity and dynamic energy: 1) cuniculi (semicircular duct) of the inner ear functions as a gyrocompass in the neural cranium due to gravity, 2) the teeth for mastication create a functionary collision of substance with mass, and 3) muscle spindles in muscles function in muscle contraction. There are also famous physiological studies of skeletal deformities by Julius Wolff (1836–1902), known as Wolff's Law on the functional adaptation of bone morphology. However, this law is restricted to very narrow conditions and over-use of the constant bias function results in discrepancies of shape

and function. The gravity action effect upon the mediums of blood and lymphofluids, and the biomechanical force on the human body, are converted into hydrodynamics concomitant with movement. Hydrodynamics induce streaming potential and, by this, bone morphogenetic proteins (BMP) are induced through the gene expression of mesenchymal cells in connective tissue, which then differentiate into osteoclasts, osteoblasts and myoblasts, conjugated with hemopoietic cells. As a result of these mechanisms, bone remodeling takes place and deformities occur as a result of unilateral, or improper action (Nishihara, 1999).

Jean-Baptiste Lamarck (1744–1829) proposed in 1809 the Use and Disuse theory for animal evolution. Wolff's Law is a part of Lamarck's theory, instructed only by skeletal morphology within one generation. Lamarck's theory has important limiting conditions of use, namely not to go beyond normal growth and healthful conditions. What does it mean when mammals exceed these conditions? Theoretically, mammals then fall ill. Mammalian babies can never eat anything during the suckling period. If they do, immune diseases such as dermatitis and epilepsy take place. As noted earlier, adult humans have several human-characteristic behaviors and structural defects compared to standard Eutheria (Mammalia). As a result of these behaviors and defects, humans can easily fall ill by means of improper energy accepted and intracellular infection by non-pathogenic enterobacteria (Nishihara, 2004).

8. THE OVERALL SYSTEM TO CONTROL MITOCHONDRIA IN WHOLE CELLS DIRECTLY IN MAMMALIA

There should be special acceptors as well as controllers in multicellular organisms, especially mammals, which control energy metabolism over all cells in the body. The special supervising acceptors for systemic energy metabolism in whole cells in mammals are the suprarenal glands, which are also supervised by the hypophysis by means of hormones. The suprarenal glands secrete adrenalin as well as mineral- and glyco-corticosteroid hormones, which control mitochondrial energy metabolism in whole cells. The control of mitochondrial metabolism in whole cells is the most important system in mammals. The accepting apparatus for these hypophysis-suprarenal gland systems are whole sensor organs of the somatic system as well as the whole gut visceral system via the epithelial body, the thymus, Waldyer's lympho-adenoid rings, and gut-associated lymphoid tissue (GALT). This system was disclosed as Selye's stress theory (Selye, 1937, 1946). He was convinced that the major immune systems of animals are carried out by the hypophysis-suprarenal gland system. However, Selye did not know that hypophysis and suprarenal

glands were acceptors of various stimuli, and controllers for energy metabolism of whole cells against the stimuli, which influence the animal body. The hypophysis secretes an adrenocorticotropic hormone as a controller of the total stimuli impacting the living energy system of the animal. He thought that there must be a close correlation between the immune system and the central nervous system because the hypophysis is a part of the limbic system of the cerebrum. However, the immune system is the cellular remodeling system conjugated with energy metabolism of mitochondria, which overcomes the aging of cells, and which is characteristic of living creatures. The limbic system is a structural anatomical ward. Also all neurons in the central nervous system have a cellular remodeling system. Therefore, there is no correlation between them, but total information from sensors in the body, and from circumstances integrated through the central nervous system, flow and transmit to suprarenal glands through hypophysis hormonally (Nishihara, 2006).

What are these total stimuli to the animal? They are substance without mass, i.e., energy and substance with mass, including oxygen, nutrition, parasitic microbes, and toxins.

Energy stimuli are heat and cold thermodynamics and atmospheric pressure, light-electromagnetic waves, sound, moisture, and biological energy.

Besides these acceptors and the common energy sensors mentioned above, mammals also have receptors and incorporate organs of the branchial respiratory and digestive gut system against toxins, parasitic microbes, namely viruses, mycoplasma, bacteria, parasites, toxic proteins, and amines. They are tonsilla or lympho adenoid tissue and thymus, Peyer's patch, epithelial body, cervical sinus, hypophysis, and suprarenal glands, which are almost all derived from branchial organs, and the gut visceral system. The above-mentioned concept of acceptors and controllers have been overlooked by conventional research. The hypophysis and suprarenal glands are acceptors not only for pressure, thermal stimuli, light and sound, but also for various kinds of substances with mass, e.g., parasitic viruses and bacteria as well as toxins. The Peyer patch is the acceptor for proteins, amines, toxins, viruses, and bacteria.

For the gut-visceral system, not only sensors for energy, namely the eye, ear, and skin, but also the sensors on acceptors for substance with mass, namely the sense of smell, the tongue, taste buds, hypophysis, thymus, GALT, and suprarenal glands, which are also the incorporation system of chemical substances as well as viruses, bacteria, toxins, and energy, and all sensors, submit to the gut-visceral system.

The hypophysis and suprarenal glands, as well as cervical sinus are also receptors of energy. Conventionally, sensory organs are considered to be limited to accept energy. However, all substances with or without mass, which enter the body from outside, are accepted as well as absorbed and acknowledged by the somato- or viscero-organs and transmitted through the nervous system as well as the blood stream system over whole body organs and cells. Animals use enormous energy during peristaltic movement of the gut visceral muscles as well as locomotive movement of somatomuscles. Plants do not have locomotive movement, therefore, plants use energy substance generated by mitochondria only for cellular respiration, namely metabolism, remodeling and reproduction. We have to remember the energy conservation theory, which states that in the ultimate condition substance with mass is equivalent to energy without mass.

9. ELECTROMAGNETIC ENERGY AND FORCE.

The embryogenic tooth germ and eye germ are histologically precisely the same. The eye is a sensor for electromagnetic waves (energy) and the tooth is a sensor for hydrodynamic waves (energy) of the masticating apparatus to crush food, namely the collision of substance with mass, i.e., dynamic force action under gravity energy (Nishihara, 2004).

Here, we have to consider energy, the correlation between force and substance with mass. The cosmos quintessentially comprises (1) space (and pressure), (2) time and (3) light (electromagnetic waves), which have a close relativity correlation, (4) substance with mass, and (5) thermodynamic energy, which rules over the other four. The author has disclosed what gravitational energy is as follows: gravitational force exclusively belongs to and acts on substances with mass and does not act in the ambit pertaining to electromagnetic energy. In the ultimate condition, a substance with mass is in equilibrium with energy; for example, in ultra-high temperature plasma, in which mass is converted into tremendous energy. However, at that instant, energy loses its attractive force, i.e., gravitation. These forces belong exclusively to substances with mass. Therefore, if they lose mass, they simultaneously lose their gravitational force (Nishihara, 2004).

Substances with mass have three states: solid, liquid and gaseous. Substances characterized by mass undergo (physical and/or chemical) modifications at a certain rate when they gain or lose thermal energy. Solid and liquid substances collide with each other. By these explosive collisions, substances with mass change into space, light and thermodynamic energy. In the case of a release of

energy, the lowest asymptotic limit exists for thermodynamic equilibrium at –273.13 °C (absolute zero).

Mammals utilize for the life system energy without mass as well as substances with mass equivalently under the energy conservation theory. The origin of the life system started initially from absorbing nutrition, oxygen and minerals, namely substance with mass, concomitant with absorbing energy. Therefore, the higher Mammalia have the absorbing system of energy and food, namely substance with mass. We call the former "sensors" or "receptors" and the latter "the gut absorbing system." The gut absorbing system is a receptor (absorber) for substance with mass from the standpoint of the energy conservation theory (Nishihara, 2006).

10. THE CELL RESPIRATION SYSTEM, THE REMODELING SYSTEM AND THE STIMULI ACCEPTING SYSTEM.

The system directly influencing mitochondria is the hypophysis of the suprarenal glands system, which supervises energy metabolism of mitochondria by means of the circulation system in whole cells of animals. What are the substances influencing energy metabolism of mitochondria in whole cells? They are 1) energy, namely heat and cold, pressure, moisture, light, sound, and electricity; 2) nutrition, minerals, vitamins, water, oxygen, namely substance with mass; 3) toxic substances; 4) parasitic microbiles; bacteria, mycoplasma, and viruses, and 5) biological energy such as mind, belief, consciousness, spirit, soul, and biological stresses. Initially, Selye's stressor included microbial infection. However, in recent therapeutics for intractable immune diseases, bacterial infections are completely overlooked. For actual animal life, stressors include not only energy as well as nutrition but also toxins, bacteria and viruses, namely substance with mass. Even for energy, Selye's conventional stress theory overlooked dynamic force, gravity energy, muscle movement, and these receptors.

Therefore, the hypophysis-suprarenal glands system has to include the all-integrated absorbing and acceptor system of not only energy, but also nutrition as well as viruses and bacteria. The gut system is the absorbing acceptor system of both energy and substance with mass, and is carried out by blood circulation of the cardiovascular system. There are three parts: 1) the branchial respiratory gut, 2) digestive tract of the gut absorbing system and 3) excretory tract, namely the genito-urinary system. This gut absorbing system functions for the cellular remodeling system in the whole animal body. There are two remodeling systems; the growth and renewal system, by means of the blood

erythrocyte system, and the cell-membrane destructive remodeling system of leukocytes, which is functional by MHC. The former is cellular metabolism and remodeling in aged cells and the latter is destructive remodeling of tumor cells, intracellularly-infected cells, and transplanted non-self organ cells by means of the membrane detector of MHC (HLA) (Nishihara, 2004).

All nutrition, minerals, vitamins, oxygen, as well as viruses and bacteria are recepted and absorbed into blood or leukocytes and delivered to almost all cells via the blood stream and lympho stream. At this time, microbes absorbed in leukocytes from the M cell of Peyer's patch are disseminated into cells by contaminated leukocytes if the body temperature is lower than 36.5 °C. This gives rise to intra-cellular infection of organ cells or tissue cells by non-pathogenic entero-virus or bacteria, and mycoplasma.

If intracellular infection occurs in some organ, the function of the cells of that organ deteriorate because of the dysfunction of mitochondria caused by contaminated bacteria or viruses. This is an immune disease (Nishihara, 2004).

The conventional interpretation of Selye's stress theory has been just half the story because it overlooked the cellular remodeling system as well as intracellular infection of the cells in the organism. Consequently, bacterial or viral contamination in all cells in whole body occurs. The initial stage of intractable immune diseases starts from intracellular contamination of hypophysis-suprarenal glands through Waldeyer lympho adenoid tissue or gut-associated lymphoid tissue absorbing into leukocytes enterobacteria or viruses by cooling the gut. After that, dysfunction in secreting adrenocrticotropic hormone takes place, and intracellular infection over all cells occurs. This is the cause of intractable immune diseases. Thus, Selye's stress theory is now completely disclosed under the energy conservation theory.

The author discloses the mechanism of the hypophysis-suprarenal gland system as the direct control system of cellular energy metabolism of mitochondria in whole cells in the animal body and this is the immune system. The immune facility is the remodeling capacity conjugated with energy metabolism. Therefore, the hypophysis-suprarenal gland system, i.e., the direct control system of mitochondrial metabolism in whole cells is the controlling system of energy metabolism as well as the acceptor of the stimuli of energy and substances with mass, including bacteria.

The cause of intractable human-specific immune diseases is brought about under improper levels of energy influencing organisms and subsequent intra-

cellular infections of specific organs by non-pathogenic parasites of enterobacteria or viruses. These intracellular parasites of specific cells hinder the energy metabolism of mitochondria, leading to deterioration of organ function and to intractable immune diseases.

Immune diseases are a hindrance of cellular renewal (remodeling), which is conjugated with the energy metabolism of mitochondria. The causes of most immune diseases are a deterioration of the mitochondrial function by various energies as well as by intracellulaly-infected bacteria or viruses, i.e., parasites. These energies are gravity, cold drinks and food, atmospheric pressure, thermal and electromagnetic stimuli, and sunlight. Most intracellular infections of cells are caused by parasitic enteric bacterium. Intracellular contamination of specially differentiated cells, e.g., neurons or hormonal glands by parasitic microbes of the gut, regardless of being aerobic or anaerobic, disturbs the specialized function of mitochondria. This is the immune disease condition (Nishihara, 2004).

11. HUMAN CHARACTERISTIC STRUCTURAL DEFECTS AND HUMAN SPECIFIC INTRACTABLE IMMUNE DISEASES.

By the development of artificial gompholic roots and artificial bone marrow chambers, the author disclosed that the causal factor of evolution is the energy generated by animals to overcome gravity, and established the Gravity Corresponding Evolutionary Theory (Nishihara 2003). From the viewpoint of energy, as well as cellular metabolism of energy, humans have the following five major structural defects or improper habitual behaviors: 1) breathing through the mouth, 2) cooling the body by air-conditioners, cold drinks, and foods, 3) workaholism without resting, 4) infant feeding of solid foods with protein instead of mother's milk, and 5) lack of natural solar light in rooms (Nishihara, 2004).

1) After acquiring speech, circa 5 million years ago, humans could breathe through the mouth, not through the nose. Only humans can breathe through mouth, i.e., mouth-breathing in mammals.

2) By cooling the gut, bacteria and protein with antigenicity are quite easily absorbed through M cells into undifferentiated mesenchymal cells (leukocytes), which change into granulocytes and disseminate bacteria into various cells in the organism, e.g., the pancreas, the joints and the gut.

3) Humans became bipeds one million years ago. After that, humans had to suffer twice the gravitational force of the earth compared to common Eutheria. Humans have to have sleep to rest their bones for at least 8 hours. Without 8 hours of rest, bone marrow ceases to generate leukocytes hemopoiesis and lymphocytes lose energy.

4) Too early feeding of protein with antigenicity is very toxic to infants until they are two and half years old. The gut of infants can absorb any kind of protein with antigenicity. After antibodies develop, allergic idiopathy as well as food anaphylaxis, autism, and epilepsy occur.

5) Lack of solar light in rooms. Sunlight is important for hemoglobin, myoglobin, and cytochrome of hemo-protein.

By these human characteristic structural defects and improper habitual behaviors human-specific intractable diseases occur.

12. MECHANISMS IN THE ONSET OF HUMAN CHARACTERISTIC IMMUNE DISEASES AND MITOCHONDRIAL DETERIORATION – Intracellular Infection of Organ Cells by Human Specific Behavior

Breathing through nose, even during sleep is most important as mouth breathing induces intracellular infection over whole body cells. As a result of low body temperature as well as a lack of rest, the mitochondria of hemopoietic cells loose their vitality, and breathing through the mouth as well as cooling the gut with cold liquids allow leukocytes infected with parasitic entero-bacillus to be disseminated into various organ cells. Then, intracellular infection of these cells takes place. Consequently, the metabolisms of mitochondria are disturbed and the function of mitochondria deteriorate. These conditions are essentially immune system diseases. As a result, the highly differentiated function of organs falls out of order. Solar light excites hemo-protein. Therefore, mitochondria recover and cytochromes are exiting allowing oxidative phosphorylation to be enhanced. By these human characteristic structural defects and improper habitual behavior intracellular infection of enterobacteria occur. After that mitochondrial deteriorations occurs in organ cells, then human specific intractable immune diseases take place (Nishihara, 2004).

Breathing through the mouth is the worst "structural defect" among mammals. As the result of acquiring the ability to speak, only humans can breathe through the mouth. From this habit, i.e., a mistaken usage of the

mouth, various maladies occur in accordance with Lamarck's Use and Disuse theory. Mouth breathing during sleep allows five kinds of lympho-adenoid tissues in the nasopharyngeal region, i.e., Waldeyer's ring, to deteriorate, thus permitting aerobic bacteria, mycoplasma, and viruses to be incorporated into lymphoid-follicles through microfold (M) cells.

In the case of nose breathing, leukocytes digest these parasites and induce the secretion of immunoglobulin A (IgA). Newly synthesized IgA are excreted through tears, snivel and saliva. In the case of mouth-breathing patients, tears, snivel and saliva dry up, allowing synthesized IgA and antigen reactants as well as undigested vital bacteria to be absorbed into the blood stream from the follicles. These then disturb the energy metabolism of mitochondria in the glomerulus of the kidneys and IgA nephrosis as well as nephritis occur. IgA nephrosis or nephritis by mouth breathing is very common in Japan and France. In both countries, mistaken methods of child rearing are still practiced. Especially, disuse of the teething ring (pacifier), results in complete, habitual mouth breathing in both France and Japan. The author has been able to completely cure patients of IgA nephrosis and acute nephritis by correct breathing through the nose (using a nostril enlarging device), getting adequate sleep (8 to 9 hours), and warming of the gut. In other severe cases of habitual mouth breathing, bacteria do not induce IgA in the follicles, but are incorporated into leukocytes intracellularly, which then spread the bacteria to other organs, e.g., the pancreas, bone marrow hemopoietic cells in joints, the bronchus, the lungs, the heart, pancreas, kidney, and subcutaneous tissue. If these patients suffer from lack of rest (inadequate sleep) as well as a cold food mania, diabetes mellitus, rheumatism, bronchitis or asthma, interstitial pneumonia, myocarditis, myositis, diabetes, nephritis, and atopic dermatitis occur. The author has been able to cure a patient who became blind from atopic dermatitis concomitant with retinitis and enabled him to regain his sight. In this case, subcutaneous inflammation by disseminated bacteria by leukocytes through mouth breathing allowed bacteria to be spread to the retina. One must never forget that the skin, the brain as well as the eyes are derived from the same exoderm. In addition, atopic inflammation can occur as there is a close correlation between organs and tissues. Diseases can be easily understood from the viewpoint of the development of ontogeny and phylogeny. In the case of patients with a cold food mania, when the temperature of the gut is lowered, intracellular infection of brain neurons occur as well as cerebral-intestinal hormones, amines, and aminoacids in the spinal cord degenerate by the deterioration of mitochondria in intestine neurons, resulting in these hormones in the visceral cerebrum to degenerate. In the central nervous system the major nutritional circulatory system is lympho-fluid and there exists a blood brain

barrier. However, this barrier is only restricted for erythrocytes and not for leukocytes. Leukocytes contaminated by enterobacteria in Waldeyer's ring moving in cervical lymphovessel to lymphonode easily enter to brain through arteria carotis interna, then leukocytes can enter into cerebral liquor through amoeboid movement passing blood vessel into tissue fluid. Then contaminated bacteria are disseminated cerebritis in new cortex or neuron in the limbic system easily take place. Migraines or depression, hallucinations, and senility result. These systemic immune diseases are induced by aerobic intracellular parasitic microbials, which are disseminated by leukocytes of Waldeyer's ring through the mouth breathing habit during sleep. They consume oxygen in specialized functioning cells of organs, causing the mitochondria to loose their special differentiated function. As a result of these immune diseases, specially functioning organs deteriorate (Nishihara, 2004).

In conclusion, multicellular animals live under sunlight and gravity energy of the earth and moon, and incorporate substances with mass from the gut. Using both energy and substance with mass, creatures remodel themselves in conjugation with energy metabolism by means of mitochondria. The vertebrates have not only sensors to recognize different energies including sound, touch, cold, heat, pressure, and moisture, but also acceptors to process oxygen, minerals, nutrition, toxins, and microbes, such as viruses and bacteria. Thus, creatures live by accepting both energy and substance with mass and, using both of them, the circulation system of energy metabolism in conjugation with remodeling work and aging of cells is overcome. Acceptors of energy are sensors of the eyes, ears, static organs, and muscle spindles as well as all somato and visceral organs, and acceptors of substance with mass, including microbes, are the gut system, incorporating into blood or lymphofluid various kind of substances. These substances, including nutrition, toxins, oxygen as well as microbes, are distributed into cells of the whole body. The control center of the substance-distributing system in blood and lymphofuluid to cells in the whole body is the direct regulation system of mitochondria. This control center is the hypophysis-suprarenal gland system. Dysfunction of this system by intracellular infection or by malnutrition, e.g., a complete lack of vitamins B or C, induces systemic dysfunction of mitochondria in whole body cells. The author has disclosed that the causes of human-specific intractable immune diseases are mitochondrial deterioration due to intracellular infection of common enteromicrobes.

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