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Establishment of a new concept of the immune system, disclosure of causes, and development of the therapeutic system of immune diseases

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Abstract—Using hybrid-type artificial organs made of bioceramics, synthetic research has been carried out to investigate the immune system of mammals. It has been shown that the causes of human systemic immune diseases are brought about by energy influencing organisms, and a hindrance of the energy metabolism of mitochondria by intracellular parasites. From this discovery, a new therapeutic system against human-specific intractable diseases has been developed and a new concept of immunology established.

From the results of these synthetic experiments, self and non-self immunology can be completely exposed as non-scientific theories like teleological adult-fairy tales, akin to the Darwinist theory of evolution.

It is shown that the driving force of evolution is a movement against the force of gravity and the mechanisms of evolution of the vertebrates is verified according to the Use and Disuse theory of Lamarck by means of experimental evolutionary studies using bioceramics. Lamarck's Theory is shown to be based on phenomena of metaplasia in molecular biology. The development of MHC (major histocompatibility complex), i.e. HLA or human leukocyte antigen, arises through the gravity-corresponding movement of the vertebrates during the second revolution in evolution, i.e. landing. The major function of MHC is to detect abnormal cell membranes, such as aged cells, neoplastic cells, and intracellularly infected cells by viruses, bacteria, and protozoa that destroy and remodel cells, and the regeneration and renewal as well as *de novo* synthesis of cells.

The tissue immune system and the mechanisms of immunotolerance from the viewpoint of Haeckel's Biogenic Law have also been studied using chondrichthyes (sharks) as archetype vertebrates. It is well known that these archetype vertebrates have the MHC gene. From this research it has been shown that the gene expression of MHC, or HLA, is triggered during acquisition of bone marrow hemopoiesis and development of sympathetic nerves concomitant with the pyramidal tract of cerebral motor nerves as well as the emergence of the homothermal system.

Thus it has been shown that the immune system is essentially cellular renewal i.e. a remodeling system; this is concomitant with the energy metabolism of mitochondria by means of the cellular digestion system of leukocytes, namely, the MHC of leukocyte membranes (HLA) that detectg deteriorated membranes of infected cells as well as tumor cells. This cellular digestion system in

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mammals depends upon the homothermal system as well as the energy metabolism of mitochondria. The therapeutic system of systemic immune diseases has developed to control the energy influencing the human body and to prevent or cure intracellular infections with non-pathogenic enteric parasitic bacteria.

Keywords: Major histocompatibility complex; artificial bone marrow; tissue immune system; mitochondria; intracellular infection.

INTRODUCTION

Today, in the life sciences, especially in molecular biology and the study of the phenomena of life, energy is completely overlooked. Protozoa and bacteria, as well as cultured mammalian cells can survive under 10 thousand times the earth's gravity. In medicine, especially in self and non-self immunology, energy is overlooked as a causal factor of immune disease. Self and non-self immunology was established by Le Douarin to describe the function of the tissue immune system, but not for understanding all kinds of diseases caused by parasites and metabolic disorders. Today, research in life science and medicine still continues under the Mass Constant Law of the 19th century but not under the Energy Conservation theory of the 20th century. Energy is substance without mass. In organisms, the gene-expression can be triggered by energy just like a catalyst in a chemical reaction. The author successfully introduces energy to the life sciences to disclose causal factors of immune disease.

This synthetic research is constructed with the following three major components: (1) Development of artificial organs and mechanisms of evolution of the vertebrates, i.e. evolution of the skeletal system as well as the hemopoietic system; (2) Development of the immune system and the mammalian immune system as well as an understanding of systemic immune disease; and (3) Development of the therapeutic system of immune disease.

RESEARCH ON THE DEVELOPMENT OF HYBRID-TYPE ARTIFICIAL ORGANS AND MECHANISMS OF EVOLUTION

Development of a revolutionizing method for creating hybrid-type artificial organs using ceramics by means of electrical energy

A revolutionizing method for creating hybrid-type ceramic artificial organs was developed for the first time in the world by means of biomechanical energy which was converted into streaming potential. This induced BMP (bone morphogenetic protein) gene expression of recipient cells *in vivo*. Using sintered hydroxyapatite, artificial bone marrow chambers have been developed *in vivo*, as well as artificial roots, on which hemopoietic cells concomitant with osteoblasts (cementoblasts) were induced in the muscle and jawbone from undifferentiated mesenchymal cells as metaplasia by means of hydrodynamic energy.

It is known that, in the Haversian system, streaming potential is generated by the hydrodynamics of the bloodstream, not only during cardiac circulation and muscle movement but also during repeated movement of the osseous system. The author considers that hydrodynamic energy is converted to streaming potential at the surface of ceramics just as in the Haversian system. To verify this, the streaming potential of sintered hydroxyapatite was measured with a physiological saline solution. The author hypothesizes that with a streaming potential of 5–10 mV, the gene expression of mesenchymal cells is triggered to induce BMP (bone morphogenetic protein) by which mesenchyme can differentiate into osteoblasts concomitant with hemopoietic cells. This is metaplasia induced by streaming potential which triggers the gene just like a catalyst in a chemical reaction. Subsequently, artificial bone marrow chambers have been developed using a titanium electrode with a 5–10 mV current. These were implanted into subcutaneous and muscle tissues and spleens of German shepherd dogs, as well as into the muscles of Triakis (shark) which has no bone marrow hemopoietic nests. In all cases, hemopoietic nests were induced around the electrode chambers, except in the spleen. *In vivo* induction of osteoblasts and cementoblasts on the ceramic surface concomitant with hematopoietic tissues from mesenchymal cells can be verified to be metaplasia by means of the surface reaction of ceramics, i.e. surface behavior induced by the ceramic components is concomitant with streaming potential generated by hydrodynamic energy.

Development of artificial bone marrow chambers. Using sintered porous hydroxyapatite, artificial bone marrow chambers were developed by the author in which mesenchymal cells were differentiated into hemopoietic cells in muscle. For this work, the author received an award from the 32nd Congress of the Japanese Association of Artificial Organs. Using adult German shepherd dogs (35 kg), two groups of experiments were carried out: (1) artificial bone marrow chambers were implanted into subcutaneous tissue; (2) artificial bone marrow chambers were implanted into dorsal muscles. After 6 months, the artificial bone marrow chambers were recovered under general anesthesia. These specimens were observed with light microscopy. In all chambers implanted into subcutaneous tissue, no hemopoietic cells were observed. In all chambers implanted into dorsal muscles extirpated, marked hemopoietic nests were observed in porous sites of sintered hydroxyapatite. Several experiments were carried out to find out the phenomena of highly differentiated functional cells by bioceramic skeletons. The author hypothesizes that hydrodynamics are converted to streaming potential at the surface of the ceramics. The author has developed *in vivo* artificial bone marrow chambers by means of the surface reaction of ceramics using hydrodynamics.

Induction of cementoblasts on the ceramic artificial root surface by means of hydrodynamic biomechanical stimuli. The author has successfully developed a bioceramic artificial root of the gompholic type around which the cementoblast, periodontal ligament and alveolar bone proper can be induced *in vivo*. To disclose

causal factors of induction of the peri-root supporting system, synthetic research on bioceramic surface behavior *in vivo* was carried out by studying the effects of the material, shape, and functional effects of the artificial root on the surrounding cells. Besides animal experiments, biomechanical numerical research using finite element analysis (FEA), as well as flow dynamics experiments using oil pressure on a ten times enlarged three dimensional model of the masticatory mandible implanted in an enlarged artificial root model, were carried out. From these experiments, surface behavior of the ceramics showed a material effect of chemical elements concomitant with the energy effect, which can induce the gene expression of mesenchymal cells of periosteum to differentiate bone morphogenetic protein (BMP), just like a catalyst in a chemical reaction. A peri-root supporting gompholic system was developed on the surface of a corrugated bioceramic artificial root by hydrodynamic stimuli, i.e. energy, in the form of fluctuating wave movements replicating the masticatory function.

Verification of the gravity-corresponding evolutionary law and Lamarck's Use and Disuse Theory by means of biomaterials in vertebrates

The essential components that define vertebrates are skeletal substances: collagen, cartilage and bone. If any of them can be synthesized intact artificially, the causes of chondrification of collagen and ossification of cartilage that occur in the process of evolution will be clarified. The reason is that in the process of the evolution of this phylum, changes from collagen to cartilage and from cartilage to bone alone are observed in terms of materials. The vertebrates pose three problems to be solved: the causes of evolution, the evolutionary biogenesis of the immune system, and the development of bone marrow hemopoiesis. These problems can be addressed all at once by developing artificial bone marrow chambers made of synthetic hydroxyapatite (HA). The development of bone marrow hemopoiesis occurs in the second revolution of evolution. The bone marrow system is essential for inducing blood corpuscles, which are responsible for digestion, respiration, metabolism, and remodeling at the cellular level: the hemopoietic system is the pivot of immune capability. Accordingly, the clarification of the mechanism of the development of bone marrow hemopoiesis leads to the solution of the three problems.

From the studies of developing artificial bone marrow chambers with hematopoiesis, it becomes evident that the evolution of hemopoiesis in endoskeletons depends on a correspondence of organisms to increased gravitational force during terrestrialization. Thence, the author proposes the Gravity-corresponding Evolutionary Law in vertebral phylogeny. The metamorphosis of the endoskeleton by biomechanical stimuli is known as functional adaptation according to Wolff's Law, which is the system of metamorphosis in accordance with the Use and Disuse Theory. It is precisely restricted to the morphology of skeletal organs occurring within one generation.

In this paper, comparative anatomy concerning skeletons, i.e. cartilage and bones of chondrichyes (shark), amphibians, reptiles and mammals is described. Skeletal

morphology of the vertebrates depends not only upon the modality of repeated movements of skeletal organs (what Lamarck called 'inner factors'), but also by biomechanical stimuli influencing the outer (external) side of organisms (Lamarck's 'outer factors', i.e. environmental factors). Therefore, if metamorphosis can be observed among the same animal kind of the same phylogenic stage, there should be differences of inner or outer factors during the evolution of these animals. Differences in the skeletal and muscle system of the same phylogenic stage should produce differences of inner or outer factors during evolution of these animals. Drastic changes of morphology and function in organs of archetype vertebrates after landing can be seen in respiratory gills, the dermal region, and inner skeletons. So, metamorphosis is shown to be a phenomenon of metaplasia, which means a change of cells from one type into another with the same genetic code by biomechanical stimuli.

In the second revolution of the vertebrates, the author hypothesizes that increased gravitational action of the earth after landing affected the blood pressure of chondrichthyes through an intensive movement to escape suffocation by moving toward water. With an elevated blood pressure, streaming potential increases and the increased currents trigger the gene expression of chondrocytes to develop bone marrow hemopoiesis as well as major histocompatibility antigens (MHC).

To verify these phenomena, the author carried out the following experiments: (1) As preliminary experiments, artificial bone marrow chambers of three kinds — sintered porous hydroxyapatite, collagen composed hydroxyapatite of adult cattle with antigenicity, and Ti electrodes with 10 mV current were implanted into the dorsal muscles of chondrichthyes and adult dogs; (2) As experimental evolutionary research, to verify Lamarck's theory, artificial landing experiments of the dog shark, Triakis, and Mexican salamander were carried out. The author has also developed a hybrid-type artificial dental root that took on the characteristics of the gompholic tooth peculiar to mammals. By development of the artificial bone marrow chamber and artificial gompholic root, the author has shown that evolution occurs according to the mechanical functions of the animal in response to the action of gravitation. Through this developmental research the author verified that newly differentiated bone marrow hemopoietic cells and cementoblasts are differentiated from mesenchymal cells as metaplasia induced by energy. The author discovered through studies on the evolution of hemopoiesis that the morphology of an organism can be changed by vicissitudes of internal or external biomechanical stimuli, i.e. energy of environmental factors, which act on the organism, and if these vicissitudes of biomechanical stimuli are transmitted to the next generation by means of discipline as energy of information, morphological changes can be transmitted. These morphological changes, a phenomena of metaplasia at the cellular level induced by hydrodynamic energy, are thence brought about chance environmental factors. Through this discovery, the Use and Disuse theory of Lamarck can be explained biomechanically in molecular genetics, and a Genuine Use and Disuse theory is proposed by author.

The Use and Disuse theory is evidenced in the second revolution of the vertebrates as increased gravity triggers genetic expression in mesenchymal cells, thereby not only producing hemopoiesis conjugated with ossification of the cartilage, but inducing major histocompatibility complex (MHC).

RESEARCH ON DEVELOPMENT OF THE IMMUNE SYSTEM AND THE MAMMALIAN IMMUNE SYSTEM

Disclosure of immuno-tolerance of archetype vertebrates by means of sintered apatite-collagen composite

To investigate the tissue immune system, pressure sintering composite of apatite-collagen with antigenicity of MHC was carried out.

An attempt was made to synthesise a composite consisting of apatite and collagen derived from cattle with antigenicity of MHC. Starting from an aqueous solution of collagen, phosphoric acid and calcium hydroxide suspension, an apatite (90 wt%) collagen (10 wt%) composite of apparent density 1.75 g/ml, Young's modulus 2 GPa, and 6.5 MPa in compression strength was successfully synthesized at 40°C and 200 MPa. It was found that the presence of liquid water in the system was essential for the sintering of the composite under high pressures. Without liquid water, the specimen that was pressure treated and brought to atmospheric pressure broke into small pieces due to residual strains. The prepared composite could be cut by a razor blade, and was stable against immersion in water. The mean size of the apatite crystals in the composite were 10 nm in width and 40 nm in length.

The development of the tissues immune system can be studied by composite ceramics, i.e. artificial bone of collagen-hydroxyapatite composite, which was sintered by high-pressure techniques under the above-mentioned method. Artificial bone marrow chambers were fabricated with sintered collagen-hydroxyapatite composite. Experimental evolutionary studies using mammals (German shepherd dogs) and chondrichthyes (Triakis sharks) were carried out by implanting the chambers into their muscles. The experiment showed that around the collagen composite chambers implanted into the dorsal muscle of dogs, marked cell differentiation as well as dedifferentiation with atypia (anaplasia) could be observed, and resembled histologically part of the intestinal digestive tract. Around the chambers implanted into the dorsal muscle of sharks hemopoietic nests could be observed that were similar to those induced by the chambers of conventionally sintered hydroxyapatite. Hemopoiesis and osteoid formation 4 months after surgery were observed around the collagen–apatite chamber implanted in the shark muscle as well as in the upper site of vertebral cartilage of the spinal cord. No hemopoietic osteoid around cartilaginous tissue in the upper site of the spinal cord was evident in control sharks. These experiments showed that archetype vertebrates are immunotolerant.

To verify the immunotolerance of lower animals, xenotransplantation of dermal grafts were performed between the following animals: Triakis and Triakis, Triakis

and Heterodontus, Triakis and Xenopus, Triakis and quails, Triakis and rats, Triakis and dogs. All skin grafts were successfully carried out.

Consequently, xenotransplantation of parts of nerves and brains were successfully carried out between following animals: A part of a brain of a hagfish to a Japanese salamander; a part of a brain of Triakis to a rat; and a part of a spinal cord of a Hagfish to the extirpated sciatic nerve of rats.

Subsequently, corneas as well as gut tissue from Triakis were successfully transplanted to those of German shepherd dog, respectively.

What is immuno-tolerance? Experimental evolutionary studies by means of the successful xenotransplantation system

It is known that primitive vertebrate chondrichthyes possess genes of major histocompatibility complex (HMC). Skin grafts from Cyclostomata (hagfish) to rats have been successful, and the corneas of sharks can be successfully transplanted to those of German shepherd dogs. In addition, a part of the intestine as well as brain and muscle of sharks can be successfully transplanted to those of dogs. These successful xenotransplantations suggest that they have no tissue immunity. This means that they are immunotolerant, just like embryos of higher animals such as reptiles, birds and mammals. The major function of MHC (HLA) is found to be the cytological digestion system of the leukocytes functioning mainly for tissue remodeling in the organism's own cells by means of abnormal cell membrane such as tumor cells, aged cells and intracellularly infected cells, as well as partly transplanted imported tissue, especially, intracellularly infected cells by the usual parasitic bacteria in the gut which change their cell membranes. Leukocytes detect altered membranes of infected cells by means of HLA; simultaneously, an anti-nucleic acid antibody is generated by leukocytes. Intracellularly infected cells become chimera cells of the human genome with many nucleic acids with parasites. This reaction is the result of the digestion of infected cells together with parasites by leukocytes.

What at is the immune system in mammals?

Haeckel's Biogenic Law states that 'ontogeny recapitulates phylogeny'. From the viewpoint of this law, the tissue immunity system of archetype vertebrates is thought to be analogous to that of the embryos of mammals. Present research aims to prove the development of tissue immunity through genetic expression by acclimatizing to gravitation during terrestrialization. In ontogeny in higher animals, embryos have no tissue immunity. This is known as immunotolerance. However, the mechanisms of immunotolerance are not known. Self and non-self immunology is in vogue in these days. This concept is defined only with regard to tissue immunity. The author proposes a hypothesis in the development of tissue immunity by the changes effected by gravity of 1 G during landing in phylogeny (from 1/6 G in sea water) as well as in ontogeny during landing from amniotic fluid by delivery. Successful xenotransplantation of various tissues between archetype

vertebrates of chondrichthyes (sharks) and mammals (dogs) indicate that sharks are immunotolerant and the genetic expression of major histocompatibility complex (MHC) in higher animals is triggered by gravity, just as development of bone marrow hemopoiesis is triggered by it in phylogeny as well as ontogeny.

From these experiments, it is shown that the emergence of the tissue immune system in higher animals coincides with the development of bone marrow hemopoiesis as a result of the action of the gravity as well as the acquisition of a homothermal system. The function of HLA on leukocyte membrane emergence is in conjugation with the homothermal system and differentiation of lymphocytes.

It is well known that archetype vertebrates like the shark have MHC. However, the author has shown that chondrichthyes are immunotolerant. Therefore, xenotransplantation between amphibians, birds, and mammals can be successfully carried out.

What does immunotolerance mean against bacteria and viruses? For surgical operations on sharks, such as xenotransplantation, aseptic treatment is not necessary. In cold-blooded animals like chondrichthyes and amphibians, bacteria and virus coexist in their body. The major function of MHC of leukocytes (HLA) is not merely to detect self or non-self by cell membranes, but to detect abnormal cell membranes of tumors, deteriorated aged cells, and infected cells intracellularly by bacteria and viruses. The function of leukocytes to detect abnormal membranes as well as generate immunoglobulin depend strictly upon the gene expression of the cells, and these leukocyte functions depend upon the homothermal system.

The strict dependence of the mammalian immune system on the homothermal system has been shown by Professor N. Hayashi through his investigation of brain resuscitation by means of cerebral hypothermia in Tokyo. Brain surgery was carried out after lowering the body temperature to 3°C from the normal human temperature of 37°C. During operation at this lowered body temperature, numerous bacteria from the gut through M (microvilli) cells of GALT (Gut Associated Lymphoid Tissue) are incorporated into in the blood stream. However, leukocytes do not digest bacteria but leave them to co-exist. If the body temperature rises intensively without washing out the gut the patient dies because leukocytes and numerous bacteria react intensively as sepsis at the normal 37°C homothermal system.

What are systemic immune diseases?

To indicate the nature of immune diseases, the author considered the synthetic regulation system of mammals at the cellular level, following comparative morphological research between protozoa and mammals.

Basic construction of protozoa and mammals at the cellular level. Research on the comparative morphology between protozoa and multi-cellular organisms of mammals is carried out from the standpoint of energy metabolism to uncover the causes of systemic immune diseases. When comparing protozoa and multicellular organisms of vertebrates at the cellular level, there are no major differences.

Therefore, it is necessary to ask, what is the difference between protozoa and multi-cellular organisms? To discover this, the basic construction of the mono-cellular organism of eucaryotae of protozoa and multi-cellular vertebrates are compared at the cellular level. Protozoa get all nutrition including oxygen by phagocytes directly from their surrounding medium, and they carry out regeneration or remodeling of a part of the organism, conjugated with energy metabolism by means of mitochondria. Through this metabolism they can overcome deterioration by aging. The metabolism of protozoa depends entirely upon the surrounding medium. On the other hand, all mammalian body cells obtain nutrition and oxygen from the blood and lymph system of the cardiovascular system. The only difference is the cardiovascular system. The gravitational action of the earth directly influences the cardiovascular system as blood pressure rises to compensate for increased gravity. There is no such influence of gravity on protozoa or cultured cells of mammals.

All cells of organs and tissues of mammals also regenerate in a part of a cell, as well as a whole cell and a whole organism (hereditary by reproduction) in conjugation with energy metabolism of mitochondria. Cellular metabolism of mammals also relies on the metabolism of mitochondria, and this metabolism entirely depends upon blood pressure and nutrition and oxygen in the blood. If mitochondria require more energy for metabolism in cells, mitochondria of the medullar cells of adrenal glands excrete adrenalin, the respiratory movement of the lungs as well as the heart are enhanced, and glycogen is released from the liver. Consequently, the oxidative phosphorylation of mitochondria in all cells of the organism are activated and body temperature, and energy, metabolize ATP, and catabolites and CO_2 are generated. Protozoa, which are single-cell organisms, also remodel a part of this cell using energy that their mitochondria generate. An adult human has 60 trillion cells and one trillion cells are regenerated daily; for this regeneration, mitochondria as well as HLA are functioning components.

Function of mitochondria in mono- and multi-cellular organisms. As mentioned above, as the basic cellular construction, protozoa and mammals utilize the same organelle of mitochondria as energy generators. In other words, almost all functions of cells in organisms are carried out by the gene expression of the organism by means of ATP generated by mitochondria.

All specialized differentiated cells in mammals, like neurons, para-neurons, respiratory ciliated cells, hormonal gland cells, salivary gland cells, hepatic cells, glomerulus of kidney, brown adipose tissue of hibernating animals, osteoblasts, and fibroblasts, have specialized mitochondria. The genome of mitochondria as well as that of the nucleus is quite similar in all specialized differentiated cells in certain organisms. Therefore, highly differentiated cells carry out their specialized function by their characteristic mitochondria. For example, in the brain about 20% of the total oxygen absorbed is consumed by mitochondria of neurons, para-neurons, and glia of the cerebrum, yet it is only 2% of the total body weight. Neuron mitochondria generate monoamines, cerebrum-entero hormone, and neurotransmitters.

Mitochondria of the pancreatic islets of Langerhans generate insulin, and those of the adrenal cortex cells generate mineral- and glycocorticosteroid hormones.

The effective target of all minerals, vitamins, essential lipids, essential amino acids, and mineral or glycocorticosteroids are mitochondria, which exist through out the body. Thus, in protozoa, mitochondria require and directly absorb oxygen and nutrition from the surrounding medium into cytoplasma. Mitochondria in mammalian cells require oxygen and nutrition including minerals which they acquire by excretion of hormones into the bloodstream. The leading metabolic functions in aerobic eukaryotae are performed by mitochondria.

Comparison of infections of protozoa and mammals. Protozoa have two infection sites, namely, membrane surfaces and intracellular cytoplasm. However, multicellular vertebrates have four infection sites — the skin surface, the digestive tract, including the lungs and the urogenital tract, the intercellular space of the cardiovascular system, and the intracellular cytoplasm.

Most epidemic diseases as well as diseases caused by pathogenic bacteria are extracellular infections for which most antibiotics are effective. Viruses and enteric parasite bacteria cause intracellular infections. Conventional diseases caused by pathogenic bacteria are exclusively extracellular infections. Only viruses and malaria are known intracellular infections.

Conventionally it has been overlooked that parasitic bacillus and bacteria without pathogenicity in the intestinal tract can easily infect cells and survive for a long time intracellularly. In conventional medicine, intracellular infections have also been overlooked.

It is suggested that all intractable diseases are intracellular infections of parasitic bacteria without pathogenicity, viruses and protozoa. Because all vital microbial organisms have their own genes, then cells with parasitic viruses, bacillus, and protozoa have chimeric modified genes. Cells with chimeric genes have a special cell membrane corresponding to the chimeric genes, as well as a special metabolic system. For example, viruses introduce their structural proteins by their gene, and malaria introduces hemopoietic cytocain of the host by its mitochondrial gene. Also, parasitic bacillus and bacteria in cells ulitise oxygen and glycogen intracellularly. Consequently, as the original mitochondria become dysfunctional, this condition of cells in human organs are certainly systemic immune diseases.

DEVELOPMENT OF THE THERAPEUTIC SYSTEM OF IMMUNE DISEASES

The nature of immune diseases in humans?

Immune diseases are a hindrance of cellular renewal or remodeling, which is complementary to the energy metabolism of mitochondria. The causes of most immune diseases are a deterioration of the mitochondrial function by various energies as well as 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 a 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.

History of diseases and history of overcoming illness

Considering the types of diseases and the history of overcoming illness, humans have conquered various illnesses, but have still not overcome immune system diseases. Human diseases are divided into the following 8 kinds: (1) Infections (a) epidemic and pathogenic, intra- or extracellular microbial infections, (b) parasitic infections, (c) chance infections of intracellular parasitic bacteria, mycoplasma, and viruses; (2) Malnutrition; (3) Dysfunction of energy metabolism, including mental disorders; (4) Exhaustion and disorders of energy balance; (5) Disorders of remodeling and differentiation (cancers and malformations); (6) Toxicity; (7) Tissue-immune reaction after transplantations; and (8) Injuries.

All these are immune diseases except injuries. The key to overcoming epidemic diseases caused by pathogenic microbes (virus and bacteria) was provided by Pasteur and Koch. Various illness caused by pathogenic bacteria were overcome by the development of antibiotics in 1970. At this stage, Lu Douarin established self and non-self immunology by transplantation of neural crests between embryonic chickens and quail. However, the results of her experiments illustrated only the tissue immune system, not the causal factors of intractable systemic immune diseases. As already mentioned above, immune diseases are intracellular infections of the parasitic microbe of the intestine, and reactions of host leukocytes against infected cells resemble those of the tissue immune reaction against transplanted animal cells. These cells change their original nucleic acid into chimera genes: consequently, anti-nucleic acid antibodies are generated. At the same time, cell membranes change their surface structure, and the energy metabolism of mitochondria in the cell is disturbed by a parasitic bacillus. As a result, the cellular function of highly differentiated cells with specialized function deteriorates by the disturbance of mitochondrial metabolism.

Intracellular infections of parasitic bacillus of the intestine are brought about by breathing through mouth as well as hyperphagia by cold ice cream and cold drinks.

Structural defects of the human body from the energy viewpoint

By the development of artificial gompholic roots and artificial bone marrow chambers, it has been shown that the causal factor of evolution is the energy generated by animals to overcome gravity, from which the author has proposed his Gravity Corresponding Evolutionary Theory. From the viewpoint of energy, humans have the following major 5 structural defects: (1) breathing through

the mouth, (2) cooling the body by air-conditioners and cold drinks and foods, (3) workaholism without resting, (4) infant feeding of solid foods with protein, and (5) lack of natural solar light in rooms.

(1) After acquiring speech, about five million years ago, humans could breath through the mouth, not only through the nose. Only humans can breath through the mouth within mammals.

(2) By cooling the gut, bacteria and proteins with antigenicity are quite easily absorbed through M cells into 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 and food anaphylaxis, autism and epilepsy occur.

(5) Lack of solar light in rooms. Sunlight is important for hemoglobin, myoglobin, and cytochrome of hemo-protein. Solar light excites the hemo-protein. Therefore, mitochondria recover and are excited, allowing oxidative phosphorylation to be enhanced. With low body temperatures 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 allows leukocytes to become infected with parasitic enterobacillus, which are disseminated into various cells. Consequently, the metabolism of mitochondria is disturbed and their function deteriorates. These conditions produce immune system diseases. As a result, the highly differentiated function of the organs become imbalanced.

Mechanisms in the onset of human characteristic immune diseases

Breathing through the mouth is the worst 'structural defect' amongst the 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 of Waldeyer's ring to deteriorate, thus permitting aerobic bacteria, mycoplasma, and viruses to be incorporated into lymphoid-follicles through microvilli (M) cells.

In the case of nose breathing, leukocytes digest these parasites and induce the secretion of immunoglobulin A (IgA). Newly synthesized IgA is excreted through tears, nasal mucous and saliva. In the case of mouth-breathing patients, tears, nasel secretions and saliva dry up, allowing synthesized IgA and antigen reactants to be

absorbed into the blood stream from the follicles. This allows the reactant to destroy the glomerulus of the kidneys and IgA nephrosis occurs.

IgA nephrosis caused by mouth breathing is very common in Japan and France. In both countries, mistaken methods of child rearing are still in vogue. In particular, the 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 by correct breathing through the nose (using a nostril enlarging device), 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, 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, mesenchymal pneumonia, myocarditis, myositis, and atopic dermatitis occur. The author has been able to cure a patient who became blind from atopic dermatitis concomitant with retinitis and was able 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, cerebral-intestinal hormones, amines, and aminoacids in the spinal cord degenerate by the deterioration of mitochondria in neurons, causing hormones in the visceral cerebrum to degenerate.

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.

Establishment of the therapeutic system in immune diseases

By breathing through the mouth as well as lowering the gut temperature to 2 to 3°C, enteric parasitic bacteria invade into the M cells of GALT. Through M cells of GALT leukocytes infected with bacteria intracellularly differentiate into granulocytes. Enteric bacteria are disseminated into various visceral organs organs as well as somatoneural, musculo-skeletal, and vascular organs through the blood-stream by granulocytes. As already mentioned, specialized functions of the highly differentiated cells of organs are carried out by their mitochondria. In some special cases of intracellular protozoainfection, such as malaria, large clusters of

erythrocytes appear in the parenchymal space of the host liver. Protozoa malaria can proliferate exclusively in erythrocytes but not in other vital cells that have nuclei. This means that mitochondria of malaria secrete some cytokine to induce erythrocyte-hemopoiesis in the host liver. Therefore, if protein (cytokine) synthesis of mitochondria in malaria is disturbed, malarial infection cannot occur. The causal factor of systemic immune diseases have been shown to be intracellular infections of non-epidemic parasitic entero-bacteria caused by inadequate energy absorption by patients. Therefore, it is very easy to prevent as well as to cure immune diseases.

Inadequate energies influencing the patient's energy metabolism of mitochondria are the over-loaded gravity action of the earth, atmospheric pressure, radioactivity, electromagnetic waves, hot and cold thermal stimuli, and stresses. Adequate energies to activate mitochondria are solar light with infrared waves and some kinds of ultrasonic waves. Skeletal rest to minimize gravity and warm drinks to avoid cooling the gut, as well as breathing through nostrils are most important to prevent infections of parasitic entero-bacteria. Diagnosis *ex juvantibus* through the regulation of energies to cure immune diseases are carried out as evidence-based medicine. The author has shown that immune diseases are induced not only by energy, i.e. substances without mass, but also by the functional disorder of mitochondria by intracellular infection of parasitic bacteria in the intestine.

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