DISCLOSURE OF THE KEY CAUSE OF INTRACTABLE IMMUNE DISEASES BY MEANS OF HYBRID-TYPE ARTIFICIAL IMMUNE ORGANS

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The author successfully developed hybrid-type artificial articulations, i.e., gompholic root as well as bone marrow chambers using bioceramics as artificial immune organs. Inside these bioceramic organs hemopoietic cells can be induced by gene expression through streaming potential generated from biomechanical stimuli. Following this development, he disclosed the cause of evolutionary changes in hemopoietic nests from the gut system into bone marrow and disclosed that the immune system is the cytological digestion of the blood and lympho-system. During evolution, the blood digestion capability in mammals changed dramatically, as erythrocytes lost their nuclei, becoming ghosts, resulting in the completion of the lympho-vessel system. From the viewpoint of evolution, mitochondria are believed to be an archetypal prokaryote that entered and lived inside eukaryote some 1.8 billion years ago. As a result, various kinds of parasites, e.g., virus, bacteria, protozoa, survive in mammals, even intracellularly.

These organisms are composed of water-soluble colloids of nucleic acids, proteins, lipids, carbohydrates and minerals, and use energy metabolism to remodel a whole or part of themselves. By using energy metabolism, and remodeling, these organisms are able to overcome aging.

The energy metabolism of organisms is carried out by mitochondria and can be greatly influenced by energy affecting the outside of the cells. The author has disclosed that the immune system is essentially cytological digestion by the blood system. There are two major types, i.e., the digestion of bacteria, viruses, proteins, and foreign bodies, and the digestion of aged cells discharged from organs, transplanted organ cells, and intracellularly-infected cells.

The leukocytes' ability to digest is directly affected by energy acting outside and inside the body.

It is well known that in gut-associated lymphoid tissue (GALT), there are many M-cells of adenoid tissue and Peyer's patches with follicles that can catch viruses and bacteria as well as indigestible proteins like prions. Under some conditions, leukocytes incorporate microorganisms without digestion and circulate in the lymph system and blood vessels, thereby spreading them to various organcells. Conventional self-non-self immunologists close their eyes to these facts. It is therefore necessary to establish the right concept of immunology by which the causes of intractable immune diseases are disclosed, and diseases are prevented and cured.

In conclusion, the cause of intractable human-specific immune diseases is brought about under improper levels of energy influencing organisms and the subsequent intracellular 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.

INTRODUCTION

The definition of the mammals is "vertebrates borne with the suckling system, which later become masticatory organ with heterodontial teeth in the jawbone". Articulation, i.e., the joint system of skeletons, including the gompholic system, is one of the most important characteristics of mammals, having important function of leukocyte-hemopoiesis. The other key characteristics are the respiratory diaphragm, the lymphovessel system, the homoiothermic system, and the genitourinary system.
The circulatory system based on hemopoiesis intermediates between the external respiration system and the internal respiration of mitochondria.
The author has developed a bioceramic artificial bone marrow chamber as well as bioceramic artificial gompholic dental roots by means of a hybrid method by which, in vivo, highly differentiated hematopoietic cells conjugate with osteoblast and cementblast induced by means of the gene expression of recipient mesenchymal cells around ceramics via hydrodynamic energy. The author has verified that hydrodynamic energy is converted into streaming potential and this potential triggers the gene expression of mesenchymal cells around ceramics. This means that a major cause of meta-morphology in evolution is the result of biomechanical stimuli, in a broad sense, which is converting to streaming potentials triggering the gene expressions just like catalysts. The mammals are composed of various kinds of structures and organs of ca. 60 billion multiple cells. These structures and organs are under control and function systemically having close interaction as one organism. What are the controlling system in mammals of these organs and structure as one creature? At first we have to know basic construction of mammals, then this can be disclosed comparing the life system of mono-cellular organisms of Protozoa to that of multicellular-mammals.
Today, in the life sciences, especially in molecular biology and 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 disclose 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 continue 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 diseases. This synthetic research is constructed with the following three major components: 1. Development of artificial organs. 2. Phylogenic development of the immune system and the mammalian immune system as well as an understanding of systemic immune diseases; and 3. Development of the therapeutic system of immune diseases.

1. Development of revolutionizing method for creating hybrid-type artificial organs - artificial bone marrow chambers and gompholic roots - using ceramics by means of electric 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, the author

developed in vivo artificial bone marrow chambers implanted into femur muscle of Japanese monkey 11 months post operation (Fig. 1, Fig. 2), as well as artificial roots 4 months÷2 years post operation implanted in dogs (Fig. 3-5), on which hemopoietic cells (Fig. 2) concomitant with osteoblasts as well as cementoblasts (hydroxyapatite artificial root for clinical use, 15 years post operation, Fig. 6) were induced in the muscle and jawbone from undifferentiated mesenchymal cells as metaplasia by means of hydrodynamics.

It is known that in the Haversian system, streaming potential is generated by 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 hydrodynamics is converted to streaming potential at the surface of ceramics just as in the Haversian system.

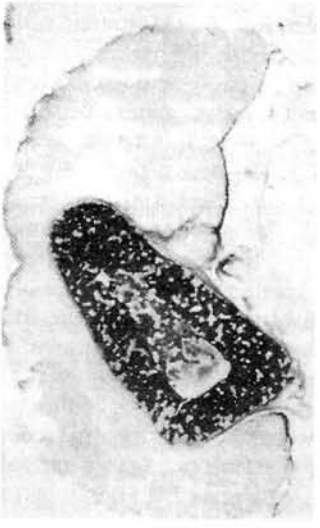

Fig. 1

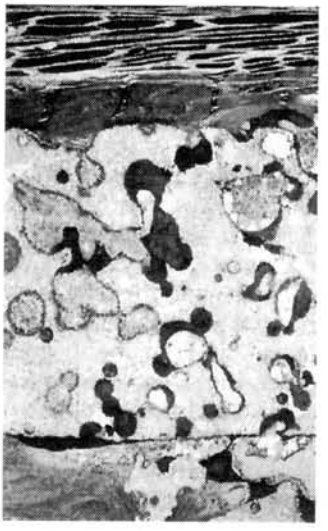

Fig. 2

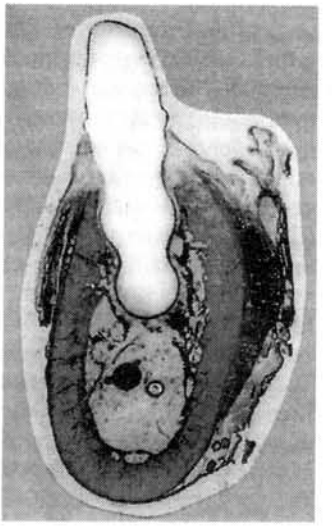

Fig. 3 ZrO_2 artificial root

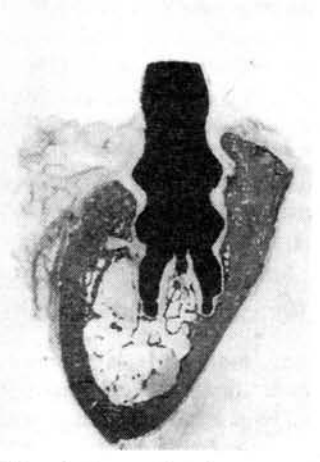

Fig. 4 Ti artificial root

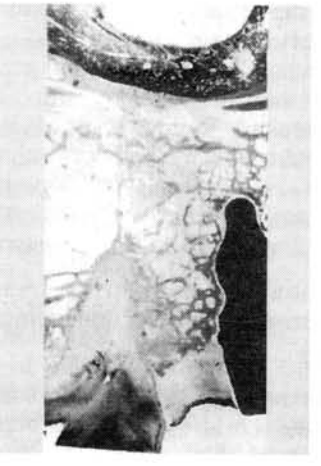

Fig. 5 Ti artificial root

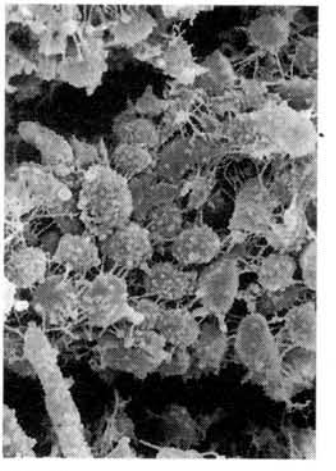

Fig. 6

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 50~100μV, the gene expression of mesenchymal cells is triggered to induce BMP 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. Subsequently, the author developed artificial bone marrow chambers using a titanium electrode with a 50~100μV, 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 in concomitant with streaming potential generated by hydrodynamic energy. Using sintered porous hydroxyapatite, artificial bone marrow chambers were developed by the author in which mesenchymal cells were differentiated into hemopoietic cells in muscle.

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. For this work, the author received an award from the 32nd Congress of the Japanese Association of Artificial Organs.

In vivo arterial organ culture chambers for autogenous liver and pancreas made of sintered hydroxyapatite were also developed and successfully connected to the femur artery of dogs for 3 months (Fig. 7). Organ culture of autogenous liver was carried out successfully for three months (Fig. 8).

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.

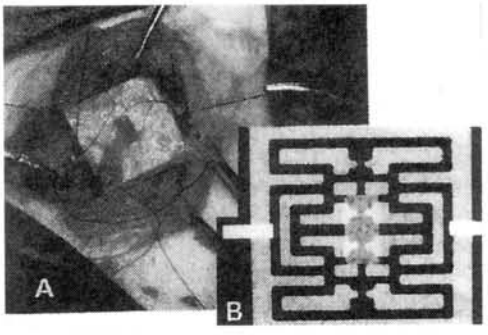

Fig. 7

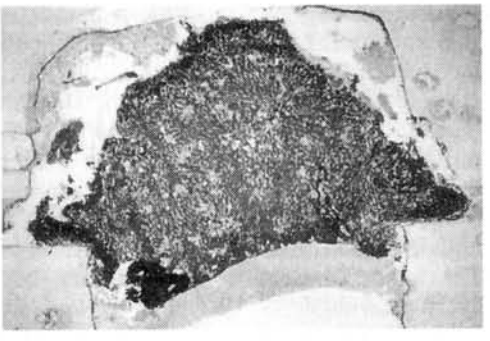

Fig. 8

2. Research on development of the immune system and the mammalian immune system

2-1) 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 (major histocompartibitily antigen complex) was carried out. A composite consisting of apatite and collagen derived from cattle with antigenicity of MHC was attempted. Starting from an aqueous solution of collagen, phosphoric acid and calcium hydroxide suspension, an apatite (90wt%) collagen (10wt%) composite of 1.75 g/ml in apparent density, with 2 GPa in Young's modulus, and 6.5 MPa in compression strength was successfully synthesized at 40° C, 200 MPa. Artificial bone marrow chambers were fabricated with this pressured 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 composed 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 which 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. Sharks are well known to possess MHC genes. As the results of these experiments, the author disclosed that archetype vertebrates are in immuno-tolerance, the same as mammal embryos. This means that even, though they have MHC genes, the genes remain dormant without gene-expression. To verify the immuno tolerance of lower animals, xenotransplantation of dermal grafts were successfully performed between the following animals: a) Triakis and Triakis, b) Triakis and Heterodontus, Triakis and Xenopus, Triakis and quails.

2-2) Disclosure of immuno-tolerance by means of the successful xenotransplantation system

It is known that primitive vertebrate chondrichthyes possess genes of HMC. The author has successfully carried out skin grafts from Cyclostomata (hagfish) to rats, and the corneas of sharks (Triakis) can be successfully transplanted to those of German shepherd dogs (Fig. 9). In addition, a part of the intestine (Fig. 10) as well as brain and muscle of sharks (Triakis) can be successfully transplanted to those of dogs. From these successful xenotransplantations, the author has discovered that they have no tissue immunity. This means that they are in immuno-tolerance just as embryos of higher animals such as Reptiles, Aves, and Mammals.
The major function of MHC (HLA; human leukocyte antigen) 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 and aged cells, as well as partly transplanted imported tissue, especially, intracellularly

infected cells by 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 intracellularly infected leukocytes. These cells become chimera cells of the human genome with many nucleic acids of parasites. This reaction is the result of the digestion of infected cells together with parasites by leukocytes.

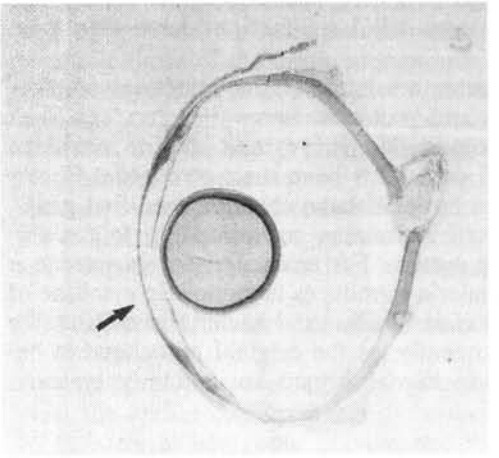

Fig. 9.A
Shark eye. The cornea (arrow) transplanted into that of a dog.

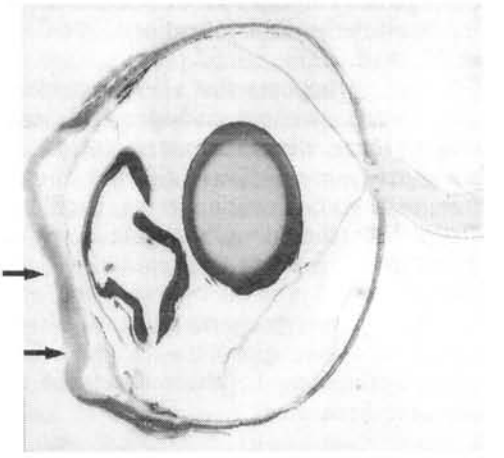

Fig. 9.B
Dog eye. Thin transplanted cornea turns into thicker one (arrow) in dog.

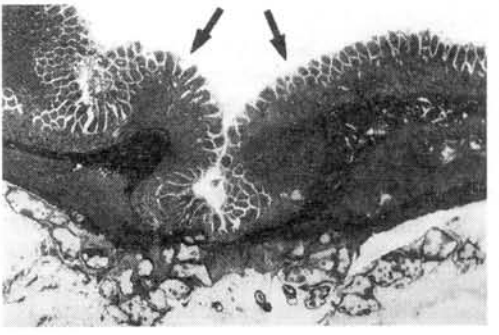

Fig. 10.A
Transplanted shark intestine (arrows) into that of a dog (2 months post operation).

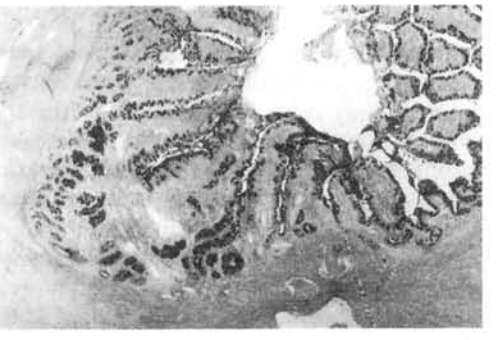

Fig. 10.B
Transplanted shark intestine with numerous chalice cells are observed.

2-3) Comparison of infections of protozoa and mammals

Protozoa have three infection sites, i.e., medium, membrane surfaces, and intra cellular cytoplasm. Also, multi-cellular vertebrates have three infection sites; i.e., 1) epithelical surface of skin, digestive tract, including lungs, and urogenital tract, 2) medium, i.e., inter-cellular space of the cardiovascular system, and 3) intra-cellular cytoplasm.

Most epidemic diseases as well as diseases caused by pathogenic bacteria are extra-cellular infections for which most antibiotics are effective. Viruses and enteric parasite bacteria cause intra-cellular infections. Conventional diseases caused by pathogenic bacteria are exclusively extra-cellular infections. Only viruses and malaria are known intra-cellular 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 intra-cellularly. In conventional medicine, intra-cellular infections have also been overlooked.
The author proposes that all intractable diseases are intra-cellular infections of parasitic bacteria without pathogenicity, viruses and protozoa. Some 30 years ago such non-chronic diseases were called opportunistic infections or for children autointoxication. Because all vital microbial organisms have their own genes, therefore, 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 cytokine of the host by its mitochondrial gene. Also, parasitic bacillus and bacteria in cells utilize oxygen and glycogen intra-cellularly. Consequently, as the original mitochondria become dysfunctional, this condition of cells in human organs are certainly systemic immune diseases.

3. Development of the therapeutic system of immune diseases

3-1) What are immune diseases characteristic in humans?

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 intracellulaly-infected bacteria or viruses, i.e., parasites. These energies are gravity, cold drinks and food, atmospheric pressure, thermal and electro magnetic 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.

3-2) 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 extra-cellular microbial infections, (b) parasitic infections, (c) opportunistic infections of intra cellular 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 above-mentioned illnesses are immune diseases except injuries.

Epidemic diseases caused by pathogenic microbes (virus and bacteria) were overcome 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 disclosed only the tissue immune system, not the causal factors of intractable systemic immune diseases.
As already mentioned above, immune diseases are intra-cellular infections of the parasitič 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 parasitic bacillus. Consequently, 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.

3-3) Structural defects of the human body from the energy viewpoint

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. 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, circa 5M years ago, humans could breath through the mouth, not through the nose. Only humans can breath 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 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. Solar light excites the hemo-protein. Therefore, mitochondria recover and are exited allowing oxidative phosphorylation to be enhanced. Low body temperatures as well as a lack of rest, the mitochondria of hemopoietic cells loose their vitality, and breathing through mouth as well as cooling the gut with cold liquids allows leukocytes infected with parasitic entero-bacillus

which are disseminated into various cells. Consequently, the metabolism 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 become out of order.

3-4) Mechanisms in the onset of human characteristic immune diseases

Breathing through the mouth is the worst "structural defect" among 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, 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 to be absorbed into the blood stream from the follicles. This allows the reactant to disturb the energy metabolisms of mitochondria in the glomerulus of the kidneys and IgA nephrosis occurs. IgA nephrosis by the mouth breathing is very common in Japan and France.
In both countries, mistaken methods of child rearing are still in vogue. Especially 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, interstitial 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 allowing 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 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, resulting in these 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.

3-5) Establishment of the therapeutic system in immune diseases

By breathing through mouth as well as lowering the gut temperature to 2~3° 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 as well as somato neural, 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, e.g., 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 with nuclei. This means that mitochondria of malaria secrete some cytokine to induce erythrocytes-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 are disclosed to be intracellular infections of non-epidemic parasitic entero-bacteria by means of 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. Skeletalrest for minimizing 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 disclosed that immune diseases are induced not only by energy, i.e., substance without mass, but also by the functional disorder of mitochondria by intracellular infection of parasitic bacteria in the intestine.

ACKNOWLEDGEMENTS

This research was supported by a Grant-in-Aid for Developmental Scientific Research (B) (1) (No. 03557107), in-part by a Grant-in-Aid for Scientific Research on Priority Area (1) (No. 05221102 and 06213102), a Grant-in-Aid for Developmental Scientific Research (B) (1) (No. 06558119), in-part by a Grant-in-Aid for Scientific Research on Priority Area (1) (No. 08233102), and a Grant-in-Aid for Co-operative Research (A) (No. 07309003) from the Ministry of Education, Science and Culture, Japan. This study also has been supported by a Grant-in-Aid for Scientific Research (A) 09309003 from the Ministry of Education, Science and Culture, Japan.

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