Great medical discoveries of the 21st century

Part I: Revitalizing stagnant medicine by establishing energy-based bioscience. Disclosure of the aetiological factors of three major intractable maladies at the subcellular level: immune diseases, carcinoma and mental illness

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For human beings today, three kinds of major intractable maladies, immune diseases, cancers, and mental illness, present urgent issues requiring the discovery of both causes and therapeutics. The author has developed an artificial bone marrow chamber as well as a hybrid-type artificial gompholic dental root using bio-active ceramics by means of inducing gene expression of mesenchymal stem cells via the hydrodynamic flow of bathing medium, which induces a streaming potential. As a result of this work, he noticed that in conventional medicine and bioscience there are three major blind spots concerning energy: "energy without mass"; the energy-generating organelles (mitochondria); and "animal biomechanical energy". To bring about a breakthrough in stagnant medicine, the author has introduced the concepts of "mitochondria", "environmental energy" and "biomechanical energy" into bioscience and therapeutic medicine. He has also introduced clinically bioresonance diagnostic methods (the Bi-Digital O-Ring Test) to disclose major causes of intractable maladies, which have been revealed as being brought about by intracellular infection of common nonpathogenic enteromicrobes, due in turn to absorbing improper environmental energies. These microbes cause deterioration of the mitochondria. Thereafter, he has established the new concept of mitochondrial energy-based medicine, which also provides insight into the evolution of the vertebrates, the unified movement of mammals, and the mechanism of the immune system. After that the author developed new therapeutic methods for the complete curing of the three different kinds of intractable maladies through treatment of intracellular infection as well as controlling environmental energy. The "intractable maladies", which are conventionally accepted as being quite different, are induced by essentially the same cause: intracellular infections by nonpathogenic and/or feebly virulent enteromicrobes due to absorbing improper environmental energies. These bring about serious deterioration of mitochondria in the cells of the infected organ. Successful therapy is discussed. These maladies can be completely cured, if treated in time.

Keywords: diagnosis *ex juvantibus*, energy metabolism, evolution, gravity, hypophysis, intermediary matter, intracellular infection, intractable maladies, mitochondrial deterioration, ontogeny, pathology, phylogeny, quantum physics, terrestrialization, thermodynamics

1. INTRODUCTION: THREE CATEGORIES OF INTRACTABLE MALADIES, THE ENERGY CONSERVATION LAW AND THE DEFINITION OF LIFE IN MULTICELLULAR ANIMALS

In today's medical science, human beings have the urgent need to address three categories of intractable maladies, viz., immune diseases, cancers, and mental illness, whose aetiologies remain mostly unknown. As a result, prevention and complete cure treatment methods for these maladies are still not available. Robert Mayer, a medical doctor, proposed the energy conservation law in 1842. Later on, the law developed into "the mass and energy conservation law," as the special principle of relativity formulated by Einstein in 1905. This law now represents a commonly held view of the world or universe in scientific circles. However, conventional medicine and life science are still based on the mass conservation law, and the above-mentioned maladies are believed to be quite different kinds of disease. However, the author previously pointed out that these three ostensibly different kinds of maladies occur in patients in advanced countries, whose habitual lifestyle and behaviour are quite similar. Most habits and lifestyles mean accepting

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and consuming environmental energy and biomechanical energy. Conventionally, the concept of energy (environmental energy and biomechanical energy evoked by the animal's own movement, as well as mitochondrial energy metabolism, which is essential for life phenomena at the cellular level) are completely overlooked. The author is convinced that if the concept of energy is introduced into the aetiologies of these maladies, clues to the unknown causes of these three categories of disease will be easily discovered. From the standpoint of the mass and energy conservation law, it is certain that all substances with mass are ultimately constructed with elementary particles. From the viewpoint of quantum theory, substances with mass and energy are, ultimately, equivalent; and the entities correlating substance with mass to energy are elementary particles.

The concept of energy—environmental energy, the energy metabolism of mitochondria and the biomechanical energy of animal behaviour—are almost completely forgotten in today's medicine. Introducing these three categories of the energy system into life science and medicine, the author has established mitochondrial energy-based bioscience and energy-based medicine.

Note that life has not yet been scientifically defined even in the 21st century. Introducing the energy concept into life science, the author defines eukaryotic life as follows: life is a hydrocolloid of organic substances, i.e., nucleotides, proteins, carbohydrates, lipids etc. with various kinds of minerals, encapsulated by phospholipid membranes in which a part of or the whole structure remodels itself by means of energy metabolism via mitochondria. Consequently, this organic system can overcome aging by the renewal of tissues or cells; that is, decreasing entropy by remodelling. Therefore, remodelling concomitant with energy metabolism is indissociable from life (Nishihara, 2004a).

2. CHARACTERISTICS OF VERTEBRATE ANIMALS

A common characteristic of animals is movement—somatic locomotive and visceral gut movements, which are 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 palaeontology and the principles of comparative anatomy. He proposed empirically: (1) the principle of subordination; and (2) the principle of correlation, stating that "Animals move and live with unity and have each a complete system. Animals can move with objective behaviour, with harmony, because of their many organs they can move with a chain reaction and react with each other" (Cuvier, 1812).

There are five major correlating systems among organs in animals. The first is derived from the biomechanics of animal movement under the influence of Earth's gravity, all of which is converted into hydrodynamic energy concomitant with streaming potential in the system of lympho and blood vessels, which triggers gene expression of mesenchymal cells (Nishihara, 1998); the second is the somatic locomotive neuromuscular system with the sensory organs; the third is represented by the visceral gut movement of the neuromuscular system of the digestive absorbing system; the fourth comprises the cardiovascular and lymphovascular systems with the erythrocyte blood system and the leukocyte remodelling system of the major histocompatibility antigen complex (MHC) or human leukocyte antigen (HLA) (Nishihara, 2004b); the fifth is the direct controlling system of energy metabolism of mitochondria in whole cells in animals by means of the hypophysis–systemic hormone system (Nishihara, 2006). Vertebrate animals with the visceral gut muscular system as well as the somatomuscular system have sensory organs and, using them, the animal controls the gut peristaltic system of eating, mastication, respiration, digestion, vermiculation and absorption as well as somatic muscle movement and reproduction. The neuromuscular system can be divided into two major systems, namely the somatomuscular–cerebro sensory organ 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. By these systems, animals can move, live, and change morphological form physiologically. Through the respiratory as well as the digestive gut system, not only oxygen and nutrition but also toxins and parasitic microbes are absorbed into the bloodstream from the gut; hormones and cytokines secreted from glands into the bloodstream can be delivered to all 6×10^{13} cells in the body. By means of the lymphovascular system, nutrient supply as well as the invasion of parasitic microbes in the central nervous system, and the remodelling of aged, tumour and intracellularly infected cells in the mammalian body (MHC is involved) are carried out.

Through these five mammalian characteristic systems, animals can live, utilizing both the energy without mass of the cosmos (sunlight and 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 system of incorporation of oxygen and nutrients into circulating body fluids as well as through the hypophysis–systemic hormonal system, the direct control system of energy metabolism in all cells, including the organ and tissue correlation system

(Cuvier's principle of correlated movement of animals), is accomplished (Nishihara, 2006).

3. BASIC CONSTRUCTION (SIMPLE UNIFIED SYSTEM) OF MAMMALIA AND FUNCTION OF MITOCHONDRIA

Adult eutheria, multicellular mammalia, have *circa* 6×10^{13} cells and many specialized organs and structures; with their complicated correlating functions they can move as if constructed from a single cell, like protozoa. The fertilized oösperm divides into multiple cells, develops into complicated gastulura, branchilura, neurura, and embryos. No scientist in the 21st century has apparently 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 2×10^{12} cells to an adult with 6×10^{13} cells with a close correlation, systemically, and a coöperating system among tissue cells and organs, which are themselves constructed from enormous numbers of cells.

First of all the multicellular human body acts as a whole, systemically, as if it were a single-cell organism (protozoan). Second, prokaryotic bacteria cannot form a multicellular organism; only eukaryotes with mitochondria can develop into a multicellular creature, implying that mitochondria have the essentially important function to enable the development of multicellular animals (Nishihara, 2006).[2] If environmental energy as well as cell respiration (viz., mitochondrial energy metabolism) and the biomechanical energy of animal movement are introduced to life science and therapeutic medicine, thereby establishing mitochondrial energy-based medicine, then all of today's medical challenges are easily and completely resolved. Consequently, dynamic medical research as well as investigations concerning the quantum mechanics of energy and elementary particles at the subcellular level have to be carried out instead of the cellular pathology established by Virchow 150 years ago, which is still the main diagnostic procedure for therapeutic medicine, only observing optically visible morphological changes; that is, trace-observation in organ cells during morbid state development at the cellular level.

4. THE CELL RESPIRATION SYSTEM AND THE STIMULUS-ACCEPTING SYSTEM

The system directly influencing mitochondria is first of all the hypophysis–suprarenal glands system, which supervises the energy metabolism of mitochondria by means of the cardiovascular circulation system in all the cells of animals. The factors influencing energy metabolism of mitochondria in whole living animal cells are:

(1) energy (viz., stimuli of heat and cold), pressure, moisture, light (electromagnetic waves), sound, radioactivity, gravity and electricity;
(2) nutrition, minerals, vitamins, water, oxygen (viz., substances with mass);
(3) toxic substances;
(4) parasitic microbes (viz., bacteria, mycoplasma and viruses);
(5) incompatible transfusions or transplants;
(6) biological energy such as mind, belief, consciousness, spirituality and biological stresses (Nishihara, 2010).

In conventional medicine, in Selye's stress theory, stressors included microbial infections. However, in recent therapeutics for intractable immune diseases, bacterial infections are overlooked. For actual animal life, stressors include not only energetic as well as nutritional shortcomings but also toxins, bacteria and viruses (viz., substance with mass). Selye's conventional stress theory overlooked energy (e.g., dynamic force, gravitational energy, muscle movement and environmental energy). The hypophysis–suprarenal glands system has to include the all-integrated absorption and acceptor systems of not only energy, but also of nutrition as well as viruses, bacteria and toxic substances.

The gut system is the absorbing acceptor system of both energy and substance with mass, and absorption is effected by the blood circulation of the cardiovascular system. There are three parts: (1) the branchial respiratory gut; (2) the digestive tract; and (3) the excretory tract, namely the genito–urinary system. This gut–absorbing system accomplishes cellular remodelling in the whole animal body. There are two remodelling systems: the growth and renewal system (by means of the blood erythrocyte system); and the cell membrane destructive remodelling system of leukocytes, which is operated by the MHC. The former is cellular metabolism and remodelling in aged cells and the latter is destructive remodelling of tumour cells, intracellularly infected cells and transplanted incompatible tissue or organ cells by means of the membrane detector of MHC or HLA (Nishihara, 2004a). All nutrition, minerals, vitamins, oxygen, as well as viruses, bacteria and toxic substances are received and absorbed into blood or leukocytes and delivered to almost all cells via the blood and lympho streams.

[2] The present author has pointed out that with conventional research methods it is difficult or impossible to disclose the mechanism of vertebrate evolution, or the principle of correlated movement of animals, or aetiological causes of intractable maladies.

When the temperature in the gut (including the throat) becomes lower than 36 °C, microbes are absorbed in the M stem cells of Peyer's patch, which change into granulocytes. The granulocytes containing microbes disseminate their microbes into other cells if the body temperature is lower than 36 °C. Consequently, bacterial or viral contamination of all cells of various organs occurs. This gives rise to the intracellular infection of organ or tissue cells by nonpathogenic enteroviruses or bacteria and mycoplasma. If intracellular infection occurs in some organ, the function of the organ cells deteriorates because of the mitochondrial dysfunction caused by contaminated bacteria or viruses. This is an immune disease (Nishihara, 2004a).

The widely accepted Selye stress theory is an incomplete hypothesis because it overlooks not only energies but also the cellular remodelling system as well as intracellular infection of the cells in the organism. The initial stage of intractable immune diseases starts from intracellular contamination of the hypophysis through Waldeyer lympho adenoid tissue or gut-associated lymphoid tissue absorbing leukocytes, enterobacteria or viruses, or by mouth breathing or by cooling the gut. After that, dysfunction in secreting adrenocorticotropic hormone takes place, and intracellular infection in various organ or tissue cells occurs. This is the cause of intractable immune diseases. Selye's stress theory is actually completely subsumed by the energy conservation law (Nishihara, 2006). The mechanism of the hypophysis–systemic hormone system as the direct control system of cellular energy metabolism of mitochondria in whole cells in the animal body is the immune system. The immune facility is actually remodelling capacity conjugated with energy metabolism. Therefore, the hypophysis–systemic hormone 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 energy stimuli and substances with mass, including bacteria (Nishihara, 2007a; 2009a; 2010).

5. THE HYPOPHYSIS (SYSTEMIC HORMONE SYSTEM): AN INTERMEDIARY ORGAN OF THE MAJOR TWO SYSTEMS CONTROLLING LIFE ACTIVITY

In the mammalian body, there are two major informational systems, namely the visceral gut system of substance information via physical media and the stimulus information via the system of brain neurotransmission. Both integrate into an intermediary organ, the hypophysis, in conjugation with the cardiovascular system. Both information systems function as the humoral information system for mitochondrial respiration. The anterior lobe of the hypophysis is derived at the pharyngula in late embryo stage from the mucosa of the primordial oral cavity, which represents the whole gut, controlling visceral gut function. It has no blood–brain barrier. The visceral substance information system functions by means of the absorbing system of the gut (digestive tract) including the lungs, by which nutrition, oxygen, water as well as toxins and even bacteria and viruses are absorbed into the bloodstream of the portal vein around the gut. Consequently, via the bloodstream all absorbed matter flows into the hypophysis portal vein. On the other side all stimuli via sensory organs as well as through somato–visceral sensory nerves are gathered through reticular formation in the brainstem into the neurons of the nuclei of the thalamus and hypothalamus in the limbic system; that is, the diencephalon of the visceral brain. Almost all informational stimuli though the sensory organ systems as well as the visceral gut neural system ultimately gather together into the neurons of the nuclei of the thalamus and hypothalamus. There, all stimuli are converted into hormones, cytokines, growth factors and neurotransmitters. These then flow gradually through axons into the portal vein in the hypophysis. All this stimuli-converted humoral informational matter is gathered and secreted into the portal vein and endocrine gland cells in the anterior lobe of the hypophysis. Here in the portal vein nutrition and oxygen as well as contaminated granulocytes from the gut system mingle with humoral informational matter from the neurons of the cerebral system (Nishihara, 2009a). The mingled blood containing humoral informational matter is delivered to all cells for the respiration of all mitochondria, including those of brain neural cells. Also, granulocytes contaminated by enteromicrobes in this mingled blood enter into the cerebrospinal fluid, whence microbes are disseminated into various sites of the brain.

The posterior lobe has been derived from the diencephalon. Therefore, the hypophysis is a go-between informational organ of the brain (i.e., the stimulus information system and the visceral gut system—the substantial information system via the cardiovascular medium system (Nishihara, 2010)). The hypophysis is constructed with endocrine cells connecting with the axis of neurons in the thalamus and hypothalamus on the one side and continuing to its portal vein on the other side, through which informative cytokines and hormones as well as oxygen and nutrition, microbes and even toxic matter are delivered to all mitochondria.

From the viewpoint of mitochondrial energy-based medicine, the renewal system concomitant with cellular respiration is the antimalady system, which overcomes cellular deterioration via aging as well as intracellular infection through remodelling (Nishihara, 2010). Not only the cerebral brain system but also the visceral gut

immune system both have the antimalady system, namely the cellular renewal system via the subcellular level of mitochondria. All cells have the same chromosomes in their nuclei as well as the same mitochondrial chromosomes at the initial division stage of stem cells. Therefore, all cells in the whole animal body, regardless of their nature, fall into a morbid condition when exposed to the six influencing factors (§4) from which their mitochondria suffer. Consequently, the function and remodelling of the cells deteriorate. This is a malady condition at the subcellular level, which can occur in all cells. Knowledge of the immune system is not appropriate to understand maladies from the viewpoint of mitochondrial energy-based medicine. Instead, the life-remodelling system concomitant with cellular respiration or conjugated with mitochondrial energy metabolism are appropriate.

The function of the visceral gut system is to incorporate substance with mass (i.e., nutrition including oxygen and water from the environment) into the creature's cardiovascular blood-circulating system via the gut system of respiration as well as digesting food and drink. Almost all nutrition is absorbed from the mucous membrane of the intestine through the portal vein system via the liver into the heart. After that the blood full of nutrients and oxygen circulates through the *arteria carotis interna* to the *supra-hypophysis arteria* into the portal hypophysis vein, into which informative matter derived from the endocrine gland cells of the hypophysis as well as from neurons of nuclei in the limbic system directly are passed, and delivered via venous blood into the cytoplasma of all cells.

6. HYPOTHESIS CONCERNING THE NATURE OF INTRACTABLE IMMUNE DISEASES

The author has hypothesized that intractable immune diseases are not autoimmune diseases but severe cases of opportunistic infections or autotoxic diseases due to enterobacterial infection (Nishihara, 2007a; 2009a). These diseases are brought about by intracellular infection in various tissues or organs by means of infected granulocytes through Waldeyer's lympho–adenoid tissue, by mouth breathing, as well as through GALT (gut-associated lymphoid tissue) and cooling the gut with cold drinks. Due to the intracellular infection, deterioration of mitochondria in infected organ cells occurs, resulting in a disturbance of the specific function of the cells. Therefore, at the cellular level, immune diseases take place due to the deterioration of mitochondria (Nishihara, 2007a).

About 50 years ago, opportunistic infection in adult patients and autotoxic diseases in infants or children in advanced countries took place even after a slight case of the common cold. These were inapparent infections by nonpathogenic common enteromicrobes of the patient's own gut. At the same time in severe cases such as infectious granulomatosis, histiocytosis X, histiogranulomatosis, lymphogranulomatosis and sarcoidosis were often observed in university hospitals in Japan. At that time the causes of the latter severe cases were completely unknown and thought to be infections by unknown pathogenic microbes. The author now considers that these maladies were only severe cases of opportunistic infection, namely infections via common enteromicrobes (bacteria and/or viruses) in the mouth, throat and/or gut, of patients who did not get enough sleep or rest (Nishihara, 2007a).

In 1972, when Japan started the relief funds measure for incurable diseases, the concepts of opportunistic infections and autotoxic diseases via common enteromicrobes were denied and forgotten. At this stage these diseases were called intractable immune diseases or autoimmune diseases and the causes were believed to be unknown or some allergy or revolting leukocytes. After that, synthetic steroid hormones were commonly used for intractable diseases. Consequently histiocytosis X or granulomatosis have disappeared; through using steroid hormones, these maladies change to simple histiocytosis (granulocytosis). Especially, after self/not-self immunology was conceived, these maladies were believed to be autoimmune diseases brought about by rebellious leukocytes. However, the author disclosed that, for example, in a case of ulcerative colitis, tremendous so-called "rebellious leukocytes", which attack submucous tissue cells in the large intestine, were actually tremendous numbers of granulocytes, which were severely contaminated by the patient's own nonpathogenic enteromicrobes intracellularly via mouth breathing as well as cold drinks or ice cream intoxication and which disseminated these enteromicrobes into submucous tissue cells in the gut (Nishihara, 2007b). Consequently, severe intracellular infection by nonpathogenic common enteromicrobes took place in all cells of the large intestine. Even with common enteromicrobes without pathogenicity, severe contamination all over the gut, viz., of epithelial cells as well as mucous gland and submucous membrane tissue cells, takes place. Consequently almost all mitochondria in the gut cells deteriorate and ulcerative infectious inflammation occurs. This process reveals the real nature of ulcerative colitis. Scientifically, leukocytes never rebel but react with some substance or microbes automatically, because all cells have simply the reactive system based on energy metabolism, which is controlled by electron transfer. "Rebellious leukocytes" are a fiction; self/not-self immunology is pseudoscience. Hence, "intractable" maladies can never be cured via therapeutic methods of self/not-self immunology. From the viewpoint of science life phenomena are simply supported as automatic reactions by electron dynamics and biomechanics. The author has instead

proposed genuine clinical immunology by which "intractable" maladies are completely cured if treated in time (Nishihara, 2009a).

7. CELLULAR PATHOLOGY, FUNCTIONAL DISEASES AND DISCLOSURE OF INTRACELLULAR PATHOGENESIS

In conventional medicine today, most organic diseases are diagnosed, categorized and treated via cellular pathology, established by Virchow in the 19th century and based on microscopic observation of morphological changes in diseased organ cells. Conventionally, most maladies are categorized pathologically as deformities, injuries, inflammations, infections, cysts, tumours (benign and malignant) and "the others", easily. The intractable maladies and physiological deformities are investigated here, except cancers belonging to "the others" or functional diseases, which show no marked change in cellular pathology by autopsy. The functional diseases are deformities (physiological) and immune diseases, cancers and mental illness. They exhibit no marked cellular morphology in pathological findings, but show functional disturbance of cells or morphological skeletal deformities (Nishihara, 1992b; 2004c). Nevertheless, conventional medical research methods for intractable maladies have been only by morphological studies of diseased organ cells via biopsies, the method of which was established by Virchow. Pathology was established to treat the morbid conditions of diseases or to determine the essential nature of structural and functional changes in organ cells caused by disease (Mihatsch, 2009). However, through observing morphological cellular changes in diseased organs, no causes could be found indicating mechanisms of disease. During the past hundred years, humans apparently never adequately considered the causes of maladies at the subcellular level but only partial causes were considered; for example, pathogenic microbes, malnutrition, hormonal deficiency or chronic tiredness.

Life is the remodelling system conjugated with energy metabolism and this is supported completely by tremendous numbers of mitochondria. Mitochondrial deterioration presages functional disturbances of cells. Disease at the intracellular level is a definitely deteriorated condition of the mitochondria. Therefore, it is enough to consider the causes of mitochondrial deterioration in order to disclose the causes of intractable maladies (Nishihara, 2010)—see the list of six factors in §4.

To find out the aetiological cause and mechanism of these maladies is quite difficult by conventional medical research methods. They can never be found by means of cooperation with each specialist in medical science in conventional branches or divisions of pathology, physiology, molecular biology, pharmacology, virology and bacteriology. Because of the dearth of concepts for environmental energy, energy metabolism of mitochondria and biomechanical energy of animal movement, the causes and aetiology of intractable diseases can not be easily discovered. Treatment of the four kinds of functional diseases; that is, physiological deformities, immune diseases, cancer and mental illness; is quite difficult even in advanced countries. Also, concerning intractable diseases the phrase "immune diseases and immune system" is inadequate because maladies occur not only by pathogenic as well as nonpathogenic microbes but also by energy or malnutrition, toxic substances and so on. This phrase belongs to the age of contagious diseases of Koch, Pasteur and Kitasato. In addition, self/not-self immunology is a completely mistaken concept. In its place the author established genuine clinical immunology to treat intractable immune diseases effectively (Nishihara, 2009c).

8. CONVENTIONAL CONCEPT OF MIND (BRAIN)–BODY (IMMUNE SYSTEM) INTERACTION AND THE OVERALL MITOCHONDRIAL CONTROLLING SYSTEMS IN MAMMALS

The symptoms of diseases are almost same in spite of different causes. For example, deficiency of vitamins, coenzymes and/or minerals (malnutrition) or exposure to agricultural chemicals induce the deterioration of mitochondria in neurons, the symptoms of which are quite the same as those of Parkinson's disease, which is often triggered by intracellular infection of neurons via herpes viruses (enterovirus) with low virulency. The word "immune" or "immunity" is strictly restricted to infectious diseases or organ transplantation problems because of immune phenomena; that is, antigen–antibody reactions occur between leukocytes and microbes with acquired immunity via antibodies or between leukocytes and transplanted organ cells with cellular immunity via the MHC of leukocytes.

To overcome intractable maladies scientifically and completely, we have to change the concept of immunology to medical therapeutics at the subcellular level (mitochondrial energy-based medicine) because mitochondria are essential organelles in cellular life. "Immunology" goes back to the age of epidemic diseases of pestilence in the 19th century. We have to change the idea of resisting maladies through immunity to the cellular remodelling system in conjunction with cellular respiration of mitochondrial energy metabolism. The age of contagious diseases and the age of infectious diseases by pathogenic microbes were already over *ca* 50 years ago. Now only intracellular infections by common enteromicrobes remain as diseases caused by unknown origin, which have been known as opportunistic infections for 50 years.

E.M. Sternberg, in her publication "The Balance Within" (Sternberg, 2001), wrote about the science

connecting health and emotion, mind/body interaction and stress (i.e., interaction of endocrine and immune systems, brain–immune connexions)—the brain and the immune system communicate emotions and disease; the immune system talks to the brain and the brain talks back. Just like Sternberg's descriptions in conventional medicine, researchers consider the brain and visceral immune system are quite different. Using the words and phrases health, emotion, mind, stress, endocrine, immune system and brain system presage unscientific conceptual confusions because concepts like emotion, mind and health represent functional conditions of the whole body (including its 6×10^{13} cells).

Moreover, Sternberg overlooked the fact that the brain is constructed with some 10^{12} neurons, which carry out cellular respiration concomitant with remodelling in conjunction with mitochondrial energy metabolism as well as reproduction of mitochondria themselves. Brain neurons themselves easily fall into a malady condition via intracellular infections. She never defines what the immune system is and therefore could not understand mental illness to be one of the immune diseases that occurs by intracellular infection in cerebral neurons. 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 mammals are the suprarenal glands, which are themselves 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. This is the most important system in mammals. The accepting apparatus for these hypophysis–suprarenal gland systems are whole sensory organs of the somatic system as well as the whole gut visceral system via the epithelial body, the thymus, Waldeyer's lympho–adenoid rings and gut-associated lymphoid tissue (GALT). This system was disclosed as Selye's stress theory (Selye, 1937). He was convinced that the major immune responses of animals are carried out by the hypophysis–suprarenal gland system. However, Selye did not know that the hypophysis and suprarenal glands are acceptors of various kinds of stimuli. (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, just like Sternberg, because the hypophysis is a part of the limbic system of the cerebrum. However, the immune system is a digestive system at the cellular level as well as a remodelling 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 feature and all neurons in the central nervous system have a cellular remodelling system. Therefore, the hypophysis is a stimulus-converting system of the brain, into which total information from environmental circumstances are gathered via sensors in the body (Nishihara, 2006).

All stimuli affecting animals, whether energy or substances (e.g., cold or heat, neural and physicochemical, nutritional, toxic, bacterial and parasitic stimuli, as well as psychological stresses) are accepted through two ways into the hypophysis: (1) via sensory organs; and (2) via the visceral system. By the first way the stimuli are transmitted to the nuclei in the thalamus and hypothalamus. By the second way substances with mass are transmitted via the cardiovascular system through the hypophysis, epiphysis and choroid plexus, which are composed of ependymal cells and pia matter (in which there are no blood–brain barriers) through the nervous system to the thalamus into the hypothalamus. There, in the neurons of the nuclei of the limbic system neural stimuli are then converted into hormones, cytokines and growth factors, which constitute the direct control system of intracellular respiration of mitochondria in all cells. They are carried through the axon to the portal vein in the anterior lobe of the hypophysis and are delivered to all systemic hormonal organs. Concomitantly, the informational substances (hormones, cytokines, neurotransmitters and growth factors as well as nutrition) are delivered over the whole body to all mitochondria. This is the hypophysis–systemic hormonal system. All metabolism based on cellular respiration in cells, each having 800 ~ 3000 mitochondria, is directly controlled by the humoral information system of hormones, cytokines, growth factors, nutrition, and toxins as well as parasitic microbes (Nishihara, 2010).

9. SPACE–TIME, SUBSTANCE WITH MASS AND FORCE, LIGHT, GRAVITY, AND THERMODYNAMICS: THE QUINTESSENCE AND THE GRAVITY EVOLUTIONARY THEORY

9.1 Life and gravity energy

The embryogenic tooth germ and eye germ are histologically precisely the same. The eye is a sensor for electromagnetic waves (light energy) and the tooth is a sensing apparatus for substance with mass; that is, for energy in the form of hydrodynamic waves during prehension, mastication, and crushing food (i.e., dynamic force action under gravitational energy) (Nishihara, 2004b,d). Prokaryote or eukaryote protozoa can live indefinitely in a gravitational field 10000 *g* but multicellular vertebrata cannot live even for one day in 7 *g*. All biomedical forces as well as gravity in animals

are converted into fluid movement with hydrodynamic potential energy (blood pressure), just like the ebb and flow of the tide caused by the Moon's gravity. Converted fluid movement of medium (i.e., blood and lympho fluid dynamic flow) provide concomitant streaming potentials, which trigger gene expression in mesenchymal stem cells. Consequently, skeletal tissue remodelling take place by biomechanical repeated movement (Nishihara, 1996a; 1997a,b; 1999a,b). In conventional bioscience this point is completely overlooked.

Multicellular vertebrate animals have sensory organs for visible light. Not only retinal cells in the eyes but also ectodermal cutaneous epithelial cells can register light energy. Energy can trigger gene expression of nuclei as well as mitochondria. In conventional bioscience the phenomenon of gene expression via energy is merely known as photosynthesis (when light strikes plants). The present author verified gene expression occurring by biomechanical repeated stimuli (energy), which are converted into streaming potential, during developmental experiments with artificial bone marrow chambers (Nishihara, Ref. Group A: 1994a; 1996a; 1997a,b; 1998) as well as the development of the gompholic artificial root (Nishihara, Ref. Group B: 1989; 1991a,b,c; 1992a,b; 1993; 1994b; 1995; 2003a).

Thermal energy also triggers gene expression of nuclei as well as mitochondria. What are the differences between cold-blooded (poikilothermic) animals and warm-blooded (homeothermic) animals? Generally, blood pressure of the former is lower than that of the latter. Blood pressure is directly related to gravity action. On the contrary, gravity influences animals only via the circulating media of bloodstream and lymphofluid (via the cardiovascular system as potential energy). Therefore, monocellular organisms or cultured mammalian cells without a cardiovascular system can live at 10000 *g*. To the organism of monocellular bacteria as well as protozoa, which are tiny pieces of matter governed by a Reynolds number < 1, gravity has no effect because the viscosity of water is far stronger than the action of gravity. Therefore, gravity strictly influences blood pressure in multicellular animals. No one else seems to have noticed this.

Cold-blooded means a low metabolic rate at the cellular level. The most characteristic difference of cold-blooded animals is in the genome size of the nuclear chromosomes. The lungfish have the largest genome size among the vertebrates, viz., 30 times larger than that of the mammals.

Poikilothermic animals have their characteristic gut system, through which enterobacteria and viruses are absorbed into leukocytes and these contaminated leukocytes circulate in whole body, disseminating microbes all over the body. Consequently, all whole cells in body are completely contaminated intracellularly and genes of contaminating bacteria and viruses enter into the chromosomes of cells in the lungfish as "junk" genes. Mammals and birds have evolved via cold-blooded animals; therefore, if they cool the gut, the system of cold-blooded animals starts to operate—enteromicrobes contaminate leukocytes, which change into granulocytes circulating all over the body, disseminating enteromicrobes into various tissue or organ cells. Thus, intracellular infection of nonpathogenic enteromicrobes occurs. Bringing enteromicrobes into leukocytes in the gut of cold-blooded animals is also a gene expression phenomenon of the leukocytes (Nishihara, Ref. Group A: 1994a; 1996a; 1997a,b; 1998; 2003a. Ref. Group B: 1989; 1991a,b,c; 1992a,b; 1993; 1994b; 1995).

9.2 Energy and substance with mass

Here, we have to consider the correlation between energy, force and substance with mass. The cosmos quintessentially comprises (1) space, (2) time and (3) light (electromagnetic waves) and gravity—these three are closely connected via relativity theory—(4) substance with mass and force, and (5) thermodynamic energy, which rules over the other four. All substances have the universal gravitational force or attraction. This is the law of gravitation in the cosmos disclosed by Newton. The present author has disclosed what gravitational energy is with respect to living creatures as follows: gravitational (attraction) force is one essence that is provided in massy substances and exclusively belongs to substances and acts only on substances with mass. Therefore, if they lose mass they simultaneously lose their gravitational force (Nishihara, 2007a). It does not act in the ambit pertaining to electromagnetic energy (i.e., light). In the ultimate condition, a substance with mass is in equilibrium with energy; for example, in a high temperature plasma, in which mass is converted into light energy. However, at that instant, plasma loses its attractive force (i.e., gravitation). 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 violent 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 –273.15 °C (absolute zero). Velocity of light is dependent upon temperature; below –273 °C (i.e., near absolute zero) the velocity of light falls to 17 m/s (Lene Vestergaard Han, 1999).

9.3 Intermediary go-between matter between substance with mass and energy

The mass and energy conservation law is now a common-sense view of the universe in scientific circles. However, no one points out the intermediary go-between matter between substance with mass and energy without mass (light; i.e., the energy of electromagnetic waves). Max Planck presented his thesis that energy levels were quantized, which originally came through his work in thermodynamics; de Broglie conceived matter waves (the union of waves and particles in a concrete fashion, i.e., the particle being a localized object incorporated into the structure of propagating waves, sometimes thought of as a pilot wave); Boltzmann assumed that gases consist of molecules and treated their behaviour using statistical methods in thermodynamics. Also, Einstein proposed the hypothesis that light is a stream of particles, or quanta (Aczel, 2001); Newton had a similar concept of light as corpuscles. Every small particle in the universe is associated with a wave propagating through space, both of which are go-between matter between energy and substance with mass. The concepts of quantum mechanics, viz., pilot wave, atom and electron, elementary particle and various kinds of energy all represent intermediary go-between matter between substance with mass and energy without mass (Nishihara, 2011).

Why does the velocity of light change at temperatures near absolute zero? Light scatters in every direction after emission; the velocity of light or electrons multiplied by time yields space and space is eternally constant. Light, space and time are trilateral forms of energy. The increased speed of electrons at temperatures near absolute zero is a phenomenon of superconductivity. These phenomena at temperatures close to absolute zero are not only one side of the genuine relativity law but also another side of the energy conservation law of the cosmos (Nishihara, 2009c). At temperatures near absolute zero, the span corresponding to 1 s at normal temperatures becomes so elongated that it equals *ca* $3 \times 10^8/17 = 204$ days. Therefore, the superconductivity phenomenon of electrons discovered by Kamerlingh Onnes (1911) confirms the principle of Einstein's relativity theory. (In contrast, Einstein explained superconductivity as a Bose–Einstein condensate.)

The principle of the invariance of light velocity introduced by Einstein is incorrect. Another error of modern physics is the concept of light velocity acceleration by means of a high-speed moving rocket. All dynamic forms of energy such as velocity, inertia and gravity belong to substances with mass. The three kinds of energy, light (i.e., electromagnetic waves), space and time, have an exclusive trilateral relationship with relativity. These three can never separate or divide and are closely related to the relativity principle through the laws of thermodynamics (Nishihara, 2010).

As mentioned earlier, gravitational energy exclusively acts on substances with mass, never on light, time and space (viz., the constructive energy principle of the cosmos) (Nishihara 2010). From this principle there is no existence of so-called black holes in the universe but a spot where the temperature is near absolute zero, at which the light velocity falls close to zero. Therefore, in 1881, A.A. Michelson's famous experiment of the acceleration velocity of light with the Earth, which moves with a rather high speed (30 km/s) in its orbit, naturally revealed no effect. He believed light emitting from a star moving at speed of light changes its wave velocity. Surely, waves of light change not in velocity but in wavelength only (the Doppler effect). Substance with mass and energy have different dimensions. Therefore, in the famous parable of Einstein of a train or rocket moving at near the speed of light, naturally no acceleration of the velocity of light occurred. Both light and sound display not only interference and resonance phenomena, but also the Doppler effect because they are waves, i.e., energy without mass. Therefore, the velocity of light can never be changed by the fast-moving Earth (Michelson) or a rocket or train (Einstein), just like the velocity of sound can never be accelerated by supersonic jets (Nishihara, 2009c). A Mach 3 jet fighter far exceeds sonic velocity, therefore an impulsive wave of a great detonating sound trails behind long after the aircraft has passed.

To recapitulate, electromagnetic radiation, light and sound are waves and waves are energy without mass. Waves from running matter change not the velocity of the wave but the wavelength. This is the Doppler effect. The velocity of light can change due to thermodynamic conditions (ultralow temperature or ultrahigh pressure) and/or in substance with mass (Cherenkov radiation). All massy substances emit light when heated but not a perfect vacuum even under strongest energy condition. However, light radiation takes place concomitant with losing mass. But gravity does not act on light energy although a light beam is concomitant with matter losing mass.

Black holes are a rather dubious concept (Nishihara, 2009c). R. Feynman remarked that "Most of the phenomena you are familiar with involve the interaction of light and electrons—all of chemistry and biology, for example. The only phenomena that are not covered by this theory are the phenomenon of gravitation and nuclear phenomena; everything else is contained in this theory" (Feynman, 1983). Therefore, gravitation is out of the dispensation of quantum mechanics but in thermodynamics. In addition, multicellular animals live under the action of gravity; however, gravitation works in

animals after conversion through hydrodynamics into streaming potential via animal movement (Nishihara, 1999b).

10. BIOMECHANICAL ENERGY AND SUBSTANCE WITH MASS TRIGGERING GENE EXPRESSION AND THE MECHANISM OF EVOLUTION IN THE SECOND REVOLUTION OF VERTEBRATES—TERRESTRIALIZATION

The author has developed an artificial bone marrow chamber using bioactive sintered hydroxyapatite, as well as a hybrid-type gompholic artificial dental root with a fibrous joint system (Nishihara, Ref. Groups A & B). This fibrous articulation tissue concomitant with osteogenesis and haemopoietic bone marrow cells can be induced by means of activating gene expression of mesenchymal cells via the biomechanical energy of rhythmical hydrodynamic movement in the animal body, which is concomitantly converted into streaming potential. By this developmental research, the present author disclosed that, under gravity, the energy of biomechanical movement that is concomitantly converted into streaming potential can trigger gene expression of undifferentiated mesenchymal cells (Nishihara, 1994a). At that stage, the author recognized that in modern medicine and life science there are still so many blind spots concerning energy. Also, the author understood perfectly why mechanisms of vertebrate evolution and mechanisms of unified systems of animals constructed with $\sim 6 \times 10^{13}$ cells and the causes of intractable maladies have yet to be disclosed. Therefore, if energy without mass is introduced as an inducing factor of evolution, and as a cause of the unified working of mammals and of human intractable maladies, a breakthrough in stagnant life science and modern medicine could certainly be achieved.

Mammals utilize for their life system energy without mass as well as substances with mass, equivalently under the energy conservation law. The origin of the life system began initially from absorbing energy, after that it started absorbing nutrition, oxygen and minerals, namely substance with mass, concomitantly. Therefore, the higher mammals have the absorbing system of energy and food, namely substance without mass as well as with mass. We call the former "sensors" or "receptors" and the latter "the gut absorbing system," which is a receptor (absorber) for substance with mass; the sensors are mostly receptors for stimuli of energy, both of which can trigger gene expression in mesenchymal cells. The functions of most sensors depend upon gene expression via energy triggering of sensory organ cells (Nishihara, 2006).

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, environmental energy, biogenetic energy generated via mitochondria and molecular genetics concerning remodelling with biomechanical energies (Nishihara, 1998). The author has also devised an experimental evolutionary study method that applies trilateral research to work at every phylogenetic stage representing evolution (Nishihara et al., 1996). From these studies the author has tried to reinterpret Lamarck's use and disuse theory (1809), Haeckel's biogenetic law (1866 and Alberch, 1994) and Wolff's law (1870), with the current level of science via unifying biomechanics and molecular biology. Following that, the author carried out research on the basic construction of mammals from the viewpoint of gravity influencing evolution (Nishihara, 2003b). The present author interprets the metamorphosis of animals' skeletal morphology in evolution to be due to biomechanical characteristics of bone and cartilage, which define vertebrate animals, and which are dually controlled—firstly by the hard-information system of inheritance (i.e., genes, DNA) and secondly by long-term habitual behaviour (constant usage of skeletal organs), which is the soft-information system according to Lamark's use and disuse theory (Nishihara, 1999a).

Another great issue in vertebrate evolution is metamorphosis during the second vertebrate revolution (i.e., terrestrialization). The author has verified Haeckel's Biogenetic Law, viz., "Ontogeny recapitulates phylogeny" at the dramatic metamorphosis stage of pharyngula by means of experimental evolutionary study method using archetype vertebrate chondrichuthyes of the dog shark (*Heterodontus japonicus*), which the present author has discovered is the real ancestor of mammals. The dog shark was artificially landed one hour every day for 10 days, after that the author observed metamorphosis of its brachial system and could compared the precise rôles of biomechanical as well as physicochemical factors influencing the transformation of organ cells. Actually, the following eight phylogenetic changes are repeated in mammalian ontogeny:

1. Morphology; the skeletal system, the viscero–cranial system, the somato–muscle system, the genito–urinary system are repeated;
2. Energy metabolism system;
3. Bone marrow haemopoietic system;
4. Nervous system;
5. Cardiovascular circulation system;
6. External gut respiration system;
7. Cytological immune system via MHC;
8. Hereditary and cytological gene expression system.

At the same time, from thinking of phylogenesis as well as ontogenesis, the author disclosed that the central nervous system, the gut visceral muscle system, the somatoskeletal

muscle system, and the cardiovascular muscle system (viz., the sole neural system and the three muscular systems) are concomitantly developing tetralaterally. In ontogeny the morphogenesis of the embryo is closely concomitant tetralaterally and never separated independently. Drastic changes in morphology as well as function of external respiratory organs occur from the gill to the lung as well as from the gill–haemopoietic organs to the endocrine glands. Naturally, metamorphoses in ontogeny are all based on the transformation of cells constructing tissues or organs. In the initial stage of stem cell division, nucleic genes in the cytoplasma all have the genetic information of the individual creature. Therefore, by metaplasia all kinds of organ cells can be induced from undifferentiated mesenchymal stem cells by some stimuli. During terrestrialization, a drastic change of the medium surrounding the animal from water to air occurs. In conventional evolutionary studies no one considered these environmental changes to be physicochemical stimulating factors inducing transformation of organs or tissues at the cellular level. Changing the medium from water to air means drastic changes of environmental factors, influencing the various kinds of cells that construct tissues or organs. These factors are the following (Nishihara, 1998):

1. During landing gravity increases sixfold from 1/6 *g* in water (due to the effect of buoyancy) to 1 *g*;
2. Water pressure becomes the pressure of one atmosphere;
3. Oxygen content of less than 1% in seawater increases to 21% in air;
4. Salt concentration of 3.5% in sea water becomes zero in air;
5. Temperature extremes of –2 ~ +40 °C in seawater increase to –70 ~ +60 °C in air;
6. Water density (0.999 g cm^{-3}) falls to 0.00123 (air), i.e., 1/800;
7. Viscosity 0.0114 g cm^{-1} s^{-1} (water) falls to 0.00018 (air), i.e., 1/60;
8. Thermal capacity—4.18 J g^{-1} K^{-1} of water falls to 1 in air, i.e. about one third;
9. Electrical conductivity—a good conductor (seawater) to a nonconductor (air);
10. The velocity of sound falls from 1500 m s^{-1} in water to 340 in air.

Consequently, the organ cells that accept or absorb these physicochemical stimuli must change into different phenotypes. What is the action of a sixfold increased gravitational force on animals? Gravity in animals acts strictly in blood and lympho fluid. Under sixfold increased gravity landing sharks (chondrichthyes) wriggle around to find water, after that the shark's blood pressure and streaming potential increase. Thereafter, sharks can survive landing. By the enhanced hydrodynamics and streaming potential gene expression of stem cells in mesenchymal tissue in the skeletal organ are triggered. Then evolutionary metamorphosis can occur. All the 6×10^{13} cells in the body (except erythrocytes) have genes to differentiate into all kinds of organ or tissue cells, just like stem cells. Evolutionary change of morphology occurs via long-term repeated biomechanical stimuli, which are converted in the creature into streaming potentials, by which gene expression of mesenchymal cells take place and remodelling of skeletal bone and muscle occurs according to Wolff's law (a restricted version of Lamarck's use and disuse theory). Metamorphoses in cells of branchial organs, the eardrum (tympanum), the lung, thymus, thyroid, parathyroid and lympho–adenoid organs take place via transformation of cells, in which gene expression of organ or tissue cells considered as metaplasia is triggered by physiochemical stimuli due to a drastic change of environmental factors. The present author disclosed evolutionary phenomena in vertebrates to have two kinds of mechanisms: (1) gene expression via streaming potential, which results from biomechanical energy; and (2) gene expression of specific organ or tissue cells by means of metaplasia via energy as well as chemical substances (e.g., heat shock and cold shock, oxygen or hormones, cytokines, and growth factors) (Nishihara, 1997b; 1999a,b; 2000; 2001; 2003b; 2004b,d).

11. CORRELATION BETWEEN SUBSTANCE WITH MASS AND ENERGY, PRINCIPLE OF BIORESONANCE FOR DIAGNOSES VIA THE BI-DIGITAL O-RING TEST, AND INTRACTABLE IMMUNE DISEASES

11.1 Principle of bioresonance

All substances with mass are ultimately constructed with elementary particles. From the standpoint of quantum theory, substances with mass and energy are ultimately equivalent. At the same time, from the standpoint of quantum mechanics, the matter that correlates substance with mass to energy (without mass), is elementary particles or electrons. In other words, the intermediary matter that goes between energy and substance with mass is electrons or other elementary particles (Nishihara, 1999b). Analogously in mammalian cells, the matter that correlates and interacts with animal organelles at the subcellular level to environmental substance or energy is mitochondria, which have in all cells essential functions of the electron transfer system conjugated with oxidative phosphorylation (Nishihara, 2008a). The mitochondrial electron transfer system shows bioresonance phenomena with elementary particles or electron spin of environmental substances or energy. Let

us consider the interaction between animal life and substance with mass at the intracellular level (viz., nutrition, oxygen, water, minerals and vitamins, toxins, antiviral agents and other medicines and living microbes (bacteria or viruses)). Life phenomena are sustained by cellular respiration (i.e., the energy metabolism of mitochondria). Without sound mitochondrial function no vital activity occurs. Animal life at the subcellular level and substance with mass exhibit *bioresonance phenomena*, detectable with the Bi-Digital O-Ring Test (Omura, 1981). The principle of bioresonance comprises the following 6 items:

1. Animal exhibit the characteristics of movement. In animals, neurons develop concomitantly with muscle cells. In animals without muscle there are no neurons, and without neurons, no muscle. The brain and spine develop conjugated with muscles;
2. In living cells, mitochondria engender the functioning current of the electron transfer system of oxidative phosphorylation;
3. Substances have electron spin and this spin and mitochondrial current in cerebral neurons exhibit resonance phenomena;
4. In intracellularly infected cells, the mitochondrial functions of the electron transfer system are disturbed;
5. Mitochondrial dysfunction results in the deterioration of cell function. The intracellularly infected organ cells can be easily detected from the bioresonance system due to functional defects of their mitochondria;
6. All cells composing somato–visceral organs, except blood cells, have connexions with cerebral neurons by means of not only the neuro–muscular but also the capillary and autonomic nervous system, and the resonance of mitochondria in neurons is reflected by the strength of somato muscle contractions (Nishihara, 2007b, 08a).

11.2 Diagnosis of intractable immune diseases via the Bi-Digital O-Ring Test and the meaning of immunity

In civilized progressive countries there are many functional maladies, the causes of which are vague and unclear according to modern medicine based on cellular pathology.

The author previously disclosed that these intractable maladies are brought about by the deterioration of mitochondria in morbid-invaded cells, which in turn is caused by the 6 items listed in §11.1. The cause of a malady can be established by anamnesis or precise observation of the patient, or via the Bi-Digital O-ring Test. The intractable maladies are what the author calls three kinds of pathological morbid conditions, i.e., immune diseases, carcinoma and mental illness. In conventional medicine these three are believed to be quite different types of maladies. However, the present author has revealed that they are all brought about by intracellular infection via common enteromicrobes without pathogenicity.

The immune diseases involve immunity, antigenic microbes, antibodies, antigen-antibody reactions and immunology. The word "immune" means being highly resistant to a disease because of the formation of humoral antibodies or the development of cellular immunity following an antigenic challenge, and "immunity" means security against a particular disease, nonsusceptibility to the invasive or pathogenic effect of foreign micro-organisms or to the toxic effect of antigenic substances. From the meaning of immune and immunity, immune diseases are strictly restricted to diseases induced by foreign microörganisms. However, in conventional medicine, it has been misunderstood that all pathogenic microörganisms as antigens necessarily induce antibodies and they respond to each other as an antigen–antibody reaction resulting in precipitation. But actually there are no diseases in the world (e.g., smallpox, cholera, anthrax, diphtheria) that are so strongly toxic that almost no patients can recover before they get antibodies induced in their serum. Therefore, instead of human pathogenic viruses, cattle smallpox viruses as well as viruses with artificially lowered virulence are used to make vaccines in animals for human use. Besides them, against the protozoa of malaria, *Treponema pallidum*, gonococcus, mycoplasma, *E. coli*, streptococcus, staphylococcus, rickettsia, dysentery bacillus, and common enteromicrobes (virus and bacteria) almost no antibodies develop. Especially, nonpathogenic common enteromicrobes, which infect intracellularly into organ cells, generate no marked antibodies but antinuclear antigens, antiphospholipid antigens or C-reactive protein (CRP) in serum. In conventional immunology these facts have been overlooked. Many maladies are triggered not only through unfavourable environmental energy, but also by nonpathogenic enteromicrobes, which are disseminated into tissues or organ cells intracellularly. In case of these maladies no marked antibody inducement occurs (Nishihara, 2007b; 2008a; 2009b,c). Therefore, there is no way to cure these immune maladies by conventional immunological methods.

12. RESEARCH INTO MAJOR CAUSES OF MITOCHONDRIAL MUTATION BY MEANS OF MOLECULAR BIOLOGY

As already mentioned, mitochondria are the most important organelles in the mammalian life system. Therefore, to disclose the cause of mitochondrial mutation and/or deterioration is today's urgent issue. It is well known that also in diseases such as alcoholism,

cancer and infection by rickettsia and viruses, mitochondrial mutation, mitochondrial disorder, mitochondrial dysfunction and mitochondrial abnormality (morphological disorder) are observed in infected cells. In today's clinical medicine, not only in mitochondrial diseases but in various immune diseases, mitochondrial mutations are commonly reported. The causes of these mutations are considered to be free radicals of oxygen generated during the mitochondrial function of oxidative phosphorylation. However, the author is skeptical about this concept of mutation; about 40 years ago he successfully defended his PhD thesis "Disclosure of Major Causes of Mitochondrial Mutation Using Yeast by Means of Molecular Biology". As this research is so important today, therefore the three parts of the thesis have been recently published (Nishihara, 2008b,c,d). The following is a summary of these three parts.

Part 1. To disclose the mechanism of mitochondrial mutation, their deformities and deterioration in diseased cells, the author carried out following model experiments using yeast (*Saccharomyces cerevisiae*): (1) Experiment for development of respiration-deficient strain using inhibitor of protein synthesis of cytoplasma (cycloheximide), of mitochondria (chloramphenicol) and of others, in culture; (2) Measurement of activities of mitochondrial DNA and RNA synthesis *in vitro* during development of respiration-deficient strain using an inhibitor of protein synthesis in culture.

Part 2. The interaction between nuclei and mitochondrial genes during development of mitochondria. To disclose the developmental mechanism of mitochondrial mutants the author carried out molecular biology experiments using wild strains of yeast and several respiration-deficient strains of different genotypes, in which the synthesis of DNA polymerase and RNA polymerase of mitochondria was observed *in vitro*.

Part 3. Mitochondrial genes. Observation of the activities of yeast mitochondrial ATPase with the administration of cycloheximide. From these experiments the author concluded that petite mutant (i.e., a respiration-deficient mutant) can be developed by an inhibitor not of mitochondrial but nucleic–cytoplasmic protein synthesis, which would disturb mitochondrial DNA polymerase as well as RNA polymerase synthesis in the cytoplasm. From the above results, the developmental mechanism of mitochondrial mutation was investigated to be a disturbance of mitochondrial DNA and RNA polymerase via cycloheximide. A possible interpretation of the above results is that coupling factor F_1 (ATPase) is controlled by mitochondrial genes, and that its genetic information is translated by the protein synthesis system of mitochondria. By disclosing the functions of mitochondrial genetic information, it is anticipated that clues will be obtained to differentiate whether morphological transformation of mitochondria in diseased or cancer cells is derived by the disturbance of the synthesis of DNA polymerase and RNA polymerase of mitochondria, which are encoded in nuclear genes. From these model experiments using yeast, one of the causes of respiration-deficient mutants was disclosed to be a disturbance of DNA polymerase as well as RNA polymerase of mitochondria.

Tremendous numbers of intracellularly infected nonpathogenic enterobacteria or viruses would induce a severe disturbance of protein synthesis in cytoplasma, comparable in effect to cycloheximide (Nishihara, 2009a). The author proposes that the major cause of intractable immune diseases and mental illness is mitochondrial deterioration due to entangled complicated intracellular contamination of low virulent pathogenic as well as nonpathogenic common enteromicrobes such as viruses, mycoplasma, ricketia, chlamydia and/or bacteria in various organ cells and neurons (Nishihara, 2008a,b,c,d).

13. ANALYSIS OF DETAILED MITOCHONDRIAL FUNCTIONS IN MULTICELLULAR ANIMALS

Mitochondria are believed to be parasitic archetypical bacteria incorporated into eukaryotic cells *ca* 2 milliard years ago. In all specifically differentiated cells except matured erythrocytes, mitochondria, viz., bacteria-like organelles with haploid genes in the cytoplasma of multicellular mammals, play an essential rôle for unified individual systems (organisms) constructed with 6×10^{13} cells. Mitochondria have multiple functions in specifically differentiated cells; several common general functions as well as special functions: (1) Mitochondria reproduce by themselves in the cytoplasma via mitosis, during which interval mitochondria stop energy generation; (2) Respiration, viz., energy generation for the needs of living cells by oxidation of organic compounds with molecular oxygen and the liberation of free energy. The mitochondria have highly ordered arrays of enzymes for the citric acid cycle, electron transport, fatty acid oxidation, and oxidative phosphorylation, by which respiration is accomplished. The mitochondria receive from cytoplasm oxidizable substrates, such as pyruvic or fatty acids, oxygen, ADP, and P_i (inorganic phosphorus), then a group of enzymes catalyses a series of consecutive transformations of these substrates, resulting in complete oxidation to CO_2 and H_2O. The electrons removed from the substrates during these oxidations flow through an organized arrangement of electron carriers, from the lowest to the highest potential, and thence to oxygen. In the course of this electron flow, much of the free energy thus made available is trapped by concurrent synthesis of ATP, the common form of energy utilizable in the endergonic processes of living cells. Thus substrates,

oxygen, ADP and P_i enter the mitochondrion, and CO_2, H_2O, and ATP as well as wasted metabolites leave it; (3) Specific information-bearing cytokines, porphyrins, haemoproteins, all hormones (including steroid hormones) are synthesized via mitochondrial function in conjunction with the nucleic gene information system. All specific cytokines (e.g., neurotransmitters in neurons or insulin in Langerhan's islets) are generated by the mitochondria inside specifically differentiated cells; (4) All kinds of gene expression of nucleic genes in the cytoplasma necessitate *de novo* synthesis of energy via mitochondria; (5) During embryogenic metamorphosis as well as evolutionary change based on metaplasia of cells and the biomechanics-based metamorphosis system (i.e., the remodelling system via streaming potential) mitochondria play an essential rôle, inducing several kinds of cytokines and growth factors in cytoplasma to develop trilaterally, i.e., the muscles and neurons as well as the cardiovascular system (Nishihara, 2010); (6) Mitochondria control cell differentiation, cell division and remodelling as well as proliferation, in conjunction with the negative feedback regulation system during growth (Nishihara, 2010); (7) Mitochondria control tremendous numbers of cells, unifying them as an integrated unit via inducing the secretion of growth factors, hormones and cytokines; (8) Mitochondria control cell apoptosis. Integrating the aforementioned various functions, mitochondria work in each cell in multicellular mammals just like humans in nations. The various organs are analogous to states or prefectures. Each cell, which has thousands of mitochondria, is like a united community. From the standpoint of reverse systems engineering, in the unified multicellular human body there exist intracellularly tiny homunculi. In the 19th century scholars tried to argue that homunculi really live inside human body cells and determine their behaviour. The present author reveals these homunculi to be the mitochondria in cell cytoplasma (Nishihara, 2010).

14. CHANGING DIAGNOSIS FROM CELLULAR TO SUBCELLULAR LEVEL, DISCLOSURE OF THE CAUSES OF IMMUNE DISEASES AND THE ESTABLISHMENT OF NEW THERAPEUTICS

14.1 Changing diagnosis from cellular to subcellular level

Since 50 years ago, when the age of organic diseases was over, diagnoses of organic diseases by means of cellular pathology via Virchow have ended. Instead of overcoming organic diseases, intractable maladies (viz., functional diseases) are now in vogue. Intractable immune maladies including cancer and mental illness can now be diagnosed accurately not by the cellular morphology of a morbid organ but by the subcellular function of mitochondria. How is the function of mitochondria in cells diagnosed? Conventional diagnoses by biopsy using microscopy or by X-ray photos or CT scans are all carried out by observing deformity of the cellular configuration or organ transformation from a standard shape (i.e., morphology). However, morphological figures exhibit no function, but only traces of constructive cellular shape in morbid organs. As already mentioned above, all substances with mass are ultimately constructed with elementary particles. From the standpoint of quantum theory, substance with mass and energy are ultimately equivalent. Mitochondrial function in diseased organ cells in patients can be detected via the Bi-Digital O-Ring Test (cf. §11). Appropriate images of patients may reveal their body cell's information including bacterial contamination. By means of the Bi-Digital O-Ring Test, the present author has established a new concept for diagnosis, viz., mitochondrial energy-based medicine, which is based on quantum entanglement phenomena (Nishihara, 2009c).

14.2 Disclosure of causes of immune diseases and establishment of new therapeutics

The present author has confirmed from clinical research that cooling the gut by just 1 °C down from 37 °C, intracellular infection by nonpathogenic common enteromicrobes into leukocytes occurs via M-cells in Peyer's patch, which develop into granulocytes. Granulocytes contaminated with numerous bacteria or viruses circulate in the whole body, disseminating microbes into various organ cells, resulting in intracellular infection of these organs. The author hypothesizes that these intractable immune diseases are not autoimmune diseases but severe cases of formally accepted opportunistic infections, which are caused by intracellular infection of one's own common nonpathogenic enteromicrobes (Nishihara, 2006). These intracellular infections deteriorate as well as mutate mitochondria, and result in functional disturbances of specialized organs, which appear as immune diseases. The author hypothesizes that human-specific intractable immune diseases are severe cases of opportunistic infections or autotoxic diseases caused by intracellular infection of common nonpathogenic enterobacteria and/or enteroviruses as a result of lifestyle changes. The author also hypothesizes that by intracellular infection of common enterobacteria and/or enteroviruses, mitochondrial deterioration and mutation takes place. With this hypothesis and understanding, the author established the mitochondria activating therapeutic method (MATM) to cure those diseases by means of prevention and recovery from intracellular infections in conjunction with nose breathing during sleep as well as warming the gut, resting the bones by lying down, moderate eating and drinking with optimal mastication,

treating periodontitis, optimal exposure to sunshine by sunbathing, and by administering suitable bifidus factors, effective antiviral agents as well as antibiotics (Nishihara, 2009a). By these remedies (i.e., collectively MATM) intracellularly infecting microbes are controlled, then mitochondrial mutation and/or deterioration easily recover and specific functions of special organ cells are restored completely. In most of the cases, the patients who had been diagnosed with intractable immune diseases in conventional hospitals showed evident recovery by these new curative methods. By the complete cures of intractable immune diseases, namely complete recovery of deteriorated mitochondria in diseased cells via MATM, the author's hypothesis is verified as diagnosis *ex juvantibus*; that is, diagnosis based on the results of treatment (Nishihara, 2009a). If intracellular infection occurs in some organ, the function of the cells of the organ deteriorates because of the dysfunction of their mitochondria caused by contaminating bacteria or viruses. These intracellular parasites hinder the energy metabolism of mitochondria, leading to deterioration of organ function and to the so-called intractable immune diseases, which are a hindrance to cellular renewal (remodelling), which is coupled with the energy metabolism of mitochondria. Intracellular contamination of specially differentiated cells (e.g., neurons or hormonal glands) by parasitic microbes of the gut, regardless of being aerobic or anaerobic, disturb the specialized function of mitochondria. This is the immune disease condition at the subcellular (i.e., intracellular) level (Nishihara, 2004).

15. GREAT MEDICAL DISCOVERIES: DISCLOSURE OF THE AETIOLOGY OF THREE MAJOR INTRACTABLE MALADIES

Conventionally, immune diseases, carcinomas and mental illness are considered to be quite different kinds of diseases. It is well known that special bacteria or viruses induce carcinoma in some cases, but the causes of most cancers remain unknown. Concerning psychiatric diseases no one thinks about causes rooted in orthodox medical science and complicated therapies have been applied since the time of S. Freud. Ten years ago the present author started a thorough clinical treatment of intracellular maladies from the standpoint of energy-based "stomato–facial and neuro–cranial medicine", which the author had previously established. In contemporary Japan too many patients suffer from atopic dermatitis, cancers and intractable immune diseases as well as mental illness. Especially, severe atopic dermatitis with severe schizophrenia have been observed. In many cases inflammatory granuloma are mistakenly diagnosed as carcinomas through using CT scans or NMR combined with cellular pathology diagnosis. Whether a malignant tumour is real or not can be easily detected by means of the Bi-Digital O-Ring Test.

Some 20 years ago the author had a very unique case of a 74-year-old male with severe periodontitis. He was referred from the internal medicine haematological division of a university hospital in Tokyo, where he was being treated with anticancer therapy under the diagnoses of chronic myelotic leukaemia, dementia and severe dermatitis. Severe carcinoma-resembling periodontitis was detected by a biopsy to be severe inflammation as a pathological diagnosis. The author told the patient to remove these teeth, whereupon he became very scared. Thereafter, the author understood his dementia was a mistaken diagnosis in the haematologic division. After removal of all remaining teeth, the patient's dermatitis as well as the so-called dementia and hyperleukocytosis disappeared completely. After that, the diagnosis was changed to be osteomyelodisplasia in the haematological division.

Since this case 20 years ago, the author realized that psychiatric disorder and atopic dermatitis as well as leukemia (cancer of hemopoietic organs; i.e., malignant tumors) were three major maladies that can be induced by severe complex infection by common enterobacteria or viruses. This mistakenly diagnosed leukaemia could never be differentiated by Virchow's cellular pathology in Japan at the time. However, the author could diagnose it by clinical symptoms such as plain inflammation of the gums, namely benign hyperleukocytosis via ultrasevere gingivitis. However, in the case of malignant carcinoma of hemopoietic organs (i.e., real leukaemia), the patient who has such a serious inflammation as ultrasevere gingivitis in any part of the body will die in two or three days after an attack of leukaemia because of deteriorated myoblasts without digestion of bacteria. But in the case of leukocytosis via such severe inflammation (periodontitis) he would never die even taking the maximum dose of anticancer agents.

The author restricts the phrase "immune system" as follows: the immune system is the antimalady as well as the remodelling system of each living but aged cell, which is concomitant with the energy metabolism of mitochondria, namely the cellular respiration system, including the cellular digestive system; that is, phagocytes of not only nutrition, oxygen and toxic matter but also inter- or intracellularly infected microbes. Therefore, the neural brain system and somato–visceral immune system are other facets of the same unified system for cellular remodelling and respiration in the whole 6×10^{13} cells, where the go-between functions are carried out via the cardiovascular blood–lympho system as well as via the hypophysis systemic hormone system (Nishihara, 2010). From this

standpoint as well as from the above-mentioned case the author has hypothesized, verified and disclosed three major intractable maladies of immune disease, carcinoma and mental illness to be almost the same opportunistic infections, which are brought about via intracellular infection with nonpathogenic common enteromicrobes.

Thus, in 1960 the age of infectious diseases caused by pathogenic microbes ended and a new age of opportunistic infections induced by nonpathogenic common enteromicrobes began. From the viewpoint of bacteriology or virology, studies on pathogenic microbes have been vigorously undertaken; they have characteristic toxins or pathogenicity. On the other hand, researchers had no interest in nonpathogenic common enteromicrobes. No one knows about their characteristics in bacteriology or virology, nor their antigenicity in immunology. At the present time in progressive countries serious medical issues are: (1) health disturbances due to drastic changes in today's lifestyle regarding environmental energy; that is, cooling the gut, bone rest shortage via short sleeping time, and mouth breathing via too much speaking; (2) newly developed but mistaken therapeutic methods using synthetic steroid hormones for severe types of opportunistic infections—a reflexion of "progress" in the biochemical and pharmaceutical industries; (3) establishment of the mistaken concept of self/not-self immunology and the consequent practice of mistaken therapy for immune diseases, cancer and mental illness; (4) a complete overlooking of gravity, thermal and biomechanical energy; (5) overlooking intracellular infection by nonpathogenic indigenous enteromicrobes, which can be commonly observed in leukocytes as granulocytosis, by which means these enteromicrobes are disseminated into various tissue or organ cells; (6) incorrect research methods of cellular pathology to disclose the causes of functional diseases at the subcellular and energy levels.

In the age of maladies caused by pathogenic microbes, diagnosis for aetiology and treatment of organic diseases was adequate with the cellular pathology established by Virchow. However, diagnosis for aetiology and treatment of functional maladies, i.e., immune diseases, physiological deformities (e.g., maldentition, malfunction of joints, and facial deformities), carcinomas and mental illness is quite difficult via cellular pathology. Functional diseases are induced by energy imbalance as well as by deterioration of cellular facilities, which are strictly based on mitochondrial functions. Mitochondrial deterioration is brought about by the aforementioned six items, i.e., toxins, malnutrition, environmental energy, pathogenic or nonpathogenic microbes and so on. The present author disclosed that these major intractable maladies all have the same aetiological origins of intracellular infection by nonpathogenic common enteromicrobes via the newly developed research methods of mitochondrial energy-based medicine (Nishihara, 2008a). Pathological conditions (maladies at subcellular level) are due to mitochondrial deterioration and the causes are limited only by the six aforementioned items. Therefore, the aetiological factors can be detected by anamnesis—asking about lifestyle, common inspection and surveillance by the Bi-Digital O-Ring Test. After detection of aetiological factors including energy, patients are treated by means of MATM, viz., effective nutrition, minerals, antibiotics, antiviral agents, environmental energy remedies and antitoxin agents as well as the remedy of correcting a mistaken lifestyle and behaviour in an integrated manner. From the author's clinical research to cure these maladies, three kinds of intractable diseases present the same morbid condition at the subcellular level; that is, the same deteriorated condition of mitochondria with three type of characteristic differences, namely immune diseases, carcinomas and mental illness. They are all caused by intracellular infection of the respective organ cells via nonpathogenic common enteromicrobes, by which deterioration of mitochondria occur.

Characteristic differences in the three maladies are as follows: (1) Intractable immune diseases—common immune diseases are induced via common intracellular infection in various tissues of organ cells (except brain neurons), in which their mitochondrial function is deteriorated, with consequent disturbance of specific cell functions due to lack of the specific cytokines that their mitochondria generate; (2) Carcinomas—these maladies are induced via mode-specific intracellular infection in various tissue or organ cells including brain neurons, in which intracellular infection of multiple viruses and bacterial contamination occurs, resulting in mitochondrial deterioration, by which collapse of the negative feedback regulation system of cell division as well as of proliferation and remodelling is brought about; (3) Mental illness—these diseases are organ (brain)-specific immune diseases in which intracellular infections occur in various parts of the cerebral neurons; e.g., (a) in the visceral brain, i.e., the limbic system; (b) in the reticular formation of the brainstem, i.e., pons and medulla oblongata, viz., the branchyal brain; or (c) in cerebellum neurons.

The symptoms and kind of the disease are decided by the site of intracellularly infected neurons. Often intracellular infection occurs concomitantly in all three parts.

16. DISCLOSURE OF ENTITIES OF THREE KINDS OF MALADIES VIA MITOCHONDRIAL ENERGY-BASED MEDICINE—PRECISE INTERPRETATION OF THE THREE KINDS

16.1 Common intractable immune diseases

These diseases are mostly human specific maladies, which *ca* 50 years ago have been known as opportunistic infections in various tissue or organs of the body resulting from chronic cold syndrome with severe fatigue. The opportunistic infections of organs at the cellular level (i.e., cellular pathology) are intracellular infections by nonpathogenic common enteromicrobes (e.g., mycoplasma, chlamydia, rickettsia and herpes or enteroviruses). These three kinds of bacteria can only proliferate intracellularly, just like viruses. As bacteria living inside cytoplasma use oxygen as well as minerals, vitamins and nutrients, consequent deficiency for protein synthesis in the cytoplasm occurs. Then mitochondrial deterioration as well as tentative mutation occurs because of a shortage or failure in syntheses of enzymes of mitochondrial DNA and RNA polymerase, which are controlled by nucleic genes in the cytoplasm. Specific functions of infected organ cells are disturbed. This is an immune disease condition at the subcellular (i.e., mitochondrial) level (Nishihara, 2007a). The immune diseases are separated into the following two groups: (1) those that occur in various tissues or organs in the whole human body *except* the brain and bone marrow haemopoietic nests in the joint system; (2) those that occur in bone marrow haemopoietic nests in the joint system.

16.2 Entities of common immune diseases occurring in various tissues or organs except for brain and bone marrow

The entities are as follows:

- Intracellular infection (abbreviated I.I.) of cartilage cells constituting synovial joints—rheumatism.
- I.I. of subcutaneous connective tissue cells—atopic dermatitis.
- I.I. of pancreas: in the case of Langerhans islet—diabetes mellitus, in the case of corpus pancreas—granulomatosis or pancreatitis.
- Interstitial pneumonia—I.I. of pulmonary as well as tracheal epithelial and stromal cells.
- Ulcerative colitis—I.I. of total mucous and villiferous epithelia of the colon.
- Crohn's disease—I.I. of mucous and villi epithelia of the total gut system.
- Retinosis, glaucoma, uveitis—I.I. of retina, uvea and ciliary body.
- Otitis, impaired hearing and tinnitus—I.I. of auditory organ cells.
- SLE, collagen diseases—I.I. of systemic cutaneous, subcutaneous and connective tissue cells as well as reticuloendothelial cells.
- Endometriosis—I.I. of endometrium.
- Hepatitis—I.I. of hepatic parenchymal cells.
- Nephritis, nephrosis and IgA nephrosis—I.I. of cells of glomerulus and mesangium.
- Asthma, bronchitis and pulmonary emphysema—I.I. of throat lympho adenoid tissue, bronchus and pulmonary epithelial cells.
- Schörgren and Behcet's diseases—I.I. of lacrimal gland, sweat gland, salivary gland cells and oral mucosal cells.
- Myasthenia gravis—I.I. of thymus parenchymal cells as well as the systemic somato muscle system.
- ALS (amyotrophic lateral sclerosis) and fibromyalgia—I.I. of the spinal nervous system conjunction with the systemic somato muscle system.

16.3 Immune diseases occurring in bone marrow haemopoiesis in the joint system

Intracellular infection in bone marrow hemopoietic stem cells easily occur via cooling the gut by ice cream intoxication or oral breathing habits and/or bone rest shortage by short sleeping. The cardiovascular vessel systems including haemopoiesis as well as the lymphoadenoid haemopoietic system are the most important intermediary go-between system of the gut and neural systems having various kinds of functions in the whole body. Therefore, once intracellular contamination occurs in the stem cells of haemopoietic nests, the haematological symptoms and disease names are legion. The therapeutic methods are the same as for common immune diseases. The following diseases occur (intracellular infection of the bone marrow haemopoietic stem cells in the joint system as well as the lymphoadenoid hemopoietic system): (1) purpura; (2) thrombocytopaenia; (3) pernicious anaemia; (4) leukocytopaenia; (5) hypoplastic anaemia; (6) leukaemia; (7) granulocytosis; (8) lymphocytosis; (9) malignant lymphoma; (10) bone marrow granuloma; (11) histiocytosis.

16.4 Carcinomas

A major cause of cancer is mode-specific intracellular infection via complicated non-pathogenic and/or pathogenic microbes in various organs or tissue cells, by which cell remodelling, division, and differentiation as well as the negative feedback regulation system of cell proliferation (viz., the important function of mitochondria in cell regeneration) are disturbed. In conventional medicine

metastasis in infectious diseases has been well documented (e.g., tuberculosis, syphilis and sarcoidosis, which are all intracellular infections (Nishihara, 2008a)). Mitochondrial deterioration due to complicated intracellular infections by several kinds of common enteromicrobes induces such severe injuries of the regulation mechanism of infected organ cells in differentiation so as to induce the proliferation of granulation tissue, just like tumours. The author has hypothesized that carcinomas are induced by deterioration of mitochondrial function affecting the negative feedback regulation system of cell proliferation via intracellularly contaminating numerous microbes. The author surveyed via the Bi-Digital O-Ring Test several patients suffering from cancer and diagnosed and treated in conventioned hospitals; e.g., cancer of glands, lungs, oesophagus, colon, pancreas, kidney and uterus; they were treated with MATM and effective medicines (e.g., antibiotics, and/or antiviral agents and dietary supplements). In many cases complete recovery was obtained, from which the author inferred that antibiotics stopped the activity of intracellularly contaminating bacteria, hence the deterioration of mutated mitochondria was reversed. It is well accepted that in cancer cells gene mutation usually occurs. However, the author is convinced that mutation takes place only in mitochondria; through curing intracellular infection with nonpathogenic microbes, general metabolism and protein synthesis in the cytoplasm should recover, then normalization of mitochondria occurs. In the author's experiments using yeast as aforementioned (§12), disturbance of protein synthesis in the cytoplasm by cycloheximide induces mitochondrial mutation, which disturbs protein synthesis of nuclear genes (Nishihara 2008b,c,d). Instead of cycloheximide, severe bacterial or viral contamination should easily induce mitochondrial mutation, but ceasing bacterial or viral activities in cytoplasma the mutation or dysfunction of mitochondria is easily recovered, because mitochondrial DNA polymerase is controlled and synthesized by nucleic genes in the cytoplasmic protein synthetic system.

As mentioned above, to recover the function of intracellularly infected cells the author has developed a new therapeutic way for activating emaciated mitochondria via MATM with thermal energy up to 38 °C ~ 42 °C and sunlight irradiation, both of which activate mitochondrial function, together with all kinds of deficient vitamins, minerals and co-enzymes as well as the three major nutrient classes (protein, lipids and carbohydrates) and amino acids, fatty acids, glycogen and lactic acid, along with water, oxygen and the minimal effective dose of antibiotics or antiviral agents. All this is effective to arrest living microbes in cytoplasma. The author applied this MATM to many cancer patients and had many cured cases. Therefore, this author's hypothesis of carcinogenesis by means of complicated intracellular infection via nonpathogenic and/or pathogenic microbes, which result in mitochondrial deterioration in the cell regeneration regulatory system, are verified as diagnosis *ex juvantibus*. If treated not too late, patients can be cured by MATM. Most anticancer medicines are effective upon the genes of the nuclei in the cytoplasma, not upon that of the mitochondria, therefore they arrest mostly carcinogenesis only but do not cure the maladies. When the author's MATM treatment coupled with surveillance by the Bi-Digital O-Ring Test and remedying environmental energy and the patient's wrong habitual behaviour resulted in complete recovery of the patient's cancer, then the causes of cancer are proved as diagnosis *ex juvantibus*. In other words, the causes of cancer are disclosed and the complete cure is evidence for the correctness of the hypotheses (Nishihara 2009a,b,c; 2010).

16.5 Mental illness

Mental illness is an immune disease caused by intracellular infection via common enteromicrobes restricted to neurons in the brain. As mentioned before, mitochondria in the specifically differentiated organ cells (neurons) have organ-specific functions of nerve cells; that is, the first is synthesis and secretion of neurotransmitters, the second is a regenerative remodelling of mitochondria, and the third is regeneration of the constructive parts of neurons and *de novo* synthesis of ATP for cellular metabolism. Via the intracellular infection of neurons, all of these various mitochondrial functions are disturbed. Among them, the most important is the secretion of neurotransmitters.

The brain is largely divided into three functional parts, viz., (1) the visceral cerebrum, namely the limbic system with hypophysis–diencephalon (interbrain) for the visceral gut muscle; (2) the branchial gut system—the cardiovascular–respiratory centre relating with the intermediary muscle of the somato–skeletal and visceral gut system, which is localized in the reticular formation in midbrain, pons, and medulla oblongata; and (3) the cerebrum sensory and muscle system, namely, the cerebral cortex of the sensory and somato–skeletal muscle system. In the case of intracellular infection of neurons in the limbic system (thalamus and hypothalamus), mental illness including psychosomatic disorders occurs. Mostly, neurons in the visceral brain and cerebral cortex are infected in conjunction with those of the reticular formation (Nishihara, 2005; 2009b; 2010).

16.6 Psychosomatic disorders concerning satiety, hunger, sleep and thermal centres of neurons in the limbic system

In the case of intracellular infection of the neurons of nuclei in the hypothalamus in the limbic system, the satiety, hunger, thermal and sleep centres are infected intracellularly. Then, psychosomatic disorder, which is accepted in modern medicine as an incomprehensible syndrome, occurs. Symptoms include: (1) hyperphagia (bulimia); (2) cibophobia; (3) anorexia nervosa; (4) insomnia; (5) aphrodisia; and (6) low body temperature. These all can be treated by antibiotics and/or antiviral agents combined with effective mineral and co-enzyme supplements as well as vitamins, and by remedies for environmental energy deficiencies; that is, bone rest shortage as well as cold drink intoxication and mouth breathing.

16.7 Psychosomatic disorders concerning the cardio-respiratory system

In case of infection of neurons in the reticular formation of the midbrain (i.e., branchyal brain), psychosomatic disorders concerning the lungs and heart occur. In this region infections in the nuclei of neurons for the respiratory system occur and in the cardiovascular system the disorder of respiration, cardiac dysfunction (i.e., hyperventilation syndrome) and panic disorder take place. Aetiology and therapy are all the same.

16.8 Migraines and major depression

In case of intracellular infection of neurons in the limbic system in conjunction with those of the branchial brain (in the reticular formation), early-stage migraine occurs, afterwards major depression takes place. In this area the serotoninergenic neurons as well as noradrenogenic neurons are intracellularly contaminated by nonpathogenic common enteromicrobes. Mostly chronic fatigue accompanies the other symptoms.

16.9 Intracellular infection of neurons in the cerebral cortex

(1) autism; (2) neurosis; (3) epilepsy; (4) dementia; (5) schizophrenia; (6) mitochondria encephalomyopathy; and (7) multiple sclerosis may occur.

The skin (cutaneous) cells and brain (neural) cells are both derived from the same ectoderm. Atopic dermatitis occurs by intracellular infection via common enteromicrobes through dissemination by contaminated granulocytes by means of the bloodstream; therefore, something quite resembling intracellular inflammation with atopic dermatitis easily takes place in the cerebral cortex. This type of slight case corresponds to neurosis and autism, and intracellular inflammation resembling "acne type" inflammation occurring in the brain cortex should correspond to epilepsy. Severe "atopic dermatitis-type" mental illness should be schizophrenia, which is concomitant with intracellular infection not only of nuclei of neurons of the limbic system but also of those of the reticular formation. In the reticular formation in the midbrain (branchial brain) there are five kinds of nuclei of neurons, viz., cholinergic, dopaminergic, serotoninergic, noradrenergic and adrenergic neurons, which have a reticular neural network in connexion with the cerebral cortex neurons. Mental illness takes place by intracellular infection in these five kinds of neurons through arterial suprahypophysis via contaminated granulocytes (leukocytes) into the anterior lobe of the hypophysis, which is derived from the oral mucosa and part of which is not genuine brain. Therefore, there is no blood–brain barrier, thus contaminated granulocytes enter into the brain–spinal liquor (lympho fluid) disseminating enteromicrobes into brain neurons. The localizations of neural cells in the brain are so complicated, and the functions of the brain are so complicated, therefore symptoms of mental illness are very convoluted.

16.10 Deranged neurotransmitters via contaminated microbes

Several kinds of biogenic amines (i.e., amino acids and their derivatives) play important rôles as neurotransmitters. Mitochondria (i.e., archaea-like parasites), having monoamine oxidase in them, oxidize biogenic amines as a neural cell function. In neurons of patients with mental illness, disorder in monoamine oxidases have been well known since *ca* 60 years. Amino acid metabolism is carried out easily and perfectly, not only by mitochondria but also by intracellularly infecting bacteria. Therefore, in microbe-contaminated neurons monoamine (e.g., tyrosine) metabolism (viz., oxidization) becomes deranged and the amount of the metabolites dopa, dopamine, noradrenaline and adrenaline increases or decreases. Thereafter, the neurotransmitter adrenaline can change into amphetamine or methamphetamine. These chemically changed substances are equivalent to stimulants inducing hallucinations, illusions and/or auditory hallucinations. The author has examined schizophrenic or depressive patients, as well as epilepsy patients, undergoing treatment in conventional mental hospitals, using the Bi-Digital O-Ring Test, disclosing contamination by nonpathogenic and/or low virulent enteromicrobes in the cerebral neurons. Following that, he administered minimal doses of effective antibiotics and/

or antiviral agents. Mostly, drastic improvements are obtained. Note that recent antipsychotics are inhibiting agents of reabsorption for receptors of dopa or dopamine, and the author's antimicrobial agents are effective for arresting bacterial activity, resulting in normalization of the amount of dopa or dopamine. A complete cure is mostly obtained, if treated in time.

In brain neurons, the major neural transmitters are acetylcholine, catecholamine (i.e., dopamine, DA), noradrenalin (NA), adrenalin (A), serotonin (SHT), aminobutyric acid and glutamic acid. These are all metabolized and oxidized not only by mitochondria but also by intracellularly contaminating bacteria. In intracellularly infected neurons, adrenaline or serotonin are oxidized by contaminated bacteria, then amphetamine or methamphetamine and LSD appear in the cytoplasm. In conventional psychiatric medicine apparently no one noticed intracellular infections by nonpathogenic microbes of brain neurons, which induce the derangement of neurotransmitters. No one thought of finding the causes of derangement, but researchers only recognized the increase or decrease and tried to normalize their amount by administering medicine. The author hypothesizes that the major cause of mental illness is intracellular infection of neural cells in the brain by common enteromicrobes without pathogenicity and/or those with low pathogenicity, which can enter by means of granulocytes containing nonpathogenic microbes from periodontitis directly or in the oral and pharyngeal cavities though Waldeyer's lymphoadenoid tissue via the suprahypophysis arteries into the portal vein of the anterior lobe of the hypophysis. In the clinic, the author surveys the patient's three parts of the brain by the Bi-Digital O-Ring Test, then administers effective antimicrobial agents. Consequent drastic recovery verifies the hypothesis. Intracellularly contaminating common enteromicrobes are quite easily controlled by minimal doses of antibiotics or antiviral agents (Nishihara, 2009c).

17. SUMMARIZING DISCUSSION

The author has disclosed the subcellular aetiologies of three kinds of intractable maladies as six factors inducing mitochondrial deterioration. These have been detected clinically during treatment from the precise observation of patients. Concerning the most important four out of the six: (1) Toxins inhibit the electron transmitting system of mitochondria immediately after administration (e.g. sarin, cyanide, carbon monoxide (CO) or agricultural organophosphorous compounds); (2) Malnutrition (e.g., complete deficiency of vitamins, co-enzymes, minerals and/or essential fatty acids as well as essential amino acids and carbohydrates); (3) Microbes, regardless whether pathogenic or nonpathogenic, especially as intracellular infection—disturb mitochondrial functions; (4) Environmental energy, especially gravity and temperature, is converted into blood pressure in higher vertebrates via hydrodynamics concomitant with streaming potential. Mitochondrial functions are strictly dependent upon environmental energy, optimal temperature as well as optimal blood pressure brought about by the struggling movement of animals against the increased effective gravity upon terrestrialization. Their functions strengthen at 38 °C to 39 °C but at 42 °C mitochondrial death occurs. At temperatures lower than 36 °C they diminish their energy-generating function. Energy as well as substance with mass can trigger gene expression of stem cells. Therefore energy can be the cause of disease—an aspect completely absent in conventional medicine.

Aczel (2001) explained the concept of quantum physics as follows: "The word itself, quantum, denotes a small packet of energy, a very small one. In quantum mechanics, we deal with the basic building blocks of matter, the constituent particles from which everything in the universe is made. These particles include atoms, molecules, neutrons, protons, electrons, quarks as well as photons, the basic units of light. At this level, suddenly, all the rules of behaviour with which we are familiar no longer hold. Entering this strange new world of the very small is an experience as baffling and bizarre as Alice's adventures in Wonderland." In this unreal quantum world, particles are waves, and waves are particles. A ray of light, therefore, is both an electromagnetic wave undulating through space, and a stream of tiny particles speeding toward the observer, in the sense that some quantum experiments or phenomena reveal the wave nature of light, while others reveal the particle nature of the same light—but never both aspects at the same time. And yet, before we observe a ray of light, it is both aspects at the same time; it is both a wave and a stream of particles.

For multicellular animals, the intermediary matter works on most sensory organ cells to induce gene expression of cellular chromosomes. In animals, only gravity and biomechanical energy function not directly but are converted into blood pressure providing fluid dynamics. Multicellular animals have two major information systems, viz., the energy information system of somato sensory organs (the cerebro–spinal–neuromuscular system) and substance with mass (the viscero–intestinal digestive and absorption system). Between these two major systems the hypophysis and the cardiovascular system act as the intermediary go-between organs and the system by which all energy stimuli are converted into humoral

information and all digested substances with mass are absorbed from the gut into the bloodstream. In animals substance with mass and energy work concomitantly together and sustain life phenomena.

In 1944 Schrödinger published his now rather well known book "*What is Life? The Physical Aspect of the Living Cell*", in which he proposed to establish molecular biology by means of the physicist's approach. He considered that the most characteristic phenomenon of life is heredity, but did not actually define "What is life?" and overlooked living energy metabolism in life, which is the most important phenomenon associated with it. He did not notice the fact that the essence of living phenomena is the system of remodelling, which is closely connected with energy metabolism; with that, the living system can overcome aging.

Some 50 years ago research on electron spin resonance started. After extensive work in this area, CT, especially X-ray tomography, NMR tomography and PET have been developed as excellent modern technologies. The results contain not only optical representations of organs but also information concerning microbes and minerals, as well as toxic substances and vitamin deficiencies. Large molecules also are waves with particle nature, hence can exhibit resonance and interference phenomena, which are exploited in the Bi-Digital O-Ring Test.

For 50 years the author has treated patients for all kinds of maladies. He remembers that before steroid hormones were commonly used, psoriasis and Vogt-Koyanagi-Harada disease (granulomatous uveitis with retinal detachment) were cured completely by penicillin. Before antibiotics were commonly used, it was often experienced that cancer patients with malignant tumours, suffering from erysipelas with severe high body temperature (39 °C) for a week, were able to recover concomitantly with the disappearance of the tumours. Today, for some kinds of malignant tumours, specific hormonal therapy is effective to treat cancer. These facts suggest that by activating mitochondria in tumour cells or immune cells patients can recover—by heat shocks of 39 °C and by solar irradiation as well as by some hormones.

Actually, the author has surveyed patients with malignant tumours as well as the other two maladies via the Bi-Digital O-Ring Test detecting intracellular infections of brain neurons by several kinds of common nonpathogenic enteroviruses or bacteria. Following that, he administered minimal doses of antiviral agents and several kinds of antibiotics with minimal doses, concomitant with solar irradiation and hot towel dressings as well as bone resting by sufficient sleeping (gravity releasing) and the complete conversion of mouth breathing to nose breathing during sleep. All of these treatments, which were mentioned before, activate mitochondria in intracellularly severely contaminated cytoplasma in diseased organ cells.

18. CONCLUSION

After overcoming epidemic maladies, contagious diseases and infectious diseases humans in civilized countries have suffered from three kinds of so-called intractable maladies; viz., immune diseases, carcinomas and mental illness, which have been considered for a long time to be quite different. The author developed a hybrid-type artificial skeletal supportive organ with the bone marrow haemopoietic system as well as with the fibrous joint system via inducing gene expression of stem cells by biomechanical hydrodynamic energy, which induces a concomitant streaming potential. During this research the author noticed three blind spots concerning energy, namely "energy without mass", energy generating organella ("mitochondria") and "animal biomechanical energy". The author subsequently established the new concept of "mitochondrial energy-based medicine", by which means he has successfully treated patients of the intractable maladies of the three categories by means of MATM remedies. He has disclosed all of them to be caused by intracellular infections of nonpathogenic and/or low virulence pathogenic enteromicrobes via improper absorption of environmental energy, which induces deterioration of mitochondria in the intracellularly infected organ cells. Via the complete curing of these maladies by means of MATM remedies, the causes of the maladies are verified as diagnoses *ex juvantibus*. The great medical discovery is the revelation that these three kinds of maladies are a simple and easy matter; they can be completely cured, if treated in time.

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