Great medical discoveries of the 21st century.

Part II: Establishment of the gravitational evolutionary law in the vertebrates‡

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In order to establish the gravitational evolutionary law in vertebrates, this paper profoundly considers what is evolution, and comprehensively examines the features of evolutionary phenomena. Energy, especially biomechanics as well as gravity and mitochondrial energy metabolism, are also carefully scrutinized and Lamarck's Use and Disuse Law and Haeckel's Biogenetic Law are revisited. The Use and Disuse Law was verified in vertebrates at a cellular level using biomaterials. The material foundations of the vertebrates are skeletal substances, namely collagen, cartilage and bone. If any of them can be synthesized intact artificially, the causes of chondrification of collagen and ossification of cartilage that occurred in the process of evolution will be clarified. Vertebrates pose three unsolved questions: the mechanism of evolution; the genesis of the immune system; and the development of bone-marrow haemopoiesis. These issues can be investigated together using artificial bone marrow chambers made of synthetic hydroxyapatite, and applying biomechanical stimuli to sintered hydroxyapatite. Development of the bone marrow haemopoietic nests occurred in the second revolution of evolution. Accordingly, clarification of the mechanism of their development leads to the solution of the other two unsolved questions. A hybrid-type artificial dental root that assumed the characteristics of the gompholic tooth peculiar to mammals was also developed. It was thereby clarified that evolution occurs according to the biomechanical functions (behaviour) of the animal in response to gravitation. In order to further elucidate the law of evolution, trilateral research methods integrating morphology, including embryology and phylogeny; the functional study of molecular biology; and molecular genetics concerning remodeling, with biomechanics were developed. An experimental evolutionary study was launched, in which energy as well as material (physicochemical) stimuli were applied to archetypical vertebrate animals from the recent epoch representing the phylogenic stage. Subsequently the author succeeded with the larva-type adult Mexican salamander to raise a reptile-type imago. From the results of these innovative studies, Lamarck's Use and Disuse Law and Haeckel's Biogenetic Law have been reinterpreted, also using present-day biomechanics, molecular biology and molecular genetics. Through these researches, close correlations between ontogeny and phylogeny via biomechanics, consistent with gravity, have been revealed. The drastic changes in morphology as well as function in the second revolution of vertebral evolution (landing) have been demonstrated to be in accordance with the Use and Disuse Law. The dormancy of the MHC (major histocompatibility antigen complex) genes in the archetype Chondrichthyes (shark) in seawater, just as in the embryo and foetus in amniotic fluid, is explained: they are in an immune-tolerant state. As verification, transplantations of many kinds of organ or tissue from shark into mammals were successfully accomplished. From the studies on relations between tooth form and biomechanics it has been shown that the function related to morphology of the tooth is one of biomechanics-dependent morphogenesis according to the Use and Disuse Law applied to odontology. Thus, the Gravitational Evolutionary Law has been established. It has the potential to save human beings from extinction by eradicating intractable refractory diseases, i.e., cancer, immune maladies and mental illness.

Keywords: archetypical vertebrate, artificial organ, Biogenetic Law, biomechanics, embryology, evolution, gene expression, gravitation, Gravitational Evolutionary Law, Heterodontus, hydroxyapatite, MHC, molecular biology, morphology, ontogeny, phylogeny, skeletal substance, Triakis, Use and Disuse Law, vertebrates

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PART I. Introduction: Unsolved and overlooked issues in modern medicine and life science

1. Three unsolved and three overlooked issues in modern life science

One of the most important aspects of zoölogy, specifically regarding vertebrate animals, is also one that is essentially ignored.

The vertebrates are constructed from numerous cells, all of which are fed by nutrients and oxygen, distributed by the blood circulated by the cardiovascular system. To maintain blood circulation throughout the entire skeletal system, the cardiovascular system has to maintain a rather high level of blood pressure—as blood is rather heavy in a gravitational field of 1 *g*. Hence the vertebrate animals live under the law of gravitation.[1]

In conventional bioscience and medicine there are three important but unsolved issues. The *first* is to discover the unifying controlling system of animals with multiple organs (ultramulticellular mammals). Without this knowledge, the causes of intractable refractory diseases as well as the evolutionary mechanism of the vertebrates cannot be understood. The *second* is to discover the causes of and therapeutic methods for intractable refractory diseases; i.e., immune diseases, malignant tumours and mental illness. The *third* is to discover the driving force of evolution, namely environmental factors such as various kinds of energy and gravity as well as physicochemical stimuli of substance with mass (i.e., oxygen, glucose, air and water).

If, however, in considering the evolutionary system we are to include various kinds of microbes with or without pathogenicity among the environmental factors, then not only contagious (infectious) diseases but also intractable refractory diseases can be included as an issue not of the immune system but of the evolutionary process, as a manifestation of degraded regressive evolution. Therefore, the three issues actually become only two. However, the author will discuss the original three problems (Nishihara, 2011) in this paper.

In conventional life science there are three major overlooked issue. The *first* is the fact that the multicellular vertebrates live under the law of gravitation without recognizing it. Higher land animals are subject to a force proportional to 1 *g* during any locomotive movement carried out at some speed, hence they change their body construction through their cellular remodeling system. On the other hand, not only prokaryote microbes or protozoa (because they are too small), but also lifeless things lacking a remodeling system, do not suffer from gravity.

The second overlooked issue is energy, viz. environmental energy, and biomechanical energy, including intrinsic gravitational energy and mitochondrial energy metabolism. Animals are subject to biomechanics, which controls their movement and behaviour. Concomitantly, cell remodeling and the inheritance concomitant with energy-induced gene expression systems are generally overlooked. *The third overlooked issue concerns* opportunistic infections of parasitic, common, nonpathogenic enteromicrobes; i.e., which live in symbiosis, as intracellular infections, in various organ or tissue cells (Nishihara, 2011).

If these three *overlooked* issues are introduced into the above-mentioned three (or two) *unsolved* issues, they might surely be solved.

With these ideas in mind, we can assert that evolution occurs via energy as well as via substance with mass by means of physiochemical stimuli, which trigger gene expression of mesenchymal stem cells as catalysts. Consequently, we can understand that evolution is attained by healthy (beneficent) remodeling, which becomes metamorphosis after several successive generations. On the other hand, intractable refractory maladies are the result of regressive remodeling, which, after several successive generations, ultimately leads to extinction.

2. The three unsolved issues

2.1 The unified control system of ultramulticellular mammals

The first unsolved issue is what, where and how the controlling life energy system exists all over complicated multi-organ creatures. At first we have to consider the major two components of the mammalian body. One is the "outer" somatic system, namely the cortex of the body, the brain–nervous system, the skeletal bones and somatic muscle systems; the other is the inner one—the system of guts (viscera).

The system mediating between the outer and inner components is constituted by the cardiovascular blood and lymphatic fluid. The mediating system carries nutrition and other factors including oxygen, carbon dioxide, nitrogen, nitric oxide, "intelligent" proteins (e.g., growth factors, hormones and neuropeptides) and microbes as well as toxins, all of which constantly enter the mediating ststem from all over the body.

The major *site of secretion* of intelligent proteins is the nucleus of neurons of the thalamus and hypothalamus in the limbic system connecting the hypophysis cells, and the *targets* of these proteins are the mitochondria in all

[1] Note that vertebrate animals on land live under energy of 1 *g* and change their skeletal forms according to their long-term repeated fixed functions (Wolff's Law of functional adaptation).

body cells. Even bacteria and viruses can enter into the cytoplasm of the leukocytes through the cell membrane, just like the rickettsiae. It is considered that mitochondria originated from rickettsia-resembling proteobacteria that had entered early prokaryote cells, after which they became, and remained as symbiotic mitochondria. Common enteromicrobes (nonpathogenic bacteria and viruses) can easily enter into leukocytes (granulocytes) via the lymphoid tissue of the gut. Then, contaminated granulocytes circulate through the portal vein of the hypophysis, after which they carry all the intelligent proteins found in the hypophysis. Only granulocytes can carry them to the targeted organ cells of glands secreting hormones or growth factors (Nishihara, 2011). Since these contaminating microbes in the granulocytes are disseminated in the portal vein of the hypophysis, the cells of the latter become contaminated with them. This is a concrete connexion between the hypophysis and the mitochondria in all body cells, which mediates between the somatic neurons and the sensory as well as the muscle systems and the gut (visceral) uptake and incorporation system of not only nutritients, oxygen and minerals but also viruses and bacteria. With these mediating systems, creatures can maintain vital activity via the blood and lymphatic circulation systems, not only via metabolizing nutrients to synthesize substances for remodeling as well as reproduction, but also via the catabolizing and excretion systems with various kinds of metabolites, organelles, aged and deteriorated proteins and cells. All cellular activities of life are carried out by the mitochondria–hypophysis system with the involvement of hormones, cytokines, growth factors etc.

This is the mitochondria–hypophysis overall controlling system (Nishihara, 2011). Without disclosing this most important issue, the causes of intractable refractory diseases and the evolutionary mechanisms of the vertebrates can never be solved.

2.2 The unified control system and gravity

It is still a challenge to find out what exactly gravity is (Feynman et al., 1995). However, higher animals (i.e., multicellular vertebrates) have been utilizing gravity for themselves without "knowing" it, in daily life as well as in evolution (Ross, 1984).

It is equally a challenge to *comprehensively* understand the actual effects of gravity upon vertebrates. How do they cope with gravity in daily life? It is necessary to sustain the blood circulation in order to live, despite the heavy weight of blood.

Then how did they deal with gravitational energy during evolution, at the second revolution of vertebrate evolution (i.e., landing or terrestrialization, which occurred in the Devonian period)? In seawater, gravity is effectively cancelled by buoyancy. Therefore, it became greater on land. Note that the archetypical vertebrates, namely the Cyclostomata and the Chondrichthyes from the Devonian period and surviving as relicts up to the present, have no lung and, unlike modern (bony) fishes, seals, whales and the like, are not neutrally buoyant. The gravity they experience in seawater is about one sixth of that experienced on land. After landing, they writhed automatically and vigorously to look for seawater, whereby they were able to increase their blood pressure. Consequently, they could adapt to the increased gravity, and became able to respire in air instead of in seawater through gills.

2.3 The other two unsolved issues

To recapitulate, the other two unsolved issues in life science and medicine are (ii) the evolutionary mechanism and (iii) the true nature of intractable refractory immune diseases, including carcinoma and mental illness. It will be shown that solving these issues also suggests therapeutic methods to combat them.

3. The three overlooked issues: energy, biomechanics, and parasitic microbes and the rôle of organelle mitochondria in the vertebrates—the new concept of intracellular infection

In conventional biology and medicine as well as in human life science, the three major overlooked issues are: (i) the effect of gravity on land vertebrates; (ii) the various types of "environmental energy" including gravity and biomechanical energy as well as the energy metabolism of mitochondria; and (iii) the parasitic enteromicrobes in the human body, namely nonpathogenic or feebly virulent common bacteria and viruses that live symbiotically in various tissue cells (Nishihara, 2011; 2012).

If we overlook the types of energy concerned with vital activities, especially the energy metabolism of mitochondria, and overlook the intracellular infection of parasitic microbes into human body cells, the unified control system of ultramulticellular mammals composed of multiple organs can never be understood, nor can the mechanism of evolution and the immune system be understood.

In biomechanics, gravitational energy is manifested in the animal body, especially the media of blood and lymph. In order for circulation to take place, blood pressure (delivered by the cardiovascular system) is necessary to counteract gravity. In animals, biomechanical force and energy are converted into the hydrodynamics of lymphatic fluid and blood when animals move around. As for the nonpathogenic microbes, parasitic common

enteromicrobes are, curiously, disregarded in today's medicine, even though contamination of blood by common enteromicrobes has been known as an opportunistic infection since *c*. 60 years ago.

In conventional vertebrate life science, the basic unit of living systems has been thought to be the cell. However, the most important system in higher animals is the energy-providing mitochondrion in cells, which has various important functions in living systems. Therefore, studying the complicated functions of mitochondria is critical for understanding the mechanism of the mammalian life system from the viewpoint of biomechanics as well as molecular biology and energy-based life science.

By introducing the concepts of intracellular infection into modern medicine we can easily understand the enigma of the causes and therapeutics of three kinds of intractable refractory maladies (immune diseases, malignant tumours and mental illness). The obligate intracellular parasites—all viruses, rickettsia, chlamydia and coxiella—are conventionally known. Common intracellular parasites—such as the tubercle bacillus—are also known. The author proposes that the common occurrence of intracellular infection of leukocytes reported in clinical studies occurs when mammals, including human beings, let their body temperature become significantly lower than that of homoiothermal animals.

Also, we can easily understand the unified control system of the mammals, which is composed of multiple organs with numerous cells in the tissue or organs of the visceral system as well as the complicated somatic systems. After that, we can understand the mechanisms of the immune system and the biomechanical mechanisms of evolution of the MHC (major histocompatibility antigen complex); i.e., the tissue immune system and evolutionary metamorphosis. At the same time we shall find out what determines the evolution of flourishing and of extinction.

It is now the time to pursue genuine theory for the immune system and evolutionary theory with genuine scientific thinking by means of real scientific methodology.

PART II. Establishing energy-based medicine and life science

4. The enigma of the three major intractable refractory diseases

4.1 Aetiological causes of three major intractable maladies at the subcellular level

In a previous paper (Nishihara, 2011), the author presented his fundamental research concerning mitochondria, and discussed the cause of mitochondrial mutation. He revealed the unified control system of ultramulticellular mammals—via the hypophysis–comprising humoral hormones, cytokines and the growth factor-integrating system. The author has developed artificial haemopoietic bone marrow chambers as well as hybrid artificial gompholic dental roots using bioactive ceramics *in vivo*, which, by means of inducing gene expression of mesenchymal stem cells via the hydrodynamic flow of blood circulation in animal muscles or in jaw bones, 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: "environmental energy"; the "energy-generating organelles, mitochondria"; and "animal biomechanical energy". To bring about a breakthrough in stagnant medicine, the author has introduced the concepts of "mitochondrion—the life energy-generating organelle", "environmental energy, especially gravity" and "biomechanical energy" into bioscience as well as therapeutic medicine. He has also introduced clinical bioresonance diagnostic methods (the neuron–mitochondria bioresonance diagnostic method) to disclose major causes of intractable maladies. By these diagnostic methods it has been revealed that intractable refractory diseases are something that is brought about by intracellular infection of common nonpathogenic enteromicrobes absorbing improper environmental energy. These microbes in cytoplasma cause deterioration of the mitochondria. Thereafter, the author has established a new concept of mitochondria-based energy medicine, which also provides the unified and organized mechanisms of regulation systems in the vertebrates by multiple tissue and organs with numerous cells. The author then developed new therapeutic methods for the complete cure of the three different kinds of intractable refractory maladies through the treatment of intracellular infection as well as by controlling environmental energy (Nishihara, 2011).

4.2 Intractable refractory diseases: caused by deteriorated cell function illness

The author developed radical therapeutic methods to treat functional diseases, namely cell function-deteriorated illness, by means of diagnosis *ex juvantibus* (therapeutic diagnosis) via neuron–mitochondria bioresonance diagnostic methods (Nishihara, 2008a). Consequently, it has been disclosed that all functional diseases are an intracellularly infected condition of a certain organ by nonpathogenic common enteromicrobes; in the organ's cells the mitochondria are deteriorated (Nishihara, 2007a,b).

Vital activity is sustained by mitochondrial energy metabolism via matter with mass as well as environmental energy. At the initial starting point of life, organisms need

the aid of appropriate environmental energy to rotate the energy whirlpool of life by means of metabolizing absorbed nutrients, which are digested within the organism.

The "three major intractable refractory maladies", which are conventionally considered as being quite different, are induced by essentially the same cause; viz., intracellular infections by nonpathogenic and/or feebly virulent enteromicrobes, which bring about serious deterioration of mitochondria in the cells of the infected organ. These maladies can be successfully cured if treated in time (Nishihara, 2007b; 2008a; 2009a,b,c: 2010; 2011; 2012).

4.3. Energy-based medicine

4.3.1 Darwinism and self–not self immunology

Conventional evolutionary theory (Darwinism or neo-Darwinism) has been much criticized, and the current hypothesis for the immune system, (based on "self" and "not self" immunology) is also subject to criticism. Influenced by these possibly mistaken concepts of science, today's medicine, especially therapeutics attempting to deal with intractable refractory diseases, is in a state of deterioration.

Both were developed by persons who, apparently, had a poor grasp of the scientific method. The author calls Darwinism "the adult fairy tale of the evolutionary hypothesis", and self–not self immunology "labyrinthine immunology". According to what is generally accepted as pseudoscience, both merit that appellation,

Conventional Darwinism emerged as a hypothesis through miscellaneous reflexions about natural history without logical thinking. In the natural selection theory that underpins Darwinism there is no impelling vectorial force of evolution generated by the creature's repetitive behaviour and movements.

Regarding self–not self immunology, there is confusion between the two different immune systems; i.e., the cytological digestion system against microbes and tissue immunity, i.e., against transplanted not self tissue and/or organ cells. The most important protein in tissue immunity is the MHC (major histocompatibility antigen complex). The self–not self immunologists insist that all animals having MHC genes can detect self or not self when an organ is transplanted from a not self animal. However, the author has revealed the enigma of immunotolerance to be *dormant* MHC.

Evolutionary phenomena as well as the tissue immune system based on the MHC constitute an automatic reactive system induced by synthesized vectors generated via repetitive movements (in the presence of gravitational energy) in animals throughout successive generations. At first we have to consider why such questionable propositions emerged in the 20th century and even in the 21st century. The author recognizes that not only grand old Darwin but today's immunologists observe a cornucopia of jumbled objects and phenomena, which they research as natural historians not as scientists, without any proper definition of the subjects under research.

4.3.2 Autoimmune diseases as a mistaken concept of self–not self immunology

After the establishment of self–not self immunology in the 1970s, the most intractable refractory immune maladies were then called autoimmune diseases. Until then they had been considered to be opportunistic infections caused by the self's own common enteromicrobes coexisting in the intestine as well as in skeletal organs. The self–not self immunologists denied the fact that the cause of these diseases is opportunistic infections. They insisted that the maladies were caused by an abnormal immune response of the body against substances or tissues normally present (autoimmunity). Surely, however, were they to have had such a mechanism, the vertebrates would have become extinct hundreds of millions of years ago.

4.3.3 Archetypical poikilothermic vertebrates with a great number of genes and immune tolerance

The immunologists have seemingly ignored the archetypical poikilothermic vertebrates, whose genome size is 30 times larger than that of mammals. Genomes had been incorporated into the nucleic chromosomes as "junk" genomes. The mammals, including human beings, evolved from the archetypical vertebrates. They easily become immune-tolerant when their body temperature decreases by about 5 °C below the norm for homoiothermic animals.

To verify this proposition, the author carried out xenotransplantation in order to solve the enigma of immunotolerance of the foetus and the archetypical animals. As is well known, viruses proliferate only intracellularly. Common enterobacteria can be intracellularly infectious under some conditions. The concept of intracellular infections of bacteria is deduced from precise clinical studies of intractable immune diseases by the present author via neuron mitochondria bioresonance diagnostic methods (Nishihara, 2008a). What happens when intracellular infections occur in organs or tissue cells? In the infected cells deterioration of mitochondria ensues and, consequently, cell functions deteriorate—for

example, the immune function of leukocytes: their ability to digest infecting bacteria is lost, because they are parasites inside cells, whose cell membranes protect them. Inside the infected cells various antibodies against these bacteria (e.g., antinucleic antibodies) are produced and presented on the membrane surface of the intracellularly infected cell. Then various kinds of leukocytes start to attack the anti-nucleic antigen on the cell surface to destroy them with their anti-nucleic antibody without success. These antibodies or CRP are observed in blood serum. Needless to say, intracellularly infected cells are originally the autogenous cells. Therefore, they may have a tremendous number of bacteria, exceeding the number of mitochondria (typically 800 to 3000 per cell). Autogenous self-leukocytes can never destroy autogenous intracellularly infected self-organ or tissue cells. Observing these ineffective intractable antigen–antibody reactions, self–not self immunologists probably mistook autogenous leukocyte attacks for an abnormal immune reaction against autogenous substances and/or normally presented organ cells or tissue, and called this condition "autoimmunity". A famous immunologist, the late Prof. Tomio Tada of the University of Tokyo, called such leukocytes attacking autogenous intracellularly infected cells, "rebels" or "antiself white blood corpuscles". He also observed that intracellularly infected leukocytes contained huge bacteria attacking white blood corpuscles.

4.3.4 Mistaken concepts of immunology based on transplantation medicine and ignoring basic life science

Self–not self immunology is based on the following two simple stories: (i) Immunologists today have negligible interest in infectious diseases (including contagious as well as viral diseases) but rather focus on MHC-immunology, namely, tissue immunity for organ-transplantation medicine. The self–not self immunologists cannot distinguish between immunology against bacteria and against viruses (i.e., microbes and tissue immunity—immunity based on MHC). Furthermore, they appear to have gaps in knowledge regarding immune tolerance of the embryo and the archetypical vertebrates—situations in which the MHC is dormant. These gaps were filled by the present author (Nishihara, 1998a,b,c; 1999a; 2000; 2003c; 2004e). (ii) Immunologists today seem to neglect modern bacteriology, physiology, pathology, vertebrate zoölogy, cellular respiration of mitochondria, and environmental medium and energy. The author introduced the aforementioned basic life science into immunology and medical therapeutics, and after that he disclosed three intractable major refractory diseases that are caused by intracellular infection with common enteromicrobes of the respective organ cells, by integrating studies of these different kinds of researches:

① Precise clinical research of intractable refractory diseases to cure and administer effective antivirals and/or antibiotics with bifidus factors, which the author detected by the bioresonance method.
② Precise research on the bacteriology of obligate intracellular parasites as well as the common properties of intracellular parasites.
③ Comparative studies between embryos of higher animals and the archetype adult vertebrate system (shark and axolotl) versus the mammalian adult system.

4.3.5 The poikilothermic animal: immune-dormant versus the homoiothermic animal: immune-activated

Archetypical adult vertebrates[2] and the embryos of higher animals correspond to the poikilothermic type. Therefore, the level of inner respiration of mitochondria is very low and, consequently, blood pressure is also low and body temperature changes with environmental temperature. With low blood pressure, embryonic and adult archetypical vertebrates have a dormant MHC. Therefore, their organs can be freely transplanted between various kinds of animals. The most important difference in the immune system, compared with ordinary adult mammals, is that the former are also dormant against microbes, recalling the tissue immunity of the MHC.

The author has discovered that embryonic and archetypical vertebrates, i.e., poikilothermic animals,[3] are both immunotolerant not only to MHC but also to microbes.

The meaning of dormant immunity against parasitic common enteromicrobes (viruses and bacteria) means that they are freely parasitic in the host cells. One consequence is that poikilothermic animals (e.g., lungfish) have a genome that is 30 times larger than that of mammals, because the entire genomes of the enterobacteria and viruses have been incorporated into the host chromosomes as "junk" genes.

Therefore, intracellular infection can easily occur not only in a child but also in adult human beings if they cool the gut and the body by 3 to 4 °C below the common body temperature of 37 °C. Therefore, if mammals, including human beings, have a low body temperature, or low blood pressure, the system of the lower vertebrates comes into play and immunotolerance

[2] We remind the reader that they are the Cyclostomata and the Chondrichthyes.
[3] Cf. the similarity of their morphologies propounded by Haeckel.

against common enteromicrobes occurs automatically. Consequently, intracellular infections occur systemically. This is the condition of intractable disease.

The autoimmune diseases established by modern immunologists are, alas, based on mistaken and biased research methods. They ignore not only energy but also bacteriology, biomechanics with gravitation, physiology, and zoölogy of both poikilothermic and homoiothermic animals.

4.4 Energy-based evolutionary law and regressive evolution towards extinction

The author has proposed that evolution of the vertebrates is closely tied to environmental factors (i.e., various kinds of environmental energy, especially gravity and temperature) as well as to physicochemical stimuli (i.e., matter with mass acts as a catalyst on mesenchymal stem cells to induce gene expression), leading to metaplasia (a kind of metamorphosis) as well as metafunctions of the cells (Nishihara, 2003b; 2004a; 2004b).

Energy and physicochemical stimuli derived from matter, as well as various kinds of microbes, are considered to be environmental factors, whether or not they are nonpathogenic. Refractory diseases induced by intracellular infection of common enteromicrobes can be considered to be an initial stage of regressive evolution.

The author proposes the Energy-based Evolutionary Law, which, he has found, is also useful for elucidating the cause of intractable refractory maladies—improper environmental energy including gravitation—alongside nonpathogenic common enteromicrobes engendering intracellular infections.

Even though evolution is induced by energy, if we suffer improper energy over many generations, there occur not only refractory maladies but also degrading regressive, evolution.

Therefore, functional maladies (i.e., intractable refractory diseases) actually are a milestone on the road of regressive evolution leading, ultimately, to the extinction of human beings.

After having solved the aforementioned great three overlooked and three unsolved issues, by treating intracellular infections via effective antimicrobial agents, the author could cure many patients of these diseases. This led him to the idea of including various microbes (viruses or bacteria), whether pathogenic or not, among the environmental factors. Intractable diseases are to be understood as regressive evolution. Therefore, the author asserts that intractable refractory maladies occur as milestones of regressive evolution leading toward human extinction.

5. Establishing genuine evolutionary science

5.1 Definition of the vertebrates, characteristic organs, and defining substance

The purpose of evolutionary science is to find out the law of mechanisms of morphological transformations of animals over ultralong intervals spanning numerous generations. This definition actually comes from Goethe, who established the science of morphology. What kind of methodology is available to discover a law behind the complicated phenomena in evolution? The author here explains his radical methodology. Conventional scientists talk about evolution as if it were made up from all kinds of animals: insects, plants, protozoa, bacteria etc., based on natural history. To break away from this confusion, we first have to define animals objectively as comprising only the vertebrates.

Next, all features related to this science have to be defined and understood by their characteristics. What is to be done next is to investigate the already-known laws of evolutionary science and certain already-known facts of organs transformed or changed in the process of evolution. Namely, to know and investigate the facts about morphologically, substantially or functionally transformed organs in the process of evolution, and to disclose the causal factors. Only after that can the impelling forces or stimuli that induce evolution be understood. These are several factors to be discussed.

The first definition is that of science itself. Its purpose is to find out the laws behind entangled and complicated phenomena connected with the chosen subject. In the present context, we must first define what the vertebrates are and, after that, observe the complicated phenomena of the subject, namely, evolution and development (i.e., ontogeny and phylogeny) of morphology as well as the functional immune system (including physiologically changed conditions via intractable diseases). After that the mechanism of evolution and development (as well as the causes of and therapeutic methods for intractable refractory diseases) can be discovered and established.

5.2 Definition of evolution in the vertebrates

We may start by asking what the vertebrates are in terms of material composition and organ specificity. The definition of the vertebrates is that they are chordates having bony placoids and a backbone, to different degrees of ossification. The definition of evolution is a transformation of shape and/or function (in the vertebrates) over ultralong intervals and that these metamorphoses include functional alterations, and they are exactly inherited. Then, what is the essential function of the gene; i.e., inheritance? It is

the transmission of biomechanical behaviour patterns. We know them as instincts.

Therefore, we may define these bony structural materials as a definitive characteristic of the vertebrates. In the evolution of the vertebrates, it is possible to observe a substantial change in both outer and external skeletal matter (i.e., placoids and spine), with collagen changing to cartilage, which in turn changes to osseous bone. A redefinition of the vertebrates, therefore, is that they are animals that possess placoids and a chordal skeleton, consisting of collagen, cartilage or osseous bone. Conventional evolutionary studies are currently at an impasse, as there have been no observations made on the effects of time, space, material and energy, which are essential for the reactions and subsequent changes, for movement and mechanical reaction, and for the metabolism of evolving animals.

The structures and organs that we may define as characteristics of the vertebrates are the spine and the respiratory system of the guts, namely the gill and lung systems. The invertebrates, for the most part, utilize the dermal respiratory system. This vertebral development of the gut respiratory system has unified the absorption of nutrition and oxygen into the alimentary canal. The change from a gill-based to a lung-based system occurred in a phylogenetic stage of the evolutionary process of the vertebrates, which may be described as the *second revolution* of this process.

5.3 Defining every relevant subject and characteristic matter to establish the gravity-based evolutionary law

For science researchers it is necessary to define every relevant subject as well as to know the characteristic matter and the mechanical systems and organs, in which we intend to establish the energy-based (i.e., biomechanics-based) immune theory. And they ultimately belong to gravity-based evolutionary law. In this section, the subjects for definition are: Firstly, what is science? Secondly, what is life? Thirdly, what are the vertebrates? Fourthly, what is energy, which includes environmental as well as biomechanical energy involving gravitation? Fifthly, what is evolution? And what is the immune system? After that, according to the definitions, observations of the subject's phenomena, namely evolution, as well as phylogeny, ontogeny and development, indicate the research that has to be carried out.

In order to introduce quantum electrodynamics as well as gravitational energy and energy metabolism of mitochondria into life science, the author has to know precisely what quantum physics is. Also he has to define the most difficult issue of gravitation, which no physicist, including Feynman, successfully handled. By introducing the concept of energy into medicine as well as life science, great advances have been made in not only therapeutic medicine but also in embryology (i.e., ontogeny) as well as in phylogenetic development and evolutionary science (Nishihara, 1999a,b; 2000; 2003a,b,c; 2004a,b,d; 2006). From comparative anatomical and physiological and molecular-biological studies of animals at different phylogenetic stages, he has disclosed radical differences between mammals; i.e., homoiothermal, versus poikilothermic animals.

6. Newton's *Principia*, Lamarck's Use and Disuse Law and Haeckel's Biogenetic Law: Methodology to establish the theory of mechanisms of vertebrate evolution

Newton (1687) proposed the laws of motion and the Universal Law of Gravitation.

His grand unifying idea of gravitation with effects extending throughout the solar system and beyond explains diverse phenomena with one principle. His brilliant and revolutionary contribution to science expounded the working of a large part of inanimate nature mathematically and suggested that the remainder might be understood in a similar fashion. By taking up already-known facts, he formed a theory that explained them in mathematical terms, deducing consequences from the theory and comparing the results with observed and experimental facts. Newton united, for the first time, the explication of physical phenomena with the means of prediction.

Prior to studying Lamarck's evolutionary law, it is necessary to know the situation of biology in his time. In 1802 Lamarck separated biology from natural history, after that he tried to propose a law of mechanism for evolution in animals based on causal laws just like Newton did for inanimate nature (Lamarck, 1809).

Around 1795 (but published later) Goethe had established the concept of "morphology" to explain the evolutionary change of animal form, asserting that the purpose of morphology is to disclose the law of metamorphosis of animal organs or skeletal parts over a long time span through many generations. Subsequently, in 1815, Lamarck proposed the Use and Disuse Law in animal evolution from the viewpoint of gravity and biology; in his Law he separated animals from miscellaneous organisms including plants or fungi. Lamarck understood that animals could live under 1 *g* of gravity on land and he knew that in seawater fish without lungs could live under 1/6 *g*, with regard to buoyancy of seawater. At that time biomechanics was not established, but in biology and zoölogy gravity was recognized because of Newton's Universal Law of Gravitation.

What is the difference between common mechanics and biomechanics? The former is lifeless and the latter deals with living animals. Then, what is the characteristic of life? The most important thing in life is to maintain remodeling of parts or whole cells or the body. By this remodeling animals can overcome deterioration caused by aging of individual cells or the whole body, namely increased entropy. When animals continue to progress for a long time over many generations, in their digestive tract, after eating foods, digestion starts and cell respiration, metabolism, catabolism and remodeling continues in the whole animal body, which gravity always affects in the vertical direction. Consequently, oro-anal polarization of the digestive tract occurs. The search to establish the laws of evolutionary mechanisms and the laws of metamorphoses in the development of vertebrate animals over many successive generations can be aided by means of already-known theories; viz. Lamarck's Use and Disuse Law and Haeckel's Biogenetic Law. Both laws are rooted in biomechanics and touch on animal behaviour and gravity (Nishihara, 1998a; 2003b).

Prior to start this search, we have to know the most characteristic substance and organs defining the vertebrates. The former are the teeth and bones, which are at different stages of ossification, and the latter comprise the gut respiration system of gills and lungs. Therefore, we can read the enigma of evolutionary mechanisms in two ways: firstly, by utilizing cartilage, bone or synthetic artificial ceramic bone; secondly, by utilizing the gut respiration system of gills and lungs, which further constitute, in essence, the haemopoietic system.

7. Lamarck's Use and Disuse Law

7.1 Lamarck's Use and Disuse Law and the Gravity-based Evolutionary Law

Lamarck (1809) proposed two laws; the first being the Law of Use and Disuse and the second being the Law of Heritability of Acquired Characteristics. Prior to his proposals, Newton (1687) has presented his laws of motion and of universal gravitation, which formed the basis of Lamarck's laws of the mechanism of evolution. From the perspective of a modern reëvaluation of Lamarck's Use and Disuse Law, one needs to integrate not only gravity, environmental energy, biomechanical energy, mitochondrial energy metabolism and parasitic microbes, but also morphology, physiology, pathology, zoölogy of poikilothermal animals as well as homoiothermic animals, molecular biology and genetics (including molecular genetics).

7.2 Lamarck's First and Second Laws

1. *The First Law: In every animal, which has not passed the limit of its development, a more frequent and continuous use of any organ gradually strengthens, develops and enlarges that organ, and gives it a power proportional to the length of time it has been so used; while the permanent disuse of any organ imperceptibly weakens and deteriorates it, and progressively diminishes its functional capacity, until it finally disappears.*
2. *The Second Law: All the acquisitions or losses wrought by nature on individuals, through the influence of the environment in which their race has long been placed, and hence through the influence of the predominant use or permanent disuse of any organ; all these are preserved by reproduction to the new individuals which arise, provided that the acquired modifications are common to both sexes, or at least to the individuals which produce the young.*

In essence, a change in environment brings about a change in needs, resulting in changes in behaviour, bringing changes in organ usage and development, bringing change in form over time—and thus the gradual transmutation of the species. Lamarck named these two laws, respectively, the "Use and Disuse Law" and, as it is commonly, although in truth erroneously, called, the Law of Heritability of Acquired Characteristics.

In trying to discern the meaning of continuous use or disuse in the First Law, and the acquisitions or losses brought about by nature (environment) in the Second Law, one should concede that both laws stand for the same meaning. However, the former indicates the causes of the strengthening or weakening, whereas the latter refers to acquisitions or losses, as the result of use or disuse by the influence of nature; i.e., the environment. The meaning of the latter half of the Second Law, "All these are preserved by reproduction to the new individuals who arise, provided that acquired modifications ... ", deserves especial scrutiny. Lamarck's words have been later misinterpreted as inheritance of acquired characters. The present author noticed that the most important function of genes is *to assure the inheritance of biomechanical behaviour patterns of animals*. All acquisitions or losses are the results of special behaviour patterns of animals in conjunction with environmental influence; acquisitions or losses via use or disuse under environmental influences are absolutely inheritable.

7.3 Difference between the First and Second Laws

The difference between the First Law of continuous use or disuse and the Second Law of the predominant use or permanent disuse of any organ under the influence of the environmental means no more than whether the voluntary use or disuse of the animal organs or the passive ones is via some environmental influence. That is to say, if the behaviour patterns are transmitted to the young or the next generation, metamorphoses occur in the young with the same genetic informational codes. And, if the metamorphoses are common to both sexes, they are transmitted to the young through reproduction. The present author again emphasizes that the essential function of the gene is to transmit behaviour patterns. We can understand this by observing the inheritance of behaviour not only in primitive organisms (bacteria or protozoa) but also in higher animals (as instincts). For example, mammalian newly born babies can always suckle. From such facts, we can firmly assert that the essential function of the gene is to transmit behaviour patterns. Conventionally, in phylogeny or in evolutionary phenomena, especially in odontology and morphology of various organs in mammals, too many acquired characters are known empirically. As the author has already noted, behaviour patterns are inherited, therefore metamorphoses according to the use–disuse law are automatically inherited. In the higher animals up to mammals, parents always bring up their babies, which suckle instinctively. Later on the parents teach their young various behaviour patterns useful to survive in nature.

7.4 Acquired character originating from changed behaviour patterns

The Second Law of Lamarck is said to be the heritability of acquired characteristics. However, changing behaviour patterns in successive generations also transform the function or shape of some organs in accordance with the changing behaviours. The transformed shape and/or function are called acquired characteristics. As a changed behaviour pattern is inherited, changed shapes or functions (commonly called acquired characteristics) are also naturally transmitted. If the informational system of the behaviour patterns in parents is communicated to the young, they grow up with species-specific characteristic shapes, because newly born babies have inherited fundamental behaviour patterns, which are called instincts (i.e., suckling, eating, breathing, digesting, excreting, sleeping and reproducing). That is to say, the mechanisms of deciding species-specific morphology and behaviour are communicated to the young via parents.

This means that animals can change the shapes or functions of their organs by habitual behaviour in conjunction with the constant genetic code. For example, human babies who have been brought up by wolves or birds grow up with behaviour patterns quite similar to those of wolves or birds. Consequently, their shapes become quite different from those of humans. Thus, communicating as well as transmitting behaviour patterns of each animal by parents or foster parents are the most important features for maintaining species-specific morphology in the evolution of the vertebrates (Nishihara, 2003b).

7.5 Lamarck's Law, under control of gravity-based biomechanics, in relation to the essential function of the genes, and molecular evolution of the genes

Lamarck overlooked the most important condition in his laws: the behaviours corresponding to use or disuse in animals have necessarily to be transmitted to the use or disuse modes of some organs, thereby conveying behaviour modes to successive generations. These transmissions are the most indispensable and essential conditions. Usually these behaviour-transmissions to the next generations are carried out via upbringing, teaching and training by parents. Later, the two laws were treated independently and the Second Law was misinterpreted as "inheritance of acquired characteristics". The Use and Disuse Law means that transmitting the habitual mode of behaviour of animals biomechanically with repeated movement to successive generations enacts the transformation of a creature's morphology according to Wolff's Law (Wolff, 1870).

This means that via the same genetic informational codes the animal's body morphology as well as its organ functions can be changed by biomechanical stimuli caused by long-term changed function. That is to say, the genetic informational codes cannot directly decide the shape or function of organs in the creature, but they can be changed with the same genetic codes according to the animal's changed long-term function(s) or behaviour(s).

For example, during the second revolution in vertebrate evolution, sharks (archetypical vertebrates, namely Chondrichthyes) were left behind in shallow lagoons distant from the sea, whereupon they writhed to seek water, with the consequence that their blood pressure increased (perhaps becoming twice as high as in seawater). If they had been able to live in waterless lagoons over a sufficiently long time span the sharks would have changed their skin, gills, cartilage and the cardiovascular system characteristically and automatically via gene *expression* of stem cells without changing the fundamental genetic codes.

During the epoch of terrestrialization, animals could accomplish their landing via overcoming increased gravity. Consequent survival and reproduction were, evidently,

also achieved. After many successive generations, various parts of the genetic codes in the chromosomes of the genital gland cells changed via spontaneous point mutations, and then genetic codes also gradually changed. This is molecular evolution of the genes (Nishihara, 2003b).

7.6 The second revolution of vertebrate evolution (i.e., landing) exhibits a typical and drastic example of Lamarck's Second Law

The most appropriate events to explain Lamarck's Second Law are the occurrences of the second revolution of vertebrate evolution, namely landing (terrestrialization) of Chondrichthyes (sharks).

7.6.1 Sixfold increased gravity changed archetypical Chondrichthyes (shark) body construction after landing

By crustal movements (diastrophism), shallow seas where archetypical Chondrichthyes (sharks) were living were transformed into shoals, hence many sharks ended up in shallows less deep than their bodies or even on land, where they writhed to seek water. In seawater, their body weight is about one sixth of *Mg* (*M* being their body mass) because of buoyancy (Archimedes' Principle). After they landed, the gravity experienced becomes effectively six times greater than in seawater and this affected the shark. Some did not survive, some others could increase their blood pressure from *c*. 15 mmHg to 30–60 mmHg by writhing around. The heart muscle became thicker via metamorphosis according to Lamarck's Second Law; sharks that survived strengthened their heart muscle through the influence of predominantly a greatly increased effective gravitational force and, concomitantly, blood pressure became higher. On the other hand, concerning the medium change (i.e., substantial variation of circumstance in the environment) a drastic change from seawater to air occurred. This indicates drastically decreased density (1/8000), the viscosity decreased (1/800), and the diffusion coefficient of oxygen tremendously increased (× 8000). As a result of these changes of various kinds, including gravity, occurring simultaneously to the archetypical Chondrichthyes, their morphology (shape) as well as their system of organs changed, namely metamorphosis occurred (Nishihara, 1999a; 2000; 2003b).

7.6.2 Medium change from seawater to air induces drastic transformation in sharks

By changing the medium from seawater to air, shark skin with placoides was transformed to hide with animal hairs, and the gill-respiration system changed into the lung respiration system.

Almost all changes occurred via metaplasia, which was brought about via gene expression of undifferentiated mesenchymal stem cells via an effectively catalytic function of energy as well as stimulation by the physicochemical properties of air or water. All undifferentiated mesenchymal stem cells have all the genes by which all of the special cells of tissues, organs, muscles and skeletons in the total animal body are generated. There are two types of metaplasia. One is induced by electricial energy derived from the streaming potential induced by the bloodstream. The other is induced by ions, or elements like oxygen (O_2), or substances like water or glucose. They all work on the genes as catalysts inducing gene expression. In order to explain Lamarck's laws according to contemporary modern science, environmental energy, molecular biology, molecular genetics and biomechanics should be introduced into conventional embryology, ontology and phylogeny (Nishihara, 2003b).

7.7 Verification of Lamarck's laws by means of skeletal organs

7.7.1 The material foundation defining the vertebrates

The author has disclosed the mechanism of the evolution of the vertebrate by means of biomechanical methods using biomaterials, i.e., via energy and material effects.

The material foundations defining the vertebrate (i.e., the characteristic defining matter of the vertebrates) are the skeletal substances, namely collagen, cartilage and bone. The characteristic organs of the vertebrates are the gut haemopoietic system, namely gills or lungs, as well as the intestinal viscera in phylogeny. The gill and lung haemopoietic systems stay in the branchial gut throughout the entire evolutionary process in phylogeny, but leukocyte as well as erythrocyte haemopoiesis in the intestine change the site of the organ according to evolutionary stages. If any of the defining matters can be synthesized artificially, the causal factors of chondrification of collagen and ossification of cartilage that occur in the process of evolution will be clarified. The reason is that in the process of the evolution of the phylum, changes from collagen to cartilage and from cartilage to bone alone are observed in terms of materials. There are three riddles concerning the vertebrates: the mechanisms of their evolution, the immune system and the development of bone marrow haemopoiesis.

7.7.2 Verification of Lamarck's Law via artificial skeletal organs

The present author has developed a method to induce artificial organs by applying biomechanical loads to

biomaterials. By using biomaterials made of sintered hydroxyapatite he has developed chambers, as well as an artificial dental root inducing the cementum by biomechanics. These two kinds of developmental research pointed the way to verifying Lamarck's Use and Disuse Law and the mechanism of the evolution of the vertebrates could be clarified.

By using synthesized sintered hydroxyapatite (i.e., the mineral substance of bone and tooth, by which the vertebrates are defined), the author successfully carried out developmental researches *in vivo* using mammals having artificial bone marrow chambers and artificial gompholic teeth, which were implanted into the muscle and into the jawbone, respectively.

On artificial roots, biomechanical energy (i.e., the micromovement of controlled mastication) was applied and, in the artificial bone marrow chambers, the hydrodynamic flow of the bloodstream as would be evoked by muscle movement was applied.

By the material effect of sintered hydroxyapatite (as catalyst) and by the biomechanical hydrodynamic flow inducing a streaming potential (as catalyst), gene expression of the undifferentiated mesenchymal stem cell around the implanted bioceramics occurs. After that, osteogenesis, osteoclasis and haemopoiesis take place around them as metaplasia. This is an example of an energy and material-induced gene expression resulting in metaplasia, in other word, the Use and Disuse Law at the cellular level (Nishihara, 1989–1997; 2004a).

7.8 Development of artificial bone marrow haemopoietic chambers and artificial gompholic dental roots and the mechanism of evolution

The riddles can be read all at once by developing artificial bone marrow chambers made of synthetic hydroxyapatite (Nishihara, 1994a; 1996; 1997; 2000; 2001; 2003a,b,c). The development of bone marrow haemopoiesis occurs in the third revolution of evolution; i.e., development of the mammals. The bone marrow haemopoietic system is instrumental for creating erythrocytes and leukocytes, which are indispensable for digestion, respiration, metabolism and supplying nutrition at the cellular level. The haemopoietic system is a pivot of immune capability. Accordingly, clarification of the mechanism of bone marrow haemopoiesis development leads to the solution of the aforementioned three riddles of medicine and life science. The author also developed a hybrid-type artificial gompholic dental root that shows the characteristics of the peculiar teeth of mammals (Nishihara, 1989; 1991a,b,c; 1992; 1993; 2004a), thereby clarifying the mechanism of evolution at the cellular level, which occurs according to the biomechanical functions of the animals in response to gravitation from the viewpoint of energy as well as massy matter as catalyst, and it triggers the gene expression of stem cells as metaplasia (Nishihara, 2003a,b). In order to elucidate the law of evolution, the author developed a trilateral research method integrating morphology (including embryology and phylogeny), the functional study of molecular biology, and molecular genetics concerning remodeling via biomechanical energy and mitochondrial energy metabolism (Nishihara, 2003a,b,c). The author also devised an experimental evolutionary study method to which the trilateral research method is applied to induce more evolved organs or tissues in the archetypical vertebrates (Chondrichthyes) (Nishihara, 2003b). With these innovative studies he tried to reinterpret Wolff's Law, Lamarck's Use and Disuse Law, and, Haeckel's Biogenetic Law with the help of contemporary science such as biomechanics and molecular biology as well as molecular genetics (Nishihara, 1998; 1999a,b; 2000).

8. Haeckel's Biogenetic Law

8.1 Revolutionary stages of vertebrate evolution

8.1.1 The relation of ontogeny and phylogeny

The Biogenetic Law has famously been summarized as "ontogeny recapitulates phylogeny" (Haeckel 1866). Ontogeny is the development of the individual after the fertilized ovum that chronologically develops into cleavage (segmentation), morula and monosomite gastrula, the genome size of which is only about one tenth that of mature mammals. At the neurula stage, duplication of the genomes occurs two or three times during development, such that at the end of the neurula stage the embryo with 32–34 somites and the full genome size is present. After pharyngula (Nishihara, 2003b), the foetus develops. This series of stages of development from ovum fertilization to the embryo, the foetus up to birth and after is called *ontogeny*.

Phylogeny is the complete developmental history of a race of animals. Research on phylogeny of the vertebrates conventionally includes comparative anatomy and embryology from the viewpoint of evolution. Four revolutions of vertebrate evolution have been proposed: the first is the development of Acanthodii; the second is the landing of the vertebrates (terrestrialization); the third is the development of the mammals; and the fourth is the development of humans.

Prior to the first revolution, the primordial revolution of the development of the monosomite archetypical Urochordata (i.e., an ascidian) was inevitable. This stage corresponds to the gastrula in ontogeny. After that primitive revolution, an independent creature with multiple somites just like the chain salpa ("sequential

ascidian") developed, which became an independent lone creature with many somites with gills and guts. Thus, amphioxus developed. This stage corresponds to the embryo in the neurula stage. After the primitive revolution, a polysomite creature with vertebrae developed. This creature continued to swim ahead for such a long time that Acanthodii, the archetypical Chondrichthyes, developed; constituting the first revolution of the vertebrates in phylogeny. This stage corresponds to the stage of pharyngula in ontogeny; i.e., the embryo after neurula in ontogeny. In this early embryo stage, we can precisely observe the process of the landing of creatures from seawater; i.e., the second revolution of the vertebrates, namely terrestrialization.

8.1.2 Ascidia: the origin of the vertebrates is also the origin of plants

For the developmental emergence of life, movement of the medium is a most important factor. Initial life in seawater would be moved by the waves. Later on, life can be said to incorporate wave movement by developing a muscle system. In such a way Ascidia developed from Bryozoa. Ascidian behaviour for respiration and digestion of foods is vermiculation of the respiratory and digestive gut. In some cases, Ascidia forget the vermiculation and they abandon their respiratory or digestive movement for wave sway. After that they lose their muscles, concomitantly with nervous tissues. This becomes the kelp, from which the plant develops. Therefore, vertebrate animals and plants are the same in their origin. However, by losing locomotion, the evolutionary mode of plants became completely different from that of vertebrate animals (Nishihara, 1999a,b; 2003b).

8.1.3 The Biogenetic Law and biomechanics in conjunction with gravitational energy

Haeckel presented eight kinds of embryo and foetus in his famous scheme comprising different phylogenic stages. Embryos in the pharyngula stage of mammals as well as birds (Aves) or reptiles are all similar. The appearance of the oronasal region of the adult archetype Chondrichthyes, *Heterodontus japonicus*, is quite similar to that of a human embryo of 35 days. Is there any common scheme or mechanism in biomechanics between them? We can easily find out that both have low blood pressure (*c*. 15 mmHg). Then, is there any common biomechanical mechanism between an adult archetype and adult mammals? In the former, the blood pressure is *c*. 1/6 of that of mammals, and the former is poikilothermic, and mitochondrial energy metabolism is *c*. 1/10 of that of mammals. The former's MHC genes are dormant, therefore, even if they are adult, they are in an immune-tolerant condition (Nishihara, 1998a,b; 1999a,b; 2003). The latter are homoiothermic. The genome size of the former is typically 30 times larger than that of mammals. This means their common enteromicrobes are completely coexistent in intracellularly infected whole cells. The mammals have evolved from poikilothermic animals. Therefore, it is sound health advice to keep one's gut warm. If mammals let the gut and somatic system cool down, the system of the cold-blooded animal is switched on. Numerous microbes are incorporated into leukocytes in Peyer's patch in the gut and they circulate through the cardiovascular system all over the body, disseminating themselves into various organ cells in the capillary regions. Then intracellular infection occurs. After that, mitochondria in cytoplasma get degraded. This is the actuality of intractable refractory diseases (Nishihara, 2010; 2011; 2012).

8.2 Biomechanical energy, hydrodynamics and streaming potential underlie the Biogenetic Law

Gene expression in undifferentiated mesenchymal stem cells occurs by these biomechanical stimuli derived from moving skeletal muscles, motion which is converted to hydrodynamics of blood and lymphatic fluid, engendering a streaming potential. Consequently, osteoblasts and osteoclasts concomitantly with haemopoietic cells were induced as metaplasia. This is an impelling force of the metamorphosis of skeletal mesenchymal stem cells, which is related to the functional transformation caused by biomechanical energy in individual vertebrates.

The most important characteristics of higher (vertebrate) animal life is that it has a *remodeling system*, by which the living organism can overcome aging and deterioration with time.

The idea is that creatures move repeatedly with some constant behaviour on Earth (with constant gravity); then remodeling gradually changes the animal body.

The conventional evolutionary hypothesis ignores energy and the remodeling system of vertebrate life. Biomechanics comprises all physical energy including gravity and all physical as well as chemical properties of matter with mass.

The author read the riddles of the evolutionally mechanism of vertebrates and proposed the "Gravitational Evolutionary Law" (Nishihara, 1998a,b,c;1999a,b; 2000; 2003b; 2004d).

After that he started to tackle the three great issues in modern medicine and life science, which are still unsolved. Two of the issues, namely the unified control system via mitochondria and the aetiological factors of

and therapeutic methods for major refractory maladies, have already been reported (Nishihara, 2010; 2011; 2012).

8.3 Observing gravitational effects on cultured chick embryos

The present author's teacher, the great morphologist the late Prof. Shigeo Miki, engaged in biomechanical ontogenic researches using cultured chick embryos. He could observe their developmental processes. Let us examine this work in some detail (Miki, 1983). During precise observation of the fertilized egg of a chicken in the early stage of ontogeny Indian ink was injected into the branchial vessels near the chicken heart from the initial stage of chicken ontogeny until the end of the embryonic stages, after that developmental metamorphosis was observed. It is well known that the embryo on the fifth day after fertilization corresponds to the terrestrialization of the vertebrates, i.e., the second revolution in evolution during the Devonian epoch. On the sixth day, the embryo suddenly loses vitality and sometimes dies. In this stage, embryos reproduce landing (i.e., terrestrialization), induced by the life-memory of genes in the embryo. In ontogeny, one to two hours correspond to 300 million years in phylogeny. The healthy embryo became weak as if it fell ill, panting very feebly. Until then the ink was incorporated smoothly into the vessels, but at this stage, the ink did not stream and broke off. Then, Miki hit on the idea that this was exactly the reappearance in ontogeny of the second revolution of vertebrate evolution in phylogeny (in the Devonian epoch). Namely, at this stage, when gene expression occurs, the embryo has the Paleozoic life memory of the Devonian, after which the blood vessels of the branchial system changed into that of the lung respiratory system. The relationships of gene function between phylogeny and ontogeny explain the concept of heterochrony in gene expression, as proposed by the late Pere Alberch; according to his theory, gene expression in the embryo occurs when it is induced by the memory of the Devonian (Alberch, 1994).

The embryo recovered after this stage, then the embryo with its branchial system changed into the foetus with a beak, which looks exactly like a chicken. In his book, Prof. Miki remarked that "quite a great metamorphosis from the shark-like embryo with gills to a chicken-type foetus with a beak was observed". He saw that the chicken behaved as if "our ancestor had been truly a shark." From this ontogeny research we can experience the evolutionary process of vertebrate phylogeny by using living embryos, because in their ontogenic development there are remarkable stages of metamorphosis after fertilization; i.e., cleavage, morula, gastrula, neurula, pharyngula and, after that, foetus development. After reading the book, the author realized that the embryo, quite resembling the ancient shark, growing weak as if it were sick, was actually repeating the process of terrestrialization in the Devonian 400 million years ago, writhing under sixfold increased gravity after landing (Miki, 1983).

8.4 The blood pressure of archetypical Chondrichthyes (sharks) in seawater and the human embryo or foetus in amniotic fluid

In seawater, gravity is weakened sixfold due to buoyancy,[4] therefore, concomitantly, the blood pressure of the great shark is only 15 mmHg. The human foetus in the amniotic fluid of the placenta has 15 mmHg blood pressure, just the same as that of the shark. After delivery, the baby's blood pressure immediately becomes 30 mmHg. An anaesthetized immovable shark with low blood pressure becomes red in the abdomen owing to congested blood, and soon dies after 10 or 15 minutes.

However, after writhing around to seek water the sharks increase their blood pressure to 30 mmHg. They can survive landing by air respiration via branchial gills. Thus, only the higher vertebrates that had accomplished landing (terrestrialization) could survive in strong gravity without buoyancy. Subsequently gene expression of undifferentiated mesenchymal cells occurred. After that various kinds of metaplasia were brought about in tissues and organs by the gene expression.

Therefore, increased blood pressure adjusted to accomodate sixfold increased gravity during landing is one of the most important causal factors of evolution of the vertebrates. They naturally utilize gravitational energy not only for evolution but also for life activity from the initial stage of their evolution.

8.5 Biomechanics and the Biogenetic Law—reading the enigma of immune tolerance via the dormant MHC genes

In the early ontogenic stages, marked metamorphosis in the embryo occurs, i.e., the stages of gastrula, neurula and pharyngula, corresponding to the phylogenic stages of the ascidia, the amphioxus and the Chondrichthyes (shark). In ontogeny, up to the pharyngula, it is called an embryo, after this it is called a foetus. Underlying the metamorphosis of animals in phylogeny is biomechanical

[4] We recall that when studying ontogeny and phylogeny, we need to study Cyclostomata and Chondrichthyes which, like the embryo and foetus, have no lungs or other buoyancy devices.

energy including gravitation. In other words, the impelling force of the metamorphosis is long-term repeated biomechanical energy derived from animal behaviour and gravitational energy, both of which vectors are synthesized.

From the viewpoint of tissue immunity, immunotolerance has conventionally been well recognized in the embryo or foetus. This phenomenon can be observed in the successful transplantation of tissue or organs between animals and their foetus or embryo. In conventional life science, it is an established theory that the foetus and embryo have no tissue immunity. Also, in archetypical sharks and Cyclostomata, the existence of MHC genes has been demonstrated. Needless to say, the foetus or embryo of mammals have MHC genes. The present author has noticed a close correlation between the archetypical vertebrate Chondrichthyes (sharks) in seawater and the embryo or foetus in amniotic fluid in the placenta from the viewpoint of gravity. In both cases, the common environmental energy factor is decreased gravity, which becomes *c*. 1/6 *g* in seawater or amniotic fluid because it is diminished by buoyancy. He guessed that the MHC genes are dormant in both foetus and archetypical vertebrate (shark); therefore, body parts of animals in seawater which have never experienced landing, can be transplanted into other animals. He inferred that the MHC genes should be triggered automatically by increased blood pressure after landing. At the corresponding time, all foetoglobulins change to the adult type (Nishihara, 1998a,b; 1999a,c; 2000; 2003c; 2004e).

8.6 Verification of MHC dormancy by xenotransplantation

The present author proposed the immunotolerance of the embryo in higher animals to be due to dormant MHC genes. There is an analogy between the archetypical vertebrates in seawater and the embryo in amniotic fluid. The author discovered that in all the archetypical vertebrates, the MHC genes are dormant even while they exist. This means that their organs or tissues can all be transplanted into other animals; i.e., xenotransplantations or interspecies transplantations must be possible.

Therefore, he attempted transplantation of the skin of Triakis to that of another individual and to that of Heterodontus (Nishihara, 1998b), the skin of Xenopus to that of Triakis (Nishihara, 1998b; 1999c), the skin of a rat to that of Triakis (Nishihara, 1999c), the skin of Cyclostomata to that of a rat, the cornea of Triakis to that of a dog (Nishihara, 2001; 2003c; 2004e), and a part of the gut to that of a dog (Nishihara, 2003c; 2004e). The spinal cord of Cyclostomata was transplanted to two ischiadicus nerves of rats, of which human beings or dogs have only one but rats have three. Hence all three were cut out and two were recovered by transplantation. All of these transplantations were successful. From these experiments the author has inferred that the immune system is part of the evolutionary system.

9. Evolution after landing (terrestrialization)

9.1 Osteichthyes (bony fishes), Amphibia and Reptiles developed from Triakis-type sharks

There are two kinds of typical shark, i.e., the common shark type called Triakis and the special large round-headed shark called Heterodontus. On the lower jaw of a shark, which derived from the first branchial cartilage, there is a large fixed tongue at the centre of the caudal portion of the lower jaw.

Dissecting the head and the fixed tongue of the shark saggitally, there, in the tongue, laminated branchial muscles on the top side and at the bottom of the caudal side a rather large branchial heart can be observed, surrounded by the pericardiac cavity; on the bottom caudal side of the heart there is a diaphragm of thin fastia, separating it from the liver. The tongue of the shark is constructed with branchial respiratory muscles and the heart including the diaphragm. By means of rhythmical contraction and release of the laminated branchial muscles via the branchial skeletal cartilage, the gill respiration movements of the branchial respiration system are carried out. The heart is also derived from the gill branchial muscles of the left and right sides, and it carries out the blood circulation through the blood vessels in gill cartilage. Therefore, it is called the branchial heart. The author is convinced that Triakis-type Chondrichthyes after landing became bony fishes, amphibia and reptiles. All of them have in common thin long tubular lungs along with thin long kidneys that extend to the abdominal cavity. Their diaphragm has nothing to do with respiration. Only bony fish acquired bone marrow haemopoiesis after landing, they lived on land after that, again they went beyond mountains into freshwater lakes or rivers. Therefore, their lungs changed into the air bladder.

9.2 Mammals developed from Heterodontus-type sharks

There are only four kinds of Heterodontus in the world. By using *Heterodontus japonicus* (dog shark) the author carried out various kinds of researches and observations. The signification of "heterodont" is the characteristic teeth of mammals. Therefore, from the viewpoint of odontology, "Heterodontus" has a profound

connotation. The dog shark actually has heterodonts, i.e., differently shaped teeth in the front, side, and molar region, namely incisors, canine, and molar types. Besides this they have masseter muscles and a remarkably large heart with a pericardiac sack occupying the full width. At the bottom site of the gill clefts, five branchial muscles protrude together to attach the pectoral fin cartilage, which is connected to the diaphragm as well as the pericardiac sack containing O_2 and CO_2.

When sharks swim with reciprocal movement of pectorial fins, the pericardiac sac concomitant with the diaphragm moves rhythmically according to the swimming fin's reciprocal movements; simultaneously, cardiac beats are supported via the air cushion of the sac around the heart. Only dog sharks and rays have heterodontia teeth. These Chondrichthyes eat whole corals and turban shells as well as crustaceans (e.g., lobsters and crabs), with an eating manner resembling mastication, their teeth having developed to achieve masticating dynamics with the crustaceans. By the acquisition thereof, naturally heterodontia development and masseter muscle growth occur. Therefore, the cardiovascular system is necessarily and extremely strongly developed.

9.3 Experimental evolutionary research methods revealing the real process of evolutionary metamorphoses

The author has proposed that animal evolution occurs not only by biomechanical energy in conjunction with gravity but also by the medium change from seawater to air, changing the physicochemical stimuli. He developed revolutionary research methods (experimental evolutionary methods using archetypical vertebrates). He applied increased gravitation to them as well as the physicochemical stimuli of the air instead of water (artificial landing). He used two kinds of lower animals: firstly, the archetypical vertebrates *Heterodontus japonicus* and Triakis to investigate changes from the branchial gill system to the lungs; secondly, axolotls (Mexican salamanders) to observe the changes of the gill arch, gill pouch and the skin as well as the skeletal and cardiovascular systems of the larva-type adult salamander to the reptile type salamander by forcing them into artificial landing from water (Nishihara, 1998a).

9.3.1 Artificial landing of Heterodontus japonicus *and Triakis—observing air cells in the pericardiac sac of the former and air cells along with the kidney and abdominal cavity of the latter*

Two kinds of sharks that are about 50 cm long were forced to land for an hour a day for ten successive days. On each day they writhed instinctively for an hour in order to survive. After that the author dissected them around the heart thorax and abdominal cavity, and the following results were obtained.

In *Heterodontus japonicus* development of two small air cells (with the right side air cell being larger and the left side one smaller) were observed between the inner and outer membranes of the pericardiac sac (Nishihara, 2003c). The latter becomes the diaphragm after the lungs are developed (Nishihara, 2003c). The right and left air cells correspond to development of the lungs of mammals. On the other hand, in Triakis development of connective tissue with numerous air cells was observed between the cartilage skeleton of the chest fins and the pericardiac sac, which form a tube-like duct along with the strand-type kidney into the abdominal cavity on the right and left sides. The results of these changes are quite similar to the lungs of amphibians or reptiles. (Nishihara, 1998a).

9.3.2 Artificial landing of several larvae-type adult salamanders

Artificial landing experiments using 20 cm long salamanders kept in fish tanks was carried out. For three months the level of water in the fish tanks was gradually decreased. After that they remained for one month with water at the bottom of the tanks. Then they were forced to land.

To observe histological changes of the skin, the skeletal cartilage, the gills, the lungs, the tongue and the heart of the salamander engendered by the landing process, several diachronic specimens were prepared. In each organ or tissue remarkable histological changes were observed, especially in the heart (3 months after landing), which had to cope with markedly increased gravity after landing. Adult salamanders of larval type developed into the reptile type only in four or five months. In the Devonian period archetypical vertebrates with gills evolved into the reptiles over *c*. 100 million years. Thus, evolutionary changes are reproducible by means of applying energy and matter influences (Nishihara, 1998a; 2000).

9.4 The distinction of the developmental system of the lungs

9.4.1 Differentiation of the mammals and the other classes

Only in the Heterodontus-type shark group, the lungs developed in a pericardiac sac around the heart during the landing process in the Devonian period. The branchial respiratory system, which is the haemopoietic system of the erythrocytes, was formed with the capillary,

respiratory epithelium and blood vessel system, developing into the pericardiac sac. This phenomenon is quite similar to the development of haemopoietic sites from the viscera of the gut into the somatic skeletal bone marrow.

The mode of development is as follows; at the initial stage of landing, the shark writhed and struggled because there was no seawater; by the vigorous movement blood pressure became higher, as the result of overwork of the heart (cardiac functions), which released gas (O_2 and CO_2) into the pericardiac sac through the thin cardiac wall from the blood corpuscles and serum. The gas accumulation around the heart soon reached a limit, then the pericardiac sac at the joint moiety of the tongue ruptured into the oral cavity, allowing air containing more oxygen than in seawater into the pericardiac sac; metaplasia to the respiratory cell system of the mesenchymal stem cells on the surface of pericardiac sac occurs.

In the pericardiac sac, the respiratory lung system developed only in the dog shark, which developed into the mammalian-type reptiles. Among the vertebrates only the mammals have no pericardiac cavity (Nishihara, 2003c).

9.4.2 The external respiration system; erythrocytes induced by oxygen via gene expression of mesenchymal stem cells

The reality of the external respiration system cytologically induces the erythrocytes via a catalytic effect exerted by oxygen. Typical of the most primitive examples is cutaneous respiration in amphibians, as can be observed in the subcutaneous layer of external gills of axolotls (Mexican salamanders) that have landed from water by means of the experimental evolutionary studies developed by the present author. In the early stage of landing round red spots lining up are observed in the subcutaneous region, in which many erythrocytes are crowded.

9.4.3 The origin of the mammalian-type reptiles; Heterodontus–Chondrichthyes, from which the mammals evolved

From the aforementioned thoughts and experimental results, the author infers that only Heterodontus (the dog shark) could develop into the mammals via mammalian-type reptiles. Let us compare the shapes and mechanics of all of the apparatus or organs of the branchial system of Triakis and those of Heterodontus. The spiracle derived from the first branchial cleft concomitant with Meckel's cartilage of the first branchial skeleton become the conductive hearing apparatus in mammals (Gaupp, 1911a).

However, the system of those of the former (i.e., Triakis) never evolved into those of the latter. As is well investigated, the development of the lungs in relation to the heart, the pericardiac sac and the diaphragm did not involve the former. Hence the present author concludes that there is no way for the reptile system to develop into the mammalian system, as it is conventionally believed (Nishihara, 2003b).

Surveying the mammals from the viewpoint of the author's newly formed evolutionary system, not only dogs, cats, raccoon dogs and seals, but also elephants, whales and dolphins through to koalas and kangaroos, all biodiverse mammals have the same system and the same mechanisms concerning the external respiratory apparatus; i.e., the nose, bronchus, lungs, heart, and diaphragm (Nishihara, 2003b).

As to their auditory conductive hearing apparatus, the system and mechanisms are all fundamentally the same in terms of comparative anatomy, although the appearances of these organs are quite different. That is to say, from the single grand design of the Heterodontus-type Chondrichthyes, mammals have developed into various types of striking diversity (Gaupp, 1911b).

10. Evolution of the immune system

10.1 Radical difference between poikilothermic animals and homoiothermal mammals. Comparison between the poikilothermic archetypical lungfish and homoiothermic mammals

10.1.1 The poikilothermic animals

The most important feature distinguishing poikilothermic animals from homoiothermal mammals between them is genome size: the genome size of the former is *c*. 20–30 times larger than that of the latter. The lungfish has the largest genome size among the vertebrates: viz., 30 times larger than that of the mammals. It has been proposed that this astonishingly larger genome size was caused by junk genomes derived from intracellular infiltration; i.e., infection by common enteromicrobes. In poikilothermic (cold-blooded[5]) animals, it is said that about 100–300 million years ago, enteromicrobes were incorporated completely into leukocytes (granulocytes) and were disseminated via blood circulation into the capillaries and into all their body cells.

Poikilothermic animals have their characteristic gut system, through which enterobacteria and viruses are absorbed into leukocytes, and these contaminated

[5] "Cold-blooded" implies a low metabolic rate at the cellular level.

leukocytes circulate throughout the body, disseminating microbes all over it. Consequently, all of the body's cells are contaminated intracellularly—genes of the contaminating bacteria and viruses enter into the chromosomes of the cells.

10.1.2 Homoiothermal mammals

Mammals and birds have evolved from cold-blooded animals; therefore, if they cool their gut, the features of cold-blooded animals start to operate in them so that stem cells in Peyer's patch incorporating enteromicrobes automatically change into contaminated granulocytes circulating all over the body, disseminating the microbes into various tissue or organ cells. Thus, intracellular infection by nonpathogenic enteromicrobes occurs. Bringing enteromicrobes into the stem cells in Peyer's patch in the gut of homoiothermic animals is also a gene expression phenomenon of the leukocytes (Nishihara, 1994a; 1996a; 1997a,b; 1998; 2003a; Nishihara, 1989; 1991a,b,c; 1992a,b; 1993; 1994b; 1995).

Having introduced cooling thermal energy and overloaded gravitational energy into the treatment of refractory diseases having hitherto unknown causes, the author has proposed the new concept of intracellular infection of nonpathogenic common enteromicrobes into leukocytes (granulocytes), which disseminate the enteromicrobes into organ and tissue cells. These intracellularly infected organ cells are the real causes of these intractable refractory immune diseases, by which mitochondrial deterioration occurs.

Mitochondrial deterioration with intracellular infection can be easily understood by considering the aforementioned cold-blooded animal examples. It is an established theory that mitochondria are some kind of rickettsia-like proteobacteria, which had been incorporated into eukaryotae *c*. 2 billion years ago; therefore, enteromicrobes of nonpathogenic and/or feebly virulent ones can be commonly incorporated into various kinds of tissue or organ cells.

Thermal energy also triggers gene expression of nuclei as well as mitochondria. What are the differences between cold-blooded (poikilothermic) animals and warm-blooded (homoiothermic) animals? Generally, blood pressure of the former is lower than that of the latter. Blood pressure bears some relation to gravity (see §2.2). On the other hand, gravity influences animals in the circulating medium of bloodstream and lymph (via the cardiovascular system as potential energy). Therefore, monocellular organisms or cultured mammalian cells without a cardiovascular system can live under 10 000 *g*. On the organism of monocellular bacteria as well as protozoa, which are tiny pieces of matter governed by a Reynolds number less than unity, gravity has no effect because the viscosity of water is far stronger than the force of gravity. Hence, gravity influences blood pressure only in multicellular animals (Nishihara, 2011; 2012).

10.1.3 Brain resuscitation via cerebral hypothermia treatment provides vital examples of the energy-based evolutionary law—warm-blooded human beings can be easily transformed into poikilothermic animals

Brain hypothermia was developed as a method by Prof. N. Hayashi after the discovery of a new mechanism of brain damage occurring when brain temperature exceeded 40 °C in patients with severe head trauma (Hayashi, 1998). After developing the methods, he carried out surgical operations in the temperature range 32–33 °C, and these operations were completely successful. After that, the patient was able to recover at the normal temperature of 37 °C but soon after that the patient died. He was surprised and investigated the patient completely, and found out that the cause of death was severe sepsis by common intestinal microbes via cooling the total body so low (at 32 °C). As the septic microbes were common enterobacteria and viruses, he tried complete irrigation of the intestine before brain surgery under hypothermia was carried out. After that he achieved completely successful hypothermic cerebral operations.

By cooling the total body temperature by 5 °C below the normal 37 °C, the body system of homoiothermic mammals changes into that of poikilothermal animals. Because their mitochondrial energy metabolism is *c*. 1/10 of that of mammals, and their blood pressure is *c*. 1/6 of that of mammals, all the cells in the body essentially change into poikilothermal animal cells, in which leukocytes incorporate a great number of enteromicrobes. Through M cells in Peyer's patch they are disseminated all over the organs and tissues in the capillary region. All these enteromicrobes are incorporated into the entire body intracellularly, then the genomes of the enteromicrobes are incorporated into the chromosomes in the nucleus as "junk" genes. This is the system of the poikilothermic animal cells.

Because the energy metabolism of their mitochondria is so low, even a great number of enteromicrobes intracellularly co-existent does not lead to deterioration of the mitochondria, nor to degradation of cell functions. As (higher) homoiothermic mammals evolved from the archetypical poikilothermic animal, if their the body temperature falls by 3 to 5 °C below the normal 37 °C, all cells in the human body effectively change into those of poikilothermic animals.

Human beings should therefore be on guard against allowing the gut to cool; e.g., by the habits of breathing through the mouth and not taking enough sleep. If not, severe intracellular contamination of enteromicrobes takes place. This is retrogressive evolution, meaning that the system of homoiothermic mammals returns to that of the poikilothermic animal (Nishihara, 2011).

10.1.4 Human beings as mammals

All highly developed mammals, including the human race, have been developed from the archetypical Chondrichthyes. Therefore, at the early stage of phylogeny in evolution, they were once cold-blooded animals. Hence, the mammals can easily revert to the aforementioned poikilothermic gut system when their whole body temperature becomes markedly lower than the homoiothermal mammalian body temperature.

When that happens, contaminated granulocytes (leukocytes) disseminate microbes all over the body. Then, intracellular infection by common enteromicrobes occurs in various organs or tissue cells. In these intracellularly contaminated cells, mitochondria become deteriorated. This condition is that of an intractable refractory disease at cellular level. Therefore, in a person who allows his gut to cool, intracellular infection occurs just like in poikilothermic animals. This means regressive evolution has started and human beings come to have a likeness to cold-blooded lungfish, with its plethora of "junk" genes. Patients with intractable refractory diseases caused by the deterioration of mitochondria, which are triggered by severe intracellular infection by common enteromicrobes, are on a path of regressive evolution towards extinction of the human race.

11. Verification of the Gravitational Evolutionary Law from the viewpoint of Lamarck's Use and Disuse Law

11.1 Evolution concerning morphology

The evolutionary phenomena are separated into three categories; viz., morphology, function, and molecular evolution, all of which are related to the genes. The author has demonstrated that Lamarck's Use and Disuse Law and Haeckel's Biogenetic Law both come from the same theory of biomechanics in conjugation with Newton's Universal Gravity Law, which is in close correlation with the essential function of genes. Genes have various and numerous functions—e.g., protein synthesis, carrying out metabolism, remodeling, cell division and differentiation, and reproduction—all of which are integrated and synthesized for the essential function of inheritance of the biomechanical behaviour patterns of animals. *The essential and ultimate function of genes is to transmit behaviour patterns of the animals*. This can be clearly seen from the instincts of animals and even bacteria. Biomechanical behaviour patterns *qua* instincts are certainly inherited by new-born babies of mammals. For example, consider the most important instinct of suckling: they know how to do it by instinct and other details are learned through experience.

Concerning shape, the long-term repeated behaviour patterns of animals determine animal morphology according to Lamarck's Use and Disuse Law. Since behaviour patterns are inherited by animals, therefore any newly obtained animal morphology via newly acquired behaviour patterns is necessarily inherited. This is Lamarck's inheritance of acquired character. The genes can never simply decide the morphology, but the behaviour patterns are inherited; shapes are decided indirectly. In ontogeny as well as phylogeny the behaviour patterns induced by environmental factors determine morphology (Nishihara, 2003b).

11.2 Evolution concerning function

Concerning functional evolution, we can observe various phenomena associated with Lamarck's Use and Disuse Law in the second revolution of vertebral evolution; i.e., landing (terrestrialization).

Gill respiration changed into lungs with the drastic medium change from water to air. On landing gravity effectively increased sixfold. To survive, the shark writhed, and after that blood pressure increased. By these drastic changes, the pericardiac cavity of the Heterodontus Chondrichthyes was enlarged, because of the accumulation of air out of the blood circulation through the thin heart muscle into the cavity. Then the accumulated air around the heart ruptured into pharyngeal region, after which air entered the cavity, then the mesenchymal stem cells in the pericardiac sac changed into respiratory epithelium resembling gill-erythrocyte-generating tissue. From the sac the lung developed (in the Devonian period). These functional changes are induced by metaplasia. The increased blood pressure also induced ossification concomitant with bone marrow haemopoiesis from the cartilaginous cells, also by metaplasia via the increased streaming potential acting as catalyst induced by the blood circulation (Nishihara, 2003b).

11.3 Evolution concerning the immune response to nonpathogenic common enteromicrobes and tissue immunity of MHC

As already described in §§4.3 and 10.1, the immune system of archetypical vertebrates (i.e., cold-blooded animals) against common enteromicrobes and obligate

intracellular parasites is quite different from that of warm-blooded higher vertebrates (i.e., homoiothermal animals). The genome size of the former is *c*. 20–30 times bigger than that of warm-blooded animals. These tremendous "surplus" genes in poikilothermic animal are all junk genes from common enteromicrobes, with which the animals completely coexist intracellularly. Genomes of coexisting enteromicrobes are incorporated into the chromosomes of the animal cells as junk genes.

In cold-blooded animals, the leukocytes never digest intracellularly infected enteromicrobes. Because of the low level of mitochondrial respiration, microbes can coexist in the cytoplasma with mitochondria, which were derived from rickettsia-like proteobacteria and parasites in eukaryota cells *c*. 2000 million years ago. In the poikilothermic animal, common enteromicrobes as well as obligate intracellular parasites can coexist completely without mitochondrial deterioration. This is the immune tolerant condition. It is the most important difference of the immune system toward common enteromicrobes and obligate intracellular parasites as well as common enteroviruses from that of higher homoiothermic animals.

Another important difference of the immune system between cold-blooded and warm-blooded animals concerns tissue immunity; i.e., the enigma of dormant MHC (cf. §§4.3, 8.5, 8.6 and 10). Based on Haeckel's Biogenetic Law, both archetypical vertebrates and embryos or foetuses of homoiothermic animals live under 1/6 *g* in seawater or in amniotic fluid; therefore, tissue immunity MHC is dormant. Immune tolerance was demonstrated experimentally in the embryos of homoiothermic animals and in archetypical Chondrichthyes (Nishihara, 1998a,b; 1999a,c; 2000; 2003c; 2004e).

11.4 Molecular evolution of animal genes

When the higher animals are engaged in newly obtained behaviour patterns, they acquire new shapes. The essential function of genes is transmission of behaviour patterns of animals; therefore, this acquired character is inherited. After long time elapses, point mutations occur in the genes of the genital cells, then new species with different proteins in various organs or tissues develop. This is molecular evolution, which occurs without objectives as well as without evolutionary relations with shape and function.

The phrase "ontogeny recapitulates phylogeny" means that the life memory in the phylogenetic part is reproduced in ontogeny as a biomechanical behaviour pattern in close relation with gravitational energy.

11.5 The gravitational evolutionary law saves human beings from extinction by eradicating intractable refractory diseases; i.e., cancer, immune maladies and mental illness

The present author has shown that three major intractable refractory diseases occur by mitochondrial deterioration through intracellular infection via nonpathogenic common enteromicrobes at the cellular level (Nishihara, 2010). He also showed that evolutionary transitions in shape and/or function occur via not only changes of animal behaviour patterns but also via changes in environmental energy or medium. The author also showed that the MHC genes in poikilothermic animals are dormant.

Bacterial or viral symbiotic conditions should be included in environmental factors. All intractable refractory diseases are in a deteriorated stage of retrogressive evolution (cf. §4.1). The present author developed therapeutic methods using antibiotics as well as antiviral agents in combination with bifidus factors, along with effective bioresonance diagnostic methods. If human beings are to control environmental energy completely, they should never let their gut and body cool down, never breathe through their mouth, and let the bones rest completely every day by getting enough sleep. Then these intractable refractory maladies can be perfectly overcome. This is the way to save human beings from extinction—by eradicating intractable refractory diseases via the new therapeutic systems of energy-based medicine, which are based on the Gravitational Evolutionary Law.

Part III. Establishing the gravitational evolutionary law via odontology

12. Substance with mass—teeth and gravity

Conventionally, evolutionary science has investigated tooth and bone without, however, asking, "What is the tooth?"

Mammalian Heterodontia have three major tooth types on the sites of the jaw: incisors, canines and molars. Mammalian characteristic molars are *tribosphenic tritubercular*. The tooth is the vehicle of masticatory function for cutting and crushing food. Hence, in the mild collisions of food in mastication, food can turn into an easily absorbable state. The tooth–collision system of occlusion and collision between teeth moving in the vertical direction is strictly defined in higher vertebrates. The arthropods like insects, lobsters, prawns and crabs have horizontally moving light jaws constructed from chitin.

13. Construction of teeth and eyes in the embryogenic stage

13.1 Construction of sensory organs in the embryogenic stage

Other important aspects of the tooth can be obtained from histological studies on organ embryology of the teeth and eyes. The constructions of both organs are quite similar with ectodermal as well as embryogenic epithelial– and mesenchymal–cell interactions.

The eye senses light with the retina, which is derived from the diencephalon (derived from the embryogenic ectoderm) and the tooth senses gravity by enamel organs derived from surface ectodermal epithelial cells.

Through food mastication (i.e., the repeated mild collisions via the dental crowns), the tooth can be said to receive gravitational energy on the surface of the enamel of the tooth crown. Then dentine of tooth crown and root, which are derived from the mesenchymal cells of the tooth germ, suffers as a vehicle of mastication force. All of the tooth organs (i.e., dentition as well as mastication apparatus including masticatory muscles) are perfectly supported by the outstandingly large trigeminal nerves in twelve cerebral neurons. In contrast, the retina (derived from the epithelium) perceives light at the bottom of the eye. The embryogenic tooth germ and the eye germ are histologically the same. The eye is a sensor for electromagnetic waves (light energy) and the tooth is a sensor for substance with mass; that is, for energy in the form of hydrodynamic waves during prehension, mastication and crushing food (Nishihara, 2004b,d).

13.2 Comparison of matter and energy in medical science versus quantum physics

Both medical science and quantum physics deal with matter and energy. However, the objectives of life science and medicine and of quantum physics are different. The aims of the former are to disclose not only the mechanism of the systemic life system of animals and to read the enigma of evolutionary phenomena as well as the riddle of the immune system, but also to discover the causes of and therapeutic ways to cure intractable refractory maladies. They remain unsolved even today. On the other hand, the aim of quantum physics is to disclose the construction and relations of the elements, i.e., the atoms and elementary particles including energy, which has no mass. The phenomena of biomechanics as well as metabolism are restricted to the reactions between molecules and matter under the classical Newton's Law of Motion and Law of Gravitation. In animal bodies all biomechanical movements and influence of gravitation are mostly converted into hydrodynamics of the medium (the blood, lymph, and the liquor fluid), which are concomitantly converted into streaming potentials.

For multicellular animals, "intermediary matter"[6] works on most sensory organ cells to induce gene expression. In animals, gravity and biomechanical energy function not directly but are converted into blood pressure. Multicellular animals have two major information systems, viz., the energy information system of somatic 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 organs and constitute the system by which all energy stimuli are converted into humoral information and all digested substances absorbed from the gut into the bloodstream. In animals, substance with mass and energy work together and sustain life (Nishihara, 2011).

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.

13.3 Energy-induced gene expression in the vertebrates

Prokaryote or eukaryote protozoa can live indefinitely in a gravitational field of 10000 *g* but multicellular vertebrata cannot live even for one day in 7 *g* because of the loss of blood circulation in the brain, due to blood congestion in the abdomen. All biomedical forces as well as gravity in animals are converted into fluid movement with

[6] Between energy and mass, such as light, heat and gravity.

hydrodynamic potential energy (blood pressure), just like the ebb and flow of the tide caused by the moon's gravity. Fluid movement (i.e., blood and lymph dynamic flow) engenders streaming potentials, which trigger gene expression in mesenchymal stem cells. Skeletal tissue remodeling takes place by biomechanically repeated movement (Nishihara, 1996a; 1997a, b; 1999a, b). Multicellular vertebrate animals have sensory organs for visible light, not only retinal cells in the eyes but also ectodermal cutaneous epithelial cells, verified in developmental experiments with artificial bone marrow chambers (Nishihara, 1996a; 1997a,b; 1998) as well as the development of the gompholic artificial root (Nishihara, 1989; 1991a,b,c; 1992a,b; 1993; 1994b; 1995; 2003a).

14. Lamarck, Haeckel and gravity

Lamarck and Haeckel knew the life mechanism of higher vertebrate animals. Animals with ultranumerous cells have a rather heavy body, and nutrients and oxygen circulate all through it via the cardiovascular system with adequate blood pressure, overcoming gravitation for the sake of cellular respiration. Higher animals live against gravitational energy without realizing it. Geckos can hang upside-down even from polished glass via van der Waals bonding to the palms of their limbs.

15. Evolutionary science, odontology and gravity

15.1 Evolution and odontology: substance with mass—teeth

The definition and characteristics of the vertebrates include the possession of a bony dermal tooth. The mammalian tooth is morphologically quite a characteristic organ, hence many leading morphologists are engaged in evolutionary research using teeth and fossils. The form of the crown and the root shape of the tooth are correlated with the feeding habits of the possessor. Cuvier, who is famous for establishing paleontology, said that the tooth is the most essential organ for animal life; from it he could guess the form of the viscera, the scalp shape, the vertebral bones and the nails of a creature. Cuvier (1812) proposed the principles of comparative anatomy, namely the principles of subordination and correlation. According to the feeding habits, the form of not only tooth crown and root but also the shape of the jawbone as well as the cranium, the face and limbs and nails are determined.

15.2 Odontologists in the American school of evolution

A particularly famous differentiation theory in odontology was that of trituberculism, proposed by Cope (1883; 1888), Osborn (1888; 1904) and Gregory (1921).

After that, the tribosphenic trituberculism theory was developed by Simpson (1936). Another important theory for tooth morphology is Butler's field theory in the jawbones (Butler, 1941). It implies that the tooth germ of the capsid changes the tooth form when it is transplanted to the molar or incisor site of a jawbone. These results concerning the relation between morphology and feeding habits or the standing site in jawbones were too difficult to enable odontologists to discern a mechanism at that time. These odontologists of the American school were called neo-Lamarckists, because they followed Lamarck's Use and Disuse Law. Cope propounded dynamic evolution theory, which encompassed consciousness and sensation. He supposed that consciousness induces the effort of using organs. By introducing biomechanics into evolutionary science, he could discern an evolutionary mechanism: behaviour patterns, including feeding habits, continued for long enough to determine the morphological as well as functional transformation. This is the biomechanics-based evolutionary law, namely the Gravitational Evolutionary Law (Nishihara, 2000).

15.3 The origin of the mammals is the Chondrichthyes Heterodontus

In odontology, heterodont teeth (i.e., three different types of incisors, canines, and molars according to erupting sites of the jawbones) are the most important characteristics of the mammals.

The teeth form of the mammals in the molar regions is made up of tribosphenic tritubercular molars. This implies the origin of the mammals is the archetypical Chondrichthyes *Heterodontus* (dog shark) (Nishihara, 2003b). They had radiated adaptively, giving rise to the tremendous biodiversity that we observe in the recent past and today. Another difficult issue in odontology is that the tooth has a function of mechanical mastication after eruption. Metamorphosis is determined by feeding habits; character is acquired by the mastication function. This tooth crown and root shape are inherited by the next generation.

Regarding the transmission of acquired characteristics of tooth metamorphosis, acquired after eruption, cf. Butler's field theory about the jawbone site (why the tooth can change its form in the jawbone). We recall that the ultimate essential function of the gene is to transmit behaviour patterns; acquired characteristics concerning the tooth form, and behaviour patterns of mastication, converted into patterns of hydrodynamics (of the blood etc.) are transmitted by the genes. Life memory, whether in ontogeny in the embryo stage or in phylogeny in the adult and growing stage, endures;

almost all hereditary transmissions concerning evolution involve hydrodynamics of blood circulation, which always works to counter gravity. Therefore, Newton's universal gravitation law is the basis of evolution.

16. Introducing energy and massy matter effects as stimuli into life science and modern medicine

It is quite understandable that *energy* induces evolutionary phenomena by means of triggering the gene expression of mesenchymal stem cells. However, it is rather difficult to understand how *massy matter* affects animals and impels evolutionary phenomena. Acting as catalyst, both affect the gene expression of the stem cells, resulting in different kinds of cells developing as metaplasia. The most difficult enigma in morphological evolution is that of mammalian teeth; i.e., the odontology of mammals (§15). The distinction of Lamarck and Haeckel is that they considered environmental factors such as energy and massy matter as physicochemical stimuli.

17. Summarizing discussion

17.1 Considering all kinds of entities relating to evolutionary phenomena

At first, what are energy and substance with mass? The author considers the differences between biomechanics and common mechanics. He has developed trilateral research methods integrating biomechanics, molecular biology and morphology, and developed artificial bone marrow chambers and artificial gompholic dental roots made of sintered hydroxyapatite. From the results of these experiments he has inferred that evolutionary mechanisms in the vertebrates occur via various kinds of environmental energy and biomechanical energy acting on animal behaviour concomitant with gravity, as well as the medium change (e.g., from seawater to air); i.e., a substance with mass effect.

Embryological studies revealed that the histology of the eye germ and the dental germ in the embryogenic stage are similar.

Through integrated research to disclose the evolutionary mechanisms, the author has verified that the impelling force of evolution in the vertebrates is a trilateral effect of environmental energy and substance with mass effects as well as the biomechanical force associated with animal behaviour patterns.

Haeckel's Biogenetic Law (i.e., the close correlation between phylogeny and ontogeny) implies that memories of life in biomechanical behaviour patterns of animals in phylogeny are inherited by the newly fertilized embryo. As Lamarck implied, the newly acquired biomechanical behaviour patterns are precisely transmitted to the next generation; newly acquired functional as well as morphological alterations are also inherited.

17.2 Differences between living and lifeless things in relation to gravity

Creatures spend time in eating and breathing. One of the characteristics of living creatures is remodeling in conjugation with energy metabolism. Living creatures can overcome aging (i.e., vital deterioration with time) through remodeling.

Gravitation works upon all things vertically. Therefore, if creatures with their remodeling system are reoriented horizontally, the shape of the creature changes. Adult Ascidia have been stuck on rocks for five hundred million years; the structure and system of their body has not changed at all. Needless to say, as lifeless things have no remodeling system, they essentially stay as they are while gradually deteriorating nonetheless.

17.3 Schrödinger's indiscretion

Schrödinger's *What is life?* (1944) aimed to establish a new concept of molecular biology, introducing the new methodology of quantum physics into conventional biology. He knew little about biology and largely overlooked energy, especially environmental and biomechanical energy including the energy metabolism of mitochondria in cells and life energy, and did not really succeed in answering his question. There are various kinds of life; e.g., viruses, prokaryotae, eukaryotae, protozoa, fungi, plants and animals; i.e., invertebrates and vertebrates. Schrödinger handled all kinds of life jumbled together as if he were a natural historian without a definition of the research subjects of life.

17.4 Lavoisier's belief in caloric and Rumford's belief in energy

In the past it was commonly thought that the images of heat and electricity as real material fluids held sway because they fitted common sense notions. The heat fluid was even given a name, "caloric", and popularized by one of the best scientists of the time, Antoine Lavoisier, who listed caloric as one of the twenty-four elements in his *Traité Elémentaire de Chimie*. By the end of the 18 century, Count Rumford began to doubt whether caloric existed or not. His experiments with the boring of brass cannons in Munich showed that he could generate as much (frictional) heat as he liked just by keeping the boring process going. This convinced him that heat could not be a real material because then the supply of the material would surely have run out at some stage (Fisher, 2004).

Even though Rumford eventually got his experiments right, they still did not convince him of his belief in energy. He simply assumed that caloric must be weightless. He believed that heat is motion and Lavoisier believed heat to be caloric. However, to discover energy's actuality is far beyond the limits of our direct sensory experience,[7] and to arrive at the belief that heat is just one form of "energy", a mysterious, insubstantial entity which, like the soul, we will never be able to touch, see, or feel, but only experience in its different manifestations, was a lengthy process in the history of science. There are many forms of energy (viz., light, electricity and heat, to name just three). Scientists believe that these are all forms of the same basic thing because they can be converted into each other in a quantitative way. The difference between weight and mass has been known since the time of Newton. Mass is an intrinsic property of an object, and does not depend on where the object is. Weight is the downward force that tips a set of scales when the object is in a gravitational field (Fisher, 2004).

17.5 Evolution-promoting factors

Both energy, especially gravity, and the physicochemical properties of massy substance (matter), trigger (one may call them catalysts) gene expressions of mesenchymal stem cells. There are three major sites of evolutionary phenomena in animals:

(1) The interfacial surface sites of animals, where dermal and cutaneous cells physicochemically interact with the surrounding medium (water or air). The most important is the cutaneous respiration system; i.e., the original respiration apparatus, which is necessarily wet.
(2) The skeletal locomotive system, which supports body weight against gravitational energy.
(3) The whole animal body cells, except for the skin. The most important energy working here is gravitation, which is counteracted by blood pressure.

All of these, i.e., the skin, the skeletal locomotive system and the whole animal body cells are influenced not only by thermal energy, atmospheric pressure, and moisture but also by common enteromicrobes as well as parasitic microbes with or without pathogenicity.

Metaplasia transforms cartilaginous cells to osteoblasts, triggered by the increased streaming potential caused by blood pressure that is raised after terrestrialization.

Metamorphosis transforms the branchial gill to the lung respiratory system. Gill respiration was derived from dermal respiration (in water). On landing during the Devonian period, the archetypical Chondrichthyes Heterodontus as well as the Triakis shark survived by writhing against the effectively increased gravity and acquired higher blood pressure. During this struggle for survival, cardiac functions were accelerated, and oxygen as well as carbon dioxide leaked from the blood through the thin heart muscle into the pericardiac sac or air bladder. Accumulation of gas in the pericardiac sac or air bladder reached a limit and it ruptured into the oral cavity. Thus, the sac or bladder become connected to the atmospheric air, in which the concentration of oxygen is thirty times greater in comparison to seawater.

The sac or bladder surface cells, which had been covered with the undifferentiated mesenchymal stem cells, turned into the respiratory cells through metaplasia. That is to say, gene expression of the mesenchymal stem cells took place, catalysed by increased oxygen.

17.6 Massy matter, energy and biomechanics

Einstein asserted that massy matter is a form of energy. Therefore, matter itself has huge potential energy independently from gravity, but it is only released in the course of reactions of the nucleus, where most of the mass of an atom resides. Commonly, we can get useful energy when matter in liquid or solid phase is driven to move. For example, when water, a matter in liquid phase, stays quiet behind a water-storage dam, the energy in the mass of water is in a potential state, therefore no momentum is exerted. However, when it flows downwards as a rushing stream to the powerhouse, the potential energy is converted into electricity. Another example is matter in the solid phase of water, namely icebergs. When they move on seawater they have great momentum (kinetic energy), but if they remain quietly like a continent, they merely have inertia.

Let us consider the effect of biomechanical energy evoked during body movements. Thinking about biomechanics, we should never forget gravitational energy. Higher vertebrate animals like mammals have evolved in the presence of all kinds of environmental energy. All vertebrates live under gravitational energy and they utilize it for their vital activity, but they have no specific organ to sense the force of gravity, apart from the fatigue of movement.

During repeated movements of animal skeletons, biomechanical energy does not influence them directly. The energy is converted into hydrodynamic flow of blood or lymph, which engenders a streaming potential, which triggers (as a catalyst) gene expression of mesenchymal stem cells, inducing osteogenesis and haemopoiesis in

[7] On this point see Bohr (1961), especially pp. 29 and 35.

the skeletal system. When animals with a gut tube in the abdomen run on the earth over a sufficiently long time span, some craniocaudal (oral–anal) polarization of the viscera occurs under gravity, effected by the remodeling system of body cells.

17.7 The vertebrates: characteristic defining substances and organs; i.e., skeletal matters, respiratory organs and gravity

The skeletal organs (bone and tooth) are composed of hydroxyapatite, which is one of the characteristic defining substances of the vertebrates, and which can support the heavy body weight, as well as strong occlusal forces. Regarding the origin of primitive respiratory organs, such as the cutaneous respiratory cells of the extremal gills of axolotl (Mexican salamander), comparative histological studies of the epiderm, the gills and alveolar lungs, using electron microscopies, reveal that both the gill sieves and the lung alveoli constitute the erythrocyte-generating haemopoietic organ system. The bone marrow haemopoietic system is also a respiratory organ system, just like the gills or the lungs.

There is a close resemblance in histology between the embryological tooth germ and the eye germ. The eye is for sight via light; i.e., electromagnetic waves. Then what is the essential nature of the tooth in physics? The essential masticating function is occlusion (collision). In mastication, each upper and lower tooth, made from rather heavy hydroxyapatite, collides with each other, each of which then moves, accelerating in the reverse direction. In a certain manner of speaking, therefore, the tooth is a gravity sensor.

Gravitational energy is the most important for vertebrate evolution. No evolution of the vertebrates occurs without it. The life system of the poikilothermic animals, which have tremendous "junk" genomes of common enteromicrobes in their chromosomes, is quite different from that of homoiothermic mammals, especially regarding the immune system. It may be inferred that the immune system also evolved under gravitational energy.

It is clear that the cause of the three major intractable refractory diseases is deterioration of mitochondria when the gut is cooled, whereupon the immune system turns into that of the poikilothermic animals. In mammals in this cold-blooded condition, a tremendous number of common enteromicrobes are incorporated into stem cells in Peyer's patch, which turn into granulocytes that disseminate the microbes all over the organ cells via the capillaries. Intracellular infection then occurs in various organs or tissue-cells. The name of the disease is given according to the intracellularly infected organs. In the case of intracellular infection of the cerebral neurons, it is called mental illness. If infection occurs in the bone marrow haemopoietic organ, the myelodysplastic syndrome or myeloblastic leukaemia occurs.

18. Conclusions

To establish the gravitational evolutionary law, the author carried out integrated interdisciplinary researches connecting environmental energy, gravitation and biomechanics, and including molecular genetics related to developmental metaplasia through the gene expression of mesenchymal stem cells induced by energy or matter working as a catalyst. These researches are summarized in the five following subsections.

18.1 The cause of mitochondrial mutation; defining mitochondria and their relation to intracellularly parasitizing microbes

(1) The author sought the cause and mechanism of mitochondrial mutation, and discovered its developmental causes—it occurred due to the disturbance of *de novo* cytoplasmic protein synthesis directed by the nucleic chromosomes, because mitochondrial DNA polymerase exists therein. The mitochondrion is considered to have been a parasite of proteobacteria *c*. 2000 million years ago (cf. rickettsia in the eukaryotae). This suggests that even in homoiothermic mammals not only obligate intracellular parasites but also common enterobacteria can easily cause intracellular infection at a low body temperature like in poikilotherms.

(2) The author proposes the new concept of intracellular infection as the cause of the three major intractable refractory diseases (immune maladies, cancer and mental illness). Note that the intracellular infection by enteromicrobes causes the mitochondria to deteriorate, hence marked cell function disturbance occurs.

(3) These results led the author to assert that the smallest unit of life is not cells but mitochondria, which he considered to be the most important individual entity in the animal body.

(4) Mechanism of mitochondrial deterioration: mutation of their biopolymers occurs via deterioration of mt-DNA polymerase, the gene for which exists in the nucleic chromosomes. Metabolic disturbance in the cytoplasm is engendered either by intracellularly infecting microbes or via antibiotics like cycloheximide, both of which disturb cytoplasmic protein synthesis in eukaryotic higher animal cells, including mt-DNA polymerase.

18.2 The mechanism of the great systemic metamorphosis and metafunction in the second revolution of vertebrate evolution, namely landing (terrestrialization)

(1) Inducement of the evolutionary metamorphosis in archetypical vertebrates occurs when Chondrichthyes adapt themselves to these two kinds of changes; viz., the medium is changed from seawater to air; and the effectively sixfold increased gravitation going from the sea to the land, according to Lamarck's first and second laws.

(2) Biomechanical research with living chick embryos revealed that the pharyngula stage corresponds to the stage of landing of the vertebrates in the Devonian period; thus, the metamorphosis of the embryo in ontogeny is biomechanically verified to correspond to the development of the amphibia or reptiles in phylogeny.

(3) Two kinds of drastic changes in environmental factors, namely medium and energy, which promote evolution, are propounded:
   (i) Changing of the ways to receive oxygen, not from seawater but from the atmosphere, induced radical metamorphosis and functional changes in the cutaneous tissues and the pulmonary organ—from gills to lungs.
   (ii) Sixfold increased gravitational energy, from 1/6 *g* in seawater due to partial buoyancy in lungless animals to 1 *g* after landing, also induces radical systemic evolutionary changes in the vertebrates. Writhing around by instinct to survive markedly influenced not only the skeletal but also the visceral muscles, the bone and cartilage, and the cardiovascular system. Blood circulation under increased blood pressure is converted into hydrodynamic energy, which engenders streaming potentials, which in turn trigger gene expression of undifferentiated mesenchymal stem cells (Nishihara, 1998). Consequently, osteogenesis as well as osteoclasis with haemopoiesis occurs, and bone remodeling takes place. These phenomena are called metaplasia.
   (iii) During the second revolution drastic changes from archetypical vertebrates (poikilothermic) to higher (homoiothermic) animals occurred:
      (a) Blood pressure increased from three- to sixfold.
      (b) Embryogenic proteins was transformed into adult-type proteins.
      (c) Dormant MHC changed into active MHC (Nishihara, 1998).
      (d) The genomes of poikilothermic animals are more than twenty to thirty times larger than those of homoiothermic animals, because of the former's immunotolerance to parasitic enteromicrobes due to low energy metabolism, hence their genomes become incorporated as "junk" genomes.
      (e) The poikilotherms' immune system of the cytological digestive system against parasitic common enteromicrobes, dormant because of low blood pressure concomitant with low mitochondrial energy metabolism, changed into the active one of homoiothermic animals. Since mammals evolved from archetypical poikilotherms, therefore, if mammals' body temperature is markedly lowered, immunotolerance against microbes is enabled and in consequence severe intracellular infections occur all over the body.

(4) Haeckel's Biogenetic Law merits fresh scrutiny. There is an analogy between the mammalian embryo in amniotic fluid and the archetypical vertebrate in seawater (both are subject to $\sim$ 1/6 *g* and have dormant MHC genes). Hence:
   (1) Studies on tissue immunity of MHC of archetypical vertebrates and embryos of higher animals in relation to the tolerance of tissue immunity were carried out.
   (2) To verify dormant MHC of archetypical sharks, tissue transplantation between the shark and various animal species were successfully carried out. It was shown that gene expression of MHC is triggered by high blood pressure induced by the increased gravitational energy after landing.
   (3) From the viewpoint of the phylogenic morphological and diminished gravitational energy effect analogy, a comparison of the archetypical poikilothermic vertebrates with the mammalian homoiothermic foetus in amniotic fluid in terms of the tissue immune system and cellular digestive leukocytes immune system, was made.
   (4) Considering the relations between the evolutionary system and the immune system, it was shown that the former comprises the latter: the immune system is part of evolutionary phenomena.

18.3 Evolution of the vertebrates occurs under biomechanical energy concomitant with gravitation as well as the medium change of oxygen. Two kinds of experiments were developed to verify the impelling force and factors of evolutionary change

(1) Trilateral research methods integrating morphology, molecular biology, biomechanics, energy and the physicochemical matter effect as catalysts. In particular:

(i) Artificial dental roots made of sintered hydroxyapatite with the triad dental supporting system were implanted into the jawbone *in vivo*.
(ii) Artificial bone marrow haemopoietic chambers were developed *in vivo*, and implanted in the muscles.

(2) Experimental evolutionary study methods. The gravitational evolutionary law was verified by using two kinds of archetypical animals: the Mexican salamander and the Chondrichthyes *Heterodontus Japonicus*.

18.4 New concepts concerning the gene and genetics of cell chromosomes and mitochondria

(1) The real function of the gene is to transmit animal behaviour patterns. Fundamental behaviours (instincts) are transmitted through the genes; other behaviours are acquired through education by parents.
(2) Energy and matter effects: energy and physico-chemical stimuli trigger gene expression.

18.5 The relation between odontology and gravity

Differences between common mechanical dynamics and biomechanical dynamics are compared with each other (see §§12 and 13.1).

18.6 Cause of illness

Considering the coexistence and parasitizing of bacteria with quiescent mitochondria in cold-blooded animals, they can live without causing any problems. However, if intracellular infections occur in warm-blooded animals with highly functional mitochondria, there is deterioration of the mitochondria, which leads to cell deterioration. This is the cause of intractable refractory maladies. Under some conditions intracellular infection by common enteromicrobes can easily occur in mammals. Therefore, microbes living as human parasites, or common enteromicrobes, whether pathogenic or not, should be considered to be one of the environmental factors in evolution.

18.7 Conclusion of the conclusions

The key factors of the Gravitational Evolutionary Law are as follows:

(1) The most important driving factor in vertebrate evolution is gravitational energy, which is vectorial and generally acting vertically in animals. The second important factor is biomechanical energy derived from the habitual behaviour of animals. Another important factor is the drastic change of physicochemical properties of the medium when some animals came to take oxygen into the body not from seawater but from the air. All energy and physicochemical properties function as stimuli triggering gene expression of the undifferentiated mesenchymal cells (i.e., stem cells) that differentiate into various kinds of specialized cells.
This is called metaplasia in histology and in pathology. Thus, function and morphology originate at the cellular level. The form of animal body organs in evolution are controlled by Lamarck's Use and Disuse Law or Wolff's Law of Functional Adaptation.
(2) For living animal cells both energy and massy matter trigger gene expression of some mesenchymal stem cells, inducing differentiation.
(3) Biomechanical force is converted into hydrodynamic blood flow, engendering streaming potential, which also induces gene expression in mesenchymal stem cells.
(4) Common parasitic enteromicrobes should be considered as an important environmental factor in vertebrate evolution. Maladies caused by intracellular infection cause evolution to regress, ultimately towards extinction.
(5) This regressive evolution can be easily prevented by controlling environmental energy, including gravitation and optimal room temperature. We should, therefore, never let our gut and rest of the body cool down. Also, it is important that we lie down when we sleep, in order to give a good rest to our bones.[8]

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