ADVANCES IN SCIENCE AND TECHNOLOGY
28

MATERIALS IN CLINICAL APPLICATIONS

P. VINCENZINI
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Reprints

9th Cimtec-World Forum on New Materials
Symposium XI - Materials in Clinical Applications
P. Vincenzini (Editor)

Invited Lecture

SUCCESSFUL DEVELOPMENT OF ARTIFICIAL BONE MARROW BIO-CHAMBER USING BIOCERAMICS BY MEANS OF EXPERIMENTAL EVOLUTIONARY STUDY -READING TRILATERAL RIDDLES OF THE VERTEBRATES-

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Artificial bone marrow bio-chambers are developed by means of trilateral research combining phylogeny-ontogeny, biomechanics, and molecular genetics. The authors successfully developed artificial bone marrow bio-chamber of hydroxyapatite(HA) and tricalcium phosphate (TCP)as well as titanium (Ti) with electricity of 10μA current and got award of the originality prize on 32nd Japanese Artificial Organ Society 1994. Combining biomechanical stimuli with biomaterials in animals, experimental evolutionary study is carried out. Hybrid type artificial organ inducing hemopoietic bone marrow tissue can be developed using hydroxyapatite and electric bio-chamber not only in mammals but in chondrichthyes and cyclostomata which are relicts of archetype without bone marrow cavity in internal skeletons. Through this new research method using bio-chamber the correlation between the evolution and immune system is studied and a new concept of immunology as cytological digestion system, as well as new revolutionizing evolutionary theory are proposed. In life science of the vertebrates we have trilateral riddles to be read, i.e., the mechanisms of evolution, the immune system, and bone marrow hemopoiesis. Hemopoiesis is major function of digestive tract of the gut in archetype vertebrates. However, in evolution the hemopoiesis in digestive tract immigrates into bone marrow cavity in higher vertebrates. In this paper trilateral riddles of vertebrates are read through investigating the cause of development of bone marrow hemopoiesis in evolution, by means of artificial bone marrow bio-chamber using bioceramics (hydroxyapatite) as well as titanium electrodes.

The present study is supported by a Grant-in-Aid for Scientific Research (A) (No. 09309003) from the Ministry of Education, Science and Culture, Japan.

1. INTRODUCTION

Hemopoietic nest are major sites of immune system [1]. Phylogenetical changes on hemopoietic nests in digestive tract of archetype into bone marrow cavity in higher vertebrates are a major issue of the evolutionary system [1,2].

The life science is classified under major three categories, i.e., the morphology, molecular biology concerning function and physiology, and molecular genetics of reproduction including tissue remodeling through gene expression. Each science of these three categories represents only one side of integrated life phenomena in an organism. Therefore, to understand characteristics of vertebrates the authors developed trilateral research [5], in which these three categories are integrated by biomechanics.

The definition of a vertebrate is "a chordate having a bony backbone, with the various degrees of ossification". Therefore, it can be said that the bone structure is the defining characteristics of the vertebrates. For this reason, the trilateral riddles of vertebrates, i. e., the mechanisms of evolution as well as the system of immunity and of hemopoiesis in bone marrow in evolved vertebrates can be clarified by investigation of bone characteristics [2]. Therefore, we can read these riddles by investigation on characteristics of hydroxyapatite as well as of the substitute of bioceramics, i.e., titanium electrodes [3-11].

Authors disclosed that remodeling of skeletal organ by biomechanical stimuli is controlled by streaming potentials, which was converted from repeating mechanical loads, i.e., biomechanics in organisms especially in skeletons [8]. Therefore, remodeling of osseous tissue conjugated with bone marrow hemopoiesis can be controlled by electric device as well as hydroxyapatite bio-chamber [7-11]. The authors developed hydroxyapatite bio-chambers and titanium electric bio-chambers with 10μA current. This research is based on trilateral research, which is integrated by means of biomechanics, molecular genetics in remodeling, morphology, and metabolism [5]. Using bio-chamber with electricity or bioceramics we can disclose the mechanisms of Wolff's law of functional adaptation of bone, i.e., the system of biomechanical remodeling in skeletal organ [9].

Applying the trilateral research on archetype vertebrates, the authors also developed experimental evolutionary research methods [9]. By implanting electric bio-chamber into sharks (chondrichthyes), which have no osseous inner skeletons with bone marrow but only cartilage ones, hemopoietic nest resembling bone marrow can be induced in vertebral cartilage.

2. MATERIALS AND METHODS

The following experiments were carried out. Details of experiments are already descried in papers [7-13].

2-1. Development of several kinds of artificial bio-chambers :

① Artificial bone marrow bio-chambers made of HA conventionally sintered by Asahi Optical Co.

② Artificial bone marrow bio-chambers made of collagen-HA composite using high pressure technique [13] sintered by National Inst. for Research in Inorganic Mat.; collagen was extracted from cow skin.

③ Artificial bone marrow bio-chambers made of titanium (Ti) mesh with a 10μA current fabricated by National Inst. for Research in Inorganic Mat [13].

2-2. Following experimental evolutionary studies were carried out using newly developed artificial bone marrow bio-chambers.

Implantation of the artificial bone marrow bio-chambers of conventionally sintered HA into vertebrates which represent each stage of phylogeny:

① cyclostomata (hogfish) ② chondrichthyes (dochishark) ③ amphibian (xenops)
④ aves (chicken) ⑤ mammals (dogs and Japanese monkeys)

2-3. Transplantation of artificial bone marrow bio-chambers into muscles of sharks and dogs , made of collagen-HA composite using high pressure sintering technique.

2-4. Transplantation of Ti bio-chamber with a 10 μA current into muscles of sharks and dogs.

2-5. Arterial bio-chamber of autogenous hepatic organ culture for mammals (dogs).

3. RESULTS

Following results are obtained:

3-1. Three kinds of artificial bone marrow bio-chambers were developed.

3-2. Experimental evolutionary studies were successfully carried out in all cases and osteogenesis conjugated with hemopoiesis could be observed around bio-chambers as follows: ① in hogfish, ② in shark, ③ in xenops, ④ in chicken, ⑤ in mammals. Induction of hemopoiesis in conjunction with osteogenesis was observed by the hydroxyapatite bio-chamber implanted in dogs(45kg) and Japanese monkeys (12kg), 3 months, 6 months and 12 months (Figure 1) after surgery.

3-3. Around bio-chambers of collagen-HA composite implanted into muscles of dogs marked cytological digestive reactions dysplasia resembling with histology of digestive tract of the gut were observed.

3-4. Induction of Leukocytes hemopoiesis was observed by the Ti bio-chamber with 10μA current implanted into subcutis of dogs 4 months after surgery (Figure 2).

FIGURE 1

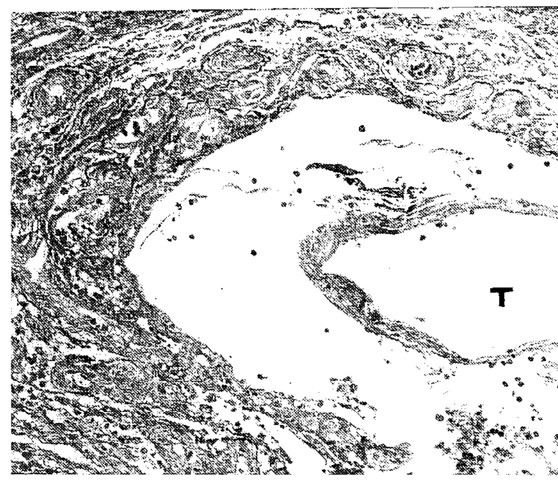

FIGURE 2

FIGURE 1 Hemopoiesis with osteogenesis in HA bio-chamber 12 months after implantation in muscles of Japanese monkey.

HA: hydroxyapatite HE: hematopoiesis OS: osseous tissue

FIGURE 2 Lymphocyte and leukocyte induction around Ti bio-chamber with 10μA current.

T: titanium

Hemopoiesis and osteoid formation were observed 4 months after surgery around the hydroxyapatite bio-chambers implanted in the shark muscles as well as in vertebral cartilage, which had been a part changed into osseous tissue . In a cross section for control of a shark (dochi), no bone marrow in the cartilaginous tissue around the spinal cord was evident (Figure 3). On the contrary, a cross section of a shark with a titanium bio-chamber with a 10μA current, 4 months after surgery marked hemopoiesis in vertebral cartilage was observed (Figure 4).

Figure 5 shows hemopoietic nest in vertebral bone of chicken (arrow), which is quite resembling that of shark (Figure 4) artificially induced by experiments.

3-5. In arterial bio-chambers autogenous hepatic organ of dogs was successfully cultured for 2 months [11]

Artificial induction of hemopoiesis was carried out successfully in all of the newly developed bio-chambers for each phylogenic species. Figure 2 shows the leukocyte and lymphocyte induction around the Ti bio-chamber with a 10μA current in a dog 4 months after implantation. Leukocyte production induced from undifferentiated mesenchymal cells by the electrical current around the Ti was observed. Figure 1 shows induction 12 months after surgery of hemopoiesis in conjunction with osteogenesis by the HA bio-chamber implanted in a Japanese monkey. Osteogenesis as well as hemopoiesis could be observed around the bio-chamber. In dog muscles around the collagen-HA bio-chambers implanted marked tissue differentiation that resembled digestive tract could be observed. On the contrary, in dorsal muscle of sharks around collagen-HA bio-chamber ordinary hemopoiesis was observed. Figure 4 shows a cross section of a shark with a Ti bio-chamber with a 10μA current and Figure 6-right shows findings of polarizing light microscope of hemopoietic nest of the Figure 4 and the left shows findings of polarizing light microscope of dorsal cartilage of control shark. In Figure 7 shows hemopoiesis and osteoid formation in dorsal cartilage 4 months after implantation of the HA bio-chamber in the shark dorsal muscle.

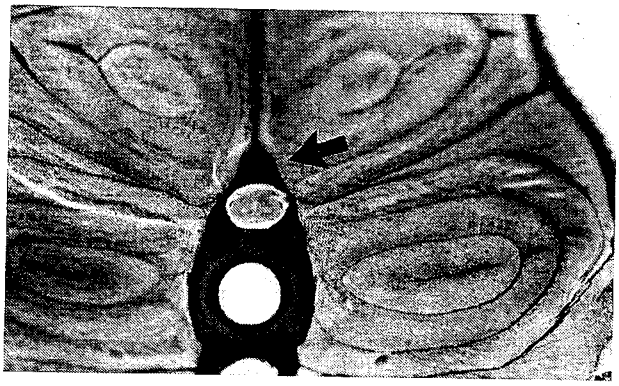

FIGURE 3

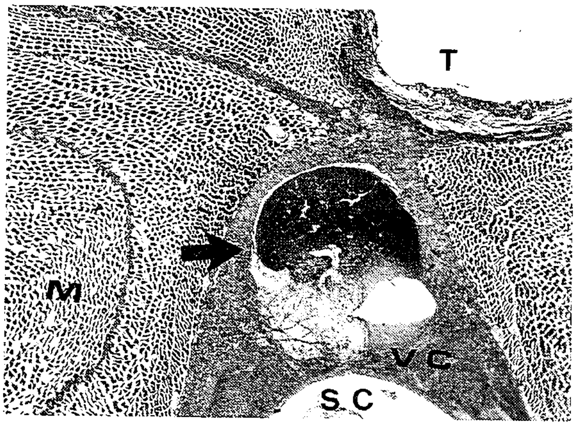

FIGURE 4

FIGURE 3 Cross section of shark vertebra (dochi) for control, no hemopoietic marrow is seen in cartilage (arrow).

FIGURE 4 Cross section of induced bone marrow (arrow) of shark vertebra with bio-chamber of Ti with current implanted in dorsal muscle.

T: titanium M: muscle VC: cartilage SC: special cord

As conclusion, through the experimental evolutionary research methods the authors are able to read trilateral riddles of vertebrates.

4. DISCUSSION

The phylogenetic transition of branchiae into the lung as well as the migration of hemopoietic activity from the spleen to the bone marrow cavity demonstrate the concurrent evolutionary changes of organ structures and functions in vertebrates in response to environmental changes, such as the effect of gravity during terrestrialization from a water environment [1,2].

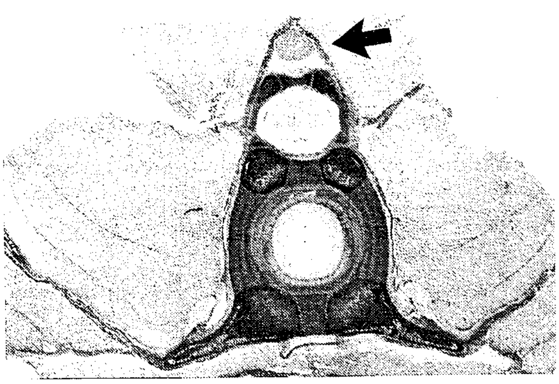

FIGURE 5

FIGURE 6

FIGURE 5 Bone marrow hemopoiesis (arrow) in dorsal bone (vertebra) of chicken, which is characteristic of the vertebrate.

FIGURE 6 Left shows shark dorsal cartilage for control (Fig 3) and the right, dorsal hemopoietic nest of the Figure 4 observed by polarizing light microscope.

The present study introduces a hybrid-type artificial bone marrow bio-chamber that uses sintered HA and tricalcium phosphate (TCP) which is able to induce hemopoietic nest in conjunction with osteogenesis heterotopically in mammalian muscles but not subcutaneous tissue [3-12]. This process is believed to proceed in bio-chambers by heterotopical hemopoiesis that is induced by the streaming potential of sintered HA or TCP, which trigger genetic expression of mesenchymal cells to drive cytocaine of the bone morphogenetic protein (BMP). In order to investigate this hypothesis, the following preliminary experiments were carried out: ① Transplantation of an HA bio-chamber with

BMP into the subcutis [9]. ② Transplantation of an HA bio-chamber with a 10 μA current. ③ Measuring the streaming potential of sintered HA using a physiological saline solution [9]. ④ Transplantation of a Ti mesh with a 10μA current into subcutis [9].

Results of the experiments demonstrated that biomechanical stimuli were converted into streaming of the organic body fluid, ultimately resulting in the induction of a streaming potential [9]. Therefore, the authors concluded that heterotopical hemopoiesis in the bio-chamber is induced by genetic expression of the mesenchymal cells. Based on this assumption, Ti artificial bio-chambers with a 10μA current were developed. To further investigate this theory from a biomechanical perspective, a trilateral research method that integrates morphology (Goethe), molecular biology (Delbrük), and physiology (Bernard) was developed. Based on this research method, the mechanisms associated with morphogenesis and function appear to originate from genetic expression, which are driven by biomechanical stimuli such as environmental factors of the gravity, thermal, and light stimuli.

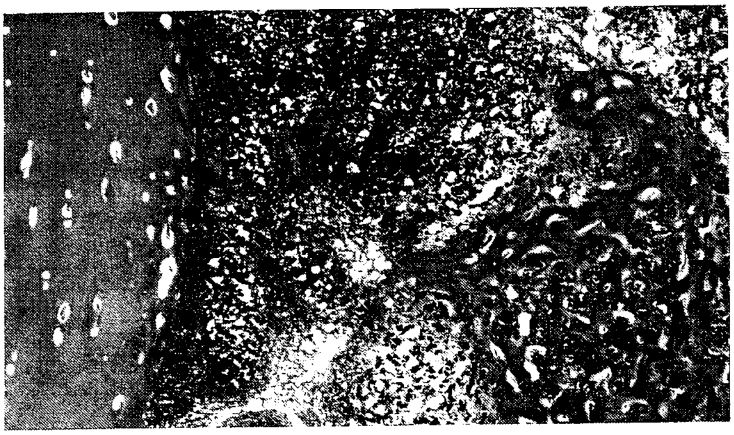

FIGURE 7

FIGURE 7 Hematopoietic nest induced by HA bio-chamber with ossification of cartilage resembling bone marrow in shark vertebral cartilage.

An experimental evolutionary study in which the trilateral research method is employed was first proposed by the present authors Nishihara in 1995 (5, 6). In this study, biomechanical stimuli are applied to biomaterials in sintered hydroxyapatite bio-chambers that have been implanted into various animal muscles during different phylogenetic stages.

A hybrid-type artificial immune organ that induces hemopoietic bone marrow tissue was developed successfully not only in mammals but also in chondrichthyes (sharks), which are relicts of the archetype that does not possess bone marrow tissue in their internal skeletons [11]. Using this method, an in vivo culture of an autogenous liver placed in a HA arterial bio-chamber that is connected to the femoral artery could also be established successfully in dogs [11].

The use and disuse theory proposed by Lamarck has been revived as a result of recent molecular genetic studies. Alberch reported that the Recapitulation Theory (Haeckel) could be explained by the Heterochrony of genetic expression [14]. Conventionally, Lamarck's theory could not be explained in mechanisms by molecular biology. However, the author Nishihara can explain by molecular biology the Use and Disuse Theory as Heterochrony (1997), because all the functions of muscle cells and osteocytes are controlled through gene expression of mesenchymal and neural cells, which are triggered by physicochemical stimuli (also considered to be biomechanical stimuli) that affect the topical cells of the organism [9]. Based on this trilateral research, evolutionary changes in vertebrate morphology can be understood as a series of biomechanical events, as described by Lamarck [9]. Thus, evolutionary changes can be induced at the cellular level in the mesenchyma of heterospecies through biomechanical stimuli. This approach is referred to as an experimental evolutionary study [9].

The present paper investigates the correlation between the immunity system and evolutionary changes. Furthermore, this paper presents a new concept of immunology that involves a cytological digestion system [11], a new theory of biomechanics-responsive evolution [9], and a simple theory to explain biological reactions.

The present series of studies were conducted based on the evolutionary theories of Lamarck, the morphological studies by Goethe, the Biogenetic Law proposed by Haeckel, the biomechanical principles outlined by W. Roux [15], the morphology of organisms presented by S. Miki [16, 17] and the molecular genetics developed by Delbrück [18]. The application of bioceramics to develop hybrid-type artificial organs was based on studies of phylogenetic transformation of osseous skeletal tissue in conjunction with hemopoiesis, that is the evolution of hematopoiesis in bone marrow.

Conventional research has only studied the effects of materials upon tissues surrounding the implanted artificial material. No marked histological changes appear to occur around the porous sintered HA implanted into the subcutis. However, if the HA is implanted into the muscle, marked heterotopical hemopoiesis in conjunction with osteogenesis occur around the HA implant [7,19]. Thus, the response in subcutis appears to differ from that of muscle. Biomechanical stimuli tend to differ between the subcutis and muscle. Therefore, not only the material effects but also the shape and functional effects, referred to herein as biomechanical stimuli, should be examined because the organism is a closed system in which internal pressure exists [11]. The stress distribution patterns around the implants are dependent upon the shape of the implanted biomaterials. Through a trilateral approach using biomaterials, tissue engineering of hybrid-type artificial immune organs can be developed. Furthermore, by introducing gravity as well as low-current energy, a simple theory to explain biology can also be established. New immunological concepts that consider cytological respiration, metabolism, and digestion in conjunction with cell differentiation by gene expression by physicochemical stimuli can also be introduced [11].

Based on the successful induction of hemopoiesis and osteoid formation by a collagen-HA bio-chamber of cow skin, chondrichthyes and cyclostomata did not appear to demonstrate any major histocompatibility antigen complex (MHC). Autogenous hepatic tissue culture was carried out successfully using a HA bio-chamber that was connected to the femoral artery of a dog. All epithelial organs derived from the ectoderm and endoderm showed epithelial-mesenchymal interaction. Because HA is a product of the mesenchyma, the use of a HA bio-chamber for in vivo culture of an autogenous endodermal epithelial organ appears to be the most appropriate bio-chamber [11].

In 1965, T. McCulloch developed the colony forming unit-spleen method during lethal-dose irradiation exposure experiments using mice, one of which he did not irradiate on the tail. That mouse did not die, despite exposure to a lethal dose of radiation over the whole body except the tail [20]. The mouse appeared to recover due to proliferation of stem cells that migrated from the tail bone marrow. E. Thomas successfully applied the principle of this mouse colony forming unit-spleen method to human bone marrow transplantation in order to treat hematopoietic disorders [21], for which he was awarded the 1990 Nobel prize for medicine-physiology.

Based on the colony forming unit-spleen method as well as research on bone marrow cells [21-23] and phylogenetic research on evolution of the hemopoietic organ [17, 18, 24,25], the concept of a hybrid-type artificial bone marrow bio-chamber was developed [26, 27]. As all mesenchymal cells that comprise the body of vertebrates have common genetic codes, undifferentiated mesenchymal cells can differentiate into various types of cells that comprise the skeleton, i.e., osseous and cartilaginous tissues, muscles, bloods, reticuloendothelial cells, lipid cells endothelial cells, tendon, and fascia.

The present results suggest that the trigger for hemopoiesis induction in conjunction with osteogenesis is a streaming potential [26-29] which is converted from fluid flow that occurs due to repeating optimal loads. Cellular functions can be categorized as follows: ① metabolism,② skeletal construction, ③ muscle activity, ④ planocytes and phagocytes for cytological respiration and digestion, ⑤ signal transmission of neural cells, ⑥ absorption of nutrients and oxygen, ⑦ excretion of catabolites, ⑧ support of metabolism for epithelial cells.

Almost all cells are capable of cell division and remodeling, i. e., regeneration. Osseous cells function as a support against mechanical stress. They form the basic skeleton of the organism in response to biomechanical stimuli. Almost all cellular functions are ultimately carried out through genetic expression of each cell.

Morphology, metabolism, and remodeling are all products of cellular function. These cellular functions are also products of genetic expression of cells. Through trilateral research that integrates morphology, metabolism, and molecular genetics of remodeling with responses to biomechanical stimuli, these three different categories can be studied as the same molecular genetic phenomenon with three different features.

Thus, genetic expression appears to be under the control of the general biomechanical stimuli. The present results demonstrate that the migration of hemopoiesis from the spleen into the bone marrow cavity occurred as a result of the gravity that became a factor during the terrestrialization period in evolution. The only difference between archetype vertebrates and higher vertebrates is blood pressure. Mammals have substantially higher blood pressure than do sharks. By loading a mechanical stress of 1G, blood pressure should increase dramatically in sharks that have very low blood pressure in water of approximately 1/6 G with buoyancy.

During terrestrialization, archetype vertebrates (sharks) initially experienced difficulty breathing due to the lack of respiration without water, and writhed in response to the suffocation. As a result, blood pressure increased. During surgery, bleeding was not apparent in most areas of shark muscle. Thus, the gravity appears to be the primary influence on the elevation of blood pressure during terrestrialization. This in turn induced a higher streaming potential [26, 28] than that in the water environment. Therefore, hemopoietic nest migration appears to be a direct consequence of the introduction of the gravity. Furthermore, these studies demonstrate that evolutionary changes in morphology result from biomechanical-physicochemical stimuli such as the gravity , thermal, and light stimuli.

5. CONCLUSION

The present experimental evolutionary study investigates the artificial induction of bone marrow hemopoiesis in heterospecies using not only mammals but archetype vertebrates, which have no osseous bone in their inner skeleton. By implantation of Ti bio-chamber with electricity into dorsal muscle of sharks, bone marrow hemopoiesis is induced in dorsal cartilage, which is characteristic hemopoietic nests of the vertebrates. Through these experiments the mechanism of development and evolution of bone marrow hemopoiesis can be clarified. Based on these results, this study presents a new concept of the immune system, a new theory of biomechanics-responsive evolution, as well as a simple theory to explain biological reactions.

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Successful Development of Revolutionizing Hybrid-type Artificial Root with Peri-root Joint

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Two kinds artificial roof of hybrid-type with peri-root joint have been developed. In the new system of artificial roots, not only morphogenesis but function of peri-root tissue induced after operation are carried out by gene expression of recipient mesenchymal cells. The first system is an artificial root which can induce the peri-root fibrous tissue with cementum around the roots. The second system is artificial root with corrugated shape of inner vehicle which is jointed with elastic materials inside of the outer vehicle. The outer vehicle is correspond to the alveolar bone proper in the jawbone. By both system bone remodeling around the artificial root can be maintained continuously.

Objective This research is aimed to develop artificial root, around which bone remodeling can be maintained perpetually.

Materials and methods Finite Element Analyses (FEA) were carried out to find out superior shape of artificial root. Animal experiments were carried out with newly tailored artificial roots. Specimens recovered from animals were compared with stress distribution patterns of FEA. Also clinical applications has been carried out.

Results Peri-root fibrous tissue with cementum can be successfully induced from mesenchymal cells of recipient animals and patients. Osteogenesis in cortical region and trabecular formation around the alveolar bone proper are coincided with patterns of the Mises equipment and the principal stress trajectory.

Discussion Around ankylotic implant bone remodeling in attaching cortices can not continue over three years postoperatively. Destructive remodeling without inflammation begins to occur after three years postoperatively. Therefore, for sufficient bone remodeling for over ten years, gomphotic joint system as stress breaker is essential. By gomphosis the tooth can be the vehicle system of occlusal multiple force, by which stresses are almost evenly scattered around the root. The gomphotic tooth is the characteristic organ of the mammal. The ankylotic tooth as well as complicated jawbone with entangled articular bones are the characteristic organs of the archetypical reptilian. The author found out from the investigation of establishment of bone marrow hemopoiesis, that the cause of evolutionary changes is biomechanical stimuli in broad sense. Therefore, evolutionary changes can be induced in present animals by biomechanical stimuli in vivo. Thus, artificial inducement of the gomphotic system as well as the ankylotic system is quite easy by biomechanical stimuli applying postoperatively.

Conclusion Two kinds of hybrid-type artificial root with peri-root articulation are successfully developed.