Send Orders for Reprints to reprints@benthamscience.ae

Open Biological Sciences Journal, **2015,** *1,* **1-6**

Open Access

The Role of Disease in Organic Progress

David Sephiashvili*

Tbilisi State Medical University, Oncologic Dispensary, Post Code 0112, Georgia

Abstract: On the basis of some paleontological readings, the main macro evolutionary changes take place **only in the period of ecological crisis**. Since the organic progress is a complication **of the internalorganization** of live systems, it may lead to a logical inference that the indispensable condition complexity of the internal organization is an alteration of homeostasis. But, a stable disturbance of homeostasis is called "disease". **Consequently, disease is prerequisite for the organic progress.**

Disease is a breakage of self-controlling and regulation, including genetic processes. How reads, interprets a damaged cell the hereditary information? In the case of a non-classical transfer of genetic information, the above-stated question deserves a specific treatment. There is reason to assume, that the **"erroneously" or "alternatively" realized genetic information in the damaged cells may become one of the major factor-provider of the evolutionary material**.

The micro-changes of the genetic activity in the damaged cells are not ignored by the "magnifying lens of natural selection". Better adapted organisms survive and multiply successfully.

The complication of the inner structure- an organic progress is an answerable reaction for the influence of pathological factors, which takes place on the historical periods (for example while global ecological catastrophes). The aim of it is a restoration of damaged homeostasis – recovering of flum, by creating the new evolution forms. Typical pathologic processes are the tools for the creation of new forms during the process of organic development (progress).

The excess of pathologic substrate detected at the onset of an individual development, both at the tissue, cellular and molecular levels, confirms that **disease played an important role in the evolutionary transformations.** Complex genetic, metabolic, morphologic changes that take place in embryogenesis are the reflection, in a tiny model, of those pathologic processes, to which adult ancestor embryos had been exposed on the corresponding stages of phylogenetic development, while **ontogenesis itself presents a short history of disease of filum.** By those characteristic nuances of the pathologic changes which take place in the developing organs, we may surmise, which pathology might have been the cause of those changes in the process of the organic progress. **Disease itself is a developing style of living matter**. Pathology, as a process of struggle for survival, is the only way, an essential condition of the progressive evolution. The progressive evolutionary objects were diseased organisms, **"hopeful patients"**. **Pathology is a lack circle of evolution theory, some kind of Terra incognita, where there is hidden the answers of many actual questions of Evolution theory**.

Keywords: Adaptation, disease, environmental conditions, homeostasis, organic progress, pathological process,.

The final goal of the progressive evolution, according to most evolutionary theories, is the adaptation of organisms to the principally new conditions of habitat. Individuals, who better adapt to these conditions, have greater chances to survive; their offspring gain victory in the battle for life and begin to multiply. The less adaptive individuals are doomed to extinction;disease and death are the final phases of this battle.

The environment of living organisms may conditionally be divided intoexternal and internal. With the help of special structures, organisms adapt to external physical, chemical, and biological factors of the environment, whereas other structures are responsible for their adaptation to the inner conditions of existence, by means of providing stability to the inner environment: homeostasis.

Since the organic progress is a complication of the internal organization of living systems, it may lead to a logical inference that the indispensable condition for such reorganization is an alteration of homeostasis, or else the necessity in the reorganization of the inner structure simply disappears.

On the basis of some paleontological readings, the main macroevolutionary changes take place in the period of ecological crisis. During "normal" the periods between crises, stasis was detected [1-3]. Therefore, if the inner balance is not disturbed, there takes place no evolution of structures responsible for the adaptation of organisms to the inner conditions of existence.

*Address correspondence to this author at the Tbilisi State Medical University, Oncologic Dispensary, Post Code 0112, Georgia;
Tel: +9950322346287; E-mail: chveniclinica@yahoo.com

2352-6335/15

A change in the outer environment may beprogressive onlyif it involves stable changes of the inner conditions of habitat;the said changes become pathogenic for the organism. At the same time, a stable disturbance of homeostasis is called "disease" [3-5]. Consequently, morbidity or disease is necessary for the organic progress.

During "normal" the periods between crises, the main cause of elimination of the less adaptive organisms is a competitive activity [6, 7]. The latter appears as a stabilizing factor inside the population. Though in case of an ecological crisis, disease may prove to be the only way for adaptation to the changed adverse conditions of habitat, as a mode of survival of the whole population, the so-called "saving reaction". It may not concern the populations that are less influenced by the ecological crisis. They may remain unchanged or choose another way of adaptation. These changes are best explained by Charles Darwin's theory [8].

In the period of global ecological crisis, morbidity inside the population and the whole biocenosis should be acute.When the influence of pathogenic factors spreads on, the process of recovery may also be prolonged. The only way of recovery and restoration is a reconstruction of old structures and functions in correlation with the new, inner conditions of habitat that is an organic progress. The latter process may be named "evolutionary recovery".

On the initial step of recovery a pathogenic process, the response of organisms to the effect of damaging factors, is not entirely adequate. The process of adaptation is achieved via non-specific, short-termed (e.g. the common adaptation syndrome) and prolonged specific mechanisms, in particular, compensatory hypertrophy of organs, hyperplasia of the damaged cells, which results in the chronic pathogenic process or lethality [3,4,9].

Organisms that are better adapted to the outer and, consequently, to the inner living conditions, under the influence of natural selection, survive and reproduce better. In the process of natural selection, the response of the organism to the action of prolonged pathogenic factors, progressively acquires an adaptive character. Non- specific factors of adaptation are replaced by specific ones on the basis of the adequate adaptive structural and functional changes.

Thus, the complication of the inner structure is an organic progress [6] that can be viewed as a response of the livingsystem to the destruction of the inner living conditions; therefore, it is aimed to recover its homeostasis. Consequently, only disease, as a process of struggle against the unfavorable inner living conditions, might really present an essential condition for the progressive evolution.

In the process of the organic progress, there appear certain groups of organisms with more composite structure which is principally different from that of their ancestors. In the following phases of evolution (until the new turn of the organic progress), there begins an irradiation of the new produced forms initiating different taxonomic units, at the same time preserving the main structural character. Surelyneither all the changes in the outer environment entailed massive pathology within the population, norall the evolutionary changes required diseases, like changing covering color, shape or size of organisms etc. These organisms did not change the main structural plan and have been well studied by Charles Darwin.

Disease is a breakage of self-controlling and regulation processes [3-5]. This is one of the definitions of disease. The destruction of the regulation processes at the genetic level should be revealed in changes of expressiveness of certain genes. Genes can be switched on mistakenly, in an unusual place and time. The mentioned changes, along with "erroneous" switching-on of recessive genes, may become a source of new signs.

The pathogenic factors of the environment causing a destruction of cell and nuclear membranes, endoplasmic reticulum, mitochondria, lysosomesand otherorganelles, changing membrane permeability, and cell metabolisms, may entail a spatial change of the gene configuration, DNA, enzymes (regulatory) and, consequently, destroy the normal process of realization of the genetic information on all its stages.

Any change of temperature, salt concentration, O_2, CO_2, acid-base balance, of biochemical medium within the cell, the intensity and character of metabolic processes which accompany pathology, may also influence the realization of hereditary information [1].

How can a damaged cell read the hereditary information? In the case of a non-classical transfer of genetic information, the above-stated question deserves a specific treatment. At all that, the importance of such factors as the place, the scale and the significance of an epigenetic regulation of the genes activity are being understood only now [1, 10-12].

During different pathogenic processes, such as dystrophy, inflammation, tumor or some other pathologies, the cells begin to produce new substances,whose synthesis is not characteristic of the normally functioning cells (enzymes, hormones, proteins, immunoglobulins and other biologically active substances). There are several mechanisms of ectopic cell secretory functioning which not completely clear [4, 5].

The above-indicated facts allow to admit that the "erroneous" or "alternatively" realized genetic information in the damaged cells may become one of the major factors, even the provider of the evolutionary material.

The micro-changes of the genetic activity in the damaged cells, however insignificant, are not ignored by the "magnifying lens of natural selection" [2, 12-15]. If in the damaged cells, the "erroneously" switched-on recessive gene/genes occasionally prove to be beneficial, they can be realized even in heterozygote position. The probability of their transfer into a dominant position becomes more and more pronounced.

By the destruction of the reparation processes, the pathogenic factors conduce to the growth of genetic changes both in the germinative and in the damaged somatic cells (physiologic theory of mutation process).It is evident that the genetic changes in the somatic cells, as well as the disease itself,cannot be inherited bythe inherited susceptibility induction via the identical pathogenic factors. If the reorganization of genome, separate mutations, and epigenetic changes (e.g. alternative splicing) in non-germinative cells

have an adaptive meaning,the possibility of its replication among the following generations in the process of selectogenesis may beup to 100% [2, 13, 14].

Can the outer factors directly influence the process of evolution? If they are pathogenic, the answer is yes. A damage may be caused by the direct action of pathogenic factors on the organism, these factors are: hypoxia, toxins, infectious agents, ionizing radiation and others. The indirect damaging effect of the outer environment appears in the situations, when individual organs, or systems, with the aim of adaptation and compensation, need to have an excessive hyperfunctioning. The excessive, non –adequate hyper-functioning, the so-called "training" of cells, organs, or systems, results in the exhaustion of adaptation-compen-satory mechanisms and, consequently, the breakage, "the damage of function and structure" [3, 4, 5]. The greater and more intensive the battle for survival, the higher the risk of decompensation of the function and the development of disease.

Ontogenesis is a short-term repetition of phylogenesis, and, perhaps, it may containcertain arguments to the advantage of the above-stated thesis. The character of the structural changes in the developing organismmay help understand the real process of origination of itsphylogenetical ancestor. The anatomy of the organisms on their earlier stages of development amazes us by the scale of pathogenisity, e.g. the massive damage and death of cells. Perhaps, the detected changes only accompany morphogenesis, orthe alteration, inflammation, circulatory destructions and other typical pathogenic processes are the indispensable attributes of morphogenesis.

In the process of ontogenesis, a degeneration and death of cells begin at different sites of the embryo. The especially demonstrative degeneration processes are seen in animals during their metamorphoses: arthropods, amphibian etc., when the degeneration and death of cell masses occur. Death of cells inevitably occurs during the resorptionof provisory organs, e.g. during the reduction of pronephros. Destructive processes take place among the vertebrates, when the shape of embryo is changed, when the separation of layers of cell masses, the development of interstice, the development of central channels etc. occur. The important fact is that the dying cells stimulate mitoses in the adjacent (neighboring) cells.

It has been discovered that the degeneration changes in spinal ganglia, somites, sclerotome and eye primordium, and also in other sites of mammalian embryo–mice, rats, rabbits, human–take place at different stages of ontogenesis.

Death of cells is necessary for the splitting or connecting of parts of organs, or the formation of space in a dense structure. Some embryologists think that such a process as the death of cells is no less important in ontogenesis than the reproduction and differentiation of cells.

In the past, I. Mechnikov spoke on the morphogenetic function of phagocytosis in adult organisms and during the development of animals. The morphogenetic role of phagocytes and inflammatory reactions is confirmed during the studies of organism's normal development processes, e.g. at the formation of auditory organs, uro-genital functionary among vertebrates and others. E. Krichinskaya studied the formation of the excretory system in a chicken embryo. According to her theory, the processes studied resembled "chronic inflammation".

The excess of pathologic substrate detected at the onset of an individual development, both at the tissue, cellular and molecular levels, confirms that disease played an important role in the evolutionary transformations. Otherwise, the morphological and functional changes in ontogenesis would have remained within the normal frame; the normal cell types, tissues, organs should have transformed into a different normal type of cells, tissues, or organs. Deformity and pathology are absolutely different notions. E.g. an organism may acquire additional extremities, the fact hideous by itself, but there may be no pathology in it. In his theory of hopeful monsters, R. Goldschmidt does not speak of hopeful patients.

As a matter of fact, on an anatomic embryo substance one can see solid damages (alteration), necroses, inflammation and other typical pathogenic processes. These are the tracks of old severe illnesses indicating that the adaptation to new and unfavorable conditions in the process of evolution had taken place via disease. The complexity of form should be discussed as a compensatory reaction of the organism to the damage in the frame of an integral system.

The above-stated idea points out that the progressive evolutionary objects were diseased organisms, "hopeful patients". Typical pathologic processes are the tools for the creation of new forms during the process of organic development (progress).

The experimentally determined morphogenetic function of different damaging chemical and physical factors can dramatically change the process of normal ontogenesis, the latter event known as morphoses.

The change of acid-based balances, oxidation-reduction processes, and other biochemical and physical data (including temperature, oxygen concentration, other gases, electrolytes etc.), that are detected duringhisto-morphologic processes, are also typical of local or generalized pathologies [9].

All the above mentioned facts lead to a surmise, that certain embryo genetic processes, that take place on cell, organ and tissue levels, resemble cell hyperplasia, organ and system compensatory hypertrophy and other compensatory processes detected during pathology, and are aimed for the adaptation of the organism to injurious conditions.

However, in an adult organism, pathologic changes take place the pathologic site, while the other organs may go on functioning physiologically, normally. Just as in an adult organism, the pathologic changes in an embryo are concentrated focusing on the active morpho-physiologic transformation (reconstruction), while other processes may go on normally. Which of the embryo genetic processes are referred to as normal, and which as pathogenic, can be identified via certain purposed investigations. They must be very important for a substantial understanding of the development of live systems.

Disease is a tool for the formation of new forms in the process of onto-phylogenesis. Typical pathologic processes underline several embryogenetic changes: dystrophy, inflammation, destruction of microcirculation, thrombosis, necroses, volemic and acidic disturbances.Through these minor, stereotypic processes, not only a variety of pathoanatomy pictures during different diseases, but also a general rich variety of living forms is created. The only difference is that pathomorphologic changes exposed in the process of evolution to a rather careful correction, during the process of natural selection, in embryogenesis, acquire an adequate, completely adaptive formative character.

The unity of pathology and development mechanisms explains why, despite the continuous complication and perfection of adaptive mechanisms, the pathologic process becomes more and more verified, and its causes more multiple and numerous. Disease is the price for progress.

Complex genetic, metabolic, and morphologic changes that take place in embryogenesis, are the reflection, in a tiny model, of those pathologic processes, to whichembryos adult ancestor havebeen exposed on the corresponding stages of phylogenetic development, while embryogenesis itself presents a short history of this disease. By those characteristic nuances of the pathologic changes which take place in the developing organs, we may surmise, which pathology might have been the cause of those changes in the process of the organic progress.

Considering the above mentioned facts, we may conclude that embryogenesis is a normal disease, and disease itself is a developing style of living matter. Pathology, as a process of struggle for survival, is the only way, a precondition of the organic process. As distinct from other types of struggle for survival, disease is a struggle of an organism with its own injurious signs and properties that is a struggle with oneself. The above-stated concept of the organic process is named morbal (morbus – disease). According to the morbal concept of the organic progress in order to make the inner structure of a living organism more complex, it is not enough to change only the outer living conditions (the so-called method of idioadaptation). A stable change of the inner living conditions or disease is necessary. It means that the degree of pathology severity in an evolutionary recovery directly correlates with the scale of the organic progress. The higher the degree of pathogenesis, the larger the scale of necessary morphophysiological conversions.

Proceeding from the above-stated facts, the objects of the progressive evolution are less adaptive organisms, the so-called "excretions", "non - hopeful" patients, sincein the process of the struggle for existence, their functional reserves and compensatory abilities are depleted, and first of all, it occurs precisely in these less fit organisms.

But how can less adaptive, less competitive organisms, whose vital capacity and fertility are much lessened by disease, not only survive, but also achieve certain dominancy in the process of differential multiplication?

On the initial stages of the organic progress that coincides with the beginning of an ecological crisis, the intensity of competition is minimal and the physical survival of the population is vital and crucial. Here disease appears not as a "sanitarian" isolating less adaptive, less competitive organisms, but as the means of their survival, adapting them to the new, adverse living factors.

As a rule, climate changes deeply narrow in the adaptive reproduction zone, the latter being the one where, on their early stages of ontogenesis, the non-mature offspring continue their life. In the period of multiplication (and the growth of young generation) the struggle for existence dramatically intensifies.

In this situation, the offspring of less competitive organisms are more vulnerable, they are directly doomed to extinction. The salvation strategy for them is their isolation from the above-mentioned struggle. The latter goal was achieved by means of changing sites and seasons of pairing, multiplication and growth of the young population, the acceleration of pubescence, being the conducive factor to the above-stated, took place mainly at the expense of the later stages of organisms' development. The changing speed of morphogenesis might also have taken place on the earlier stages of ontogenesis.Speeding up or slowing down the tempos of different organs' and systems' development,might have led to large morphogenetic changes. Thus, the compensation of dysfunctions, the adaptation to pathogenetic living factors was achieved. In the case, when the mature generation in the process of survival appears in the role of a rival, a competitor of their own offspring, very often the only chance to save the non-mature, forming offspring, is a migration of the parental organisms to the new, non-adaptive niche, perhaps ever before the struggle begins in the reproductive zone. After the migration of the parents is over, the heat of the competition in the reproductive zone decreases, and the survival chances of the young generation of the hopeful patients considerably increase.

In its turn, the young generation remaining in the reproductive niche until the process of formation is over, that is until it has reached puberty, is also obliged to migrate into a new, non-adaptive zone, where its morphogenesis ends under the influence of the pathologic living conditions.

Whereasin the initial stage of the progressive evolution, the response of an organism to a damage, that is a pathologicalprocess, has mainly a destructive character, in the new, non-adaptive niche, part of the migrated organisms perishes, often without reaching puberty.

For all that, in the final analysis, "migration" is an adaptive process, because as a result of the parental organisms' self-sacrifice, there survives the main living force of the species, the potential of its development and its posterity.

Thus, the cause of organisms' death in the process of the organic progress is not acutedeterioration of the environmental living conditions as the active migration of organisms into the unfavorable pathological conditions of existence. It is difficult to explain what underlies "migration".In the initial stage of the organic progress, the primary living conditions, in connection with the ecological crisis, change themselves, which may be named "passive migration". The cause of "migration", in some cases, may become a direct action of the pathogenic factors (hypoxia, toxemia, viruses, radiation etc) on the structures responsible

for the behavior of organisms, such as homeostatic, orientation reactions and reflexes.

Later on, "migration" in the pathogenic niche might have been initiated by some inner factors. In the latter situation, there appear certain signs of sexual selection; the specific place and time of sexual reproduction. The newly acquired, progressive evolutionary innovations (including behavioral ones) can simultaneously combine the functions of genital characters, and this fact partly explains the fatalism of developing organisms, so characteristic of this evolutionary phase. Hoverer, the phenomenon of "migration" cannot be treated as only sexual behavior, because the latter, in its essence, presents a specific revelation of the general survival manner. It might be called "entelechon", an inherent effort for development.

Colonizing the new niche, the latter being without any competition in it, the diseased organisms acquire almost an inexhaustible reserve for the gratification of their living requirements. Therefore, the organisms having had weaker competition abilities and fertility in the old niche, having been doomed to extinction, having had a more expressed altruistic character, and having a capability of self-sacrifice, acquire an opportunity of developing and reproducing under the new living conditions. From this point of view, disease is a "saving reaction", the last chance of survival for the less adaptive organisms [16, 17].

Towards the end of the organic progress, the viability and fertility of the diseased organisms gradually increase, their number progressively grows up and, since the resources of the niche are limited, eventually the morpho-physiological progress yields to Darwin's evolution, where more competitive, healthy and self-preservation-oriented organisms survive. Altruism resigns itself to the struggle for existence.

Thus, all along the organic progress, organisms with a better developed capacity for self-sacrifice, altruism, eventually manageto survive and reproduce, rather than the organisms with stronger self-protecting qualities. The offspring of the organisms with a more revealed altruism have better chances for survival and reproduction. Selection in the organic progress favorsaltruistic organisms. So, altruism as such, the capacity for self-sacrifice rather than the struggle for existence, proves to be the main motive force of evolution. It is an absolutely different, specific, non-characteristic style of existence for livingorganisms of today. It is characteristic of the progressive evolution subjects, and is the main condition of the organic progress. Alas, we can only see the incredibly ethical and beautiful world of the past from afar. To penetrate it, to study its laws and regularities, one can only manage through learning the laws of the progressive evolution.

In conclusion, proceeding from the above-stated ideas, it should be noted that the main object of the study in question, the organic progress theory, is the phenomena of disease and diseased organism.

Disease as such, is a peculiar Terra Incognita, where clear answers to many actual questions of the modern theoretical biology, may be found.

RESUME

The environment of the living organism which is conditionally divided into external and internal and where the processes of organic progress take placeisconsidered in thisarticle. It is proved that the unique and necessary organic progressthat is harmful for internal environment is homeostasis permanent disability that is a disease.

Realization of dominant and recessive status of genes is defined by regulating system of expression of genes. Breaking of normal functioning of this system, may cause the changing of the status of genes as well among them the "involving" of recessivealleles. Breaking of autoregulation process is illness. It makes us think that the pathology may be the only revealing and may be even main supplier factor of recessive genetic information.

If the genes involved in damaged cells by mistake, will have an adaptive character,then in the process of natural selection, their expressiveness andpenetrance will gradually increase and harmful dominant genes will be eliminated.

The necessary and the only condition of complication of inner organization of a live system–organic progress may be only the inner existing circumstance harmful for organism – breaking of homeostasis and "Firm breaking of homeostasis is illness". Referring to it, Sickness, as one of the ways for struggling for existence, should be a necessary condition of organics progress. The other forms necessary for the existence nowadays, are the pre conditions of only idioadaptation and horizontal evolution.

Organic progress is an answerable reaction on the impact of pathological factors, which takes place on the millennium periods (for example asglobal ecological catastrophes). Its aim is the restoration of damaged homeostasis of phylum, by creating the new evolution forms – (Evolutionary recovery), though it does not mean the full removal of the pathological process. Pathological process, as a means of creating new evolution forms is further kept on the certain stages of ontogenesis (for example in the case of embryogenesis).There are still left typical pathological processes in the basis of these changes: dystrophy, necrosis, inflammation, circulatory damage and the others. But in the process of natural selection, pathological changes obtain an adaptive, expedient character. Due to these changes, a variety of not only path anatomic forms, but also that of general alive forms is created. As far as homeostasis is broken, and pathology is great, the scale of necessary evolution reforms becomes greater.

Ontogenesis (embryogenesis) is a short history of illness of phylum, as the sickness itself is a form, value of developing theliving matter organism. As a fuel progressive changing coincides the ecological catastrophes, competitiveness is minimum and the fighting obtains the decisive meaning to the harmful inner (and out) conditions of existence.– So illness is a process of differential saving and multiplying of less adapted organisms. On the other hand, this issue is beyond the evolution theory and general biology and is the object of studying the sciences of philosophy, religion and other sciences.

Pathology is a missing link of evolution theory, some kind of Terra incognita, wherethe answers of many actual questions of Evolution theory are hidden.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Tokin BP. The general embryology. Higher School: Moscow 1987.
[2] Yablokov AV, Yusufov AG. Evolutional teaching (Darwinism), Higher School: Moscow 2006.
[3] Zaychik Sk, The bases of general pathology. Moscow, ELBI 1999.
[4] Ado AD. Questions of general nosology. Moscow: Medicine, 1985.
[5] Dilman VM. Four models of medicine. Leningrad: Medicina 1987.
[6] Bruce SL, Niles E. What is punctuated equilibrium? What is macroevolution? A response to Pennell. Trends Ecol Evol 2014; 29: 185-6.
[7] Futuyma DJ. Evolution: Sunderland, Massachusetts. Sinauer Associates, Inc: 2005.
[8] Robert L. Perlman, Evolution and medicine. Oxford University Press 2013.
[9] Strukov AI, Serov VV. Morbid Anatomy. Moscow: Medicina, 1995.
[10] John N. Thompson, Relentless evolution. University of Chicago Press 2013.
[11] Sam CB, Geoffrey JC, Annabel LS, *et al.* How does ecological disturbance influence genetic diversity? Trends Ecol Evol 2013; 28: 670-9.
[12] Wallace A. Evolution: A developmental approach. Wiley-Blackwell: USA 2010.
[13] Ayala FJ. Darwin's greatest discovery: design without designer. Proc Natl Acad Sci USA 2007; 104: 8567-73.
[14] Bowler PJ. Evolution: the history of an idea. University of California Press: USA 2003.
[15] Nei M. Mutation-driven Evolution. Oxford University Press: UK 2013
[16] Davidovsky IV, Silvestrov VE. Regarding the definition phenomena of illness. Archive of Pathology and Laboratory Medicine 1966.
[17] Davidovsky IV. Methodic base of pathology. Archive of Pathology and Laboratory Medicine 1968.

Received: July 22, 2014 Revised: September 19, 2014 Accepted: October 10, 2014