New direction for medical research

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CORONARY ARTERY DISEASE HISTORY OF CURRENT KNOWLEDGE

The epidemic of cardiovascular disease is beginning to ease with fewer acute myocardial infarctions, deaths and strokes. In the USA, the epidemic of cardiovascular disease appears to have peaked in 1980 for men and in 2000 for women. In developing countries, the epidemic continues to rise. There is some fear that advancing obesity and diabetes will cause the current decline in the disease most responsible for the death and disability. How did medical science achieve these goals?

In 1950, myocardial infarction was a mystery. A seemingly healthy young male or older grandmother would suddenly be struck down with chest pain followed by a sudden death or 50% mortality within the hospitalisation. In 1948, the National Heart Institute began a longitudinal study of 5209 inhabitants of Framingham, Massachusetts. The purpose of the study was to identify risk factors for development of disease. The study has expanded and now includes children and grandchildren. It identified smoking, cholesterol, hypertension, diabetes and inactivity as characteristics that were associated with disease. These factors, although statistically significant, had no apparent direct link to the process of myocardial infarction.

Coronary thrombosis was a term for myocardial infarction, but at that time thrombosis was not clearly demonstrated. Post mortem examination often lacked a clot or was confused with post mortem clotting. The theories of coronary thrombosis versus demand outstripping supply due to vessel narrowing by atherosclerosis were debated until 1986 when angiography demonstrated clot within the vessel of a patient suffering from acute myocardial infarction. Once clot was definitively identified, fibrinolysis, antithrombotics and anti-platelets were developed, attacking the clot that was at least linked to the disease process. Trials began to test the hypothesis that if a blood clot could be dissolved, outcomes would be better. These trials were successful and have helped curb the rising death rate. The trials did not shed any information as to the reason for the clot formation.

Atherosclerosis was the substrate that coexisted in most cases. Cholesterol could be found in these lesions. In homozygous familial hypercholesterolaemia, death occurred while still in childhood. The cholesterol hypothesis was born, and treatments of elevated cholesterol improved outcomes. Linking cholesterol to an acute thrombosis, however, was problematic. Animals could be made hyperlipidaemic and grow atherosclerotic plaques but would not suffer from an acute thrombotic event. Thirty-five per cent of coronary events occurred in individuals with a total cholesterol under 200 mg/dl. The link to acute thrombosis again was not strong. Inflammatory cells and thinning of the plaque pointed towards a new theory of coronary thrombosis, that of inflammation.

The new paradigm in the aetiopathology of myocardial is inflammation. Inflammation of blood vessels with its interaction with the clotting cascade could be directly linked to the onset of the clinical syndrome. Inflammation weakens the lipid filled plaque wall. The thinned plaque ruptures; exposing the blood vessel to thrombogenic factors, and attracts clumping platelets to initiate clots. Coronary atherosclerosis is present in 75% of individuals over the age of 21. This fact has been known since the Korean War. Inflammation occurs in a smaller percentage of individuals, explaining why acute events are less frequent than the prevalence of disease. The lack of an inflammatory process in animal models explains why they do not have events. Inflammation of the vessel wall is more difficult to visualise than clots but appears to be the initiating culprit prior to a thrombosis. Recent studies demonstrate that attacking inflammation can be a preventive strategy. Many of our therapies that have been shown to decrease mortality after myocardial infarction also have anti-inflammatory properties.

Inflammation still has not been accepted as a cause for myocardial infarction. It has taken 60 years to almost arrive at this conclusion.

Proposed fundamental laws of biology

1. Biology must be consistent with the fundamental laws of physics and chemistry.
2. Life, as opposed to non-living, exhibits negative entropy developing order out of chaos. (The energy to support negative entropy is yet to be defined.)
3. The cell is the fundamental unit of biology.
4. The cell must be in homeostasis with its environment. (This property allows for evolution. The environment changes life.)
5. There must be a distinction between self and the environment. (Immunity and inflammation are the defences against invaders from the environment.)
6. Electromagnetic information transfer is necessary for development and regeneration. (Life, regeneration of tissue will not exist in a non-electromagnetic environment, denervation.)

BRIEF EXPLANATION OF THESE PROPOSED LAWS

‘Biology must be consistent with the fundamental laws of physics and chemistry’

From Sir Isaac Newton to Einstein and beyond, we have a number of laws that explain motion in space, electromagnetic radiation, energy and mass, elements and their interactions. Physicists are still trying to explain the order of the universe and how the atom stays together. Any interaction within biological systems must behave according to these laws. These laws are expressed in mathematical terms and in the final achievement will explain the very smallest structures and forces that describe the atom and the organisation of the Universe from the beginning to its still undetermined future.

Life as opposed to non-living exhibits negative entropy developing order out of chaos (The energy to support negative entropy is yet to be defined)

Self organisation in the universe has no accepted law. Dark energy and dark mass have been proposed as the energy required for organisation of the universe. In biological systems, there has been no explanation of how a cell organises itself; nor is there a solution for how a simple seed
sprouts utilising water, local material, CO₂ and photons, and grows into an organised 300 foot sequoia. Two separate cells combining to organise a single cell would not be predicted by the laws of thermodynamics. Growth and repair of injuries have to overcome powerful forces that cause disorganisations. With advanced age, life eventually loses its battle with these forces, resulting in repair failure, debility and death. Death occurs when the life force of organisation is depleted, and the organism crumbles into decay. The mathematics of self organisation is in its infancy.

The cell is the fundamental unit of biology

All of the information that will define the organism (collection of cells) is within the structure of a single cell. The cell is responsible for growth and development, repair and regeneration. If this function is faulty, the organism will be redefined or a disease state will be recognised. The cell of sexual union contains all of the information for growth, maturation and repair. This cell continues to exist after the organism is developed and continues to perform repair and replacement. If this cell or a cell line originating from this cell is lost, repair will cease, and the organism will deteriorate. New therapies must always be evaluated by how they affect the progenitor cells. Differentiation of organs, location of the organ and regeneration of senescent or damaged tissue depend on a single cell and the response of the cell. Disease states occur when the normal function of the stem cells is inhibited, blocked or destroyed. Disease can occur if there are too many stem cells or too few, throwing the balance towards regeneration or degeneration. Proteins produced by the cells are determined by the genetic code of the cell. These codes determine the function and type of cell. These codes ultimately determine the interaction with other cells.

The cell must be in homeostasis with its environment (This property allows for evolution. The environment changes life)

All biological systems have to interact with the environment for fundamental building blocks, nutrition and energy. What the environment has to give is what the organism must use. In this way, the environment can shape the organism. From the Archean to the Neogene, life has changed, and according to Darwin, life has evolved. During these time periods, the environments have changed. Successful organisms have the ability to adapt to these changes, while unsuccessful organisms become extinct. It is unlikely that humans will reign forever, but will be replaced by those suitable for the future environments. The current environment of excess calories and decreased energy expenditure has evolved some individuals into larger bodies with type II diabetes.

There must be a distinction between self and the environment (Immunity and inflammation are the defences against invaders from the environment)

In the biosphere, there are many competing life forms that utilise the same resources. This competition breeds survival traits. Some symbiotic traits help both organisms to survive. At other times, competition requires one organism to dominate others. The evolution of the immune system was necessary to combat viruses and invasive bacteria. The collection of cells had to determine self from non-self and the risk of the non-self, and then develop a protective defence. Self needs to be protected from the environment and competitors. It is a complex process that has evolved multiple pathways with multiple checks and balances. Regeneration and replacement of senescent cells also utilise this system to process the dying cells. Inflammation utilises cellular components (endothelium, T cells, B cells, dendritic cells, leucocytes, eosinophils, basophils, monocytes, macrophages, mast cells, plasma cells and platelets), humeral elements (immuno-globulin IgG, IgM, IgA, IgE, natural antibodies and immune antibodies) and signalling proteins (complement cascade, tumour necrosis factor, intercellular adhesion molecule, monocyte chemotactic protein, bradykinin, histamine, interleukin, platelet-activating factor, prostaglandins, leucotrienes, selectins (L, E, P) and other cytokines). Reactive oxygen species produced through inflammatory pathways are deadly molecules that can cause direct injury. The inflammatory pathways are more complicated than the coagulation pathways and have proven to be far more difficult to target in therapeutics. Inflammatory and coagulation pathways are intertwined with inflammation resulting in thrombosis and anti-coagulation reducing inflammation. Many of the pathways have self regulation, so disturbing one pathway may enhance other pathways. The inflammatory pathways are also instrumental in repair and regeneration. Senescent cells are labelled by natural autoantibodies and reprocessed by macrophages. Disruption of one pathway may have deleterious effects when other pathways compensate for the disruption. The above system has evolved to protect us from the environment and functions as a regenerative tool removing senescent and injured cells. When this system shifts out of balance, disease processes become evident. Colagen vascular disease occurs when self is misrepresented as environment, and innocent bystanders are attacked. Infections that are relatively benign can cause the immune system to over-react again damaging innocent bystanders. Freedom from disease occurs when there is a balance in the inflammatory response between the host and the environment.

Electromagnetic information transfer is necessary for development and regeneration (Life regeneration will not exist in a non-electromagnetic environment, denervation)

The world in which we evolved did so with an electromagnetic environment that deflected ionising radiation. Life may have never started without the iron core that rotates and generates those forces. Communication among cells is vital to survival. The beating heart, muscular contraction and the brain are bathed in electrical forces. Development from a single cell to a complex organism requires direction, differentiation and ordered growth. The cells are propagated in the bone marrow and released into the general circulation where they nestle into the endothelium or organ niches. They randomly circulate until they detect and replace a senescent cell. The senescent cell during apoptosis has a shift in internal proteins that changes its polarity, resulting in an electromagnetic attraction. The replacement cell then differentiates according to cell-to-cell information transfer at the level of the cellular membrane. If there is a failure of information transfer or a breakdown in the electromagnetic forces, the default differentiation is a fibroblast and scar. In the developing embryo, the neurontube electrically directs growth. Denervation results in atrophy. Denervation causes failure of regeneration.

Molecular genetics

The assumption is that life sprang from the primordial soup when molecules under the influence of law 2 became self organising. The cell, fundamental building block, has its information stored in DNA and uses this information to produce
various proteins and peptides that determine the function of the cell. Promoters turn on and off genetic traits. Signalling proteins are released from cells to influence cells that are remote. An example of this function is brain naturetic peptide, produced by cardiac cells to help regulate filling pressures within the heart. This peptide influences many cells of diverse nature from muscular arterial and venous cells to kidney cells and endothelium. These peptides influence the genes within the cell of the nucleus to turn on protein factories that will relax the muscle or make membranes more permeable. The net effect is to lessen filling pressures. When cells are damaged, they send signals to progenitor cells to increase production. The role of inflammation is to protect from foreign invaders and replacement of senescent cells. Their role is not well understood but is controlled by multiple signalling proteins and multiple feedback loops. The genetic machine involved in these loops needs further definition. Many diseases are caused by a primary problem in the DNA code, and the best fix is to correct the code. Most diseases, however, are a result of proliferation or degeneration influenced by inflammation. Molecular genetic manipulation of cells may make the perfect cardiac replacement cell, but without engrainment, healing will not occur.

The fundamental laws can work in concert with molecular genetics to promote repair of damaged tissue. Any new therapy or model of a disease process has to fulfill all of the above fundamental laws to be successful in describing a disease process or designing a therapy to combat a disease process. Understanding growth and development, the degeneration and the eventual death of an organism must follow these rules. The beginning of life and the evolution of life needs to be compatible with some fundamental laws.

**CORONARY ARTERY DISEASE MODELLED FROM THE FUNDAMENTAL LAWS**

Utilising the proposed fundamental laws of biology, coronary atherosclerosis and thrombosis and repair will be investigated.

Laws 3, 4, 5 and 6 will be utilised.

Law 3: ‘The cell is the fundamental unit of biology’.

The endothelium is the largest organ in the body and is replaced by circulating progenitor cells. Failure of repair of the atherosclerotic plaque leads to thinning with risk for rupture. In vascular-disease patients, smoking, hypertension, age and lack of exercise are associated with decreased levels of circulating progenitor cells.\(^{21-26}\) These known risk factors can be linked directly to a thrombotic event by failure to repopulate damaged endothelium. Preventive strategies such as exercise,\(^ {27,28}\) statins\(^ {29} \) and enhanced external counterpulsation\(^ {30,31} \) increase circulating stem cells and decrease events. All of the risk factors discovered by the Framingham Study can be reflected in the quantity of circulating progenitor cells, and this factor is directly linked to acute ischaemic events.

Law 4: ‘The cell must be in homeostasis with its environment. (This property allows for evolution. The environment changes life.’)

The environment includes all of the potential invaders and nutrients. In simple terms, you are what you eat. In more complex terms, there is a constant interaction with the environment which can shape health and disease. It is not by chance that developing countries are seeing an increase in cardiovascular death.\(^ {32} \) As their environment becomes more western, their disease processes become more western. Dietary changes such as switching to oil-based cooking from direct heat, more processed as opposed to fresh produce, increased salt content and excess calories all contribute to new disease processes. The rise and fall of acute rheumatic fever and rheumatic heart disease was more of an environmental change than the advent of penicillin. The epidemic of rheumatic fever began to decline before penicillin was invented.\(^ {33} \) The cholesterol-filled macrophages are the result of an overabundance of cholesterol in the bloodstream. The excess cholesterol in these cells targets them for destruction by the immune system, which is responsible for finding and replacing senescent cells. Type 2 diabetes is an evolution within one generation. Greater access to simple sugars, the miracle of the light bulb allowing greater time to consume and sedentary behaviour burning fewer calories have evolved a new larger species with a waist circumference greater than 40 inches.

Law 5: ‘There must be a distinction between self and the environment. (Immunity and inflammation are the defences against invaders from the environment.)’

This law is closely linked to Law 4 in that the environment poses a threat to the organism. Immunity and inflammation are necessary for an organism to survive in an unfriendly environment. Bacteria are everywhere and have colonised the gut. The environment and the gut are in homeostasis, and there is a symbiotic relationship. The gastrointestinal tract is the portal for most elements from the environment. We must be in homeostasis with these elements. Foodstuffs are taken into the gastrointestinal system. This system regulates the nutrient intake and also responds to foreign invaders.\(^ {34} \) It is not surprising that the liver and spleen, which act to detoxify foreign invaders, are located just off the gastrointestinal tract. The respiratory system also has to contend with airborne invaders. The entire system is posed to detect a threat, remember the threat and cause demise of the threat. If the system is kept busy and is not overwhelmed, the organisms will remain healthy. If unsuccessful in its battle with the foreign invader, the organism will simply become nutrients for the invader. If the immune system responds in an overwhelming manner killing off the invader with excessive toxins, the inflammation may spill over and injure the organism. There have to be checks and balances to keep the immune system reacting properly and not over-reacting. In regard to coronary disease, the immune system may be prompted to react to cholesterol-filled macrophage, and the resulting inflammation thins the fibrous cap of a plaque. The inflammatory response and clotting system are interwined, making a direct link to a coronary thrombosis.\(^ {35-38} \) In an adult-onset diabetic, the high glycaemic diet may feed the gut bacteria causing an ‘algae bloom’ in the number of bacteria. The inflammatory response to contain the excess bacteria spills over to the blood vessels, increasing the risk for vascular disease and acute myocardial infarction.

Smoking involves inhaling foreign substances that cause an immune response. This immune response may be the link for this risk factor. Chronic inflammation from periodontal disease\(^ {35} \) and rheumatoid arthritis\(^ {36} \) can also stimulate the immune system and may be why these individuals have more cardiovascular events. Under-developed countries have greater exposure to waterborne illness, keeping the immune system occupied by fighting foreign invaders. There are not enough immune resources to react to blood vessels. Westernised countries have fewer invaders from their water systems, and the immune system has resources that can over-react to blood vessels lined by lipids. These patients tend to have elevated high-sensitivity C reactive protein. Flu vaccines,\(^ {37} \) statins,\(^ {9} \)

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*Heart Asia 2010*
exercise, anticoagulants, antiplatelets, \(\beta\) blockers, angiotensin inhibitors and other useful therapies all have an influence on the immune system, reducing inflammatory response to blood vessels. This law would suggest that inflammation is the direct cause for initiation of myocardial infarction.

The immune system, in addition to fighting foreign invaders, is intimately involved in repair. Through autoantibodies, senescent or injured cells are identified and removed so replacement cells can rejuvenate. Law 6, therefore, depends on law 5.

Law 6: "Electromagnetic information transfer is necessary for development and regeneration. (Life, regeneration of tissue will not exist in a non-electromagnetic environment, denervation.)"

Progenitor cells are propagated in the bone marrow and released into the general circulation, where they nestle into the endothelium or organ niches. They randomly circulate until they detect and replace a senescent cell. The senescent cell during apoptosis has a shift in internal proteins that changes its polarity, resulting in an electromagnetic attraction. The replacement cell then differentiates according to cell-to-cell information transfer at the level of the cellular membrane. The senescent cell is then removed by the inflammatory system. If there is a failure of information transfer or a breakdown in the electromagnetic forces, the default differentiation is formation of a fibroblast or scar formation.

In myocardial infarction, the dying cells stimulate an inflammatory response. If the inflammatory response is overwhelming, the information transfer will be blocked, and scarring will result. In transmural myocardial infarction, the electrical conducting system is damaged, so the electromagnetic environment is changed to denervation. Without this signal, all reparative cells will become fibroblasts by default. Both of these conditions make recovery from myocardial infarction unlikely. This model would suggest that therapies that slow apoptosis, decrease inflammation, increase progenitor cells and restore innervations will be successful in regeneration of myocardial tissue after myocardial infarction. Multiple simultaneous interventions will be required.

NEW DIRECTIONS FOR RESEARCH

Achievements have been made from the identification of risk factors for cardiovascular disease. The risk factors are only weak predictors because of patient biological diversity. Two patients with identical risk factors can have very different outcomes. Since the population is not uniform, it takes many subjects to prove that a risk-reduction therapy is beneficial. Demonstrating a change in a biological marker by a therapy will have a more predictable outcome with fewer patients. Law 3—"The cell is the fundamental unit of biology"—suggests that the measurement of progenitor cells should be used as a biological marker. Law 5, there must be a distinction between self and the environment, suggests that the measure of inflammatory response should be used as another biological marker. High-sensitivity C reactive protein may be one of those markers. Other as-yet undiscovered markers for inflammation may be better.

Research utilising the tools of molecular genetics should concentrate efforts on understanding law 5—"There must be a distinction between self and the environment. (Immunity and inflammation are the defences against invaders from the environment.)" This law is the most pivotal and modifiable of all the laws. It is also the most difficult to comprehend, so a physical example will be used. Inflammation is like the fulcrum of a scale balance, lying between regeneration and degeneration. The fulcrum of this scale can move, increasing or decreasing inflammation to rebalance the changing forces of degeneration and regeneration, which sit on opposite ends of the scale. A balanced scale supporting regeneration and degeneration results in health. Cytokines, the upregulation and down-regulation of inflammation, the feedback loops, the effects of modulating these pathways and inflammatory markers will be the work of the basic scientists in molecular genetics. The genes that control inflammation and how they are regulated will be the answers for chronic disease conditions. The cell itself may be the target for therapies in the future by manipulating genes. A 90-year-old progenitor cell that has trouble replicating could be altered by increasing telomere length, then reinfused into the body and again become efficient in regeneration and repair.

Clinical trials of the fundamental laws will employ multiple simultaneous interventions. A cardiovascular example will be used to illustrate this. Patients who present with a large anterior myocardial infarction complicated by ventricular fibrillation cardiac arrest have a terrible prognosis from both the heart and the brain recovery. The multiple interventions in this individual may include: cooling to slow apoptosis, coronary intervention to open the artery, standard antiplatelet and anticoagulant therapy, statins, angiotensin-converting enzyme inhibitor, \(\beta\) blockers (all of which decrease inflammation), plasmapheresis to remove cytokines and modify inflammation, injection of progenitor cell or enhanced external counterpulsation therapy to increase circulating progenitor cells, and electrical stimulation of the infract zone to mimic the normal electromagnetic environment in both the brain and the heart. The goal is to fully resuscitate and regenerate the brain and the heart. The benefit can be measured, but it will be impossible to determine which intervention is more efficient.

In more practical terms, these laws can be applied to individual patients. Patients must understand that exercise will increase circulating progenitor cells to rejuvenate and repair their bodies. They need to exercise and take their statins to reduce inflammation and their risk of acute coronary thrombosis.

In summary, this paper has introduced a new paradigm in medicine that explains wellness and disease in a new manner. New concepts always begin outside normal conventional thinking. These concepts have to be tested, confirmed and applied to other conditions to become established in mainstream medicine. The realisation that cardiac tissue could be rejuvenated was the initial stimulus to the discovery of these concepts. The model of fundamental laws has helped the author understand some mysteries: the function of a patent ductus in utero allowing blood to bypass the lungs, growth retardation in children with VSD, pulmonary hypertension of VSD, growth spurt in children with VSDs as they develop Eisenmengers, pulmonary hypertension of cirrhosis and others. The fundamental laws suggest new therapeutic modalities to treat myocardial infarction, sepsis, shock, pulmonary insufficiency from the flu, unsightly scars, ageing and others. The laws will help us understand the influence of our environment on our health. Understanding the cell at the molecular level and at the total organism level is a requirement. New therapies should be evaluated in how they influence the number of circulating stem cells, inflammatory system, electromagnetic homing of the progenitor cells and cell-to-cell communication that are dictated by the fundamental laws. The paper has referred to these six concepts as laws. These
concepts are really postulates. The readers will hopefully prove them to be laws.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Heart Asia 2010:113–117. doi:10.1136/ha.2010.001966

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