



## Review Article

## Concept generation and integration in surgical pathology

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## ABSTRACT

This presentation emphasizes the importance of concept generation in the undergraduate medical education. It is primarily based on molecular genetic advances. It is implicated in the understanding of various normal human biomolecular activities based on the intrinsic molecular integration and unification of diverse biomolecular activities to provide best possible service for the survival of human being. Disruption of these molecular integration pathways results in various disease manifestations. The concept generation should form the basic foundation in surgical pathology teaching in the undergraduate medical education without which it remains a disjointed discourse. We have highlighted the process of concept generation and presented few examples and we aim to stimulate medical graduates to generate their own concepts based on their own observations. They should be able to integrate various associations with future molecular advances to enhance their understanding and improved clinical outcome as most treatment in near future will be based on molecular basis.

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## 1. Introduction

As a complementary adjunct to age old philosophy and contemporary concept of pedagogy the “concept generation” seems to be a timelier deserved paradigm shift in teaching methodology. This is all the more relevant in the context of ever mounting modifications of teaching methodologies by medical educationists with expertise and experience. Concept generation in Medicine is an important and integral part of medical education. This provides a clear base for the undergraduate students. Concept generation i.e. acquiring the ideas, is the most critical step in the engineering science in the design processes.<sup>1,2</sup> but concept generation and concept integration has not been widely used in medical education. Establishing links of various established facts into a meaningful acquisition of information is integration. Integration of basic sciences in health’s course is essential to the understanding and treatment of the escalating number of illnesses.<sup>3</sup> Most of the medical institutions presently follow integrated medical

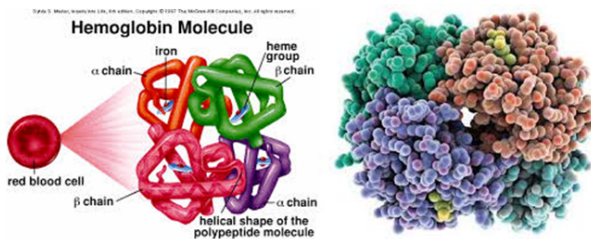
education which is not without its own shortcomings. The frequently quoted negative aspects of integrated medical education are 1. dissemination of fragmented knowledge, 2. lack of comprehensive understanding based on concepts, 3. content over - load. Concept generation can serve as an anchor or a guiding light in the maze of complex bio-molecular mechanisms involved in pathogenesis and development of diseases. The concept generation basically underscores the synchronization of our normal activities due to inherent molecular integration and unification of various organ systems to present us ample services for our survival for a finite period of life time. The site of all intrinsic knowledge is our DNA. Our DNA determines the duration of our survival and diseases we suffer and when we die.<sup>4,5</sup>

Biological matter is comprised of small molecules (e.g., water), macromolecules (biopolymers), supramolecular assemblies or macromolecular complexes, which assemble into subcellular particles and cells, which in their turn form supra-cellular systems such as tissues and organs. One of the key ingredients of biological systems is represented by the intricate, specific or non-specific, intra- and inter-molecular interactions, which determine the structure and, further, the

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biological structure-related links. Spatial packing or folding of macromolecules, such as proteins, nucleic acids or polysaccharides, is regulated by intramolecular interactions, which occur between segments of the same molecule. Equally important for the 3D structure of macromolecules are intermolecular interactions with solvent molecules (constituted by water molecules in biological systems), ions, and various small molecules from the cytosol. Intermolecular interactions between macromolecules are mostly conducive to formation of supramolecular structures such as protein complexes, which could be either transitory (e.g., binding of oxygen to hemoglobin) or permanent, relative to the lifespan of a cell or a superior organism (e.g., the tetrameric complex of hemoglobin).<sup>5</sup>



**Fig. 1:** 3D model of haemoglobin taken via open goggle search site to highlight the molecular integration.

### 1.1. Need for concept generation

From the undergraduate students' feedback, the medicine is too vast and too complex to master it- especially the pathophysiological mechanisms implicated in disease production. So the miniaturization of complex process in to one or two word concept can help to summarize and help to decipher the complex knowledge underlying the clinical manifestations. In this context the essence of our knowledge should facilitate our metamorphosis from bench to bedside. For, after all we are trained and destined primarily concerned with appreciation of signs and symptoms of diseases.

We further, learn from our post-graduate students-feedback that they feel that most undergraduate tutors teach by "Cut and Paste" in power point presentations. This raises the question of the quality and extent of genuine knowledge a medical teacher is actually providing his pupils in basic fundamental way and not simply repeating book-knowledge often delivered by their peers and teachers. The dismal current trend among tutors who have become slaves to power point presentation has made the marvelous art of pedagogy almost meaningless. Compounding this is the conspicuous lack on the part of teachers to elucidate and elaborate the intricate and evocative mechanisms of disease. In short, the noble art of teaching and inspiring students by elucidation of fundamental as well as thrilling mechanisms underlying diseases has been relegated to the background by

dispassionate tutors.

### 1.2. Steps of process of concept generation.

The process of concept generation can be summarized in following steps which are self explanatory. 1. Observation→ 2. Analyzation→ 3. Rationalization→ 4. Conceptulization → 5. Integration→ 6. Unification.

### 1.3. Molecular observation and integration

Molecular observation and integration is the quintessence of the concept generation based on sound molecular foundation. We can visualize the various molecules integrated to form a haem molecule, with capacity to hold one molecule of iron each in each of 4 pyrol rings of haem molecules to carry a life sustaining Oxygen molecule to sustain aerobic respiration in living organisms including in human as shown above diagram. The beauty and unique function of this molecule is appreciated by its capacity to give up and take another molecule ( carbon-dioxide) at different sites with different affinity for the gases for the survival of its host. This crystallizes genuine integration and unification at molecular level. Similar subtle molecular observation and integrations have been high-lighted by recent researches in GIT of absorption of dietary methionine to cysteine and reabsorbed of same at brush border of proximal renal tubular epithelium via transmembrane transportation in case of cysteinuria. Further molecular researches have highlighted the integration of various genes in entirely dissimilar organ system especially genes involved in normal kidney development are found to be involved in neonatal aganglionosis.<sup>6</sup> Another good example are the genes involved in ciliopathies and production of cystic lesions of various organ systems including kidney, liver, brain and lungs, dextrocardia and cardiomyopathies of heart and infertility.

The link between PLOD 2 gene and scurvy merits mention here. Most pathological changes of scurvy can be attributed to failure of synthesis of collagen due to vitamin C deficiency. Scurvy patients have defective blood vessels because collagen type IV is a chief component of blood vessel walls, skin, and specifically, the basement membrane zone between the epidermis and the dermis. Vitamin C facilitates hydroxylation and crosslinking of pro-collagen catalyzed by lysyl hydroxylase. Lack of vitamin C lessens transcription of pro-collagen. Furthermore, deficiency of ascorbic acid causes epigenetic DNA hypermethylation and represses the transcription of various types of collagen found in skin, blood vessels, and loss of vascular support, leading to frequent hemorrhages.<sup>7</sup>

### 1.4. Integration- making connections

Students learn medicine in a fragmented fashion. They know, for example, that a. too much uric acid (UA) causes

gout, and b. that ATP in the body provides energy, and that c. DNA and RNA are nucleic acids. They do not appreciate, however, that UA is a purine and that adenosine is another purine, that adenine plus ribose- a sugar makes a nucleoside, and that adenosine can attach to phosphates both to participate in nucleic acid metabolism as well as to provide energy. To provide another example, students know that superficial cysts are fluctuant, and that Pascal's law states that pressure in a fluid is transmitted equally in all directions, but they do not put these facts together. Or that students know that osmolality derives from the number of particles in a fluid, and that Avogadro's constant is  $6 \times 10^{23}/\text{mol}$ , but they do not put the two facts together to explain why sodium (and not albumin or red blood cells) is the major contributor to serum osmolality. Put another way, they do not see the connections. They have not acquired the skill to integrate various facts into a meaningful actionable clinical knowledge.

### 1.5. Hypothesis generation

A universal mode of contemplating on scientific practice involves categorizing it as hypothesis- or data-driven. One facet of daily routine scientific practice that is beginning to attract more attention is integration. Then, using some examples from molecular systems biology, we can show how integration works in a range of situations to generate astounding insights and even novel arena of research. Current milieu of data-intensive large-scale studies favour indubitably pragmatic integration; likewise it promotes achieving the obligatory implications for meta-methodological accounts of scientific practice. We conclude that the comprehension of imminent integration must be coupled with its dynamic benefit for philosophy of science and scientific practice in general.<sup>8</sup>

Further, needless to reiterate, the impact of genetic alterations that can have wide spread effects in human body which may be more complicated as a result of the cross-talk between these genes and its interface with other ecological micromolecules agents like microplastic nanoparticle acting as hormone-disruptors. These microplastic are found to promoting male gynecomastia in young ones and children, and obesity, diabetes and cancers in adults respectively. Recent reports suggest that endocrine disruptors may leach into the contents of bottles made from polyethylene terephthalate (PET).<sup>9</sup>

### 1.6. Central Dogma of Genetics

It is well recognized that every medical discipline is connected to human well-being through the mechanism of gene expression, environmental influences and inheritance.<sup>5,6</sup> Genetics underscores many biochemical pathways, physiological processes and pathological mechanisms.<sup>6</sup> Hence, the concept of integration is well exemplified

by the central dogma of genetics that translates the information encoded in DNA genetic molecules to RNA and to protein molecules to perform certain function. The same information present in the protein molecules can be reverted to DNA molecules via reverse transcriptase technology. This enabled the molecular scientists to create new human embryo from a matured skin cell nuclear DNA. Similar ability exists in the stem cells present in various organs to form mature cells and to transform mature cells to stem/ progenitor cells. This reversibility highlights the fact that information code / knowledge in DNA and protein molecules are same but only in different forms thus promoting a hypothetical concept of "one in all and all in one". Since the molecular genetic code in DNA is in different form (nucleotides) and different form in protein but carrying same message/ information code / knowledge, this supports the hypothesis of "simultaneously same and different concept".

In the modern medical education the above concept can be easily integrated into vertical and horizontal integration concept. Medical educationists can integrate both type of integration by introducing case scenarios with multidisciplinary clinical cases example like- a 5 year child with skin rash and vesicles on face and arm is brought to a pediatrician- now discussion can involve students and group of experts on the subject- dermatologist, immunologist, pathologist, microbiologist, pharmacologist, geneticist and anatomist.

### 1.7. Our narrative

Our narrative is based on simple truth of deeper science based on molecular integration and it must be told as simple as childhood- Nanny's stories which were easy to remember and usually carries great moral values. Can we tell our medical stories with such knowledge and skill in a simple conceptual basis? So that our students can remember this as the foundation on which to build future knowledge. Hence concept generation is important and unique way to make the very complex subjects into a simple one

### 1.8. Thinking medical doctor

The basic motive of medical education is to create a conscious thinking-medical student, who can think and analyze complex question like how the hundreds of trillions of cells in human body with each cell having a nucleus with 46 chromosomes with complex of DNAs holding all the information or knowledge about everything about life and death including recreation of its own species function normally. How they are preserved and what type of basic laws govern them? What type of quantum or physical law or force control them at subatomic level? According to recent medical genetic researches everything in life is controlled by its DNA and its intrinsic milieu and it must follow certain

universal laws/ ways to survive otherwise lives cannot exist in vacuum without regulation. Thus, we can label it as Laws of survival based on genetic principles and it has four principle sub-laws according prevailing genetic information based on recent genetic findings.

#### 1.8.1. Law of survival and death

The code or information of survival and death are encoded on our genes. There is a fine balance in such genes of opposite actions. Example are pro and anti-apoptotic genes, cell cycle genes and its controller genes, house-keeping genes, telomerase genes and other related genes involved in sensing genetic defects, excision and repair of damaged DNA nucleotides. We also must appreciate that same gene may have multiple functions at entirely different organ system as controlled by interaction between various genes and its controlling genes and cytokines. These genes basically do crosstalk to each other and get information from external sources via signaling molecules thus controlling the survival and death of each cell in our body. Further according to survivability and reproductive capacity of these genes, our cells, tissue or organs have long being subdivided into labile, stable and permanent types. Thus, various types of injuries to these organ or tissue cause different types of cellular reaction and clinical outcomes. Example of fatal ischemic injury to cardiac myocytes or neurons in myocardial infarction and stroke respectively highlights the susceptibility of these permanent cells.

#### 1.8.2. Law of middle path

In most of our biochemical, molecular and cellular functions and processes there are checks and balances to maintain the normal homeostasis in our body to function at optimal level. This has been highlighted by middle path of Buddhism or the “Yin and yang” philosophy of Confucius-faith. Genetically compared with the balanced telomeres at the end of a chromosome to maintain a normal genetic homeostasis and survival and immortality of a neoplastic cell because of its ability to secrete enzyme telomerase that prevent shortening of telomeric ends in ageing.

#### 1.8.3. Law of intolerance to extremism

Extreme genetic alterations are not tolerated by our DNA/ genes because it is incompatible with human survival. So, it kicks in apoptotic process and commits suicide or become unviable. Hence, extreme ideas or extreme views are always rejected by human society.

#### 1.8.4. Law of unification and integration

Human body has various cell types of various functional and regenerative capacities organized into various organ systems which are ultimately integrated as one functioning unit to serve one purpose that is the survival of human being. This highlighted the concept of unity of one and all

in one concept. Below we present concepts generated on each major topic / subjects most based on embryologic and molecular basis.

### 1.9. Concept on various organ system

#### 1.9.1. Neuroectodermal system: theme concept - “Beauty and Brain”

We can summarize it in a simple word of Beauty and Brain. This basically integrate sensory-motor, autonomic, endocrine, skin and other sensory organs in the body as one organ system based on embryologic origin. Although embryonically all are derived mainly from ectodermal germ cell layer but as they differentiate and mature into different cell line to perform different function there occur genetic alterations suitable for that function. Thus, we can conclude that physiology determines its microanatomy or microanatomy determines its physiological function. In fact, both are determined by the pre-programmed genetic program hereditarily carried in the germ cells which is carried to the next generation - pointing towards immortality of genetic information or genetic knowledge. In other word man may die but genetic knowledge survives.

Central nervous system is the control tower of all human activity and the master of this control tower is the neuronal cell. The network of these neurons controls our sensory, motor, endocrine and autonomic activities. The unique plasticity of CNS is well known which is further enhanced by presence of stem cells, intact blood brain barrier (BBB) maintaining autoregulation of pressure and constant hemodynamic state needed for such vulnerable permanent cells to hypoxia and hypoglycemia. So such important and unique but vulnerable organ is protected by a rigid bony cage from external factors and injuries. But this protective shield can become fatal in case there is increase in intracranial pressure due to any causes or pathology which may lead to increased intracranial volume, displacement of cerebral tissue, midline shift, herniation, coning, respiratory failure and death. Hence cerebrovascular diseases are one of the most common cause of mortality and morbidity.

Likewise endocrine system is also source of humoral system responsible for growth, development and normal homeostasis of male and female species and its reproductive capacities. So while CNS is the control Tower of human life, endocrine system can be summarized as The Orchestra ruled by its Band-Master- Pituitary to control our various internal humoral function which works in unique feedback system controlling actions of higher centers by the products of lower target organs. This again highlights the unique check and balance in normal humoral status maintaining normal physiology.

### 1.9.2. Lymphohaemocardiorespiratory system: theme concept - “not an empty vessels”

Without the presence of lymphohaemopoietic cells we can consider cardiovascular system as empty vessels. Further, cardiorespiratory system as only a conduit or channels to carry the most vital life-sustaining oxygen molecules and nutrients and defense forces for our survival and protection from infection and trauma. These defensive hemopoietic cells use their surface molecules as “pass-word” to transit various barriers to go the internal organs to fight infection or injuries and help in healing. Uniqueness of hemopoietic cells is the expression specific surface antigen or receptors at various stages of their development which can be detected via flow-cytometry or immunohistochemically on the cells that permit a higher level of tumour sub classification-not possible for other system and their neoplasms like carcinoma and sarcomas.<sup>10</sup>

Respiratory System: theme- “let me live, let be breathe”

Theme could be Harmonium with a song- “let me live, let me breathe.”

Oxygen is essential gas for human survival and its efficacy largely depends on the patency of supply pipeline and integrity of pump- the heart and the filtration plant-the lung.

1.9.2.1. Hypothesis on neoplastic transformation. Lymphohaemopoietic cells of mesenchymal origin and its neoplastic transformation is quite different than neoplastic transformation of epithelial cells of ectodermal germ cell origin or endodermal germ cell layers which is known to occur through process known as “Multistep Carcinogenesis” in which transformation of a mature cell to metaplastic to dysplastic to neoplastic phenotype is preceded by series of nuclear DNA mutations. This process is slow and progressive and takes severe years to reach malignant neoplastic stage via multistep carcinogenesis.

Lymphohaemopoietic cells are mobile cells of mesenchymal germ cell origin hence the concept of metastasis does not apply to these neoplasms and their neoplasms are different than of those arising from surface lining epithelium. Most arise from chromosomal translocation like the tumors of musculoskeletal system. These cells do not possess a basement membrane like epithelial cells.

### 1.9.3. Git-hepatopancreaticobiliar and cns system

Theme concept “Entry into a lover’s heart is via his stomach” holds good for above integrated system functionally and structurally via vascular system. Gastro-intestinal system integrates hepato-pancreatico-biliar system embryologically and CNS via vascular system and can lead to hepatic encephalopathy/coma if hepatic failure occur in cases of drug-induced or alcoholic or viral hepatic injuries.

4. Genito-renal and reproductive system are integrated for your Recreation, reproduction, propagation

of species and its waste management system. Two kidneys are major excretory filtration plant connected with drainage pipeline to maintain homeostasis in acid-base balance along with other electrolytes and hormonal functions.

### 1.9.4. Genetics and perinatal diseases

Theme: “we are what our genes are.” Or “We are reflection of our genes”

Development of most human diseases is intimately related to individual’s precise genetic make-up, genotypes. Environmental factors have strong and complex role in most multifactorial genetic diseases including diabetes and neoplasms.

## 2. Musculoskeletal system

Theme: “Everybody loves to dance”

A simple act of walking is a complex exercise which needs lot of co-ordination of many organ systems to accomplice it. Pathological lesions of this system is vast which are mainly neuro-muscular system including lesions of neurons, nerves, bones, joints, soft tissues, muscle, ligaments, tendons, fibro-histiocytic tissues, vascular, lymphatic and subdermal tissue of the skin.

### 2.1.

#### 2.1.1. Cell injury and cellular adaptation

Theme concept- “when in Rome do as Romans do”

That is what our cells do every moment and adapt to changing environment. Our cells are in constant state of flux or constant struggle against the external environmental forces for survival. Our cells tolerate these external insults to large extent and adapt to injurious agent and return to normal state once the injurious factor is neutralized or overcome but in extreme cases the cell may die. So cellular adaptation is a process of survival strategy of the cell which varies according to specific types of cells as mentioned earlier and also on the type and severity of injurious agents.

The various mechanism and agents of cell injury can be anoxia, hypoxia, ischemia, trauma, free radicals, inflammation, autoimmunity, various physical, chemical, hot and coldness, nutritional, infectious or genetic factors/ mutations. The cells reaction to above agents is stereotype depending on the degree of severity and kind of cell involved. So it varies from hyperplasia, hypertrophy, atrophy, metaplasia, grades of dysplasia, dystrophic changes, calcification, cellular depositions, infiltration or degenerative changes. The injury may be too severe to cause irreversible change of apoptosis- suicide or necrosis of the cell or tissue or organs.

#### 2.1.2. Inflammation

We can put people “in-FLAME” by our thought, action or our speech. THIS IS INFLAMMATION. The famous

four cardinal signs of inflammation was highlighted by famous pre-Christ age medical expert CELSUS in 30-388BC and the 5<sup>th</sup> sign of inflammation of “*functio- laeso*” was added by Virchow in 1821-1902. These manifestation are mainly due the vascular endothelial reaction to the cytokines released due to various injuries.

### 3. Discussion

Integration of Basic sciences in clinical practice is essential for undergraduate education which sharpen students' thinking skill, logical reasoning, critical thinking, problem solving decision making and creativity.<sup>11</sup> Many newer concept in teaching learning sessions have evolved and successfully applied in various teaching learning setting including self-directed learning and problem solving settings or small or large group settings.<sup>12-15</sup> We delivered concept on clinical scenarios that help the students to better understand the pathophysiological mechanisms in our reverse teaching research.<sup>16</sup> In this presentation we highlighted the point that medical science is not just fact based science and it has no other narrative except for death and diseases. Medical science and medical education has a definitive narrative based on philosophy of life that is based on core value of molecular integration as encoded in our genes. When these molecular integration is disrupted we suffer the consequences of these genetic alteration as disease manifestation. So delivery of medical teaching is the art and science of medical education not entirely based on scientific facts based on researches/ science but also based on philosophy of life based on immortal principles highlighted by our genes that control our every activities. Pathology is study of and application of pathophysiologic mechanism in understanding the human disease at cellular and molecular level via morphologic, ultra-structural, or biochemical study and observations and integrating those changes with the spectrum of changes observed in organs, tissue and body fluid.

Concept generation is essential element of an eloquent delivery in health care system. It is an important aspect of good teaching.<sup>17</sup> Concept generation on various topic help students to conceptualize the whole area of complex disease processes on a particular topic or subject in one or two easy and simple sentences or proverbs with examples of daily life. That should form the fundamental basis or skeleton or thread on which other peripheral knowledge can be built. The human disease is a complex process where various biochemical mechanisms and cellular or genetic complexity are involved. For the beginners in medicine that may be quite perplexing and daunting task.

### 4. Summery

Concept generation is essential element of an eloquent delivery in health care system. It is an important aspect of

good teaching. Concept generation on various topic help students to conceptualize the whole area of complex disease processes on a particular topic or subject in one or two easy and simple sentences or proverbs with examples of daily life. That should form the fundamental basis or skeleton or thread on which other peripheral knowledge can be built. The human disease is a complex process where various biochemical mechanisms and cellular or genetic complexity are involved. For the beginners in medicine that may be quite perplexing and daunting task.

In this presentation we tried to establish that medical science not only as rigid fact based discipline but as medical science that has a narrative based on certain philosophy of life purely based on genetic information technology conveyed through gene expressions which are under certain regulation. The molecular genetic information as bio- informative studies has generated billion terabytes of information and which need to be integrated into useful clinical information not only in dollar value. Our narrative is that all information is inside our genes in all in one and one in all concept but simultaneously same and different concept-an unthinkable and imperceptible concept.

Based on this concept in this presentation we have generated simple easy to remember concept as common proverb or simple words for each of group of organ system and disease –processes. These words or concept encode the inner meaning of these topics. This should help undergraduate student to understand the difficult pathophysiologic mechanisms in simple form. These concept generation, integration and unification of theme teaching in pathology can be summarized as harmonization of normal human activities due to inherent molecule integration and unification of various organ system to provide best service for the survival of human being.

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None.

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