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Beyond a Simple Concept of Constancy of Homeostatic Control or of the Disease State

Lawrence M. Agius
Department of Pathology,Institute of Health Care
St. Luke's Hospital, Gwardamangia, University of Malta, Malta, Europe

Abstract: Within a framework of operative control of cellular homeostasis one would necessarily have to conceptualize a system of mechanistic pathways that is essentially transformed as this affects organs and tissues within a given organism. Suppression would appear to perhaps constitute the main form of controlling influence governing not only such potential transformational events towards disease states but also the intrinsic operability of the genome as an operative system of the integral organism as a whole. It is perhaps in such terms that neoplasia and neurodegeneration would appear to constitute systems of de-suppression of such pathways as differentiation/de-differentiation and proliferative/non or anti-proliferative activity with neoplastic transformation, or with apoptosis/anti-apoptosis and cell necrosis in neurodegeneration.De- evolution in terms of desuppression of biologic and homeostatic systems of control might actually constitute the single integral substrate for pathobiologic transformation from a healthy to a diseased state of the organ and organism. A concept of intrinsic rhythmicity of evolution and de-evolution, of suppression and desuppression, or activation and de-activation, would appear to constitute a series of basic mechanistic pathways that would go beyond a simple concept of transformation of events and of attributes not only in the maintenance of homeostasis but also within the realm of the disease state. In such a system, one might in the final analysis have to consider a complex interplay of metabolic and mechanistic pathways that interactively participate at multiple different levels of operability in ensuring the switching on and off of induced effects within a system of identifiable form and function. In a final analysis, therefore, both biology and disease in molecular terms would have to take into consideration the essential attributes of constitutional change that both require suppression and desuppression, activation and de-activation, evolution and de-evolution in an overall process contrary to the concept of constancy of homeostatic control or of static maintenance of health.

Key words: Homeostatic, control, neurodegeneration, disease

INTRODUCTION

A central issue regarding pathobiology of disease concerns the active maintenance of integral cellular processes determining the viability of that cell. Indeed, strict considerations of the individual cell particularly in terms of mechanisms for maintaining this viability are bound not to take account of whole systems of homeostasis at a tissue and organ and even multi-organ level. The whole concept of tissue and organ differentiation within and as part of an integral organism is one that does not revolve simply around dynamics of effective regulatory control or even of homeostatic efficiency. For example Wnt proteins transmit many intercellular signals involving cell proliferation or apoptosis, cell fate determination, differentiation or stem cell maintenance in a single interactive system implicated also in the development of diseases ranging from osteoporosis to neoplasia[1]. Indeed, it would appear that viability of a given strictly individual cell is fundamentally a fallacious point of reference.

On the other hand, organ rather than cellular viability as with brain or heart would potentially constitute effective terms of reference with regard to the nature of homeostatic mechanisms regulating pathways of compensation or decompensation.

The individual cell is itself paradoxically an expression of such an organ homeostasis that would in turn perhaps help account for vital aspects of differentiation evolving from cellular to tissue and to organ level.

A whole supporting array of biologic systems enhancing various types of tissues that include also vasculature and nerve supply in an organ such as the heart or brain might be operatively homeostatic even in terms essentially independent of concepts of dynamic considerations arising concerning a cell such as the cardiomyocyte or neuron. In this connection, for

Corresponding Author: Lawrence M. Agius MD., Department of Pathology, St. Luke's Hospital, Gwardamangia, University of Malta/ Institute of Health Care, Malta, Europe Tel: 00356 21451752 / 00356 25951663
Fax : 00356 21223190/ 00356 21224286

example, endothelial cells play a crucial role in controlling vascular tone and homeostasis, especially in terms of expression of pro-atherosclerotic and anti-atherosclerotic genes via acute production of autocoids and the levels of autocoid-producing enzymes[2].

Certain fundamental aspects involved in integral organ physiology, biology and as a consequence also in pathology would perhaps affect the organ, principally in an indirect manner and be conceptually accounted for simply in terms of integrity of the whole organism beyond individuality of its organs and tissues In fact, it would appear that physiologic and pathologic aspects of involvement must in an important sense not be restricted simply to cellular pathology.

In a more fundamental sense, conceptual frameworks of physiology and of pathology cannot be reduced to just cellular forms of involvement. There would appear to exist a need for active incorporation of supracellular concepts of integration of systems of homeostasis and of dynamic regulation concerned specifically with essential integrity of organ and organism. Hence, for example, the liver plays a crucial role as the only organ to produce glucose used by skeletal muscle during exercise[3] .

Such considerations are borne out when one considers how a conceptual framework of integrity of the organism would not truly resolve itself simply in terms of a series of organ and tissue inter-relationships physiologically, pathobiologically or even anatomically.

In a real sense, a cellular basis as a system of integration of body systems would for example prove paradoxically incapable to account for how cardiac or cerebral function has evolved in developing a maintained system such as the blood-brain barrier.

In other words, there are aspects of the very nature of organ and organismal physiology and pathology that go far beyond cellular physiology and cellular pathology. It is for such reasons that concepts of mechanical frameworks determining selective vulnerability of the neuron, in terms of essential neuronal viability, or of specific viral neurotropism would fail to account for observed dynamics of neuronal injury or death[4] Selective vulnerability of neurons would have to be incorporated within schemes of selective vulnerability of whole regional groups of neurons, in turn specifically characterized in terms of regional neuronal group in brain or spinal cord as an organ, and furthermore within a context of specified nervous system versus organism as a whole[5].

Only in this way might one account for apparent contradictory aspects of homeostatic pathways that would allow pathways of selective neuronal vulnerability to both develop and be maintained in the face of such upsets as relative oxygen lack or ischemia as seen with hippocampal cortical neurons[6].

In this sense, perhaps, one might perhaps realize that concepts of selective neuronal susceptibility are in real terms only an active expression of frameworks of operation determining primarily organ and organismal integrity rather than individual cell viability.

Furthermore, such considerations might be crucial when considering disturbed mechanisms of maintenance of viability of cells particularly as exemplified by the pathologic states of neurodegeneration. In a sense, neurodegeneration would represent an essential failure of maintenance of viability mechanisms on the part of the body as a whole that would specifically derive from all or most cells in the body, including neurons, that have developed from a single fertilized ovum.

In this connection, it would be for such reasons that conceptual aspects of malignant transformation of a particular cell and of a particular cell type could also be so misleading.

In a sense, malignant transformation would be a disease of the whole body, not simply in terms of its essential metastatic spread and the consequent death of the organism, but especially with regard to a neoplasm that is paradoxically a focal lesion that evolves systemically.

It would appear that an essential quality that ensures integrity of maintenance of homeostasis would develop at the time of fertilization of the ovum. In some way, the fertilized ovum truly embodies not only the source of the whole organism that subsequently develops but also the source mechanisms crucially influencing subsequent possible pathologic involvement as with neoplasia.

Such a concept of the fertilized ovum incorporating subsequent possible forms of pathologic involvement is the environmental and microenvironmental influences to which the cells and organism are exposed, including the responses and compensatory mechanisms that would be set in motion as a result of such exposures.

Also to be considered is the real phenomenon of an increased susceptibility of the neuron to hypoxia when contrasted for example to the fibroblast.

Hence, there would appear to exist such a profound integration of a vast range of factors determining selective vulnerability of a cell such as the neuron to hypoxia that in a sense perhaps one would have to understand the hypoxic event itself in terms not only of the individual cell but especially in terms of cells as essential components of an integral organization of tissues or organs within a complete organism.

Even in terms of neoplasms such as pancreatic carcinoma, for example, a microenvironment of low oxygen

in the neoplasm might actually influence tumor growth as well as neovascularization[7].

Such considerations would appear to depend on a single essential genome for the entire organism and of a single genome type within the full setting of that particular species as the human.

It would appear that only such an approach in terms of integral overall properties and natural pathologic attributes could account for the neuron is so exquisitely sensitive to hypoxia, or for neurodegeneration as inexorably progressive till death of that neuron, or for malignant transformation such an integral and analogous counterpart of the normal physiology of the cell with paradoxically abnormal expression of increased cellular mitotic activity In a final analysis, selective suppression as the single prime target to achieve when pathologic insults involve the cell and the organism as a whole, accounting thus for such diverse phenomena as malignant transformation, hypoxia and neurodegeneration.

Combinatory and associative interactions of multiple genes towards cell biologic de-evolution in the development and progression of neoplasia: A particularly interesting form of association is the inheritance of distinct phenotypes along non-Mendelian lines, particularly in the case of multiple different phenotypes associated with mutations of the same gene.

Disorders such as diabetes mellitus and schizophrenia would appear to be truly non-Mendelian in terms of inheritance patterns at least in part because of epigenetic events related to a variability in disease phenotypic expression in spite of involvement of the same gene.

Different mutations of the same gene might possibly follow different inheritance patterns particularly if these patterns of incidence are evaluated purely in terms of specific phenotype occurrence.

One reason might actually be that a multigene causation is possibly involved in inducing the clinical state of schizophrenia. In what ways might a multi-genetic mutational lesion lead to such nonMendelian inheritance patterns?

Certainly, in general terms, it might be true that certain individuals are particularly characterized by a predisposition for multiple mutations/deletions in different multiple genes, seen not only in the conceptual scope of such conditions as Fragile chromosomes or of Bloom's syndrome or Xeroderma pigmentosum but beyond such a concept in terms of facilitated association[8]. It might very well be true that certain genes tend to be concurrently mutated or point deleted in certain genomes. Such a phenomenon of association of mutations in multiple genes in the genome of the same individual might very well be prone to constitute a fundamental predisposing set of conditions such as schizophrenia or neoplasia.

In fact, it may even be instructive to compare predisposition patterns leading to schizophrenia with those leading to neoplasia in general outline terms. A fundamental aspect of both these two groups of disease categories might very well incorporate both a predisposition and an actual pathologic effect of lesion infliction—that in fact multiple genetic alterations might occur that on the one hand predispose to the actual occurrence of genetic mutations/point deletions and on the other hand result in dynamics of such involvement by genetic mutations/point deletions themselves.

In a sense, perhaps, in trying to understand the incidence of several disease states, including for example atherosclerosis, arterial hypertension, and perhaps also a full set of other disease entities, one might be confronted by the occurrence of two fundamentally distinct genetic phenomena—one of disease predisposition and another of actual infliction and development of the genetic lesion or lesions. In this regard, for example, post-translational mechanisms of endothelial nitric oxide synthase regulation by bradykinin may operate in blood pressure regulation and vascular homeostasis via systems involving protein-protein interactions with caveolin 1, the BK B2 receptor and heat shock protein 90[9]. These two sets of fundamentally distinct groups of genetic events would appear capable of influencing the expression of the disease phenotype in terms of associative effects and of epigenetic events. Also, for example, some rapid actions of steroid hormones on the vascular system such as increased alpha- adrenoceptor numbers, reduced prostacyclin production, and inhibition of NO synthase appear mediated by non-genomic responses in vascular tissues[10].

Hence, genetic events concerned with both predisposition and also with actual infliction of lesions to the genome might in some way, as seen for example with a large variety of neoplasms, be considered in strict relation to certain epigenetic phenomena. Such epigenetic events might not simply relate to susceptibility traits that would either increase or decrease predisposition of a particular cell genome to neoplastic transformation but also participate in associative aspects of enhancement between different genes in the same cell genome. In similar or analogous terms, for example, changes in the patterns of gene expression through regulatory transcription factors are crucial components of the

machinery that determines cellular responses to oxidative and redox perturbations[11].

Hence, it might very well be true that associative predisposition with subsequent enhancement of occurrence of both genetic lesions and also of actual clinical expression of such genetic lesions might constitute a fundamental background and operative platform both for the development and progression of neoplasia.

Neoplasia as a clinico-pathologic phenomenon would appear so intimately embedded within the cell biology of the individual as a fundamental de-evolution of the biologic state itself of the cell, that understanding its pathogenesis particularly would necessitate considering the whole cell genome a platform from which both facilitation of development of lesions and of expression of such lesions would evolve or de-evolve in terms of associative transformational events. In this sense, for example, cellular adhesion molecules of the cadherin, integrin and immunoglobulin superfamilies are important to both growth and metastasis of many cancers including malignant melanoma which tends to show well defined sequential stages in growth and spread[12].

It is this extraordinary combinatory interaction between multiple genes in a cell genome that would allow de-evolution beyond any measure of control as a phenomenon of malignant transformation concerned especially with alternative mutual inhibition/disinhibition between cell proliferation and cell differentiation as a neoplasm develops and progresses. Indeed, the stromal microenvironment surrounding tumor cells would appear to constitute a system of interactive communication involving also fibroblasts and inflammatory cells in a three-dimensional extracellular matrix.

Such a concept would go beyond a simple action of matrix metalloproteinases in degrading extracellular matrix in cases of infiltrating neoplasms[13].

An integrated multi-organ functionality far beyond any simple additive effect of individual organ functionality in terms of physiologic homeostasis and metabolic pathways: It might very well be valid to consider combined liver and kidney physiology to constitute one essential integral unit in terms not simply of metabolic synthesis and processing on the part of the liver on the one hand, but also of excretion by the kidney on the other.

In simple terms, it might be more realistic to consider renal physiologic roles to encompass within an overall scheme of homeostasis as an integral part of the central metabolic machinery of the body in considering actual mode of approach and mechanics of metabolic processing.

It would appear likely that kidney and liver physiology are indeed an integral part beyond specific individual organ characteristics and properties in physiologic and homeostatic control and biochemical metabolism.

Such a concept would appear well illustrated by metabolic defects such as primary hyperoxaluria where renal transplantation would actually result in excessive production of oxalate by the liver.

It might certainly appear conceivable to consider an integral axis of functionality between liver and kidney physiology and metabolism, an axis that would be represented by the nature of inter-organ cooperative effects beyond a simple concept of additive effect in overall physiologic and biochemical dynamics of the body as a whole.

Certainly, it might be particularly significant that individual organs are not simply essential and separate stations of metabolic processing of particular biochemical pathways—an essential concept of the coordinative efforts of all organs of the body might necessarily go beyond simple additive effects in a serial or successive fashion as would be seen with blood delivery of various metabolites to individual organs. In this sense, for example, neurobiology of sympathetic responses to changes in osmolality has implications for body fluid and cardiovascular physiology in maintaining normal cardiac output and arterial pressure[14,15].

Such a concept would apply for example to a system of crosstalk between phosphorylation sites in the case of endothelial nitric oxide synthase[16].

Even such global pathobiologic processes as heart failure and hypertension and even dynamics of widespread infections would in a sense have to incorporate an interactive series of events between individual organs. In a final analysis such upset of mechanisms and of dynamic inter-relationships between most of individual organs in the body would help account for definitive improvement or deterioration of a patient's condition afflicted by significant disease. Elucidating the essential nature of inter-organ functionality within a global physiology and metabolism of the body would constitute an essential aspect of health and of disease.

Molecular events beyond transformational events leading to disease states: Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) would be particularly interesting and valuable since they constitute an imaging mode of investigation directly and dynamically elucidating the influx and efflux along distinctive biochemical pathways in turn affected by disease processes.

Such insight into basic and essential molecular pathology of any disease involvement, might be achieved in neurodegeneration. Such insight would potentially redefine disease in basic terms with regard to the essential nature of pathologic involvement. Such a seemingly powerful approach in detecting and elucidating disease processes that originate, evolve and progress in an organ might allow redefinition of forms of pathologic involvement beyond simple states of disease entity.

Preclinical features and evolving progression might be suggestive of possible modes of intervention in manipulating or aborting disease processes early in their course.

Neurodegeneration is an excellent example of a black box that has so far been difficult to translate in simple equations as mechanisms or as transformational events. Even in terms of synaptic homeostasis and plasticity, for example, alpha and beta CaMKII are inversely regulated by activity in hippocampal neurons (as noted in culture); a swing in alpha/beta ratio shifts toward alpha during increased activity and beta during decreased activity in a system that would result in opposing effects on unitary synaptic strength as well as mEPSC frequency.

Such type of concept would help better account for integrating effect even of degree of activity in determining synaptic function or dysfunction as in neurodegeneration[17].

Even basic mechanisms that allow essential transformation from a healthy cell to a diseased cell would eventually be better delineated beyond simple morphologic lesions. The genome might constitute highly dynamic interactions even as applicable in terms of living processes of action and reaction in disease. The living state as a permissive series of cascade type events towards transformation within cells, tissues and organs, would be exquisitely susceptible to the development of disease in terms indeed that might arise from aspects of integral organization or organs and tissues as represented in terms of homeostasis and regulatory systems of influence.

Rhythmic cyclical activity patterns inbuilt in cell biologic mechanisms as central to basic concepts of feedback control, of threshold phenomena, of even basic properties of the so-called homeostatic control of constancy of the micro-environment: The co-transporter model is one that would indicate a striving for integration taking advantage of such co-transportation. In the case of the Na+-glucose cotransporter, the actual activation and deactivation cycling of the transporter is tied up with cotransportation of sodium and subsequent ingress of glucose and water into the cell.

A combined phenomenon of cyclically regulated degrees of conformation of the receptor might develop in response both to ligand binding and to voltage membrane changes. Additionally, the actual cotransportation of glucose and Na+ by the same transporter would appear to ensure a cyclical phenomenon in the activation/deactivation of the same cotransporter as a central mechanism of operability.

In sustained cyclical activity biologic mechanisms essential for viability of cells might be central to a concept of homeostasis beyond simple maintenance of constancy of the internal micro-environment. In this regard, for example, the cryptochrome 1 and 2 genes are necessary for the generation of circadian rhythms; indeed, cryptochromes would in particular appear functionally implicated in the homeostatic regulation of sleep beyond simple genetic considerations[18]. In a real sense, a cyclical model of processing and of operability might help ensure maintenance of reactive adaptability. Even a concept of compensation in the face of altered micro-environment might represent an essential biologic need for inbuilt cyclical and rhythmic operability beyond an essential scheme of constancy[19]. In fact, any concept of strict conditional maintenance of constancy of biologic phenomena might appear intrinsically paradoxical.

Pathobiology would appear to arise as an intrinsic consequence of cyclical operability of biologic mechanisms with a tendency to blur transition from a biologic to a pathobiologic state.

Beyond even the idea of normal constancy and of maintained health, cell biology would constitute an interactive series of processes with inbuilt interactions ranging from hyperpolarization and depolarization, to ingress and outflow of substances, or to activation/deactivation of enzymes, ion channels and transporters.

Even such applied concepts of an essential series of inbuilt rhythmic cyclical activation as negative and positive feedback mechanisms of control, of thermostat control of body temperature, of even threshold concepts for the elicitation of an all-or-none phenomenon might be better accounted for by concepts involving integrative resolution along pathways of either resolution or progression that however are paradoxically evolving in an interactive manner.

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