DISEASE AS INSTABILITY, ERROR AND ENTROPY

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THE ROLE OF THE MINIMUM ENTROPY PRODUCTION PRINCIPLE

In scientific medicine causes (etiology) and mechanisms (pathogenesis) of diseases are identified on the basis of biochemical and physiological changes (the physiopathological approach). Etiopathogenetic studies, however, provide information only on the mechanisms of the diseases. The problem arises as to whether thermodynamics may help to identify more general and common features of the biochemical and physiological alterations in diseases.

Living organisms are irreversible thermodynamic systems which build up and maintain their genome-codified, evolution-selected, structures by extracting energy and matter from the environment. Associated with auto-duplication and transmission of information by the genetic code, the variation-selection process leads to evolution towards increased complexity and hierarchical organization.

Evolution of life from the simple to the complex is accompanied by development of highly specialized metabolic pathways for exploitation of environmental resources. The advantage of a new species depends on the ability of exploiting the resources of new and unexplored ecological niches. However, the problem of evolution is not only that of diversifying but also that of rate control and efficiency in order to limit the parallel increase of the rate of entropy production [1]. Natural selection of the best fits is the result of optimization processes [2] with respect to the parameters of diversification, rate control and efficiency.

While without the complex metabolic pathways most of the environmental resources would remain unutilized or exploited at extremely low rates, organisms could not survive without combining the availability of new pathways with that of highly sophisticated mechanisms of control and efficiency, where control means primarily limitation of the reaction rates, and efficiency means attainment of constant stationary states of minimum entropy production.

THE COMMON FEATURES OF DISEASES AND THE STABILITY AND EFFICIENCY OF BIOLOGICAL PROCESSES

Since multicellular living organisms are characterized by stability of their internal milieu, the search for features common to all diseases has been largely focused on the alteration of homeostasis. In diseases homeostatic mechanisms often operate under modified conditions with diminished adaptation to the external environment and larger fluctuations of the internal environment. This has favored the view of diseases as consequences of a reduced capacity to maintain the internal milieu constant: alterations of homeostasis as common features of diseases and disease as decreased autonomy from the environment [3-5].

A general problem is the contrast between the specificity of the mechanism leading to each disease and the multiplicity of the kinetic mechanisms responsible for autonomy: no alteration of a specific kinetic mechanism can characterize all diseases; alternatively, no disease can involve the alteration of the multiplicity of kinetic mechanisms responsible for the constancy of the internal environment. Since each disease is characterized by the alteration of a specific mechanism, the concept of the disease as a consequence of a diminished autonomy with respect

to the environment must be moved from the level of the alteration of the specific kinetic mechanisms responsible for the autonomy to that of the general principles determining the stability of the biochemical and physiological parameters of living organisms. This leads to the concept of the alteration of homeostasis as part of the more general concept of the alteration of the constant stationary states of maximal efficiency and of minimal entropy production characteristic of living organisms.

An example of the close relationship between the concepts of homeostasis and that of stability is provided by the limited variations of the concentrations of cell constituents in spite of the large variations of their reaction rates. Consider the homeostasis of Ca^{2+}, a fundamental second messenger for intracellular reactions in secretion, proliferation, contraction and so on. Ca^{2+} homeostasis depends on a number of mechanisms such as the release of Ca^{2+} from IP_3-dependent and -independent stores, *e.g.* the operation of a number of transport mechanisms on the plasma membrane and on the membrane of other subcellular organelles, the effects of several mediators and hormones. The purpose of these mechanisms is that of regulating the Ca^{2+} concentrations in order to keep their range on one side relatively constant and on the other side enough sensitive to small variations in concentrations in order to be compatible with the requirements for signal transmission [6,7].

With stability of Ca^{2+} concentrations being essential for cell survival, most cell pathological processes are accompanied by alterations of Ca^{2+} stability. However, cell survival depends on the stability of many other constituents. Hence, alteration of Ca^{2+} stability is only one of the many stability alterations occurring in cell pathology. Furthermore type and mechanism of alteration of Ca^{2+} stability vary according to the nature of the pathological process [6,7]. Once moved from autonomy of the internal environment to that of stability of the biochemical and physiological parameters, the concept of the diminished homeostasis overlaps with that of the alteration of the stationary state, of the regulation of the ensemble of processes maintaining biochemical and physiological stability. The theoretical framework to understand this regulation is provided by the mathematical methods of stability analysis used in electrical engineering to control the stability of circuits and systems under changing conditions. The same analysis is applied to understand the stability phenomena in evolution, ecology, economy, sociology and so on [8].

THE STABILITY OF THE STEADY STATES

While the second law of thermodynamics predicts a generalized drive toward entropy production it does not specify the rate at which entropy production occurs. According to Onsager's principles, far-from equilibrium irreversible processes occur at maximal possible rates and therefore also produce entropy at maximal rates [1].

Prigogine [9] has however demonstrated a theorem of minimum entropy production, according to which, under constant Gibbs energy gradients, irreversible processes are directed towards lowering the value of entropy production per unit time and towards achieving stationary states of minimum energy dissipation. These minimum entropy production states cannot be left spontaneously, since internal changes take place after perturbations which bring back the systems to the initial states. Although, strictly speaking, the theorem is valid only in close-to-equilibrium domains where thermodynamic flows and forces are linearly related, the Onsager reciprocity relations apply and the

phenomenological coefficients are constant. Its more general validity has been argued by others (see [10]).

Living organisms are dissipative systems operating in far-from equilibrium domains and therefore in principle out of the range of validity of the minimum entropy production theorem. However living organisms are also constituted by a hierarchical organization of intermolecular forces-stabilized structures, the thermodynamic consequence of which is extending the range of validity of Prigogine's theorem. A typical example is the behavior of mitochondria which tend to achieve spontaneously a condition denoted as static head, that is of minimum entropy production [11-14].

THE STRUCTURAL ALTERATIONS

Several examples favor the concept that decrease of stability and increase of energy dissipation are common features of diseases. Consider first a mitochondrion *in vivo* or *in vitro* under static head conditions. While the rate of ATP synthesis depends on that of ATP utilization, the respiratory rate in static head is minimal as determined by the proton motive force whose dimension in turn is determined by the relative rates of the reactions generating and using the force: one of energy conversion into ATP synthesis and another of energy dissipation into passive proton diffusion and slips. The integrity of the inner mitochondrial membrane is the natural tool to achieve constant stationary states of minimum dissipation. Inner membrane damage leads to increased proton leaks and slips, and then to increased energy dissipation and higher respiratory rate. *In vivo* this is however a transient followed by recovery of the original inner membrane integrity and steady state.

Because of the multiplicity of hierarchically organized structures, the dissipation function of the organism is the sum of those of its subsystems, and the transition from low to high and then back to low dissipation of the whole organism during diseases reflects the behavior of one of its subsystems. Alterations of stability and efficiency occur at several levels of organization: subcellular organelles, cells, organs and apparatus. In some cases the alterations are of such an intensity to become incompatible with survival unless reduced by drugs.

Consider the cell damage *in vivo*. Mitochondrial respiration is stimulated to provide the ATP required for cell regeneration and duplication, *i.e.* synthesis of proteins, phospholipids and other constituents. The increase of respiration is accompanied by increase of blood supply, of venous return and of cardiac output. The entire cardiovascular system is shifted to levels of higher activity and of higher dissipation. The activity of the whole cardiovascular system returns to the low dissipation steady state parallel to the levelling off of mitochondrial respiration.

Consider the operation of the plasma membrane Na^+/K^+-ATPase. Maintenance of Na^+ and K^+ gradients across the plasma membrane depends on pump and leak mechanisms: the gradients generated by the pump are abolished by ion passive diffusion. The efficiency of the system depends on the tight control of ATP hydrolysis tending to limit hydrolysis uncoupled from ion transport and on the low ion permeability tending to limit passive ion diffusion. The integrity of the plasma membrane is the tool to insure both the tight control of the ATPase and the low ion passive diffusion. Membrane damage results in decreased control of the ATPase and increase of ion diffusion. *In vivo* the condition of high ion permeability of the plasma membrane is necessarily a transient state, after which the cell is either eliminated or regains its original structure.

Consider the alterations of the nervous system following ischemia, trauma, Parkinson's disease and so on. The enhanced stimulation of excitatory amino acid receptors, such as the NMDA receptors, leads to increased influx of Ca^{2+} into the neuronal cell, through the specific receptor regulated channels, and to alteration of Ca^{2+} concentration stability. The increased concentration of cellular Ca^{2+} activates a number of disruptive processes such as increased proteolysis and increased production of NO [6,7,15].

THE INCREASE OF ERRORS

The number of molecular symbols transmitted by self-reproducible units is inversely proportional to the average error per symbol and this sets up an upper limit for the number of digits to be transmitted [2]. During phylogenetic evolution complex mechanisms have been selected in order to correct for errors and allow for proper genome decodification. Transmission of genetic information continues to play a role also after ontogenesis. First, all proteins undergo a continuous turnover. Second, in some tissues cells are duplicated as a whole. Third, after disease-induced cell death, multiple cell regeneration and even organogenesis are necessary for repair. However transmission of information is subject to entropic drive since the fidelity of self-reproductive processes depends on thermal noise, *i.e.* on the not very great distance between the energy of interaction of the elementary step of the information transmission mechanism and the level of thermal energy.

Increases of rates of error transmission or decreases of efficiencies of spontaneous error correction result in generation of diseased cells. A large variety of alterations, from aging to genetic diseases, from tumors to metabolic defects, from autoimmune diseases to degenerative diseases, is attributed to increased rates of error production as due either to a genetic program, or to accumulation of altered genes responsible for deleterious effects or to error catastrophe [16,17]. Whatever the specific mechanism, aging is generally accompanied by an increased mutation rate, in some cases favored by environmental factors as indicated by the rapid aging induced in rats by exposure to radiations.

In some cases the molecular basis for the alteration of stability has been identified, in malignant hyperthermia a mutation in the ryanodine receptor - the Ca^{2+} channel of the sarcoplasmic reticulum. The specific mutation - Arg-Cys in position 615 - causes an increased opening probability of the Ca^{2+} channel and increased Ca^{2+} release from the sarcoplasmic reticulum. The consequences of the increased concentration of cellular Ca^{2+} are: activation of metabolism, muscle contraction and hyperthermia [15].

Mutations of the mitochondrial DNA may play a special role in alterations of tissues depending on high rates of oxidative phosphorylation [18]. Alterations of the mitochondrial DNA would then be involved in a variety of diseases such as, to mention a few, ischemic heart disease, late-onset diabetes, Parkinson's disease, Alzheimer's disease and aging.

CONCLUSION

The effect of the intermolecular forces-stabilized structures - the information which is selected during evolution, transmitted by the genome and decodified during ontogenesis - is that of favoring the evolution of the irreversible processes of living organisms toward stationary states of great stability and minimum dissipation [9]. A variety of processes, specific for each disease, causes alterations

of these intermolecular forces-stabilized structures. The consequence is the shift of one of the subsystems, and as a consequence of the organism as a whole, to diminished stability and efficiency of the stationary states.

Cessation of alteration is generally followed by repair, reconstruction of the native, genome-codified, structures and reestablishment of the stable and efficient stationary states. When however the disease is accompanied by loss of information the reconstruction is incomplete and the dissipative systems reach a new stationary state different from that predicted by the genomic code. In a wide number of diseases the lesion resides primarily in storage or transmission of information.

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