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Research Article

Entropy as the Driving Force of Pathogenesis: an Attempt of Classification of the Diseases Based on the Laws of Physics

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Abstract. In nature, every physical process involving matter is ruled by the second law of thermodynamics (the total entropy of an isolated system can never decrease over time, and is constant if and only if all processes are reversible). The living cell being a material system should comply by releasing entropy either into the body or into the outside environment. In case of pathologies, entropy cannot be fully exported outside the body and stays inside the body either in the form of intracellular biomass, of extracellular waste products. We propose hereafter, a new way of classifying diseases by looking at the kind of entropy which cannot be easily excreted outside the body. In such a classification, inflammatory diseases play with entropy through increased heat, biomass synthesis (proliferation of lymphocytes and neutrophils) and secretion of pro-inflammatory proteins (waste products from the cell's point of view). In the case of chronic inflammation, it induces mitochondrial impairment, owing to the increased osmotic pressure associated to hyper-osmolarity leading to cancer and degenerative diseases (DDs). In the special case of degenerative diseases, cellular entropy is mostly released in the form of wastes, such as amyloid plaques or Lewy's bodies, and not as proliferating cells as in cancer. Consequently, despite quite different symptoms, these two diseases are proposed to be Janus-like twins, meaning that a remedy active against cancer, should also be active against various forms of DDs.

Keywords: entropy, inflammation, cancer, extracellular pressure, classification of diseases.

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INTRODUCTION

Life appeared on earth over 3,6 billions years ago. Life is a robust phenomenon with similar concentrations of sodium, potassium and chloride in every living cell. Moreover, similar lipoproteins constitute the membranes and the nucleic acids are always built with the same bases.[1]

Metabolism corresponds to a set of life-sustaining reactions that are doomed to generate entropy. Conversion of food into energy and heat (catabo-

lism) generates a large entropy flux. Heat is then released in the environment. Entropy can also be transduced into the building blocks of life such as proteins, membranes or nucleic acids (anabolism) with elimination of wastes. In a previous paper,[1] we have shown how it is possible to classify biological molecules into food and wastes, according to their intrinsic entropy content. From such a standpoint, secretion of hormones, growth factors or any other small molecules should be considered as generation of wastes, triggering a mandatory response of the cell. It follows that any kind of "waste" should be considered as a potential signaling molecule. This new positive interpretation of "wastes" is a key step allowing deep-rooting of life processes into thermodynamics.

As previously stated, in order to be a spontaneous chemical process, metabolism should always lead to a global increase of entropy. This has allowed deriving a fundamental law of life[1] stating that the sum of the entropy of the biomass created added to the entropy of the wastes secreted by the cell added to the heat released should be higher than the entropies of the ingested nutrients. If one considers the cell as being the inside, to comply with the second law of thermodynamics, the excess entropy has to be exported outside the original cell. The excess entropy can be exported either in the form of radiation (heat) or in the form of matter named in biology: biomass.

Biomass can be exported in the form of the extracellular secretion of molecules. The secreted molecules can be simple deposits of proteins such as amyloid plaques or can be released in the blood and absorbed by other cells. Some of these molecules have special signaling properties and modify the activity of the target cell. Hormones are secreted by the sexual organs and are secreted, first, in the extracellular space then in the blood stream. These hormones bind to specific receptors and are taken up by target cells whose genetic activity they modulate. Similarly, lactate released by glial cells is secreted by the glial cells. Lactate is uptaken by the adjacent neurons, enters the Kreb's cycle and is burnt releasing entropy outside the body in the form of heat.

Entropy of the primary cell can also be released in the form of a daughter cell. The division of the primary cell in two different entities decreases by two the entropy of the original cell.

Thus entropy can be released either in the form of heat or in the form of supplementary cells and/or cellular waste. Heat will be released outside the body but waste and biomass will stay outside the original cell but inside the body.

Taking these premises for granted, it follows that diseases are also regulated by the second law of thermodynamics. Accordingly, it appears that diseases are similar across species. For example, cancer,[2] but also inflammation and degenerative diseases[3] have been described across species in almost every metazoan. Life expectancy, physiology and metabolism are deeply linked. This was demonstrated through allometry, the study of the relationship of body size to anatomy as first outlined by D'Arcy Thompson.[4] Thus, Atanasov has evidenced a linear relationship between the total metabolic energy per life span and the body mass of 95 mammals[5]. Similarly, Levine correlates the life expectancy with the rest heart rate.[6]

Today diseases are understood by the biologist as a cascade of events resulting in organ failure or in cancer. In deep contrast with biology, physics and thermodynamics do not look for detailed mechanisms, diseases being the mere consequences of fundamental laws. The goal of this paper is to better understand diseases by classification according to the second law of thermodynamics. Hereafter, by focusing on clinical symptoms such as the ones described by the physician, it is possible deducing the physical laws at stake.

As of today changes in the cycle of life are understood as the staightforward consequences of biological mishaps. They can also be described by the way the affected cells release entropy.

Most common diseases (if not all) and conditions can be understood by the modulation of entropy secreted by the cell. Entropy synthesized by the cell can either be exported outside the body in the form of heat or be secreted outside the cell in the extracellular space or stay inside the cell. From the cell's point of view the synthesis of another cell is a way to decrease the entropy by two.

1) **Conditions with heat release:** circadian rhythm and ovulation

During the circadian rhythm, there is an oscillation of the body temperature. Temperature is higher in the evening and lower in the morning.[7] At night a decrease in body temperature and cell proliferation as well as the release of hormones such as steroids are observed.[7]

At time of ovulation, there is an increase in body temperature. The sexual hormones are released by the ovaries as cholesterol derived, entropy rich, molecules. The hormone will bind to the receptor and interact with the genome. Entropy will be released mostly in the form of heat.

2) **Conditions with biomass synthesis:** childhood growth

Infancy and childhood are characterized by body growth. Growth starts with fecundation and suddenly

stops shortly after puberty. Body growth is harmonious and is partially controlled by mechanical constraints.[8]

ATTEMPT OF CLASSIFICATION OF DISEASES

As of today, diseases are classified by symptoms and affected sites. We will try to classify the pathologies by the typologies of entropy. In a few rare diseases, the amount of entropy can be increased or lowered.

Diseases with increased entropy synthesis: drug abuse, hyperthyroidism.

During hyperthyroidism there is increased heart rate, weight loss, diarrhea, nervousness, irritability, increased perspiration and hand tremors. All these symptoms are caused by increased metabolism secondary to enhanced hormone secretion. During drug abuse like cocaine or heroin, there is increased heart rate, respiration and euphoria.

Diseases with decreased entropy synthesis: hypothyroidism, hibernation, abuse of sedative

On the contrary, during hypothyroidism, constipation, feeling of tiredness, depression and slow heart rate are observed. Abuse of sedative may result in somnolence, amnesia and possibly dementia.

DISEASES WITH INCREASED BIOMASS SYNTHESIS AND WASTE SECRETION

Some benign tumors secrete proteins that are excreted in the blood stream. These proteins secreted by the cell could be considered as waste-signaling products. Other proteins have no peculiar biological functions. Benign prostatic adenoma secretes a glycoprotein: Protein Specific Antigen (PSA) which can be measured in the blood stream and used as a diagnostic tool. When present in the blood, this PSA has no known biological function. Other benign tumors can secrete hormones which can be toxic. Best known are the thyroid adenoma. Some of these benign tumors secrete high level of T3 and T4 thyroid hormones which can, in turn, be toxic to the heart or the brain (thyreotoxicosis).

Sclerosis, cancer and neurodegenerative diseases also experience increased biomass synthesis and waste products secretion. They will be discussed later in the paper as they are the direct consequence of inflammation.

Diseases with increased waste secretion and temperature: infection and cell death

Hyperthermia is present in most acute infections, but also during tissue necrosis (like cardiac infarct). During infection or cell death there is an increase secretion of pro-inflammatory proteins or CRP. During cardiac infarct, multiple proteins present in the myocardial cells such as troponin are released in the blood stream.

DISEASES WITH INCREASED TEMPERATURE AND BIOMASS SYNTHESIS

We were not able to isolate any disease displaying increased temperature, biomass synthesis and no increased waste production.

Diseases with increased heat, biomass and waste synthesis: This is the signature of every kind of inflammatory disease.

a) **Acute inflammation**

As stated by Galen about two thousand years ago, inflammation can be stated as «tumor, dolor and calor». During the inflammatory process there is increased heat, synthesis of biomass and increased waste secretion.

Inflammation can be caused by a different set of circumstances such as heat, cold, chemical or bacterial and viral injuries. The name of the inflammatory diseases varies upon the affected organ (Table 1 and 2). To name a few, hepatitis, Crohn's disease, ulcerative colitis, meningitis or bronchitis…

Some inflammatory diseases are confined to one organ (for example asthma or psoriasis) but may also extend to several organs (scleroderma, rheumatoid arthritis…).

Inflammatory diseases have all in common an increase in extracellular osmolarity. In every inflammatory fluid there is increased osmotic pressure (9, 10, 11 and references therein). The increased osmotic pressure results from an increased oncotic (and osmotic) pressure because of the presence of abnormal level of proteins in the extracellular fluid. This is in line with the fact that the concentration of protein in the extracellular fluid is pathognomonic with inflammation.[12]

Increased osmotic pressure results in cytokine and lymphokine secretion as well as the immune response.[13,14]

The waste products secreted during the inflammatory process are well documented. They are the C-Reac-

Table 1. Entropy release by the affected cell.

	Heat	Biomass	Waste
Circadian rhythm: day	yes	no	no
night	no	yes	yes
Growth	no	yes	no
Glands	no	no	hormones
Infection	yes	no	pro-inflammatory cytokines
Cell death (infarct)	yes	no	yes (troponin)
Benign tumors	no	yes	PSA/ hormones
Degenerative diseases	no	yes (inflammation)	yes (amyloid plaques, Loewy's body)
Cancer	no	cell multiplication	yes (tumor markers)
Inflammation	yes	immune system activation	yes (CRP)
Ageing	no	yes (inflammation)	yes (CRP)

Table 2. classification of diseases.

Organ	Inflamatory disease	Sclerosis	Diseases resulting from metabolic rewiring
CNS	Encephalitis Meningitis	Multiple sclerosis Lateral amyotrophic sclerosis, Schizophrenia	Glioma, neuroblastoma, Alzheimer, Parkinson, Huntington's disease
CV	Myocarditis Pericarditis	Atherosclerosis	Heart failure
GI	Crohn's, Ulcerative colitis	Dysfunctional colonic syndrom	Adenocarcinoma, Squamous cell carcinoma
Reproductive Organs	Salpingitis, Orchitis Endometriosis	Infertility	Seminoma, Adenocarcinoma
Liver	Hepatitis	Cirrhosis	Heart failure, hepatocarcinoma
Breast	Mastitis	Adenoma, Fibroma	Adenocarcinoma
Skin	Erysepelas, sun burn	Lupus, Psoriasis, sclerodermia	Basal cell carcinoma, melanoma
Lung	Flu, bronchitis	Chronic bronchitis Emphysema Pulmonary fibrosis	Squamous cell carcinoma, respiratory failure
Joints and Bone	Arthristis	Arthrosis Osteopenia	Sarcoma
Muscle	Myositis	Sclerosis	Sarcopenia, Sarcoma
Eye	Inflammation	Glaucoma, Cataract, Near sightedness	Macular degeneration
Immune system	Infection	Cytopenia, Myelofibrosis	Lymphoma, Leukaemia
General	Inflammation	Ageing	Ageing

tive Proteins (CRP) and numerous cytokines and lymphokines which can be assessed in the blood.[10]

This increased secretion of lymphokine and cytokine will result in vasodilatation, increased vascular permeability and leukocyte extravasation. The activation of the immune system caused by these lymphokines and cytokines results in phagocytosis and cell death.

b) **Chronic inflammation and its consequence: sclerosis**

Chronic inflammation is secondary to the persistence of the inflammatory agent. For example, hepatitis because of persistent alcohol consumption or unrelenting auto immune disease will result into cirrhosis (sclerosis of the liver). Similarly, persistent bronchitis secondary to excessive smoking will result in change in the

lung architecture with lung fibrosis and/or emphysema[15] (Table 2).

In the confined environment of the affected organ, the intracellular pressure must be equal to the pressure in the extracellular space. The increased multiplication of the epithelial cells will increase mechanical loads on the surrounding fibroblasts. This increased pressure results in the secretion of collagen by the fibroblasts.[16]

Chronic inflammation has another consequence: the occurrence of cancer[17] and neurodegenerative diseases.[18] This may be in part because of the change in tissue architecture secondary to fibrosis.[19]

Cancer cells usually originate from the epithelium on the lumen of an organ. In the case of sclerosis, the architecture is distorted resulting in loss of polarity of the epithelial cell. Numerical models demonstrate that the loss of cell polarity alone, is enough to induce an invasive, fractal, dendritic pattern such as seen in cancer. This transition shows a sequence of morphologies in the following order as a function of loss of polarity: first an apparently normal but already diseased tissue, then metaplastic followed by a dysplastic tissue, and eventually carcinoma first, *in situ*, then invasive carcinoma.[19]

c) **Cancer and neurodegenerative diseases**

Because of the Warburg's effect, cancer has a defective metabolism.[20,21] The glucose is mostly degraded into lactic acid which is secreted, as a waste, in the extracellular space. Lactic acid is a nutrient for the surrounding benign cells (inflammatory cells, fibroblast or vascular cells).[22]

Lactic acid is an energy rich molecule. Its release by the cancer cell results in a drastic drop in energy yield[1]. A molecule of glucose fully burnt by a normal cell releases 36 molecule of ATP. The same molecule of ATP releases only 2 molecules of ATP in a cancer cell. The energy yield is divided by at least 10 times resulting in a decrease in heat export outside the cancer cell[1]. To compensate this decrease energy yield, there is increase uptake of glucose such as seen in PET scan.[1]

Cancer could be viewed as the consequence of increased osmotic or oncotic pressure. Recently Hamraz[23] has demonstrated that increased osmotic pressure such as seen in inflammation is enough to induce the Warbug's effect. The addition to the cell culture medium of mannitol or other osmotic agents induce an increase in glucose uptake and an inhibition of the mitochondrial respiration. Moreover, treatments aiming at restoring the normal metabolic profile inhibit tumor growth.[24]

Degenerative diseases are also induced by inflammation. For example, Alzheimer's disease can be caused by repeated trauma over a long period.[25] In Alzheimer' s disease the waste products stay in the vicinity of the neurons to form the amyloid plaques. Upon examination under the microscope there is a coexistence of intense apoptosis of neurons and proliferation of the inflammatory and the glial cells (increased biomass synthesis).

In cancer and in degenerative diseases there is metabolic rewiring with decreased ATP synthesis.[20,21,26,27] The main difference between cancer and degenerative diseases is the intracellular pH. In cancer cells the intracellular pH is alkaline.[20,21] There is decrease synthesis of CO_2 and carbonic acid resulting in the alkalinisation of the intracellular medium. Alkaline pH is responsible of unrelenting cellular growth.[28] To the difference of cancer cells, the main nutrient of neurons is not glucose but lactic acid.[29] Accumulation of lactic acid results in an acidic pH and cell death.[30]

CONCLUSION

Modern medicine is characterized by a hyper-specialization with the consequence of classifying the various diseases of the body into unrelated categories. For instance, the rheumatologist takes care of the bones and joints while the pulmonologist considers only the lung. Such a wide diversification of medicine goes in the opposite direction of physics which eagerly looks for unification. This is a very strange situation as both medicine and physics play with systems made of matter. It follows that if the race for unification observed in physics is a wise goal, the same goal of unification should apply to medicine. In this paper, we proposed a very first step towards unification and classification of diseases. The red lead of our classification was the entropy concept, the single known concept ruling time evolution for every kind of material system. We do hope that the usefulness of the proposed classification will be demonstrated in a very near future. We are sincerely convinced that deep-rooting biology into physics, as done here, should not only be useful for healing diseases but also crucial for the survival of humanity. This is because our modern civilization is currently overwhelmed by wastes with the consequence of heavy pollution of air, water and soils. But, as explained here, wastes management should be synonymous of entropy management. Accumulation of wastes, i.e. entropy that is not released in the form of heat into the intergalactic space, means accumulated disorders with only one possible outcome: death. This applies to a human body, as well as to the whole earth. Time is then ripe enough to put entropy management at the very heart of any kind of living system.

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