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Is the Second Law of Thermodynamics Able to Classify Drugs?

Laurent Schwartz[1,*], Luc Benichou[2], Jules Schwartz[1], Maxime Pontié[3], Marc Henry[4]

[1] *Assistance Publique des Hôpitaux de Paris, Paris France*
[2] *Paris-Est Créteil University (UPEC) School of Medicine. Créteil, France*
[3] *Université d'Angers, Faculté des Sciences, Groupe Analyses et Procédés, (GA&P) 2 Boulevard. Lavoisier, 49045 Angers cedex 01*
[4] *Institut Le Bel, Université de Strasbourg, UMR 7140, 4 rue Blaise Pascal, 67070 Strasbourg*
*Corresponding author. Email: dr.laurentschwartz@gmail.com

Abstract. Specialization characterizes pharmacology, with the consequence of classifying the various treatments into unrelated categories. Treating a specific disease usually requires the design of a specific drug. The second law of thermodynamics is the driving force both for chemical reactions and for life. It applies to diseases and treatment. In most common diseases, there is a metabolic shift toward anabolism and anaerobic glycolysis, resulting in the release of entropy in the form of biomass. In accordance with the second principle of thermodynamics, treatment should aim at decreasing the entropy flux, which stays inside the body in the form of biomass. Most treatments aim at increasing the amount of entropy that is released by the cell in the form of thermal photons. As clinically different diseases often requires similar drugs, this calls for reinforcement in a quest for a single unified framework. For example, treatment of aggressive autoimmune diseases requires the same cytotoxic chemotherapy than for cancer. This strongly suggests that despite their apparent disparity, there is an underlying unity in the diseases and the treatments. The shift toward increased entropy release in the form of heat offers sound guidelines for the repurposing of drugs.

Keywords: Pharmacology, Alzheimer, psychiatry, cancer, entropy, pHi, mitochondria, lactic acid, paradigm shift.

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1. INTRODUCTION

This paper is one of a series of publications trying to merge medicine back into physics. Accordingly, the combination of theory and subsequent experiments was the cause of major progress in physics. We aim at describing diseases and thus treatment as physical features. But in medicine, measurements of physical data such as calculation of entropy are missing. Entropy production and dissipation has never been measured in human cells. We are, at a stage, where we can only raise hypothesis based of indirect markers of the fluctuation of entropy.

We have based our reasoning on data based on the metabolic flux centered by the mitochondria, the place within a cell, providing the maximum production of entropy as heat. We also have used clinical data. For example, if the patient is more active (like after treatment with thyroid hormones) one can assume that the entropy flux has increased. Similarly, if the temperature decreases (like after antibiotic treatment for infection) one may deduce that there is a decrease in entropy released in the outer space. In this paper, we have tried to merge biological and medical data, focusing on their impact on entropy. The second law of thermodynamics tells us that entropy can only increase in a closed system. When discussing the second law of thermodynamics, one should always define its reference. Here we consider the human body as the reference point. The entropy can be excreted from the patient and thus locally decreases. But, the entropy of the universe is always going up, as the contribution from our body, compared to the Sun-Earth system, is almost negligible.

2. BACKGROUND

In the vast majority of diseases, there is a shift toward increased synthesis of biomass. In cancer, there is increase in cellular proliferation. In neurodegenerative diseases, there are protein deposits like the amyloid plaques in Alzheimer's disease or the bodies of Lewy in Parkinson's disease. In inflammation, there is secretion of proteins such as lymphokines and cytokines and proliferation of inflammatory cells.

The Nobel Prize, Otto Warburg (1883-1970) in the 1920s, first described this shift toward anabolism in cancer cells. The Warburg's effect is a modified cellular metabolism based on aerobic fermentation, which tends to favor anaerobic glycolysis rather than oxidative phosphorylation, even in the presence of oxygen.

In epithelial cells, the Warburg's effect results in cancer[1]. The Warburg's effect is a bottleneck. The cells cannot burn the glucose because the pyruvate cannot be degraded in the Krebs' cycle. Evidence of the central role of the Warburg's effect comes when the researcher injects into cancer cells, with a micropipette, normal mitochondria. The growth will stop. These cells have become benign. The injection of the nuclei of cancer cells into normal cells does not increase growth. These cells can still burn glucose because the mitochondria are normal and do not form tumors [1 and references therein]. The inhibition of the oxidative phosphorylation results in the activation of the anabolic pathway, such as the Pentose Phosphate Pathway (PPP), that is necessary for DNA and RNA synthesis [1 and references therein].

The Warburg's effect results in the release of lactic acid in the extracellular space, the concomitant activation of the Pentose Phosphate Pathway, and anabolism[1]. The Warburg's effect results in the synthesis of new proliferating cells[1]. More recently, metabolic shifts have been described in Alzheimer and Parkinson's diseases[2,3]. Similar shifts toward anaerobic glycolysis have been described in most common disease. To name a few, among others, as published in[4]: autism[5,6] schizophrenia[7], Alzheimer[3], Parkinson's disease[8,9] Huntington's disease[10], stroke[11,12], infection[13], fibrosis[14,15], cirrhosis[16,17], emphysema[18], arthritis[19], scleroderma[20], lupus[21,22]. To the difference to the Warburg effect, these shifts toward glycolysis and increased lactate secretion may be transient and reversible in the presence of oxygen[4].

In biology, like in physics and chemistry, we are dealing with intertwined variables. In physics, Newton's law links forces to momenta. In chemistry, the ideal gas law links pressure, volume, temperature and the amount of matter. In biology, the release of entropy in the form of heat, oxidative phosphorylation, high mitochondrial activity and acidic intracellular pHi are linked if not synonymous. It seems that there is a shift to mitochondrial impairment in almost every disease, resulting in increased lactate concentration. These diseases appear to be a consequence of impaired mitochondrial function and increased entropy release in the form of biomass.

In cancer, mitochondrial impairment results in cell proliferation and tumor growth. In Alzheimer disease, there is an abnormal secretion of amyloid plaques, in Parkinson's disease, there are intracellular deposits (Lewy bodies) [3 and references therein].

A basic equation for cellular life taking into account that cells are open systems have been previously proposed[4,23-25]:

$$\text{foods (in)} = \text{biomass (in)} + \text{heat (out)} + \text{wastes (out)} \quad (1)$$

where "in" and "out" refer to a system surrounded by a containment able to exchange heat and matter between the inside and the outside of the cell.

Catabolism powered by oxidative phosphorylation is another word for entropy release in the form of heat. Anabolism through fermentation is another name for entropy release in the form of biomass[24].

Thus, from a thermodynamic standpoint, diseases can be classified according to the second law of thermodynamics. The cell feeds on low entropy molecules such as glucose to release higher entropy molecules such as CO_2 and ATP[23]. To comply with the second law of ther-

modynamics, the cell absorbs and degrades low entropy compounds into heat or biomass with a neat production of entropy[24].

Differentiated cells release their entropy in the form of thermal photons[25]. Proliferating cells have lower mitochondrial activity and release their entropy in the form of biomass. Differentiated cells have an increased mitochondrial activity [26–29], resulting in the release of entropy in the form of heat. Differentiated cells have a basal oxidative metabolism. The efficient TCA cycle degrades glucose into pyruvate [1,30]. The oxidative phosphorylation of acetyl-CoA into mitochondria yields large amounts of entropy-rich ATP and releases carbon dioxide and water as entropy-rich waste products.

This is the opposite of proliferative cells. Biomass synthesis and cell growth requires a rewiring of the carbon flux. Here, the PPP acts as a shunt for glycolysis, generating nucleic acid precursors for DNA replication [1,30]. Poorly differentiated cells release their entropy in the form of biomass[25]. Undifferentiated cells have lower mitochondrial activity resulting in alkaline pH and lower transmembrane potential, and increased cell division[31].

Cells oscillate between two modes of entropy production. Differentiated cells release entropy in the form of heat. They have high ATP production, increased transmembrane potential, increased ionic concentration, intracellular acidic pH, and low water activity. On the other hand, proliferative cells have decreased ATP synthesis, diluted ionic content, low transmembrane potential, alkaline pH[26].

During adulthood, respiration is predominant[32]. Childhood and aging are more anabolic than adulthood. In childhood, anabolism results mostly in growth. In aging, anabolism results in age-related diseases such as cancer and Alzheimer's disease. Most drugs impact both anabolism and catabolism. For clarity, we will focus on what appears to be the main target of the drug.

3. ATTEMPT OF CLASSIFICATION

Diseases can be described as a perturbation of the flux of entropy[24]. Most drugs should be described based on their impact on the entropy flux. Drugs have been designed to target a specific receptor. As a key opens the lock, the active compound binds with its receptor and modify the fate of the targeted cell. This view of pharmacology has yielded tremendous results, most recently, with the advent of targeted therapies. Our goal is to complement this approach with the necessary compliance to the second law of thermodynamics. But most drugs have multiple effects on entropy. For example, as we will discuss later, thyroid hormones increase entropy production, decrease the release of entropy in the form of biomass and shift toward the release of entropy in the form of thermal photons.

A) Drugs increasing the release of entropy

Some diseases are a consequence of a decreased metabolic activity, resulting in decreased production of entropy. A decrease in physical and psychological activity is the hallmark of these diseases. In hypothyroidism, there is constipation, somnolence and sometimes depression[33].

Treatment with thyroid hormones results in increased heart rate, weight loss and excitability[34]. Thyroid hormones result in increased entropy flux, but also in a shift toward increased release of thermal photons. Overdose of thyroid hormones may result in hyperactivity, fever, mania, diarrhea and increased heart rate. These are indirect signs of increased production of entropy.

The mechanism underlying the regulation of the basal metabolic rate by thyroid hormones remains unclear. It has been suggested that these hormones uncouple substrate oxidation from ATP synthesis. A molecular determinant of the effects of T3 could be uncoupling protein-3 (UCP-3)[34]. Such uncoupling from ATP synthesis results in increased secretion of heat in the form of thermal photons[35].

Amphetamines are a class of psychotropic drugs with high abuse potential, as a result of their stimulant, euphoric and hallucinogenic properties. Amphetamines are synthetic drugs, of which methamphetamine, amphetamine, and 3,4-methylenedioxymethamphetamine ("ecstasy") represent well-recognized examples. Resulting from their amphiphilic nature, these drugs can easily cross the blood–brain barrier and elicit their well-known psychotropic effects[36]. Both cocaine and amphetamine induces the secretion of uncoupling protein, resulting in thermogenesis[37].

Cardiac stents reestablishes the blood flow to the diseased heart and peripheral tissues, resulting in the restoration of the metabolism and increased entropy production. Antiarrhythmic and cardio tonics increase the efficacy and improve the contraction of the heart, which leads to increased quantity of blood flow to the peripheral tissues. It results an improvement of metabolism and increase production of entropy and a better well being of the patient.

The drugs aiming at treating cardiovascular diseases are numerous. They, all, aim at increasing the efficacy of

the cardiac pump. Digoxin intensifies the phosphorylating activity of mitochondria[38]. Digoxin stimulates the mitochondrial activity and thus decreases the amount of entropy released in the form of biomass. Digoxin has been repurposed in the treatment of cancer[39]. The addition of oxygen to patients with cardiac or pulmonary failure results in better mitochondrial efficacy and enhanced synthesis of thermal photons[40].

Table 1. Drugs and devices increasing entropy production.

Thyroid hormones[34,35]
Amphetamines[36,37]
Cocaine[37]
Cardiac stents
Digoxin[39,39]
Oxygen[40]

B) Drugs decreasing the flux of entropy

Caloric restriction, without malnutrition, delays aging[41] and extends life span in diverse species including humans. Caloric restriction delays the onset of age-associated pathologies. Specifically, caloric restriction reduces the incidence of diabetes, cancer, cardiovascular disease and Alzheimer's disease[41].

The brain has the highest energy consumption of the body (around 20% of the body oxygen and 25% of the glucose) while representing 3% of our body's mass. Biological conditions, which decrease mitochondrial energy yield, would impact brain functions, increasing vulnerability to brain disorders[42].

Drugs, which decrease the metabolism, slow down the flux of entropy. Anesthetics such as lidocaine, an amide local anesthetic, decreases glucose uptake through the reduction of the expression of GLUT1 and HK2. Lidocaine inhibits the enhanced glycolysis and glycolytic capacity induced by LPS in the macrophages [43,44]. Similarly, halothane anesthesia decreases glucose uptake because of transient inhibition of brain phosphofructokinase[45].

Intraperitoneal injections of phenobarbital decrease the concentration of glucose-6-phosphate and fructose-6-phosphate and result in the depression of the motor activity. The finding of decreased hexose phosphates in the brain supports the hypothesis that central depressant drugs suppress glycolysis in the central nervous system in vivo possibly by a diminution of glucose phosphorylation[46].

Propofol is another of the most commonly used sedative. This drug inhibits anaerobic glycolysis and the Krebs' cycle. Consistently, propofol inhibited the expression and glycolysis proteins (GLUT1, HK2 and LDHA)[47].

Conventional medications against seizure reduce neuronal excitability through effects on ion channels or synaptic function. Recently, it has become clear that metabolic factors also play a crucial role in the modulation of neuronal excitability[48]. In 1955, Greengard[49] demonstrated that anticonvulsant prevents the rise in oxidation such as seen during seizures. The clinical effectiveness of a variety of diets based on metabolism, especially for children with epilepsy refractory to medication, underscores the applicability of metabolic approaches to the control of seizures and epilepsy. Such diets include the ketogenic diet. A promising avenue to alter cellular metabolism, and hence excitability, is by partial inhibition of glycolysis, which has been shown to reduce seizure susceptibility in a variety of animal models as well as in cellular systems in vitro. One such glycolytic inhibitor, 2-deoxy-d-glucose (2DG), increases seizure threshold in vivo and reduces interictal and ictal epileptiform discharges[50].

Anxiety could be viewed as a shift toward the transient Warburg effect. An argument for a mitochondrial explanation of anxiety is stress's capacity to trigger the shift toward a decreased energy yield of the mitochondria. For example, catecholamines induce Warburg's effect and the secretion of lactate[51]. In times of stress, catecholamines can bind muscle cell receptors and trigger the breakdown of glycogen to lactate, diffusing out into circulation and used as a fuel. Similarly, hypoxia is a risk factor for anxiety[52]. Hyperventilation is a cause for hypoxia, which leads to anxiety and panic attacks[53]. Sleep apnea causes a panic attack[54]. In 1967, Pitts and McClure suggested that a raised lactate level in blood and body fluids causes all symptoms of anxiety[55]. Leibowitz and Hollander has confirmed their work[56,57]. Since then, Sajdyk demonstrated that the infusion of lactate results in anxiety in rats. Significant changes in regional blood flow in panicking patients but not in the non-panicking patients occurs after lactate infusion[58]. The amygdala processes and directs inputs and outputs that are key to fear behavior. It directly senses that reduced pH and increased CO_2 content, inducing fear. Buffering pH attenuated fear behavior[59]. Anxiolytic drugs are, to a large extent, effective in ameliorating anxiety symptoms. Diazepam boosts mitochondrial respiration in the nucleus accumbens[60].This change of pH may be a consequence of change in the transport mechanisms of bicarbonate ions[61]. Likewise, several antidepressants with anxiolytic capacity have been reported to improve mitochondrial activity such as monoamine oxidase inhibitors[62], selective serotonin reuptake inhibitors (SSRIs)[63].

Table 2. Drugs decreasing entropy production.

Caloric restriction[41]
Anesthetics[43-45]
Sedative[46,47]
Anxiolytics[48]
Antiepileptic drugs[48-50]

C) Drugs increasing the release of entropy in the form of biomass

Metabolic syndrome is the consequence of diets rich in fructose. Intake of fructose causes an anabolic syndrome with increase in visceral adipose deposition and de novo lipogenesis[64]. The risk of developing cardiovascular disease and type 2 diabetes increases with the occurrence of metabolic syndrome. In the U.S., about 25% of the adult population has metabolic syndrome, a proportion increasing with age, particularly among racial minorities[65].

Insulin is an anabolic hormone. In type-1 diabetes, there is weight loss and hyperglycemia, which may result in coma. To the opposite, treatment with excess insulin may cause weight gain[66-68]. Long-term uses of corticosteroids have been used to increase muscle strength and performance. Anabolic steroids have been used to enhance recovery after massive stress and exhaustion[69].

Estrogen suppression results in anabolism. Ovariectomized rats eat more and gain weight more rapidly than sham-operated rats. Estradiol (E_2) treatment attenuates food intake and body weight gain in ovariectomized in rats[70]. Women gain weight at menopause.

Table 3. Drugs increasing the release of entropy in the form of biomass.

Diet rich in sugar[64]
Insulin[65]
Long-term corticosteroids [67-69]
Estrogen[70]

D) Drugs excreting entropy as waste products

From a thermodynamic standpoint, urine, and feces are waste products. Their elimination relieves the body from entropy-rich products. Diuretics, emetics, and laxative should be considered as lowering the entropy of the body. Radiation therapy (RT) is a therapy using ionizing radiation to control or kill inflammatory and cancer cells. RT has been extensively used for the treatment of inflammation, but this indication is slowly disappearing because of the risk of radiation-induced malignancies. RT may be curative in several types of cancer if they are localized to one limited area of the body. RT kills both cancer and normal cells. Cytotoxic chemotherapy activates the concentration of radicals species, such as the ones induced by radiation therapy. This is evident by the elevation of lipid peroxidation products; the reduction in plasma levels of antioxidants such as vitamin E, vitamin C, and β-carotene; and the marked reduction of tissue glutathione levels that occurs during chemotherapy. Those agents that generate high levels of Reactive Oxygen Species (ROS) include the anthracyclines (e.g., Doxorubycin, Epirubicin, and Daunorubicin), alkylating agents, platinum complexes (e.g., Cisplatin, Carboplatin, and Oxaliplatin), epipodophyllotoxins (e.g., Etoposide and Teniposide), and the Camptothecins (e.g., Topotecan and Irinotecan)[71]. After successful radiation therapy or chemotherapy, there is a sharp decline in the number of cancer cells, resulting in decreased tumor mass.

Table 4. Drugs excreting entropy as waste products.

Diuretics
Laxatives
Emetics
High dose cytotoxic chemotherapy[71]
Radiation therapy[71]
Surgery (organ removal)

E) Drugs increasing the release of entropy in the form of heat

Sport increases the activity of the mitochondria, thus the release of entropy in the form of heat. Increased activity has been shown to improve survival from cancer[72] and memory in Alzheimer's disease[73].

Inflammation is part of the complex biological response of body tissues to harmful stimuli, such as pathogens, or irritants and is a protective response involving immune cells, blood vessels, and molecular mediators. The function of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and initiate tissue repair. Inflammation (a clinical feature) is closely related to hyperosmolarity (a physical feature)[74-76]. Animal models of inflammation demonstrate that, in an inflammatory fluid, whatever its cause, there is an increased protein content resulting in increased osmolarity (oncotic pressure). On the other hand, increased osmolarity, whatever its cause, results

in inflammation[74-76]. Increased extracellular osmolarity increases cytokine synthesis and secretion and results in the proliferation and activation of immune cells. There is an inflammatory component in every major disease[4]. There is a concomitant rewiring of the metabolic fluxes, with an increase in secretion of lactic acid.

The increased pressure such as seen in inflammation inhibits the mitochondria and induces the secretion of lactic acid[77]. The increased secretion of lactic acid, a stigma of the metabolic shift toward anabolism, feeds on the inflammatory cells and plays a part in the immune response such as seen in all these diseases[4]. This is in line with the concomitant finding of inflammation, mitochondrial impairment, and lactic acid secretion in most chronic diseases. Intraperitoneal injections in rats of hypertonic solutions result in the secretion of lactate by the brain cells.

Non-steroidal anti-inflammatory drugs (NSAIDs) alleviate inflammation, the cyclooxygenase (COX) enzyme. COX synthesizes prostaglandins. NSAID decreases the synthesis of pro-inflammatory molecules by enhancing the mitochondrial activity[78].

There is also increased osmotic pressure in cancer[4]. Increased pressure has recently been discovered as one of the reason for the Warburg's effect[77] The Warburg's effect is present in all tumors[25]. To compensate the reduced energy yield, there is massive glucose uptake, aerobic glycolysis, with an up-regulation of the PPP resulting in increased biosynthesis leading to increased cell division. The massive extrusion of lactic acid contributes to the extracellular acidity and the activation of the immune system [4,24].

Anticancer drugs have been designed to kill cancer cells, but most drugs also target the Warburg effect, thus decreasing the synthesis of biomass and stimulating the excretion of entropy in the form of heat. Injection of radio labeled glucose (PET scan) allows assessment of the efficacy of treatment. The decrease in uptake of glucose correlates with the efficacy of radiation therapy[79], chemotherapy and hormonotherapy[80].

Accordingly, cancer treatment should aim at restoring the oxidative phosphorylation. Lipoic acid targets the pyruvate dehydrogenase and increases the oxidative phosphorylation[81]. Hydroxycitrate inhibits the citrate lyase and decreases the efflux of citrate into the cytoplasm, enhancing the energy yield of the mitochondria[82]. The combination of these two drugs decreases the growth of tumor and prolongs the life of the mice[82]. Inhibition of cancer growth appears universal (independent of the primary site).

Methylene Blue (MB) is an FDA drug discovered in 1878. It has already been rigorously studied and used in humans for over 120 years[83]. Methylene blue functions as an alternative electron carrier, which accepts electrons from NADH and transfers them to cytochrome c[84-86]. It decreases aerobic glycolysis and enhances oxidative phosphorylation. Methylene blue reverses the Warburg's effect and inhibits proliferation of cancer cell[87].

Antidepressants target the mitochondria at multiple levels [83, 84, 88]. Bachman studied the effects of five antidepressants, two phenothiazines and one butyrophenone on respiratory functions of rat heart mitochondria[89]. All compounds increased oxygen consumption and caused uncoupling of oxidative phosphorylation.

Table 5. Drugs increasing the export of entropy in the form of heat.

Sport[72,73]
Anti-inflammatory[78]
Low dose cytotoxic chemotherapy
Hormonotherapy
Drugs targeting the mitochondria/metabolism[85]
Antidepressants[88-89]
Drugs enhancing the memory[84]

CONCLUSION

In conclusion, we have been able to propose a qualitative classification of drugs for a wide range of diseases. Such classification derives directly from equation (1) that is based on the facts that living cells are open systems that are not at thermodynamic equilibrium. Rather, living cells, through their metabolism, produce continuously a large amount of entropy. Such entropy is released in part as heat, i.e. as infrared radiations having a wavelength larger than 10 μm (far-IR). In our classification, drugs do not change the entropy content of substances fueling their metabolism, which that are the three main ways of producing entropy. It should be clear that thermodynamics of irreversible processes allows derivation of equation (1). See references[23-25] for technical details. This explains why me must put focus on entropy rather than energy. The next step will be to associate to each drug its irreversibility potential (IrP). This would then allow moving from a qualitative classification to a quantitative one. If the corresponding computations are not difficult, there are tedious owing to the huge amount of drugs available in medicine.

It also follows from the presented approach that drugs can be repurposed. To convince the reader, we will take some examples. A first one is methylene blue (MB). This drug has a wide spectrum of action: malaria,

leprosy, depression, neurodegenerative diseases or more recently cancer[69]. In psychiatry, methylene blue has been used for over a century. It was tried successfully to treat psychotic and mood disorders and as a memory enhancer in fear-extinction training. Particularly promising results have been obtained in both short- and long-term treatment of the bipolar disorder. In these studies, methylene blue produced an antidepressant and anxiolytic effect without the risk of a switch into mania. Long-term use of methylene blue in bipolar disorder led to a better stabilization and a reduction in residual symptoms of the illness[83]. In addition to protect neurons, MB's effects have been associated with improvement of memory and behavior in a network-specific and practice-dependent fashion. Specifically, low-dose MB has shown cognitive-enhancing effects in a considerable number of learning and memory paradigms, including inhibitory avoidance, spatial memory, fear extinction, object recognition, open-field habituation and discrimination learning[83]. Yet another example is lithium that appears both effective in bipolar and in cancer[90]. Finally, it is worth noting that anticancer agents have been repurposed in the treatment of autoimmune diseases[91]. We do hope that the classification proposed here, based on physics and not on biology, will helps in repurposing old drugs. This would strongly reduce the cost of the treatments, with the additional advantage of escaping from troubles linked to patents. Accordingly, most old drugs are now in the public domain and would then be easily available for emergent countries.

Seen from a biologist's perspective, most metabolic pathways appear to be connected to each other. But from a physicist standpoint, they all point towards an increase in entropy flux within the body. Whatever the causes (i.e., genetic defect, inflammation, or toxicity of xenobiotics), they all converge toward a shift in the type of entropy that is released in the environment. In other words, most, if not all diseases have in common a decreased activity of the mitochondria. The synthesis of thermal IR photons decreases, and there is a concomitant increase in biomass synthesis. This can be addressed by the treatment of the primary cause (for example a genetic defect) or by medication targeting the mitochondria, such as Methylene Blue. To proceed toward a better outcome, the treatment needs to be evaluated and integrated into more comprehensive and global theories, accounting with principles of physics. It then follows that the goal of modern pharmacology may be to address treatment able to modulate entropy input or output to the desired organ.

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