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Psychosomatic Molecular Mechanisms of Metabolic Syndrome and Type 2 Diabetes

Part 1. A Theory for Modelizing the Cytoplasm and Diseases

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Abstract

In the first part, the author presents his cytoplasmic model, which was first published in Hungarian in 2007. He modelized the cytoplasm of the animal/human cells with three constituents: 1) Cytoplasm Builder Ions (as K^+, Mg^{2+}, Zn^{2+}, HPO_4^{2-}, and $H2PO_4$-), 2) ATP, and 3) Functioning Proteins (enzymes). The three parts of cytoplasm are equally vital - they can only increase or decrease in unison. The author presents four models that were born at different eras and based on various logics - independently of each other, but they point in the same direction. The author's model suggests well the relations of anabolism vs. catabolism as well as the occurrence of vicious and virtuous circles. It is presented how could this cytoplasm model be of some help in modelizing diseases and healing. Even a quick recovery from an illness can be dangerous, even deadly, if the physician does not consider the hazards of instability.

It is known the second messenger and signaling functions of almost all physiologic ions of the cell, so it is not too bold to assume that the prevailing Momentary Intracellular Ion-Pattern as a whole has an essential, perhaps the primary signaling function. It would be the so-called 'software of the cell.' It seems that H+ concentration (pHi) is the most crucial of all ions to maintain homeostasis, Therefore, regulation wants to preserve the permanence of pHi. The endeavor to keep original pHi at all costs can develop metabolic dysregulation. (See Part 2.)

Practically essential issues such as Refeeding Syndrome are also analyzed. The author points out that there are so many errors about diagnosis and treatment in this issue because the pathogenesis does not refer to one but several disorders; therefore suggests a new terminology classification. The author also reinterprets Locus Minoris Resistance (the Place of Less Resistance) theory and declares that the occurrence of a vicious circle in biology is not random; it is a consequence of the Second Law of Thermodynamics, and such it is a frequent phenomenon. In all these issues, the cytoplasmic model guides us.

Keywords: Exploitation Syndrome; Momentary Intracellular Ion-Pattern Signaling; Modelizing of Cytoplasm; The Place of Less Resistance; Second Law of Thermodynamics; Utilization Syndrome

Abbreviations

ADP: Adenosine Diphosphate; ATP: Adenosine Triphosphate; BCM: Body Cell Mass; BMI: Body Mass Index; CBIs: Cytoplasm Builder Ions (K^+, Mg^{2+}, Zn^{2+}, HPO_4^{2-} and H_2PO_4- together) – these also called 'intracellular ions'; COPD: Chronic Obstructive Pulmonary Disease; CrP: Creatinine Phosphate; EC: Extracellular; EC Ions: Na^+, Ca^{2+}, Fe^{2+}/Fe^{3+}, Cu^+/Cu^{2+}, H^+, Cl^-); FFM: Free Fatty Mass; IC: Intracellular; LBM: Lean Body Mass; LBN: Lean Body Nitrogen; N: Nitrogen; Nae: Exchangeable natrium; OHS: Obesity Hypoventilation Syndrome; OSA: Obstructive Sleep Apnea; OSAS: Obstructive Sleep Apnea Syndrome; $PACO_2$: Partial Arterial Pressure of Carbon Dioxide; PCO_2: Partial Pressure of Carbone Dioxide; pHi: Intracellular pH; Pi: Inorganic Phosphates together; RDA. Recommended Dietary Allowance; RFS: Refeeding Syndrome; Se-Pi: Serum phosphate level; SRH: Sleep-Related Hypoventilation; TBK: Total Body Kalium content; TBW: Total Body Water; T2D: Type 2 Diabetes.

Introduction

The author of this book had learned at the university that Type 2 Diabetes (T2D) is not an endocrine but rather a metabolic disorder. Characteristics of living organisms - namely nutrition, respiration, movement, excretion, growth, reproduction, and sensitivity – are based on anabolic overactivity. In insulin resistance, these basic phenomena are impaired because insulin is the primary anabolic (or anti-catabolic) hormone [1]. Damaging in insulin action (insulin resistance, T2D) consequently means a catabolic overactivity. In living matter, the cytoplasm is surrounded by a cell membrane. It takes care of the uptake of nutrients and excretion of the waste products. Is there a simple way to explain metabolism? What would

be the base of cytoplasmic modeling? We can start with two fixed points. ("Give me a place to stand, and I shall move the earth." Archimedes). The first is that all biological energy comes from the high energy phosphate bonds of the ATP/ADP system; that is why it is easy to calculate with it. Secondly, it has now been proven that the Second Law of Thermodynamics can also be applied to the partly opened, partly closed biological systems as well [2]. Previously this was not thought to be applicable. To understand the essence of metabolism, we need to know how anabolism and catabolism occur. The author of this book recreated a cytoplasmic model in which the three main participants have equal importance, as their quantity can only increase or decrease in unison during one of the two opposing processes, (which can occur simultaneously, namely anabolism versus catabolism). The three protagonists of the cytoplasm are 1) The biological energy of the ATP/ADP system, 2) the enzymes of cytosol, and 3) ionic molecules which act on the active sites of the enzymes (e. g., Mg^{2+}, K^{+}, H_2PO^{4-}/HPO_4^{2-}, Zn^{2+}): The amount of three participants increases during anabolism but which one of them is the primary mover?

The author of this book had begun for four decades then continued to develop this cytoplasmic model - initially in a deductive and then inductive way - to help understand the essence, course, complications of illnesses, recovery from a disorder, and death. Also, one of the primary goals was to understand the difference between psychological and somatic diseases and how they could cause each other. The model seems to have been useful help as the author has come to such conclusions that others have not thought them.

The author hypothesized the second messenger function of Intracellular Ion-Pattern as a whole [3]. He also pointed out that H^{+} concentration and pCO_2 play a distinctive role, and they have priority in the regulation of the body - resulting in many complications and metabolic disturbances during human stress-response.

Modelizing of cytoplasm and diseases

The second law of thermodynamics also has a role

If we want to create biological laws and models, we need to find well-measurable and reproducible components. These are the ATP content (concentration) of the living cell and the amount of cytoplasm in the cell itself. ATP is continuously recycled, and it can be used again and again. It is a fundamental principle that healthy cellular ATP production accommodates to energy needs, and at the same time, the regulation maintains a constant level of cytoplasmic ATP concentration [4]. The availability of ATP will decrease if severe illness or a metabolic disorder develops. ATP molecule, in addition to its metabolic functions, is also involved in signal transduction. The decrease of ATP production is not specific to one disorder, it can be a consequence of any one. The ATP content of cytoplasm and the amount of cytoplasm the organism have a crucial role in health and life expectancy. If the concentration of ATP in a cell drops under 30-40%, the cell will die [5]. By the age of 20, a person reaches the highest cytoplasmic mass /Body Cell Mass (BCM) or Lean Body Mass (LBM)/ - they represent the amount of cytoplasm. It loses 25% of BCM on average during the aging process by the age of 75 [6] (Fig. 5.). By contrast, fat mass increases up until 70-75 years of age (which masks the LBM and BCM losses). Losing 50% of BCM is incompatible with life [7]. It may occur as a result of further aging or a chronic condition such as cachexia. Longevity, life expectancy, and BCM are, therefore, closely related [8]; this is one of the biological manifestations of the Second Law of Thermodynamics. To the best of our knowledge, this is why a human cannot live - theoretically – for more than 120 years. Increased fat mass or the decreased sensitivity of adipose tissue to insulin shorten longevity, We can draw some general conclusions about the parameters of human tissular masses on average - primarily of European and North American people - during their lifetime. The author created figures 5, and 6. for illustration, relying on scientific references. The color red stands for BCM, i.e., the functioning cytoplasm, blue signifies the space belonging to the water and exchangeable sodium (Nae), yellow stands for connective tissue and ochre for adipose tissue. Fig. 5. illustrates the changes in these three tissue types and free water in time on a healthy adult. Fig. 6. shows the alteration rates of the tissue of a malnourished patient.

- The absolute value of the functioning cytoplasm (BCM) does not correlate necessarily with body weight and, consequently, with BMI.
- Under pathological circumstances (in cases of most of the chronic diseases) BCM decreases faster than it does in healthy control subjects.
- The amount of adipose tissue usually increases with age (up to age 70-75), but there are several exceptions. The growth of fatty tissue, in contrast with that of the connective tissues, is reversible.
- When the decrease of BCM approaches a critical mass (about 50%) it will result in the death of the subject.
- Life expectancy is related to BCM while inversely related to the fat tissue mass of the body.

What are the most important components that make up cytoplasm?

Fauna includes countless creatures, and each one of them is different. It is not easy to find universal principles or those forces which build up cell characteristics for each of them. Three facts tend to indicate that the conclusions of the author of this chapter are real: 1) Others had achieved similar results with a different way of thinking - independently of each another. 2) These theses have still not been refuted. 3) The principles appear to be applicable in practice, as well.

The author of this book presumes true that the membrane-surrounded cytoplasm, in addition to the essential water, consists of three equivalent units interacting with each other. 1. Those pro-

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teins which have an active site and are functioning as enzymes. (Their amino acid sequence is encoded in both DNA and RNA.) 2. Cytoplasm-Builder-Ions, which are accumulated in the cytosol with biological energy by the cell membrane and can bind to sites of the enzymes. These include some metal ions (as Mg2+, K+, Zn^{2+}), other ions (as HPO_4^{2-}, $H_2PO_4^-$, HCO_3-, OH-), the ionic form of some trace elements and some vitamins (e.g., Vitamin B1). 3. High energy phosphates, first of all, ATP/ADP system.

Both protein synthesis and cytoplasmic ion transport are very energy-demanding processes; the last ones use at least one-third of the ATP-consumption. Protein enzymatic function also needs the presence of right ions in a sufficient concentration that binding to the active site. However, ion transporters and exchangers situated in the membrane are also proteins. ATP synthesis is also inseparable from the intact and highly arranged protein-structures (mitochondria) as well as the specially composed intracellular (and intramitochondrial) ion milieu. That is, the amounts of the three major cytoplasmic components (ATP, Cytoplasm-Builder-Ions and proteins) logically change in a parallel manner. The empirical facts largely support this rule. Metabolism is the result of two opposing processes, anabolism versus catabolism. The breakdown of cytoplasm takes place in an utterly different way from its build-up, although when the sizes of the two are the same, a quasi-steady state is achieved. In this state, the proportion of each cell component can be well studied. (A true steady-state does not exist in biology, according to physicists).

ATP and other high energy phosphate molecules

Adenosine triphosphate (ATP and other high energy phosphates) is the only commonly used chemical energy source available for cells to fuel their biochemical processes in flora and fauna. Among organic phosphates with high energy phosphate bonds, ATP and ADP have the most crucial role. The muscle cells also contain creatine phosphate (CrP). They are not able to directly utilize it; first, its high energy phosphate bond should be taken over by ADP. This means CrP is an emergency energy source that can be mobilized immediately. Every process that demands energy, uses the chemical energy of ATP, so a daily amount of 100 - 150Mol of ATP should be produced and metabolized by people each day. It corresponds in magnitude to our body weight. It also means that each ATP molecule is regenerated about 500 to 750 times a day. It is our great fortune when establishing a cytoplasm model - that all living organisms gain biological energy from the only existing system. Fortunately, the regulation system works with relatively simple principles. The "goal" of the energy supply systems is to secure the stable, normal ATP level of cytosol among different conditions. The author of this book does not know that a "supernormal" ATP level would exist in the cytoplasms of cells.

While we are young and healthy our energy supply will decrease below the normal level only in the case of an enormous strain, and even after that, it is able to recover. The reserve energy level of creatin-phosphate of muscles will decrease first, while the ATP concentration remains at the normal level in the long run. It seems that physiological protein/ATP (or Nitrogen/ATP) quotient is constant in steady-state and is a characteristic of the given cells. Das clearly described how the cell maintains a continuous level of ATP [4]. If the ATP concentration of a cell falls below normal, the concentration of extracellular ions (Na^+, Ca^{2+}, Cl^-) in the cytosol will increase, while that of Cytoplasm-Builder-Ions (CBIs) will decrease at the same and by a similar extent. If the ATP concentration of the cytosol drops below 30-40% of the normal level, the cell can die [5].

Cells require a constant supply of energy to generate and maintain the biological process, which keeps them alive. The primary energy source for metabolism is glucose, which is catabolized in three subsequent processes: glycolysis, tricarboxylic cycle, and oxidative phosphorylation. The intact mitochondrial activity has a decisive significance since most of the ATP production (over 90%) happens here. It is no coincidence that mitochondrial damage or dysfunction is considered to be the leading cause of several significant metabolic disorders. The concentration of ATP in the cells can vary within a limited range. The mitochondrial membrane potential and proton gradient (ΔpH) together form the transmembrane potential of the hydrogen ion, briefly the electrochemical potential of hydrogen ion of the inner mitochondrial membrane. All these are generated by the proton pump of the mitochondria, which is the base of ATP production. Changes in ionic conditions can cause malfunctioning mitochondria. If the ATP level decreases due to the imbalance of production and consumption, intracellular acidosis and depletion of intracellular pH buffers will develop. As a result, catabolic pathways begin.

Momentary Intracellular Ion-Pattern, as a whole, controls cytoplasmic enzyme functions

According to the author of this book, cytoplasmic ions have a much more significant role than most clinicians and researchers think. All enzymes have active sites to which can connect with their specific ions with charges and turn enzymes on or off. They are now known almost all ion seconder messenger and (or) signaling roles of almost most ions. H^+ (or OH^-) ions can also join side chains of enzymes, thereby contributing to the secondary or tertiary structure of them. This H^+ ion functions are not specific to a certain enzyme but are possible with most enzymes. The importance of pHi (cytoplasmic H^+ concentration) is highlighted. The change in H^+ multiplies the enzyme actions by affecting most of the enzymes similarly. (In the first approach, intracellular acidosis "cools" metabolism, reduces ATP metabolism, while alkalosis, on the contrary, "heats" metabolism, ATP turnover, and arousal.) These result in very significant metabolic changes (decrease or increase) [9].

Ca^{2+} ion as a second messenger (or a „signaling intermediate")

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was one of the first knowns [10]. Its concentration in the cytosol can change by three orders of magnitude in a fraction of a second and therefore plays a central role in the fast signaling system. The H^+ concentration of cytosol also can change rapidly, for example, due to changes in pCO_2 and catecholamine levels. The effect of intracellular pH alterations is complex. In part, it directly affects almost all enzymes by binding to side chains of proteins and alter their secondary structures. Partly because changes in cytosolic pH are altering the transmembrane permeability of the Ca^{2+}. An increase in pH (H^+ decrease) results in hyperarousal neuronal function, too. Already in the early 1960s, it was observed that alkalosis accelerated the movement of unicellular cells while acidosis was retarded and stopped actions [(Taylor, 1962). The rise in HCO_3^- has a compensatory effect on the increase in pCO_2.

Chronic hypercapnia, as a consequence of the spillover effect, it results in a decrease in Cl^- but also affects the other cations and anions to a lesser extent. That is, both hypercapnia and hypocapnia rearrange the entire ionic milieu inside and outside the cell. Changes in intracellular pH have primary importance to cells, so the body responds to small changes with active hormonal-humoral and direct membrane ion pump changes. There is only a moderate amount of literature despite the importance of the second messenger/signaling of H^+ [3]. It is already evident that the cytosolic pH has robust cell signaling. That is why the cells try to restore the original cytosolic pH with all the tools available. Sodium belongs to the second messenger signaling system that also changes rapidly in direction to downwards concentration gradient, can transport, and influence some ions.

While the cytoplasmic concentration of Ca^{2+}, H^+, and Na^+ can change rapidly (within one second), other ions exchange only slowly, over hours and days, and therefore, those belong to the slow signaling system. (Phosphates appear to be a transition between the two groups, as a significant increase can develop in a few minutes. See Part 2. of this book). The signaling role of both phosphate and other ions (magnesium, zinc, potassium, chloride) are well known in the literature [3]. A long-lasting alteration in the concentration of a single ion can lead to a change in the entire intracellular ion pattern. The concentration of an ion can alter in one of many ways: through osmolality, cell electricity, cell energetic state, anion/cation equality, ion transporters, neurohormonal effects, ionic synergism or antagonism, etc. In mental stress, the author of this book discusses changes in the body's carbon dioxide level, which leads to H^+ change in the first step, Then HCO_3^- level changes in the second step; further phases cannot be predicted due to a ripple effect.

In summary, the intracellular ion-pattern acts in a whole, as a second messenger signaling-modifying system, direct cellular metabolism [3]. It seems that the above mentioned is a brand new signaling theory because a recent review [11] did not speak about the ions (except Ca^{2+}) as potential signaling molecules. To the best of the author's knowledge, he was the first to explain this theory [3]. In this case, we know exactly where and how do signaling ion act, they are coenzymes.

Models of cytoplasm -- based on the triad of Cytoplasm-Builder-Ions--ATP--proteins

Sick cells cytoplasm model and theory

The intracellular and extracellular behavior of electrolytes came to the focus of attention in the 1940s and 1950s. As flame photometry spread in the clinical practice, hyponatremia became known as the most frequently occurring electrolyte imbalance. On the other hand, it became apparent that sodium accumulates while the potassium level decreases inside the body's cells. Researchers reasonably linked these processes to the newly discovered Na^+-K^+-ATPase and its dysfunction or the lack of ATP. (This is the enzyme, which pumps potassium into the cytosol, while Na^+ to the extracellular space. It is a very energy-demanding enzyme: it utilizes about 10% of the ATP consumption.) The phenomenon was first named *Tired Cell Syndrome,* then Sick Cell Syndrome [12]. It was found that, due to a variety of diseases, the levels of potassium, magnesium, and inorganic phosphate - the so-called CBIs - decreased in the diseased cells. At the same time, the levels of sodium, calcium, and chloride (the so-called extracellular ions) were increased [13]. The extent of intracellular ion changes was correlated to the severity of the disease. (Intact-ischaemic-necrotic heart tissue.) Several studies investigated the intracellular ion-composition in a variety of diseases, often parallel to high-energy phosphates, but rarely observed all electrolytes together, although the data are consistent with the theory. Initially, intracellular edema occurs, which correlates to sodium level, which decreases later due to the degradation of proteins. The amount of high energy phosphates (ATP, ADP, CrP) usually decreases parallel to the level of CBIs. Sick Cells have decreased resting membrane potential, which is closely related to the chemical potential of the potassium (IC/EC gradient) in serious injuries [14], while hyperpolarisation will develop in moderate damage [15]. That is because the passive permeability for K^+ exceeds that of other ions by two magnitudes. The potential was created by all the ions together, more precisely by ion pumps, first of all by the Na^+-pump (Na^+ -K^+-ATPase). Therefore, the resting transmembrane potential is generally a good indicator of cellular health and metabolism [14], as well as their ATP and cytoplasm content (Figure 2 and 7). Cunningham pointed out that diseases affecting particular organs (e.g., congestive heart failure, kidney failure) also exist in a localized form of the given organ as well as in a generalized (decompensated) way. The decreased intracellular K^+/Na^+ ratio (due to the disease of the given organ) in the skeletal muscle tissues could only be measured in the latter case. It also manifested in the reduced resting potential. (The decreased intracellular K^+/Na^+ ratio and that of the resting membrane potential correlated with the severity of the diseases.) According to the writer of this book, Cunningham pointed out fundamental theoretical and practical.

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The measured membrane potential is further complicated with the fact that the membrane permeability of K^+ and Na^+ can alter. The expected membrane potential can be calculated from the Goldman-Hodgkin-Katz equation. That is why the resting transmembrane potential was slightly increased while a subclinical skeletal muscle injury (chronic experimental alcohol intoxication at dogs) reduced skeletal muscle contents of phosphorus, magnesium, and potassium. The active and passive potassium transport increased, potassium permeability may also be elevated. In diseases, serum Mg^{2+} level does not show cytosolic Mg^{2+} content. An early investigation of intracellular ions shows that the proportion of potassium, magnesium, and phosphorus do not alter significantly, that is their amounts similarly decreased to protein during the atrophy of skeletal muscle. Alcoholic myopathy is a classical Sick Cell Syndrome [15]. It is easy to see that almost any structural or metabolic damage will eventually also result in a decrease in ATP formation, then can lead to ATP deficiency, thus the ion-pumping mechanisms cannot work because of the lack of energy. As a consequence, the concentrations of CBIs (K^+, Mg^{2+}, $H_2PO_4^-/HPO_4^{2-}$) ions decreases, while the amount of 'extracellular ions' (Na^+, Ca^{2+}, Cl^-) will increase in the cytosol.

Sick Cell Syndrome can also develop in the case of severe magnesium deficiency. After seven weeks of the magnesium-deficient diet, classic Sick Cell Syndrome electrolyte correlation developed in skeletal muscle in the dog with focal necrosis, rhabdomyolysis, and convulsive seizures [16] (The potassium deficiency was only moderate.) Experimental magnesium deficiency also can result in depletion of high energy phosphate, which may cause Sick Cell Syndrome to develop. Experimental Mg^{2+} also can result in focal myocardial necrosis, calcification, and fibrosis in animals [17]. Experimental phosphate depletion was achieved by diet- and genetically-induced hypophosphatemia in mice. Insulin-stimulated ATP synthesis was reduced by 50%. After reaching euphosphatemia, the mitochondrial ATP synthesis was normalized. Conclusion: the average serum phosphate level is essential to insulin-stimulated ATP synthesis. Phosphate depletion or hypophosphatemia may be a cause of ATP deficiency, as such, of the Sick Cell Syndrome [18]. Potassium deficiency rarely causes Sick Cell Syndrome because metabolism disturbance rarely results in severe hypophosphatemia, which can lead to a lack of ATP. N. B. Extracellular phosphate transport to the cytosol and into the mitochondria is crucial for insulin-mediated ATP synthesis.

Quamme's review [19] indicates that based on balance studies, it is established that deficiencies of intracellular ions (phosphate, magnesium, potassium) usually develop jointly, and their severity is also in correlation with each other. Deficiencies often (but not always) are manifested mutually in the extracellular compartment, too. Unfortunately, the Sick Cell Syndrome expression and concept have not been used for decades, although it points to an important theoretical and practical issue: intracellular metabolism disorders due to ATP deficiency usually reduce the amount of three intracellular ions (Mg^{2+}, K^+, Pi) simultaneously and during parenteral nutrition. They should be replaced together in appropriate proportions.

Static cytoplasm model

After observing a wide range of various animal tissues (from unicellulars to mammals), Wacker and Williams declared a rule [20], which shows that the ratio of K^+, Mg^{2+}, and inorganic phosphates (P_i) concentrations are relatively constant. Their rate also correlated with the cytoplasmic ATP and protein (N) content, in steady-state, when the anabolism and catabolism balanced each other out (Figure 1). The author of this book names this rule the Wacker-Williams Formula. Wacker and Wiliams claimed that the principles defining the distribution of ions in tissues are similar in human organs and animals, down to the level of unicellular organisms. E. g., the K+/N ratio is roughly constant in the entire fauna. The first evidence was provided by Moore [21]; they concluded that each gram of nitrogen bonds 3mmol of potassium, in the cytoplasm of a healthy human. The rule is still considered valid, although later measures indicated that the K^+/N ratio is about 2mmol/g on average. According to them, the TBK/BCM ratio was 109.1 mmol/kg. The total potassium content of the body (TBK) can be observed by measuring the natural ^{40}K isotope. Measuring TBK is considered one of the best methods for determining the cytoplasm mass of the human/animal body. Knowing TBK, the fat-free body mass (FFM), lean body mass (LBM), as well as lean body nitrogen (LBN) and the body cell mass (BCM) can be calculated, too. A correlation was found between TBK and the other three parameters. Moore's approach needed clarification because only the cytoplasmic proteins have metabolic activities and bind K+ and other ions, while the skeletal proteins do not. Similarly, the adipose tissue also has no (only minimal) metabolic activity. Hence the actual value of the K^+/N ratio is tissue-dependent. The Wacker-Williams Formula [20] was well ahead of its time. It was almost completely forgotten, in fact, barely quoted.

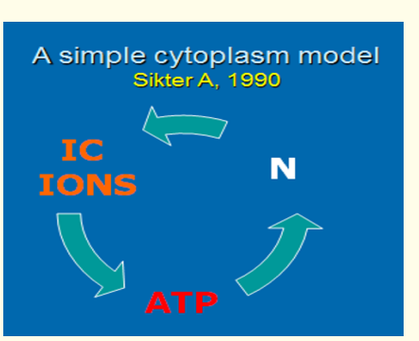

Figure 1: A simple cytoplasm model:

(the three cytoplasm components are in balance)

N=protein-based structures, mostly enzymes of cytoplasm;

IC ions =Intracellular ions = Cytoplasm Building Ions (CBIs): K^+, Mg^{2+}, Zn^{2+}, inorganic phosphates.

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The Wacker-Williams Formula has not yet been proven to be verifiable in cases of chronic diseases, neither in the relation of ions and proteins nor in that of ions, protons and ATP - even though the authors presumed that it is. In some cases, however, the correlations are already known. In malnutrition (e.g., in anorexia nervosa), the total potassium content of the body parallelly decreases with protein decrement. In the case of protein-energy malnutrition, the K^+/N ratio does not change, but the amounts of exchangeable Na^+ (Nae) and total body water (TBW) increase while K^+ content significantly decreases, hence the amount of Nae/K^+ increases. In the case of malnutrition as a result of chronic alcohol abuse, intracellular K^+, Mg^{2+}, and Pi deficiencies also occur together [15]. K^+ and Mg^{2+} deficiencies correlate to each other in diseases. K^+ and Mg^{2+} deficiencies relate to each other in various conditions and illnesses. Quamme examined the correlation of K^+, Mg^{2+}, and Pi deficiencies [19]. Iseri [13] described that K^+, Mg^{2+}, and Pi concentrations were decreased by 50 - 60% in tissues affected by myocardial infarction, tissues were taken from patients died the disease (Figure 2). In the same places of infarcted myocardium samples, Na+ and Cl- concentrations were found to be significantly exceeding those measured in control.

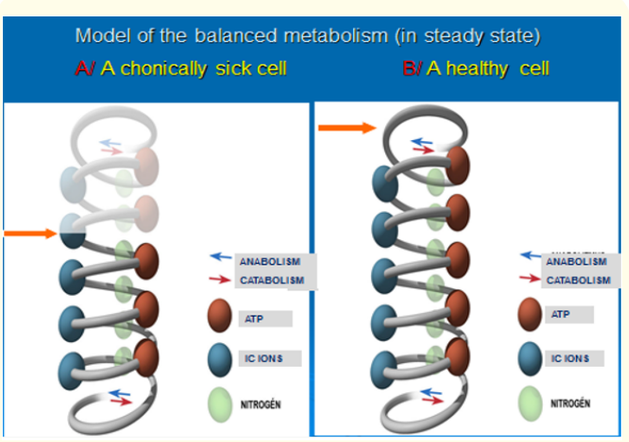

Figure 2: The model of the balanced dynamic metabolism (steady state).

A: Chronically diseased cell

B: Healthy cell.

Theoretically, a healthy (3B) and a sick (3A) steady state are also possible. The rise of the spiral also symbolizes energy levels, marked by an orange arrow. The magnitude of energy levels may be given by e.g. the IC K+ concentration or the resting membrane potential but also by the ATP or N concentrations.

IC IONS= CBIs.

Dynamic cytoplasm model and theory – catabolism versus anabolism

The dynamic "CBIs – ATP – proteins" model can be an excellent candidate to describe the cytoplasm and to achieve a strategic medical approach in analyzing diseases. The three most definitive components of the cytoplasm are closely related to each other. This relation is evident because they mutually influence each other's function and their cytoplasmic concentration. Claude Bernard introduced the Milieu Intériur theory, and this cytoplasm model fits it, even though Claude Bernard's thesis initially referred to the extracellular space and most researchers still think so. According to the author of this book, Bernard's premise can primarily relate to the intracellular ionic milieu. This model may be a reinterpretation of the axiom phrased by Claude Bernard. The intracellular ionic pattern should not change, to prevent alterations in the cytoplasmic function, however, if this structure should be subject to changes (and it obviously will), the other components will change, too. Are there any general rules applying to these changes? Can there be such rules at all? The present chapter focuses on this issue. The composition and concentrations of ions in the cell (and in the all ionic spaces bordered by cell membranes) are not only determined by physical characteristics (Donnan balance) but also by biochemical processes.

The author of this book has been developing this model for four decades. The idea emerged first in 1976, and the author has been working on the details ever since. Conclusive evidence, a jigsaw puzzle of facts complementing each other, and clinical experiences validate this model. The theory is indirectly proved by similar ideas, which came to similar conclusions and cytoplasm models. The authors of the models did not know each other. They followed different logical pathways. The similarity of the four models described here has never been presented together until 2007, the author of this book published [22], the model of the author of this book was first published in 1990 as a Hungarian pharmaceutical patent of the author. Administering the mixture of the Cytoplasm Builder Ions (K^+, Mg^{2+}, Zn^{2+}, HPO_4^{2-}, and $H_2PO_4^-$) salts together in a given proportion can help the cytoplasm of cells to recover after cessation of various disorders or in cases of chronic diseases. The salt mixture can also decrease the functional complaints caused by hypocapnia breathing disorders. That is why the patent was extended to the United States as a Method for Treating Panic Disorder [US. patent No: 5,348,74, filed: NOV. 11th. 1992]. Both patents expired.

The principal statements of the dynamic cytoplasm model (theory) are the following

- There is a strict correlation between the ions (which use chemical energy for accumulation in the cytoplasm: CBIs) and the ATP-concentration in the cytoplasm. On the other hand, the cytoplasmic level of antagonistic (so-called extracellular extracytoplasmic) ions shows an inverse correlation to the level of ATP.
- If the metabolism of cells suffers any damage (catabolic stress) or cell membranes are damaged. It can necessarily result in a deficiency of chemical energy (ATP) (as is predicted by the Second Law of Thermodynamics).
- As a result of ATP deficiency, the concentration of CBIs decrease (while that of 'extracytoplasmic ions' increase) in

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the cytosol, which may start a vicious circle process as a result of cascading effects of feedbacks.

- The decline of cell proteins correlates to the decreasing ATP and concentrations of CBIs.
- The progressive deterioration of cytoplasm is known as catabolism. It is important to note that catabolism is not a reversal of anabolic pathways, it takes place in different ways by different enzymes. The process is usually similar in various diseases. In sick cells, the concentrations of proteins, CBIs, and ATP decrease simultaneously as the amount of cytoplasm declines (Figs. 2. and 3.). In the case of the organic disorders, this deterioration of the cytoplasm first affects the sick organ itself or a part of it. As the disease progresses, the symptoms of the sick cell syndrome can extend to other organs, too. We can observe that the "decompensated" illness becomes general in the organism. However, the decline of the cytoplasm and the CBIs' deficiency are not uniform all over the body as certain organs will be more affected or, by contrast, less prone to adverse changes.
- Life is a history of alternating anabolic and catabolic processes (Figs. 3. and 4.). In healthy adults, catabolism and anabolism balance each other out more or less, resulting in a (quasi) steady-state (Figs. 3A and 3B). In the case of diseases, metabolic processes shift towards catabolism (resulting in a negative N balance) and may be followed by anabolism (recovery). Nevertheless, in chronic diseases, the energy balance can be stabilized at a lower energy level than the physiological. Growing up in children is a continuous anabolic process (it is a not-steady state) that can occasionally be interrupted by catabolic periods (caused by diseases).
- In the course of catabolic processes accompanying diseases, the CBIs flow into the extracellular space and then get excreted from the body. Hence, recovery presumes the simultaneous input of CBIs (K^+, Mg^{2+}, Zn^{2+}, Pi) in the proper ratio. If all the CBIs are available at the same time in the necessary amount and proportion, they will have a curative effect in convalescence or chronic diseases (in steady-state), even in doses below RDA, if the diseased tissues are still able to regenerate (to recover). Other necessary components for regeneration are taken up by the body in the form of food. If the therapy works, the appetite of patients increases significantly, and the spiral of vicious circle shifts towards anabolism, where the rotational speed may be prompt and continuous (Fig. 4.), a virtuous circle can develop.
- NB: According to the author of this book, the CBIs together in the right proportion may have curative effects for a variety of diseases, even if their respective amounts are under the amount of RDA (=recommended dietary allowance). One could say, "this would be a panacea, although such medicaments do not exist." The answer: it is not a medicament, but a physiological salt-combination in physiological amount. Its dosage is set to restore the ideal amounts of lacking components. The virtuous circles explain the low doses. (But only if the processes are at least partially reversible.) The expression of Golden's "catch up weight gain" [23] has a similar meaning to that of the virtuous circle of the author of this book.
- The Dynamic Cytoplasm Model (anabolism vs. catabolism) may also be given as a mathematical formula. „Anabolic ions" in the cytoplasm (provided in the numerator) show a positive correlation between the nitrogen of cytoplasm proteins and ATP while „catabolic ions" (in the denominator) an inverse relation to them, where k_1 and k_2 are constants.

$$\frac{[K^+]\times[Mg^{2+}]\times[HPO_4^{2-}+H2PO_4^-]\times[Zn^{2+}]}{[Ca^{2+}]\times[Na^+]\times[Cl^-]\times[H^+]\times[Cu^+ + Cu^{2+}]\times[Fe^{2+}+Fe^{}}$$

$$= [k_1 \times N] \times [k_2 \times ATP]$$

Equation

Growth cytoplasm model; Type I -- Type II nutrients

Golden, a pediatrician, who was employed by WHO, dedicated his life to save and refeed malnourished children in impoverished countries. He achieved outstanding results in decreasing the mortality of undernourished children. In 1991, he published his theory that had been proven valid by practical results [24]. He claims there are Type I and Type II essential nutrients. Type I nutrients include those where deficiency results in specific symptoms (such as the lack of sufficient vitamin C intake causes scurvy, while the same in the case of iron a type of anemia).

By contrast, the lack of Type II nutrients results in a single symptom: the growing of cytoplasm stops (in the case of children, it means growth and development also stops). Hence, he claims that the cytoplasm is a substance where the Type II nutrients are present at a constant ratio. Even if a single "Type II nutrient" is missing, It will not result in a lower quality cytoplasm; it will no produce it at all. Type II nutrients include essential amino acids, K^+, Mg^{2+}, inorganic phosphate, and zinc. These Type II nutrients are the same as those cytoplasm-builder nutrients, which were presented by the author of this book [22]. Golden's statements [24] are consistent with the three theories mentioned above, which cannot be a coincidence. There are some differences too.

Golden pointed out that sodium has a dual property [24]. One part of the natrium is a Type II nutrient, and increase proportionally with other CBIs. Its other part is "exchangeable" (Nae); unnecessary, harmful for the building and working of cytoplasm - if its amount increases in the cytosol. Golden's statement, that sulfate is also a Type II nutrient, is exciting and needs some further study, as all his published and to be published papers, too.

In his previous papers, Golden often tackled the role of zinc in the rehabilitation (refeeding) of severely malnourished children. Zinc is often a limiting factor in the development and refeeding of

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children. One of his particularly important claims is that in the lack of zinc, the body of children will not produce cytoplasm but use the energy uptake from food to create fat. The ratio of fat/lean tissues increases [25], and the development stops. Zinc is essential for the synthesis of nucleic acids, and proteins. In the case of poverty, a monotonous diet is frequent that will surely be deficient in one or more Type II nutrients. The nutrients uptake becomes fat if it cannot synthesizes lean tissues; this is the 'back-up nutrient' that probably will never be burned. A Type II nutrient-deficient condition may be a real etiology of obesity [24]. Electrolytes are just as essential as the amino acids themselves, for the production of cytoplasm. These are present in the cytoplasm in strictly defined concentrations. We should note that the importance of inorganic phosphate as a nutrient is equal to that of essential amino acids in cytoplasm production.

Some lessons from the Cytoplasm-Builder-Ions--ATP--proteins model

Refeedins Syndrome versus Exploitation and Utilization Syndromes

Refeeding Syndrome (RFS) is a potentially fatal condition caused by the rapid initiation of refeeding after a period of undernutrition [26]. On the other hand, there are severe problems with the definition and management of RFS, and it is understudied or forgotten [26]. After studying many papers regarding, the author of this book raises whether it is not a problem with the name? He thinks the term should be split at least three parts, mainly according to clinical manifestation and the severity of the syndrome. His suggestion: RFS should be kept only for the traditional form. "Refeeding is the process of re-introducing food after malnourishment or starvation. Refeeding Syndrome is a serious and potentially fatal condition that can occur during refeeding. It is caused by sudden shifts in the electrolytes that help your body metabolize food" (Butler: Internet: Healthline, 2017). Its signs and symptoms are summarized by reviews. The author of this book proposes to rename the other acute and subacute forms to Exploitation Syndrome, which better expresses pathophysiology of the disorder. He anticipates that according to his cytoplasmic model, it should also be a chronic form of the syndrome, which would get the Utilization Syndrome name. (The Alcohol Withdrawal Syndrome is slightly different from others because of the root cause.) N. B., All these acute recovery syndromes can develop because the mechanism of healing, replenishment of tissues is 'speed up' - a virtuous circle is created. However, there are not enough cytoplasm builder (Type II) nutrients in the extracellular space, so the construction becomes destruction.

In these syndromes, it is obligatory that the catabolism of the body suddenly switches to the anabolism. A prerequisite for this is that the organism's metabolism should be at least partially reversible. According to the cytoplasm model mentioned above (Figure 3), the catabolism of the cells works in a vicious circle, which must be slowed down and then stopped by counter-regulation. Otherwise, the cells would die. The stop is followed by a virtuous circle of the anabolism (Figure 4), which spins in the opposite direction; it can accelerate a lot if the metabolism is potentially less damaged. The recovering tissues require many phosphates and other CBIs for ATP formation and cytoplasm production. There are no warehouses for CBIs, so they (K^+, Mg^{2+}, Pi, Zn^{2+}) in the body; they had departed via kidneys during the catabolic period. Due to the sudden recovery of cells, the phosphates and other CBIs absorbs quickly into the cytoplasm. Unfortunately, the extracellular space is a relative bottleneck for CBIs, because they are presented here at very low concentrations -- compared to the intracellular ones. That is why the lack of Pi, K^+, Mg^{2+}, and Zn^{2+} will be developed extracellularly.

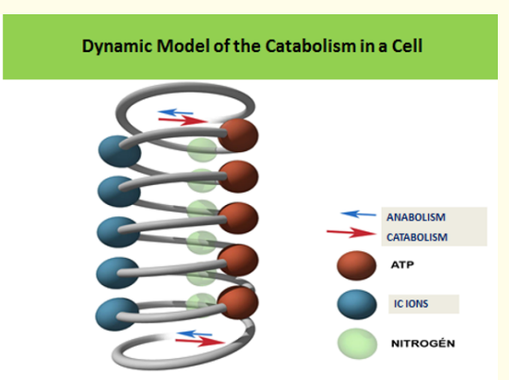

Figure 3: The dynamism of catabolism.

Catabolism is the final merged pathway of the cytoplasmic degradation: the concentrations of N, ATP, and IC ions all decrease, in a parallel fashion.

IC IONS= Cytoplasm Building Ions.

(A vicious circle.)

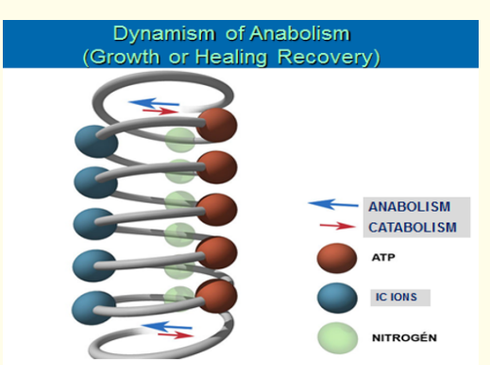

Figure 4: The dynamism of anabolism, (Recovery or growth.)

In anabolism, the concentrations of the N, ATP and IC ions (=CBIs) increase together in the cytoplasm.

(A virtuous circle.).

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Each cell has to fight alone for essential (Type II) nutrients, so tissues battle each other, too. The cells having more reduced metabolism do not obtain enough phosphate and CBIs, and cannot produce enough ATP. Critically lowering ATP levels can lead to the death of cells [5], tissues, and, ultimately, the body. It is tragic because the instability of the metabolism causes death during recovery.

According to this proposal, the initiator of the metabolic instability would be the incorrect food intake in the case of RFS. While in the case of Exploitation Syndrome, a sudden begin of the recovery of a severe disease triggers the worsening, the date is often not apparent. In the alcohol withdrawal, the withdrawal itself causes severe metabolic imbalance, which is reversible immediately with the giving back the alcohol; this will restore the pathologic, but stable balance. The Subacute Alcohol Withdrawal Syndrome hinders the abstinence [27]. The Utilization Syndrome would be a theoretical expression, would apply everyone. Circumstance-induced lesser or greater stresses (e. g., nutrition, mental stress, and meteorological changes) can cause fluctuations of the CBIs in the extracellular space. They can affect the functioning of cells, tissues, and, above all, the nervous system. In this way, it could cause complaints or worsen of different diseases.

When the US Army liberated the prison camps in Burma, the prisoners were severely malnourished, but they otherwise healthy young soldiers. They were suddenly fed with large volumes of food, rich in proteins. Many of them died of malignant cardiac arrhythmias or congestive heart failure. (Delirium developed at many patients though they had not consumed alcohol for years). Hypophosphatemia, hypokalemia, and hypomagnesemia usually go along with the RFS. All of these ions play a vital role in the pathophysiologic mechanism of RFS. Hypophosphatemia is the most crucial symptom of the RFS; this clarifies the pathophysiology, too.

Ancel Keys, professor of biology and physiology at the University of Minnesota, was commissioned by the US government in 1944 to develop a method for proper refeeding. The population of Europe was starving, and it was feared that many would die once they liberated. Ancel Keys kept 36 volunteers on a "limited diet" for six months between 1944 and 1946 and wrote up his experiences in his two-volume book „The Minnesota Starving Experiment" [28]. Unfortunately, it was late. Information was gathered from American military physicians of The Second World War [29]. They experienced that refeeding with skim milk was associated with a marked decrease in the morbidity of RFS. It was probably the consequence of the high phosphate and mineral content of the milk-whey. Laboratory testing was not possible among camp conditions.

Keys solved the pathophysiology of RFS [28]. The inadequate refeeding increased an enormous amount of raise of amino acids in blood serum. The CBIs (K^+, Mg^{2+}, and Pi) shifted into the cells together with amino acids to build cytoplasm. It resulted in an extracellular deficiency of these ions. The hypophosphatemia (lack of phosphate in the blood) is the most prominent one of these. The "hungry tissues" took up the mentioned ions aggressively, using lots of ATP-energy. Those cells, tissues, and organs having a less efficient metabolism will lose this fight for the CBIs. The ATP deficiency will limit the uptake of nutrients such as Pi. The ATP level will further decrease in these cells, which causes vicious circles and critical energy deficiency. When lacking Pi, cells will produce less ATP (see the formula of ATP production: ADP+ Pi =ATP). When the ATP level falls below 30-40% of the physiological value in the cytoplasm, the cell will lose its integrity and die [5]. Some tissues have higher metabolic rates and increased capacity to produce ATP compared to others. The ability of different tissues to tolerate ATP deficiency is not the same either. In the Refeeding Syndrome, ATP and cytoplasmic deficiencies most often occur in the heart and the brain cortex.

A particular case of the RFS is the Hyperalimentation Syndrome, when RFS is elicited by nutritionally incomplete food or infusion. Up to the most recent times, parenteral nutrition was the most common clinical form of RFS. Administering infusion lacking in phosphates can cause immense iatrogenic damage to patients. However, hypophosphatemia can still reach 34% during parenteral nutrition after was started refeeding [26]. According to them, RFS is a well-described but often forgotten condition. Severe, life-threatening hypophosphatemia can be about 1% among hospitalized patients, but serum Pi is not a rutin blood test in most hospitals. A guideline - was published in the UK in 2006 - also recommends additional Vitamin B1, Vitamin B complex, and Ca^{2+}, the mandatory Pi, K^+, and Mg^{2+} supplementation [26]. Many prefer enteral feeding (via nasogastric tubes) to the parenteral solution. In catabolic stress, the aggressive parenteral refeeding can be lethal [7].

From catabolic stress to the Exploitation Syndrome

In this section, the author of this book discusses a syndrome quite similar to the Refeeding Syndrome. He proposes to differentiate Exploitation Syndrome from RFS. The Exploitation Syndrome was firstly described in Hungarian [22]: the pathophysiology and the clinical symptoms and blood-test are similar to RFS, but the starting point is different. The primary state of Exploitation Syndrome: there is a hyperacute disorder, in which severe catabolic stress is the leading sign (the causes are various). Catabolic stress always affects the touched tissues by reducing their capacities to ATP production, resulting in a decrease in CBIs and proteins in parallel with ATP. I.e., the amount of cytoplasm decreases (or ‚becomes thinner' because the volume of the cytosol sometimes even may increase), but the rates of the cytoplasm constituents each other do not change significantly. In that case, if the vicious circles are managed to slow down and stop (sometimes with medical help), and then the tissues of the body will start recovering, and anabolism begins. It can occur the deficiencies of the CBIs in the serum if the

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improvement is rapid and the mass of regenerating tissues are large enough. It can suddenly develop hypophosphatemia, hypokalemia, hypomagnesemia. Of which severe hypophosphatemia may be lethal. The clinical picture is very reminiscent of Refeeding Syndrome - but it is not. Namely, it is not the nutrition that triggers the symptoms, but the sudden change in the tissue's ability to regenerate - switching from severe catabolic stress to recovery, because the phenomenon can occur without food intake [30]. The state is often lethal, but without blood tests (monitoring of the mentioned electrolytes), remains unclear, which was the cause of it? Some can write it at the expense of the catabolic stress, although individuals have already been starting to recover. N.B. If the serum levels of CBIs are high (or extremely high) and then suddenly drop, it is the Exploitation Syndrome. The clinician has to notice when metabolism turns to the anabolic direction and intervene! The to-do is the same as for RFS: regular fast supplementation with electrolytes, first of all, with phosphates.

In the case of catabolic stress, after a while (usually some days), catabolism slows down and then stops; otherwise, the patient would die. Then the direction suddenly changes to anabolism, which can be a similarly fast process as catabolic one. From the clinical signs, the time of turning is not always apparent; on the contrary: the condition of the patient may even get worse due to the severe phosphate and electrolyte deficiency. Therefore, in acute and hyperacute disorders should be monitored the electrolytes, especially Se-Pi. Previously Matz noticed parallels in the pathophysiology of treated uncontrolled diabetes and the Refeeding Syndrome, but he did not refer to a group of diseases [31], differentiating it from RFS.

The author of this book demonstrates the Exploitation Syndrome using a paper published by a team working at a transplant clinic in Los Angeles [30]. Baquerizo and his team performed a retrospective analysis of 112 patients with acute liver failure at whom the transplantation was to be expected. The first few days after the damage of the liver, serum phosphate levels significantly exceeded the normal values in every case. In the instances where serum P_i was still high on day 5th, the patients had no chance to heal spontaneously, regardless of the etiological factor (paracetamol intoxication, poisoning with amanita mushroom, acute viral hepatitis). By contrast, those patients whose serum phosphate concentration reduced below the normal level on day 5th had a good chance of spontaneous recovery. In the latter case, remission occurred only in 51%, if patients were not given intravenous phosphate infusion. If phosphate infusion was given, and serum phosphate levels elevated to the normal, the remission achieved 100%. In this group, the liver transplantation and death was avoided in every case. When the phosphate level decreased spontaneously into the physiological range on day 5th, the remission was 30% without phosphate infusion. However, in the instances when serum phosphate level was raised from the low normal range into the normal high range (by "aggressive phosphate supplementation"), the healed cases increased to 74%. The authors explain the decrease in serum phosphate level - correctly - with fast remission of the liver. If a rapid recovery of liver tissue starts, the liver utilizes the inorganic phosphates (P_i) for the formation of ATP. Phosphate supplementation doubled the number of recovered patients. It means that the starting up of spontaneous recovery is essential for healing; however, the supplementation of the utilized essential Type II (cytoplasm-builder) nutrients is also needed. (Results would be probably even better if the others CBIs were also supplemented). It should be noted that literature attributes the hypophosphatemia in similar cases to „phosphate wasting kidneys." It wouldn't explain why the prospects the better are, the lower the Se-Pi levels on Day 5th? N. B., The high degree instability is life-threatening, even if the changes show the correct direction.

Exploitation Syndrome will occur when during any severe disease, the pathologic process passed over the peak, and robust remission is starting, if the regenerating tissues take up CBIs too suddenly (because of their mass is large or the recovery is extremely rapid). It can result in hypophosphatemia, hypokalemia, hypomagnesemia, and the lack of Zn^{2+} in the serum. Severe hypophosphatemia (Se-Pi <0.4 mmol/L or 1 mg/dL) is particularly dangerous as it can cause immediate tissue degradation and necrosis. When CBIs are transporting into the cells, their deficiencies will develop in extracellular space, mostly as a result of the electrolyte utilization of anabolic processes of the regenerating tissues. During the progression of the disease, the metabolic spiral starts "spinning" to the direction of the red arrow (Figure 3), while in regression, it starts spinning to that of the blue arrow (Figure 4). Lack of the CBIs in the extracellular space occurs in the second case as the ions released from cells had already left the body. Monitoring serum phosphate levels is one of the most reliable methods to assess the direction of metabolism in the body [30]. However, its results can only be adequately evaluated if we consider the clinical picture and the dynamics of the ongoing disease, knowing its physiopathology. Basing on his experiments with rats, Henry declared as early as in 1979 that the amount of inorganic phosphate intake needed for producing new cytoplasm was proportional to that of N of newly formed proteins [32]. That corresponds to the Golden's Type II Nutrients Theory [24].

Acidosis is one of the most potent stressor stimuli of catabolism [33]. As a result of acidosis, CBIs migrate into the extracellular space and then get excreted with urine. During recovery from acidosis, not only N (proteins) but also CBIs should be back. An excellent example of this was a case study when the respiratory acidosis was normalized by using respirators. However, the patients could not be disconnected from respirators till serum phosphate levels restored with supplementation or by mobilizing phosphate from the bones [34]. When acidosis also is developed in the intracellular space, it is always accompanied by intracellular K^+ deficiency. When acidosis is corrected, extracellular hypokalemia will develop. We

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can help recovery from intracellular acidosis by giving potassium to the patients.

During recovery from diabetic ketoacidosis, patients usually suffer from severe hypophosphatemia [35], accompanied by hypokalemia and hypomagnesemia [31]. It may even develop potentially lethal hypophosphatemia; however, serum phosphate levels usually get back to normal within a few days without phosphate supplementation. It is generally accepted that the potassium should be supplemented while phosphate supplementation recovering from the diabetic coma only recommended in severe hypophosphatemia, in the form of potassium phosphate buffer. Giving potassium phosphate infusion to patients suffering from diabetic ketoacidosis carries the hazard of hypocalcemia that does not respond to Ca^{2+} supplementation in many cases. It can only be cured with magnesium supplementation [36]. It can be a consequence of functional hypoparathyroidism or Hungry Bone Syndrome (see Part 2. of this book). Matz pointed out at first, the similarities between uncontrolled diabetes and RFS [Matz31]. He estimated the number of ions missing from the impacted tissues at 350-1000mmol K^+, 70-140mmol P_i, and 25 - 50mmol Mg^{2+}, and others claim the deficiencies are even more severe [35]. On the first day of diabetic ketoacidosis, serum Zn^{2+} level was also significantly lower than the normal, getting back to the physiological level after two weeks [37].

Trauma, burn injury, but also surgery, can cause severe catabolic stress [38], which in turn often results in a significant loss of body weight. In these cases, the Exploitation Syndrome can develop (usually in the first 14 days); immediately after remission starts. Often, the beginning of recovery can be identified only by a blood test of serum phosphate levels [30]. Mineral supply mostly lags behind demand during rapid recovery from diseases. It often results in a lack of the CBIs both in the extracellular and intracellular spaces. The risk of hypophosphatemia is increased by head trauma, hyperventilation, parenteral feeding rich in carbohydrates, but low in phosphates, the hypothermia impacting the entire body or just some organs. Hyperventilation and glucose (in the presence of insulin) increase the shifting of phosphate into cells. Hypothermia reduces metabolism in tissues, and the released CBIs are excreted from the extracellular space via the kidneys by an increased diuresis. Poldeman, and Girbes reported the almost obligatory development of hypophosphatemia (83%) as well as hypokalemia (34%) and hypomagnesemia (46%) the day after patients underwent open-heart surgeries with cardioplegia, even though patients were preventively given K-Mg supplements and the cardioplegic solution also contained potassium and magnesium [39]. Hypophosphatemia is also common in cryosurgery, and patients with hypophosphatemia more often suffer from adverse reactions. Hypophosphatemia increases the mortality in the case of burnt patients. Parenteral phosphate supplement had a beneficial effect in the case of 16 patients with severe burn injury [40]. After abdominal surgery, hypophosphatemia was reported for 28.8% of patients; The mortality among patients having hypophosphatemia was significantly higher (30% vs. 15.2%). Once serum phosphate was normalized again by intravenous infusion of giving glucose phosphate, the cardiac index increased from 3.82 to 4.52 on average ($p < 0.01$). However, both could be reduced by proper electrolyte therapy. It was verified by Muth, who gave K-Mg-Pi-Zn salts containing infusion during the convalescence period after surgery, thus significantly reducing the duration of remission [41]. The convalescence from hyperacute nontraumatic diseases forms a critical group; a classic example is the acute, fulminant liver failure, already was referred above [30]. The liver has a relatively big mass and remarkable recovery capacity. That is why the liver is particularly exposed to a manifestation of the Exploitation Syndrome.

Alcohol Withdrawal Syndrome

Chronic alcohol abuse is everyday, grave sanitary, and social issue, for example, because of the development of addiction. In the case of regular alcohol consumption, malnutrition and deficiencies of essential nutrients are inevitable [42]. Knowing its pathophysiology, it is evident that the acute and subacute forms of Exploitation Syndrome occur during the attempts of withdrawal, e. g., delirium tremens can develop, and make withdrawal impossible. In the acute case, the success of the withdrawal is not usually dependent on the patient. He or she should choose between a clinically severe, potentially fatal disease, or relative well-being. What happens during the withdrawal? The regular consumption of alcohol keeps the malnourished body in balance relatively. The withdrawal of alcohol immediately triggers the mechanism of Exploitation Syndrome in the potentially ready-to-recover body. (The younger and healthier the patients is, the more explicit the withdrawal symptoms are.) I.e., severe hypophosphatemia, hypomagnesemia, hypokalemia [15,35], lack of Zn^{2+}, and thiamine will occur in the extracellular space, and also in several tissues with less proper metabolism. The mechanism is similar as discussed above, though the client knows according to his previous experiences that a glass of alcoholic drink helps. It restores the balance, which is pathological but at least eliminates hyperacute symptoms.

One of the most important causes of hypophosphatemia during alcohol withdrawal is hyperventilation [35]. Acute or decreasing pCO_2 cross cytoplasm-membranes without delay, it will alkalinize the interior of the cells. The falling of H^+ concentration (rising pH) increases metabolism [9], ATP utilization, in this way, the glucose utilization and ATP production. This process needs phosphate too, that is why phosphates transported into cells. (This is also one of the hypotheses of the author of this book. Others explain the phenomenon due to glycolysis increase. The two do not contradict each other.) Roelofs had shown that Subacute Alcohol Withdrawal Syndrome appears to have a close relationship with hyperventilation and anxiety [27]. The author of this book

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hypothesized that if we could prevent hyperventilation and anxiety periods developing during withdrawal, it would be a great help to patients' well-being and success in withdrawal, And indeed, according to his experience, administration of CBIs together at levels below the RDA significantly aids alcohol withdrawal and hinders the development of craving [22]. Others [42,43] also had concluded that proper nutrient intake aids in relapse prevention. We need to note that the mineral composition should also contain HPO_4^{2-} /$H_2PO_4^-$ mixture in the appropriate ratio.

Utilization Syndrome --a prevention strategy

Catabolism and its alterations with anabolism are not always rapid and explicit as it was described in the previous section. It is not still easy to recognize the acute Exploitation Syndrome, but it is even more difficult or impossible to identify its chronic form, the Utilization Syndrome. In this case, the serum electrolyte levels neither help much, so it is important to clarify the basic principles. Golden [24] declared that cytoplasm production is always limited by that Type II essential nutrient, which is available in the lowest amount. The production of cytoplasm will stop even if a single component is missing. Cells and tissues can only access the essential substances from the extracellular space. Thus, we can consider the serum concentration of cytoplasm-builder nutrients as a starting point. If we make the logical separation between inorganic and organic cytoplasm-builder nutrients, we will know that they mutually depend on each other as well as on the concentration of ATP (Figures 1., 2., 3. and 4). It means that not only CBIs but also essential amino acids should have physiological serum levels. As we do not eat nutrients but food (with a random nutrient composition) there will always be some among the dozens of cytoplasm-builder nutrients that are available only in low or normal-low concentrations. Hence, it will always be a component, which momentarily is the lowest serum concentration (related to normal levels); in this way, it limits cytoplasm production, cell regeneration, or the growth of children. Without detailed investigation, we cannot know which type II nutrient is the limiting factor of the cytoplasm building, and we can give a mixture of CBIs.

Among the cytoplasm-builder ions, the magnesium is the most popular, there is an enormous amount of data available about it, and above all, about deficiency and its supplementation trials, for example: [44]**.** However, it cannot be recommended as medicine alone only in a small number of diseases. There were high hopes in the past and also are in the present, related to it, but the evidence is not always inconclusive. They prefer to associate magnesium deficiency with the heart or the central nervous system, but we know that it is an essential part of every cell. When Mg^{2+} supplementation is not successful enough, we can conclude that it may be lacking, but not it is the limiting factor in the cytoplasm production. NB: cytoplasm builder nutrients can only be supplemented together.

It has been collected sufficient evidence on the role of potassium as a prophylactic agent against diseases [45]. Giving potassium in doses exceeding the RDA or maintaining normal high potassium levels were proved to be an efficient prophylactic agent for hypertension, stroke, kidney stones, carbohydrate intolerance, and cardiac arrhythmias. High potassium intake has an independent protective effect on the kidneys, regardless of hypertension. Furthermore, the high K^+ intake also protects the heart and bones. However, today's 'Western diet' does not contain sufficient amounts of potassium (RDA=2500-3500mg).

Monographies prove that zinc is "everywhere," playing a role in everything of the body's cells, similarly to magnesium. Zinc deficiency is often a limiting factor; inhibits cytoplasm production, regeneration, and growth [23,24,25]. There is evidence that zinc provides a versatile prophylactic nutrient, too. It is best known as an agent that protects the immune system, the intestines, the liver, and the nervous system, promotes the physical development and growth in children, and reduces mortality in malnutrition. It is also essential that the zinc is a prophylactic protector against free radical reactions and some certain complications in diabetes [37].

The status of the phosphates (Pi) as cytoplasmic ions are specific. It is said, we take up enough phosphate with a regular diet. If it right, despite that, it cannot prevent intracellular phosphate deficiency as incorporation into the cytoplasm is only possible proportionally [24]. Paradoxically, excess phosphate intake may result in cytoplasmic phosphate deficiency as a consequence of the relative inhibition of $Mg^{2+,}$ and Zn^{2+} absorption. Indeed, we talk about not one but two ions here ($H_2PO_4^-$and HPO_4^{2-}), which form together an efficient intracellular buffer system. The deficiency of alkali elements (or the H^+ load) is the first, which impairs the function and integrity of the cytoplasm and the body (e.g., the skeletal system), so protection is needed against such stresses. We can conclude that the intracellular deficiency of the K^+, Mg^{2+}, Zn^{2+}, phosphates, and alkali elements usually occur together, and we can be returned these elements into the cytoplasm only together in the right ratio.

Many other factors should be worth to mention discussing apropos of prevention, and the physical exercises are probably the most important of them. Physical activity, as good stress, promotes "internal feeding" that is the flow of cytoplasm-builder nutrients into the extracellular space from the muscles provides normal-high serum levels of them, and the redistribution of CBIs [46]. Regular training also increases the mass of skeletal muscles that turn also serve as a "storage facility of the cytoplasm-builder (Type II) nutrients". Finally, we can burn excess fat during exercise. N. B., The Increase of the cytoplasmic volume of the body raises life expectancy.

There is a robust correlation between muscle and bone masses [7]. Similarly to that of skeletal muscles, bone mass reaches its

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maximum at the time of reaching adulthood (around 20-25 years of age). The bone and muscle weight of those doing heavy physical work athletes will always exceed those of their physically not-active peers. The skeletal muscles and bones are physiologically the earliest responders for the diseases; they are the physiological Places of Less Resistance. They protect the rest of the organs of the body, providing cytoplasm-builder (Type II) nutrients for the common extracellular space. After the regression of the disease, these nutrients are then taken up again by muscles and bones. A disease always attacks structures and functions of the cells, in this way, also the ATP production.

Locus Minoris Resistentiae -- the Place of Less Resistance

The Latin term Locus Minoris Resistentiae refers to the organ that has the Place of Less Resistance of the body against certain diseases [47]. In any internal organ of the body can be lesser resistance due to the altered congenital or acquired defense capacity, a catabolic process can develop more easily than elsewhere in the body. The cytoplasmic model of the author of this book shows what its exact pathophysiology would be.

During Refeeding and his companions (Exploitation and Alcohol Withdrawal) Syndromes the „hungry cells/tissues" pick up at a rapid pace the phosphates and other CBIs. Severe hypophosphatemia, hypomagnesemia, and hypokalemia will develop. The hypophosphatemia is crucial because the weaker tissues do not get enough P_i and consequently, they cannot produce enough ATP to live. If the intracellular ATP level drops below 30-40%, the cell, the tissue will die [5], which eventually results in the death of the patient. At the same time, with the slower feeding and giving more CBIs, the individual had every chance for healing.

Severe hypophosphatemia, caused by Refeeding or other similar Syndromes, can lead to severe damage or destruction of almost all tissues [35,38], though most easily the skeletal muscles, heart and brain. That is why the elevation of serum creatine-phosphokinase level is also an early sign [35], but the most common lethal complication is heart failure. The cases include heart failure, central nervous system dysfunction (delirium), but also rhabdomyolysis, hemolysis, thrombocytopenia, granulocytopenia, respiratory failure, hepatopathy, tubulopathy; sometimes the one, sometimes the other. There are many reasons what are the causes of the current person's Place of Less Resistance. Genetic reasons play an essential role in this, just as the organ that has not entirely recovered from various diseases, that is chronically ill having more deficient metabolism, having less ATP producing ability.

The body also has a physiological organ ranking of the Places of Less Resistance. (It probably developed during the phylogeny.) In healthy adult humans, starvation and malnutrition will affect first the mass of the skeletal muscles (decreasing its cytoplasmic volume) [7], the bone tissue closely follows it (Figure 8). The heart and the brain are somewhere in the middle, while the liver, the kidneys, spleen, and the immune system are the most resistant to starvation (i.e., the lack of cytoplasm-builder nutrients) [7]. Skeletal muscles and bones represent the most substantial proportion of cytoplasmic masses and are capable of reversible way to lose a significant amount of it to protect other vital organs. That is why we need to build robust musculoskeletal systems at a young age to protect the rest organs and increase our life expectancy.

There is a robust correlation between muscle and bone masses [7]. Similarly to that of skeletal muscles (Figure 8), bone mass reaches its maximum at the time of entering adulthood (around 20 - 25 years of age) (Figure 5). The bone and muscle weight of those doing heavy physical work athletes will always exceed those of their physically non-active peers. The skeletal muscles and bones are physiologically the earliest responders for the diseases; they physiologically have the Places of Less Resistance. They protect the other organs of the body, providing cytoplasm-builder (Type II) nutrients for the common extracellular space. After the regression of the disease, these nutrients are then taken up again by muscles and bones. A disease always attacks the structures and functions of the cells, in this way, also the ATP production. After it, the cytoplasm can degrade. (Fat tissue practically does not contain cytoplasm.).

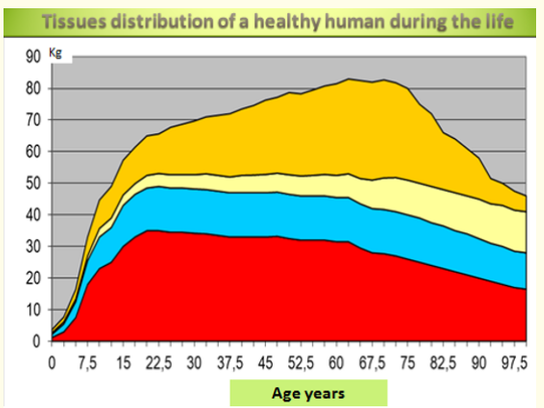

Figure 5: Changes of the three types of tissues and free water and their distribution in a healthy human subject during the life.

Red=Body Cell Mass (The Functioning Cytoplasm)

Blue=Extracellular Water-Spaces Together

Yellow=Connective Tissues

Ochre=Adipose Tissue.

'Losing muscle mass' as a defensive mechanism of the organism against the attack of diseases: it sounds like a surprisingly bad solution at first, but if we think about it, any other solution would only be worse. The resulting changes (such as decreased organic and inorganic bone mass, osteopenia) can be reversed even after long periods of malnutrition if the patient can receive later all the

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necessary cytoplasm–builder nutrients [48]. However, if the patient continues to lose weight, the mass of cytoplasm in other organs will also decrease, first in the heart or the brain (Figure 8). The fact that muscles (together with bones) also serve as a readily available stock of nutrients explains why it is beneficial having strong muscles in various diseases (including cardiac disorders). It is very tragic if one of the other organs (most often the heart or brain) gets ahead in the organ ranking of the Place of Less Resistance (Figure 8). (There can be many reasons for this, e. g., genetic defects or survived organ damages, which did not heal.) In this case, this vital organ attracts several harms and deteriorates rapidly. According to the hypothesis, monitoring and supplementing cytoplasm builder nutrients can help in these conditions. After following more than 6000 patients for five years, it can be stated that regular physical activity is an essential and efficient tool for preventing dementia. Others found similar results for different diseases (ischemia, stroke, diabetes mellitus, osteoporosis) [49].

If an organ is damaged severely by a disease, it becomes the Place of Less Resistance of the body. Skeletal muscles and bones have that the necessary mass to transmit enough cytoplasm-builder nutrients to the other organs in the emergency. For practical reasons, it is imperative to understand that the benefits of all these processes are to prevent the reduction of the serum electrolyte levels of CBIs. In other words, if the standards of extracellular space cytoplasm builder nutrients could be maintained at a normal high level, this would be essential protection against both cardiac and CNS degenerative diseases (Figure 6 to 8).

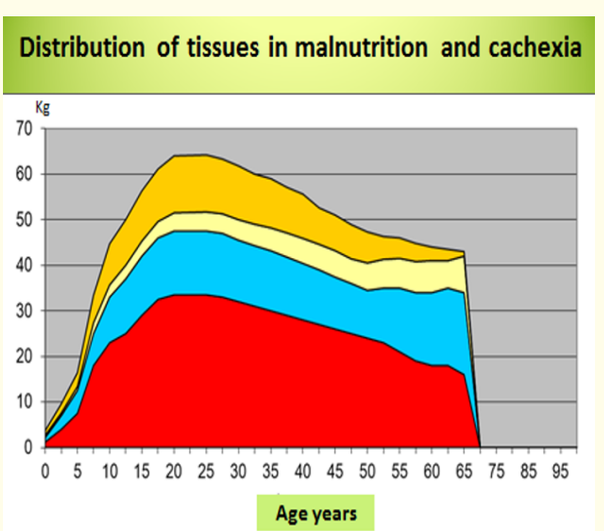

Figure 6: Distribution of Tissues In A Malnourished Patient.
Red=Body Cell Mass (The Functioning Cytoplasm)
Blue=Extracellular Water-Spaces Together
Yellow=Connective Tissues
Ochre=Adipose Tissue

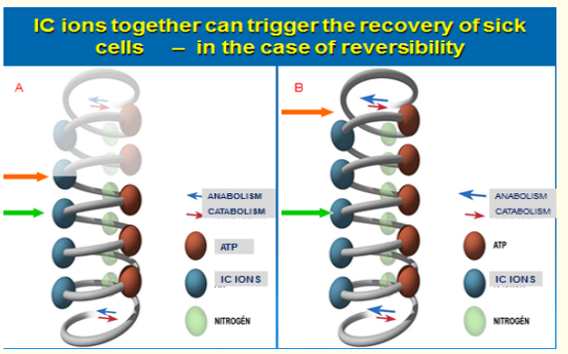

Figure 7: In reversibility, the combined supplementation with all the IC ions (e. i. Cytoplasm Builder Ions) can trigger repairing processes in chronically diseased cells. The green arrow represents the membrane potential threshold, the orange one, the resting membrane potential. Theoretically, if the concentration of Cytoplasm Builder Ions decreases in pacemaker cells, the N content of these cells, as well as their resting membrane potential, will also decrease, approaching the threshold potential (Fig. 7A). Assuming a constant velocity of the spontaneous diastolic depolarization in the sick foci, the 'firing' rate increases, resulting in an increased probability of ectopic beats. If cytoplasmic ions can be allocated to the cells by supplementation, the resting membrane potential will rise again, and the firing rate decreases together with the probability of ectopic beats (Fig. 7B).

IC IONS =CBIs=K^+ + Mg^{2+} + Zn^{2+} + HPO_4^{2-} /$H_2PO_4^-$.

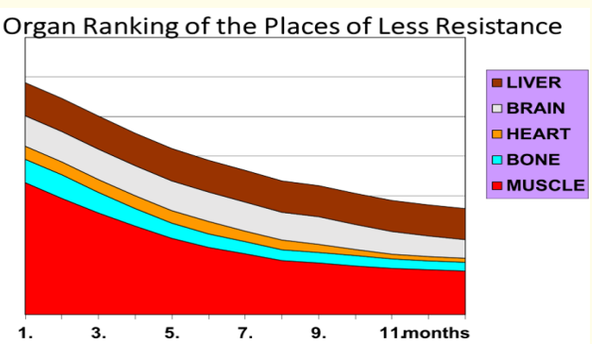

Figure 8: The figure shows the weight loss of organs during sustained semi-starvation. During the first eight months, the mass of muscle and bone only decreased. After there, the heart and brain started to decline. The liver remained intact all the time.

The Substrate Cycle was known initially also as a 'futile' cycle. There was not seen the sense that the same chemical reaction or process, which were also run simultaneously in the opposite direction and produce only heat energy. Newsholme and Crabtree discovered this thermodynamic mechanism of the Substrate Cycles, which is now entirely accepted [50]. The importance of the theory is that the increased heat generation helps to control the weight of

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the body. However, the disclosed process may also be essential to stabilize and balance the metabolism (catabolism vs. anabolism). In this way, it can play a vital role in maintaining the homeostasis of the body. The theory claims that various organs release cytoplasm-builder amino acids and other nutrients and then are taken up again and again by the same organs at varying degrees. Hence, they appear in new organs all the time and get redistributed and recycled. (In steady state, the volume of amino acids released and taken up are more or less equal.) About 80% of amino acids serving as cytoplasm-builder nutrients come from decomposing and recycling the body's proteins. The Substrate Recycling process may be a base for the theory of Locus Minoris Resistentiae. All the organs submit their cytoplasm-builder nutrients to the shared extracellular pool of them. Then each one takes out what they need, more correctly for which they have enough ATP-energy. It is an example of the struggle for life, a "civil war" that can also lead sometimes to the destruction of the "state" of cellulars/tissues and organs. That is why the physician has to be smart.

Conclusion

In the first part of his book, the author shows what a cytoplasmic model he has developed over a decade of work and how he further developed it. He has applied the model to understand the pathophysiology of stress-related civilization diseases. According to his model: the prevailing Momentary Intracellular Ion-Pattern controls the enzymatic functions of the cell, according to the hypothesis, (so-called Cytoplasm Builder Ions and other ions together) and can, therefore, be called the "software" of that cell. A living cell can balance itself if it receives the necessary nutrients and is not affected by a damaging agent. After a catabolic shock, one part of the cytoplasm will be degraded, because wherever it is damaged, it will also affect energy production. CBIs, ATP-energy, and cytoplasmic proteins will decrease parallelly. Then metabolism will be stabilized at a lower energy level, it can rebuild itself if all cell-builder nutrients are available, and the cell is not irreversibly damaged. Nutrients in the body need to enter the intercellular space to get into the cells, which is often a 'bottleneck'. Partly that is the cause that destabilizes the metabolism during sudden recovery from malnutrition. Another lesson: during recovery, phosphates become the most crucial nutrients, although most clinicians do not consider them much. (Many think that they are more harmful than useful.) This paper deals in detail with Refeeding Syndrome and similar disorders. It also introduces two new terminologies invented by the author; one of them is 'Exploitation Syndrome,' and the other is 'Utilization Syndrome.' They have great importance in clinical practice.

The Second Law of Thermodynamics plays a crucial role in how one can be modelizing the author's disease hypothesis. The amount of human cytoplasm increases in weight until about 20 years of age, and improvements in vitality, followed by a gradual decrease in cytoplasmic mass, including ATP and body's ATP production capacity. It is important to mention the role of the vicious circles in the development of the diseases and their opponents during the recovery (virtuous circle). The events of vicious circles are not accidental but inevitable. Life (living cells) exists at a higher energy level than the environment; it will come down sooner or later. An unstable organization that reaches a lower energy level gets among new conditions, many of which harm it - making it more unstable, etc. It's like a stone rolling down from a hill, and it rolls faster and faster. However, the body has defense mechanisms, counter-regulation systems, which slow down and then stop it. It can climb back from there to higher energy levels, even at a faster pace (virtuous circle), if all the nutrients and all their conditions are simultaneously available.

The Locus Minoris Resistentiae (the Place of Less Resistance) has got a new interpretation by the cytoplasm model of the author. Some diseases target specific receptors, cells, tissues, or organs. Other conditions, on the other hand, can damage the whole organism and to all its cells, though not to the same extent. E. g., such are toxins as alcohol, drugs, general oxygen deficiency. It is also the case with CO2 deficiency or excess (hypocapnia or hypercapnia). Although the stressor effects of these usually are not recognized by most clinicians because they develop so frequently, they are nearly a common phenomenon. The lack of cytoplasm-builder (Type II) nutrients as hypophosphatemia in the Refeeding Syndrome can often be deadly. The hypophosphatemia will attack first the Place of the Less Resistance of the body [35]. Because these general stressors affect the whole body, each cell has to fight on its own. Cells that are more sensitive or have a low ATP productive capacity due to chronic disease or genetic defects will be defeated. At the same time, as they catch harm themselves, other organs will be relatively protected. Physiologically, some tissues are less resistant to general stress, such as skeletal muscle and bones. There is an organ ranking of Places of the Less Resistance [7]. Both muscles and bones have large volumes and capacity and can, eliminate, at least reduce particular harm for a long time- while they are reversibly damaged. From this Locus Minoris Resistentiae theory, many things become apparent to a clinician.

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