REVIEW

Endobiogeny: A Global Approach to Systems Biology (Part 2 of 2)

Endobiogeny：一种系统生物学的全球方法（第 2 部分，共 2 部分）

Endobiogenia: un enfoque global de la biología de los sistemas (parte 2 de 2)

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THE BIOMARKERS
Experimental and Clinical Basis for the Biomarkers Used in the Biology of Functions

Endobiogeny and the biology of functions are based on four scientific concepts that are known and generally accepted: (1) human physiology is complex and multifactorial and exhibits the properties of a system; (2) the endocrine system manages metabolism, which is the basis of the continuity of life; (3) the metabolic activity managed by the endocrine system results in the output of biomarkers that reflect the functional achievement of specific aspects of metabolism; and (4) when biomarkers are related to each other in ratios, it contextualizes one type of function relative to another to which is it linked anatomically, sequentially, chronologically, biochemically, etc.

As will be shown in this article, the relationship between various hormones and particular biomarkers is a long and well-established fact based on modern physiology and scientific method. The indexes composed from these biomarkers have been derived through inductive reasoning and confirmed by more than 30 years of clinical practice. The indexes have not been individually validated in the peer-reviewed literature. It stands to reason that if the correlation of the biomarkers, directly or indirectly to endocrine activity is sufficiently demonstrated, this biological modeling system may be a more valid assessment of biologic activity than the current methods of biomarker evaluation.

Bone Marrow: Complete Blood Count

Life is permanent dynamism, and the circulation of blood ensures this dynamism. Blood plasma is a conduit of information, a delivery system of nutrients, and a remover of metabolic waste, but it is the cellular elements—white blood cells (WBCs), red blood cells (RBCs), and platelets—that serve to deliver oxygen and defend, heal, and protect the body. The endocrine system as the manager of metabolism determines the rate of production of cellular elements from the bone marrow. Thus blood is the foundation of life, and the endocrine system as the manager of blood is the manager of this foundation. The evaluation of blood cells reveals how the endocrine system manages life.

In the biology of functions, more than 60% of biomarkers used are derived just from the cellular elements of blood, made in the bone marrow (Table 1). The com-

Table 1 Biomarkers Used in the Biology of Functions

Origin	Biomarker	Value	Conversion
Bone marrow cellular products	Red blood cell	per µL	$\div 10^6$
	White blood cell, total	per µL	$\div 10^3$
	Neutrophil	%	None
	Lymphocytes		
	Eosinophils		
	Monocytes		
	Basophils		
	Hemoglobin	g/dL	None
	Platelets	per µL	$\div 10^3$
Bone marrow-serum interaction	Erythrocyte sedimentation rate	mm/h	None
Bone stroma enzymes	Osteocalcin	ng/mL	Proprietary
	Alkaline phosphatase bone isoenzyme	%	Proprietary
General enzymes	Lactate dehydrogenase	IU/L	Proprietary
	Creatine phosphokinase		
Endocrine	Thyroid-stimulating hormone	µIU/mL	None
Electrolytes	Potassium	mmol/L	None
	Calcium, total serum	mmol/L	$\div 2$

plete blood count (CBC), then, is the basis of the biology of functions. Androgens and estrogens stimulate the proliferation of red and white blood cells, respectively. Thus, sex hormones are the foundation of the CBC—hence of life—and the initial point of study in the biology of functions. (The bone stroma, discussed below, plays three key roles: protection and nourishment of the marrow, regulation and assistance in global energy management, and communication of the state of the peripheral terrain to the central nervous system).[1-3]

The roles of androgens, and then later estrogens, as the basis of life are evident from the time of conception. For the first 17 days, it is the mother's hormones that the embryo shares. At day 18 of life, the yolk sac becomes the first endogenous source of RBCs.[4,5] Rich in androgen receptors, the yolk sack stimulates erythropoietin, which itself plays a role in yolk sac maturation of RBCs,[5] establishing the key role of androgens in the foundation of structure.[6] The liver is an intermediate source of red blood cells,[4] also under the management of androgens.[7] By 34 weeks of gestation and throughout the remainder of life, the bone marrow, stimulated by androgens and estrogens, becomes the source of the majority of blood cells.[8]

In summary, the activity of androgens and estrogens is reflected in the output of red and white blood cells by the bone marrow. The evaluation of this activity, called the Genital Ratio, is used in the majority of indexes of the biology of functions. To accept the hypothesis that red blood cells are a biomarker of androgen activity and that total white blood cell count is a biomarker of estrogen activity at the level of the tissues is to accept the foundation of the majority of indexes of the biology of functions.

Red Blood Cells

Based on studies over the last 50 years, we postulate that RBCs are a biomarker of the *functional* role of androgens in metabolism. These studies demonstrate that the administration of androgens stimulate erythropoesis, the development of RBCs.[9-15] It is our belief that using RBCs as a marker of the functionality of androgens may prove to be more clinically relevant than quantitative measurements for four reasons: contradictory studies regarding serum levels of androgens and clinical effects, the complimentary nature of estrogens, the role of genomic vs non-genomic effects, and genetic variations in intracellular (IC) conversion of androgens.

Limits of Quantitative Measurements of Androgens. Multiple studies have positively associated elevated levels of serum androgens, RBCs, or both in hypertension,[16-19] thrombus formation,[20-28] impaired insulin sensitivity,[29,30] and insulin resistance.[31] However, low serum levels of androgens have also been positively associated with the same disorders.[32-35] For example, while androgens are positively associated with dyslipidemia, they have also been associated with a reduction in triglycerides and LDL.[21] Thus, evaluating serum androgen levels may be misleading.

Protective Role of Estrogens? For years, it was believed without strong evidence that delayed cardiovascular mortality in women was due to a protective effect of estrogens. Prospective studies of estrogen supplementation demonstrated not only that supplemental estrogens offered no benefit but that they elevated the risk of cardiovascular events.[36-38] The lack of definitive protective effects of estrogens and the harmful effects of elevated and low serum levels of androgens in some men and not others suggests to us that it is the relative ratio of androgens to estrogens that is clinically relevant, not the absolute quantitative value of either in isolation.

Are Androgens Harmful in and of Themselves? Studies suggest that androgens alone are not predictive of life span or risk of death from cardiovascular disease in men[39-41] or women.[42-45] Rather, androgens appear to be but one of many factors in a complex interplay of endocrine drivers of metabolism that influence the development, progression, and severity of a wide range of disorders from vascular disease[16,46] to Alzheimer's disease.[47] This may be one reason that assessments relying on serum androgens measurements alone have been inconsistent or contradictory.

Determining Androgen Function: Genomic and Non-genomic Effects. Androgens, like most other steroidal hormones, have genomic and non-genomic effects.[48] The ability to evaluate the relative impact of non-genomic vs genomic affects in a particular individual may help solve the conundrum of whether high or low androgen activity is protective or harmful.

The genomic effects of androgens are what have been associated with serum levels of androgens. In contrast to the non-genomic effects, these effects take hours to occur and are linked to many of the classic effects associated with androgens deemed to be harmful when dysregulated. These effects include smooth muscle proliferation, migration, and vasorelaxation; increased monocyte migration and foam cell production; and increased apoptosis.[48]

Non-genomic effects occur within seconds. Mechanisms of action are believed to include a novel membrane-bound receptor, second messenger activation, and sex-hormone binding globulin receptors. Many of the non-genomic effects of androgens are physiologically beneficial and explain the protective effects of androgens observed in studies. They include relaxation of smooth muscle, increased neuromuscular signal transmission by calcium regulation, improved neuroplasticity, cellular proliferation and migration, and modulation of the transcriptional effects of classic androgen receptors.[49,50] What is clinically relevant is that these non-genomic effects cannot be blocked by drugs that block androgen receptor activity. This may explain two observations: (1) the variability of responsiveness to androgen blockers and (2) factors of risk and protection from disease cannot be reliably assessed by quantitative measurement of serum androgens, sex hormone binding globulin, or free androgen levels—because their effects do not rely solely on receptor activity.

Determining Androgen Function: Metabolic Pathways. There are a number of other factors adding to the difficulty of equating quantitative levels of testosterone (free or total) with androgen functionality. Recent studies have demonstrated in vitro and in vivo sex-based variability in androgen receptor sensitivity and concentration in various tissues.[43] Approximately 5% of testosterone is converted within the cell to either dihydrotestosterone (DHT) or estrogens.

In summary, the individual effects of testosterone on the body can vary based on (1) genomic effects, (2) non-genomic effects, (3) receptor concentration, and (4) IC conversion tendency between DHT and estradiol. The net effect can be an amplification of genomic or non-genomic effects (DHT) or a counter-balancing effect (estrogens). Therefore, we believe that RBCs may be a useful biomarker reflecting the global degree of tissue functionality of androgens when evaluated relative to other factors.

White Blood Cells

WBCs, also known as leukocytes, are blood elements that mature in the bone marrow then enter the circulation. Leukocytes consist of five types of cells that arise from a common hematopoetic precursor. White cells differentiate into neutrophils, monocytes, eosinophils, basophils, and lymphocytes. Estrogen stimulates a proliferation of leukocytes in the bone marrow.[51] Leukocytosis is associated with high estrogen states such as pregnancy[52] and autoimmunity,[53] as well as during the acute phase of infections. Thus, we believe that total WBC count can be considered to reflect the basic tissue effect of estrogens throughout the body.

Limits of Quantitative Measurements of Estrogens. The challenges of evaluating the role of estrogens in human physiology are far greater than for androgens, which is why specific aspects of estrogen activity requires more than a single biomarker.

Estrogen activity is complex, varied, and fundamental to human life. It involves endocrine and metabolic functions, both genomic and non-genomic in nature. Of all sex steroids, estrogens require the greatest number of metabolic conversions, being derived as such: cholesterol → progesterone → androgens → estrogens. Estrogens can be produced in the ovaries, in the adrenals, and by peripheral conversions in various tissues.[54,55] The pattern of estrogen production (central vs peripheral, adrenal vs gonadic vs hepatic) varies based on hereditary factors, age, and parturition status and is affected by endocrine disrupters.[54-57]

There are multiple active forms of estrogens (estrone, estradiol, and estriol) as well as varying degrees of activity of estrogen metabolites. There are two types of estrogen receptors (alpha, beta), which have opposing activity with respect to cellular proliferation and various metabolic function. There are genetic polymorphisms in p450 metabolism of estrogens and polymorphisms with respect to receptor sensitivity, concentration, and rate of aromatase activity as well as non-genomic effects, which in sum all impact the effects of estrogens.[58-64] In their review of estrogen metabolism, Zhu and Conney conclude,

> Studies that identify genetic and environmental factors influencing estrogen metabolism at or near estrogen receptors in target cells may be of considerable importance since these factors could profoundly modify the biological effects of estrogens in complex manners depending on the pathways of metabolism that are affected and the biological activities of the metabolites that are formed. Such effects need not be associated with an altered profile of estrogen metabolites in the blood or urine.[61]

Estrogens: Beneficial or Harmful? As with androgens, clinical trials are conflicting with respect to the beneficial or harmful role of estrogens in the body. The protective role of estrogens in cardiovascular disease has come under question, as we have discussed above.[36-38,54] With respect to cancer, estrogens can promote or lower the risk for cancer in and of themselves and in conjunction with other hormones.[65-68] The contradictory nature of estrogen's effects on telomere length and the role of telomere length in cancer serve as another good example of the limitations of both quantitative hormone measurement and single-cause theories of disease. Estrogens increase telomere length. Women have the longest telomere length when follicle-stimulating hormone and estrogen peak during the menstrual cycle.[69] Telomere length is positively correlated with the rate of apoptosis and inversely associated with the risk of cancer. However, estrogens also cause leukocytosis, which is associated with shorter telomere length, less apoptosis, and greater risk of cancer[69,70] Telomere length alone, like quantitative levels of estrogen, does not appear to be a sufficient indicator of the global effects of estrogens on the terrain.

The Case for Multiple Biomarkers of Estrogen. In conclusion, estrogens have various sources of origin, various rates of metabolism, and changing concentrations and receptor densities throughout life and can be affected by and affect other hormones in the body, as well as being disrupted by endocrine disrupters. Mounting evidence suggests that serum and urinary levels of estrogen and their metabolites may not be sensitive or specific enough measures of the effects of estrogens.

We hypothesize, based on experimental evidence and clinical studies, that specific functional effects of estrogens can be inferred through the evaluation of particular serum biomarkers in and of themselves, as well as in conjunction with other biomarkers in increasingly complex ratios. In the biology of functions, this assessment of estrogen function is accomplished by evaluating six different biomarkers: (1) total WBC count, (2) percent neutrophil count, (3) percent monocyte count, (4) percent lymphocyte count, (5) thyrotropin-stimulating hormone (TSH), and (6) serum osteocalcin. Of these, WBC

count is used as a general marker of global estrogen effects on tissues and is the most foundational. Through the use of the genital ratio or its variation, the corrected genital ratio (see "Indirect Indexes"), WBC count can be used to evaluate the structural, functional, and adaptive role of estrogens in the body.

Neutrophils

Neutrophils are a type of leukocyte that arise from granulocytes in the bone marrow. While the total leukocyte count (WBC count) reflects global tissue effects of estrogens, we hypothesize that neutrophils can be used to assess particular aspects of estrogen activity, namely immune regulation and anabolism of tissue.

The Direct role of neutrophils is to participate in the immunologic response of the organism to aggressors. This can occur through inflammation[71] or phagocytosis of microbes and cellular debris.[72] Neutrophilia, absolute or relative, is associated with the anabolism of tissue, such as during pregnancy,[71] wound healing,[73] autoimmune disease,[74-76] and cancer.[77-81] Estrogens are associated with these same events: preeclampsia,[71] autoimmune diseases,[82] and cancer,[60] as well as wound healing.[83-88] The majority of patients suffering from autoimmune disease are women, which implies a role for estrogens in the etiology of these disorders. New-onset autoimmune disease is frequently diagnosed in the peripartum period, and flare-ups of existing disease often occur during pregnancy as estrogen levels increase up to 100-fold from nonpregnant levels.[89,90]

Neutrophils ordinarily exhibit a short half-life of 3 to 6 hours, requiring a constant production by bone marrow to maintain normal circulating levels. Estrogens affect neutrophil populations in two ways. They increase the total production of neutrophils in bone marrow,[91] and they inhibit apoptosis of circulating neutrophils, which increases the relative percentage of neutrophils in the total leukocyte differential, even when the leukocyte count is within normal limits, ie, in noninfectious states.[92] Estrogens manage the production and maintenance of neutrophils; thus, estrogens manage a particular aspect of immunity related to inflammation, host-defense, autoimmunity, and cancer. Therefore, neutrophils may be considered as a biomarker of the role of estrogens in immunologic, inflammatory, and anabolic activity within the body.

Monocytes

Monocytes are WBCs derived from monoblasts in the bone marrow. They play an important role in the immune system, combating foreign organisms in the blood through phagocytosis and the release of proinflammatory cytokines. After 24 to 72 hours of circulation, they migrate into extravascular tissue where they differentiate into macrophages or dendritic cells (histocytes).

Typically, monocytes represent 3% to 8% of the total leukocyte population. Follicle-stimulating hormone (FSH) stimulates estrogen production and estrogens suppress monocyte production.[93] During adaptation, as FSH and estrogen levels rise, monocyte levels should fall, indicating an anabolic response commensurate to the initial anti-anabolic activity of cortisol. The lower the monocyte count, the greater the influence of FSH and estrogen on the adaptation response, but this needs to be evaluated relative to the eosinophil count, which reflects the role of adrenocorticotropic hormone (ACTH) on adrenal stimulation, as well as other factors.

Conversely, monocytosis is inversely related to the relative efficiency of FSH in stimulating estrogen production. In menopause, monocytosis is observed.[94] Monocytosis also reflects a relative or absolute insufficiency of estrogen's activity during adaptation[95] and is associated with increased risk of mortality in multiple diseases marked by dysregulation of the immune system such as lupus,[96] autism,[97] asthma,[98] sepsis,[99] atherosclerosis,[100] myocardial infarction,[101] myeloproliferative disorders, and leukemia.[102-107] Thus, monocytosis implicates a terrain that is more favorable to inflammation and altered immune states: in other words, a terrain of dysadaptation of estrogen activity.

As the bioavailability of estrogens and androgens are inversely related to each other due to the activity sex hormone binding globulin,[108] and as monocytosis reflects a relative insufficiency of estrogens during adaptation, monocytosis also reflects a more predominant peripheral androgen activity relative to that of estrogens.[109]

Eosinophils

Eosinophils are a subpopulation of white blood cells. Fundamentally, the role of the eosinophil is to serve as an indirect method of adaptation and congestion when the adrenal cortical response is not sufficiently adapted to the needs of the organism.

While estrogens, as noted above, have a general effect on the proliferation of all leukocytes within the bone marrow, it is ACTH and cortisol that affect the circulating levels of eosinophils. The degree and intensity of ACTH activity on the adrenal cortex is proportional to the level of circulating eosinophils. Thus, the greater the ACTH solicitation of adrenal activity is, the greater the rise in eosinophils.[110,111] Eosinophilia, relative or absolute, is proportional to the degree of adrenal insufficiency, which is proportional to the demand for ACTH and inversely proportional to the efficiency of cortisol.[112,113]

On the other hand, cortisol is inversely related to the eosinophil count because it reduces circulating eosinophils in three ways: (1) suppression of eosinophil maturation, recruitment, and survival[114]; (2) sequestration of mature eosinophils in lymphoid organs[115]; and (3) stimulation of eosinophil apoptosis through transcriptional up-regulation.[116] The greater the degree of circulating cortisol, the lower the eosinophil count. The lower the circulating cortisol activity, the higher the eosinophil count.

While eosinophils cannot replace the complex roles that cortisol plays in the body, they can compensate in

part for some of the adaptive functions of cortisol with respect to immune modulation. Eosinophils have direct antimicrobial effects through the production of RNase enzymes[117-126] and the generation of reactive oxygen species and are immunomodulatory through antigen presentation to T-cells.[127-133] Indirectly, they are an indirect source of histamine, which modulates the immune system.[134,135]

In summary, eosinophil count is used in the biology of functions to assess the intensity of the ACTH solicitation of adrenal activity (positively correlated) and the relative efficiency of cortisol activity (inversely correlated). The less efficient the adaptation response is, the lower the circulating cortisol levels, the greater the role of ACTH in re-stimulating the adrenal cortex, and the higher the circulating eosinophil count will be. Eosinophils also contribute to the evaluation of inflammation, thrombosis, and immune and other activities.

Basophils

Basophils are the least populous of all white cells. Basophils have been likened to circulating mast cells and play a role in the innate immune response, particularly against allergens[136] and parasites.[137] Basophils share similar receptors to eosinophils, such as eotaxin, and may serve as a tertiary method of adapting the adrenal response to aggressors in the face of inadequate cortisol response and insufficient eosinophil response. They are found in high concentration in the circulation and extracellular (EC) spaces of the skin and lungs in patients with atopic disease.[138] The percent basophil count on differential is used in only one index in the biology of functions but indirectly in all indexes in which the total WBC count is used.

Lymphocytes

Lymphocytes are a subset of leukocytes that are the direct mediators of immunity. The lymphocyte count is the sum of all three subsets of lymphocytes: natural killer (NK), T, and B cells. NK cells are part of the innate immune system. They survey and directly attack viruses and tumors. T and B cells comprise the adaptive immune system. T cells manage cell-mediated immunity through the secretion of cytokines and regulate the activity of other immune cells and lyse cells infected by viruses. T cells also play a role in immunoregulation. B cells form antibodies specific to a unique aggressor and retain a memory of the aggressor in case of future aggression. Lymphocytes play a role in cancer surveillance, immunity, and autoimmunity. The concentration of total circulating lymphocytes can be related to three factors: cortisol, estrogen, and TSH.

Cortisol is inversely related to lymphocyte counts. It reduces the circulating concentration of all three subtypes of lymphocytes and augments destruction of lymphocytes.[139-142]

Estrogens are also inversely related to lymphocytes. There are several lines of evidence and clinical observations related to this. Estrogens directly inhibit the proliferation of lymphocytes.[143] In high-estrogen states, such as pregnancy, there is a relative suppression of lymphocyte proliferation in order to reduce immune attack by the mother against the fetus.[52] Autoimmune disorders occur disproportionally in females who tend to have higher levels of estrogen activity and estrogen variability.[144] There is an additional risk of developing autoimmune disease in the peripartum state when there is a terrain of hyperestrogenism and thyroid over-stimulation.[145,146] Estrogens augment the infiltration of lymphocytes into various tissues, reducing the level of circulating lymphocytes.[144]

The relationship between serum TSH and peripheral lymphocytes is positively correlated to the metabolic needs of the body and the degree to which TSH is used to modulate thyroid activity.[147,148] When the lymphocyte counts are elevated, serum TSH levels tend also to be elevated, and the body tends to be in a state of increased need of thyroid activity. For example, in subclinical hypothyroidism, there is an increased appeal to TSH to stimulate the thyroid. These patients have lymphocyte counts that are elevated relative to euthyroid patients and/or in an absolute sense. When the body's demand for thyroid hormones have been met by exogenous administration of thyroxine, lymphocyte counts reduce from their pre-intervention levels.[149]

In disorders of thyroid overactivity, such as Grave's disease or autoimmunity, there is diminished appeal by the thyroid to TSH for stimulation. One does find diminished peripheral blood lymphocytes in these patients, though not consistently.[150] As we will demonstrate later in this article, other assessments of thyroid function (see the sections on lactate dehydrogenase and creatine phosphokinase) help further contextualize thyroid efficiency.

In summary, lymphocytes are inversely related to the degree of cortisol and estrogen activity in adaptation and tissue anabolism. The greater the degree of cortisol expression and/or the greater the predominance of estrogen activity, the lower the lymphocyte levels. Lymphocytes are directly related to the degree of appeal to TSH to regulate thyroid function. The higher the lymphocyte count, the greater the appeal to TSH is and often the greater the degree of thyroid insufficiency. Conversely, the lower the lymphocyte count, the more successful TSH has been in modulating thyroid activity regardless of the serum TSH level.

Platelets

Platelets are circulating blood cells that arise from megakaryocytes in the bone marrow. Platelets have four direct functions in the body: hemostasis, repair and growth of connective tissues, transport of various factors, and modulation of inflammation. The hemostatic function of platelets has been observed for more than 120 years and is well characterized.[151] Platelets secrete numerous growth factors for the regeneration of connective tissue once hemostasis has been achieved, including platelet-derived growth factor, insulin-like growth factor

1, fibroblast growth factor, and others.[152,153]

In general, platelets are adsorbers of numerous factors in the blood, such as clotting factors and calcium, which allows them to participate in immediate hemostatic activity.[154] In addition, platelets serve as the direct transporter of serotonin from the enteric cells where they are produced. Serotonin aids in intestinal motility and carbohydrate absorption.[155] Serotonin also plays constitutive roles in the regulation of bone density.[1,156-158] Thus, platelets contribute to these physiologic activities as a serotonin transporter.

Platelets participate in proinflammatory activity, adapting innate and adaptive immune mechanisms through the expression of chemokines and cytokines and receptor-receptor interaction with leukocytes.[159] Platelets also contain histamine, which is secreted before aggregation occurs.[160]

In the biology of functions, after the total WBC and RBC count, platelets are the most important biomarker derived from the bone marrow. Through the starter index (discussed below), they are used to correct the genital ratio (RBC:WBC) in order to evaluate the role of genital hormones during adaptation. The genital ratio corrected is used in more than 50% of the indexes of the biology of functions. Platelets, along with other factors, are used to assess histamine activity, risk of thrombosis, thromboembolic phenomena, adrenaline activity, and peripheral serotonin activity.

Hemoglobin

Hemoglobin (Hg) is a metalloprotein found within RBCs. Each red blood cell contains four Hg subunits with an iron molecule in the center of each Hg subunit. The direct role of Hg is to bind and deliver oxygen from the lungs to the tissues and bind and deliver carbon dioxide from the tissues back to the lungs. Thus, Hg plays a role in acid-base balance as well as oxygen delivery.

Hg is an important determinant of the oxygen content of arterial blood, based on the equation of the calculation of arterial oxygen content (C_A):

C_A = [Hg (g/dL) × 1.34 × arterial saturation of blood (percent)] + [0.0032 × partial pressure of oxygen (torr)]

For a given saturation of blood and rate of consumption of oxygen, the lower the hemoglobin content is, the lower the oxygen content will be. Thus, the more the cardiac output must increase in order to maintain an equivalent rate of oxygen delivery. This can be expressed in the following equation, based on a rearrangement of the Fick equation:

$Q = (VO_2/(C_A - C_V)) * 100,$

where Q = cardiac output, VO_2 = oxygen consumption, C_A = arterial oxygen content, and C_V = venous oxygen content.

In vivo and clinical studies demonstrate that in both children and adults, iron-deficiency anemia up-regulates alpha-sympathetic activity regardless of the origin of the anemia (genetic, hemorrhagic, renal, acute or chronic) resulting in cardiovascular diseases such as cardiac remodeling and coronary ischemia.[161-166] Anemia appears to alter the normal adaptive response to stressors, resulting in overadaptation.[167]

Based on these observations, we hypothesize that Hg can be viewed as a marker of the degree of alpha-sympathetic activity in adaptation. Because the general adaptation syndrome is initiated by alpha-sympathetic discharge (ie, noradrenaline), Hg comes to play an important and pervasive role in the biology of functions.

Bone Stroma-derived Enzymes

Two key stroma-derived enzymes are osteocalcin and alkaline phosphatase bone isoenzyme. In addition to their bone-related activity, they have direct effects on non-bone metabolic activity. These biomarkers in particular and the skeletal system in general inform the central nervous system of the state of the internal milieu, helping it modulate basal and adaptive capacities to meet the needs of the organism.[1-3]

Osteocalcin. Osteocalcin is a noncollagenous protein. Within the skeletal metabolism, it plays an important role in osteoblasty, fixing ionized calcium to hydroxyapatite crystals. In its nonskeletal role, osteocalcin plays a key role in global energy regulation and adaptation in at least three ways:

1. **Glucose regulation:** It improves the production and secretion of and cellular sensitivity to insulin, as well as the rate of glucose metabolism.[2,3,168-170]
2. **Fat regulation:** It increases the metabolism of adipocytes.[2,3,170]
3. **Adenosine triphosphate (ATP) production:** It augments the number and efficiency of mitochondria both in part from its role in glucose regulation and independent of this role.[2]

Serum osteocalcin measures the inactive carboxylated form. When osteocalcin is decarboxylated to its active form, it enters the tissues. The less active osteocalcin is, the higher the serum levels. The more active a role it plays in global metabolism, the lower the serum level.

Osteocalcin regulates and is subject to regulation by various anabolic hormones. Serum osteocalcin is inversely related to insulin-like growth factors (IGFs)[171] and estrogen activity. Estrogens stimulate osteoblasts to fix calcium, which requires active, carboxylated osteocalcin, which results in a decrease in serum decarboxylated osteocalcin.[172-174] TSH levels vary inversely with serum osteocalcin levels.[175-177] Serum osteocalcin is directly correlated with tumor growth in both hormone independent and hormone-dependent tumors.[178,179] The wide-ranging impact of osteocalcin on the structure (bones) and function (metabolism) of the body cannot be overstated, thus its key role in the biology of functions, where it is involved in over 60% of the indexes.

Alkaline Phosphatase Bone Isoenzyme (APBi). Alkaline phosphatases are hydrolytic enzymes that work in an alkaline environment. They hydrolyze phosphates to be (re)used in the formation of proteins and nucleotides and in the mineralization of bone. Though present in all tissues, they are concentrated in the liver and bile ducts, bone, intestine, and placenta, for which isoenzymes have been identified.[180]

APBi is present in the plasma membrane of osteoblasts. It is an indicator of bone mineralization[181] and bone turnover. APBi is influenced by thyrotropic hormones in managing bone density.[176] APBi is inversely associated with the efficiency of IGFs,[182,183] but the strength of this association depends on other factors as well. APBi's relationship to IGFs implies a relationship between serum APBi and all the activities in which the IGF family plays a role, such as energy production through regulation of glucose entry into the cell, membrane permeability, free radical production, ATP production, inflammation, etc. APBi is also an indicator of dysregulated growth and is associated with acute lymphocytic leukemia, Paget's disease, and metastasis of cancer to the bone.[180]

Systemic Enzymes

Creatine Phosphokinase. Creatine phosphokinase (CPK) is an enzyme that manages the ultra-acute energy needs of the body. It manages the homeostatic state between ATP and adenosine diphosphate (ADP) and the reservoir of phosphate between creatine and phosphocreatine. Based on computer modeling paradigms and in vitro experiments, phosphocreatine, not ATP, carries the majority of energy produced by oxidative phosphorylation out of the mitochondria into the cytoplasm.[184]

When the cell has sufficient ATP, it donates a phosphate to creatine, creating phosphocreatine and ADP. Phosphocreatine is a stable reservoir of phosphate. When the cell needs an immediate augmentation of ATP, phosphocreatine donates a phosphate to ADP, which then becomes ATP. During periods of sudden increases in metabolic demand throughout the body[185] and in tissues with chronically elevated energy requirements, there is increased demand for CPK to transfer phosphate from ADP back to ATP. This allows for instantaneous availability of energy without de novo ATP production.[184] The enzyme CPK catalyzes both reactions (Figure 1).

Skeletal and cardiac muscles contain the greatest concentration of CPK as they have the greatest needs for ultra-acute adaptation of energy. In general, when there is insufficient response to a metabolic demand, cells die, either by apoptosis or necrosis,[186] resulting in either case in elevated amounts of CPK in the serum. This is classically observed during exercise[187] and rhabdomyolysis.[188] Thus, serum CPK is proportional to the rate of muscle turnover and the metabolic role of androgens (which anabolise muscle) but not in a strictly linear way nor as the sole determinant of these functions.[189]

Elevated CPK levels in the serum are also associated with myocardial infarction[190] but lack sensitivity and specificity as a sole biomarker of acute myocardial infarction.[191] Biomarkers such as total white count, total neutrophil count, and platelets increase the sensitivity of the diagnosis and risk of mortality, which is consistent with the endobiogenic posit that multiple biomarkers are required to accurately assess complex physiologic events.[192,193]

CPK levels correlate with the degree of ATP flux due to insufficiency of oxidative phosphorylation, ie, mitochondrial strain but again, not in a strictly linear way. As a method of assessing oxidative deficiencies, serum CPK levels alone are neither necessary nor sufficient, but one of many associated factors,[186] as is evidenced in cases of chronic fatigue syndrome where patients have normal cytochrome enzyme activity.[194] Subclinical thyroid dysfunction (SCTD) has been associated with elevated morbidity and mortality in diabetes and cardiovascular disease, both of which are disorders of deranged redox states.[195-197]

CPK is inversely related to thyroid metabolic activity[198,199] and may be elevated in hypothyroidism and SCTD. CPK has been shown to be inversely related to free T3 and free T4 levels in both the diagnosis and treatment of hypothyroidism.[200,201] However, in any particular patient, the correlation is not linear, which supports the endobiogenic theory that quantitative expression of thyroid hormones is neither sufficiently precise nor reliable to determine the actual metabolic impact of thyroid hormones on cellular metabolism.

Lactate dehydrogenase. Lactate dehydrogenase (LDH) is an enzyme that catalyzes the inter-conversion of pyruvate and lactate (Figure 2). Aerobic respiration, using glucose as a substrate, is the most efficient manner
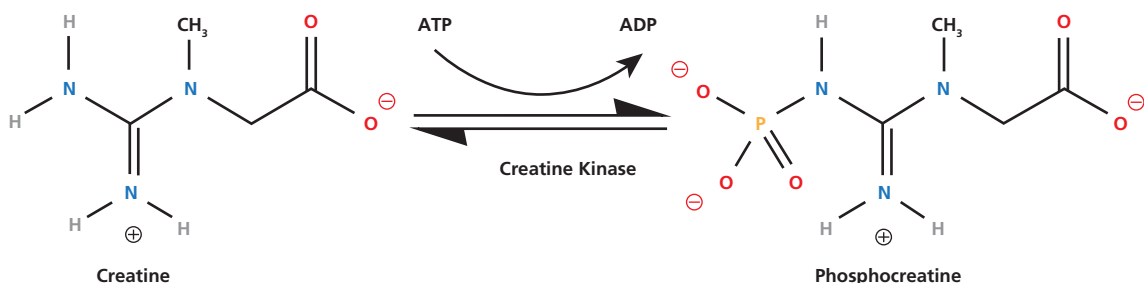

Figure 1 Interconversion of adenosine diphosphate (ADP) and adenosine triphosphate (ATP).

of ATP production in the cells. The preferential pathway in the cell is to metabolize glycogen to glucose to pyruvate. Pyruvate is then converted to acetyl-CoA, which enters the Krebs cycle. When there is an insufficiency of coenzymes in the Krebs cycle and/or oxidative stress, LDH activity increases in order to convert pyruvate to lactate. Lactate generates ATP by anaerobic metabolism but at a much lower yield than is attained with aerobic metabolism of glucose. LDH also converts lactate back into pyruvate to produce glycogen as energy storage for future use.

LDH is contained in large amounts in the liver (the direct storage site of glycogen), as well as cardiac muscle (a major consumer of glucose) and in certain tissues and red blood cells but is found in the serum at low levels. An elevation of LDH in the serum represents a state of impaired oxidation of glucose relative to the demands of the organism, as seen in cardiac ischemia,[202,203] muscle turnover,[186] rapid cell and tissue growth,[204] hemolysis,[205,206] and cancer.[207-209]
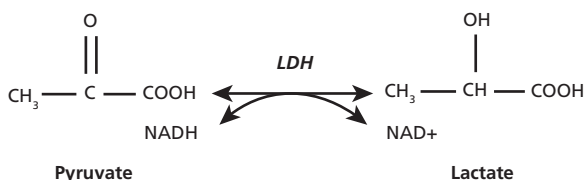

Figure 2 Lactate dehydrogenase (LDH) conversion of pyruvate and lactate.

Endocrine

Thyroid-stimulating hormone. TSH is a glycoprotein created in and secreted from the anterior pituitary gland. In clinical medicine, it is considered strictly within its intrathyroid activity of stimulation of thyroxine (T4) and triiodothyronine (T3), ie, merely as a barometer of thyroid function. Based on more current studies and the endiobiogenic theory of terrain, serum TSH levels have key intra- and extrathyroid implications that should also be considered if the clinical significance of a serum TSH level is to be properly contextualized.

Euthyroidism is defined as normal thyroid function that occurs with normal serum levels of TSH and T4. It has been assumed that TSH and serum levels of T4 have an inverse linear relationship based on classic feedback loops and that this relationship is a reliable indicator of the sufficiency of thyrotropic regulation of metabolism.

There are a sufficient number of anomalies to this assumption that raise questions about its validity. For example, euthyroid sick syndrome is defined as a clinical condition with normal thyroid function with a normal TSH levels but low serum T4 and T3. Subclinical hypothyroidism is a condition in which there is a functional hypothyroid state based on an elevated serum TSH but a normal serum T4. Subclinical hyperthyroidism is a functional hyperthyroid state based on a serum TSH value below the normal limit but normal T4. Finally, patients with normal serum levels of TSH, T4, and T3 may present with symptoms consistent with

hypo- or hyperthyroidism. See the section on creatine phosphokinase for a further discussion of the functional evaluation of thyroid metabolic activity.

More recent studies demonstrate that serum TSH lacks a log-linear relationship to thyroid output of free T4 (fT4) and free T3 (fT3) (Figure 3). In their evaluation of 3223 untreated patients referred for thyroid testing, Hoermann et al found poor correlation ($R_2 = 0.236$) between TSH and fT4. For example, a serum TSH of 1.0 mU/L (normal 0.4-4.1 mU/L) was associated with a fT4 anywhere between 4pmol/L and 28 pmol/L (normal 9.5-25 pmol/L). Conversely, a free T4 of 14.5 pmol/L was associated with TSH between 0.1 mU/L and 100 mU/L.[148]

In our opinion, the serum level of TSH only reflects the responsiveness of the thyroid to stimulation without determining the final degree of metabolic efficiency of T4 or T3 or the degree to which thyroid catabolic activity has been adapted to anabolic demands from estrogen.

TSH has a number of extrathyroid relationships and functions independent of T4 or T3. TSH receptors are found in divergent tissues throughout the body.[210] TSH activity is augmented by estrogen.[212-214] TSH is
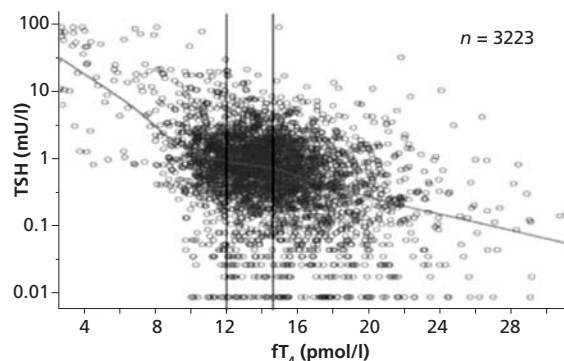

Figure 3 Thyroid-stimulating hormone (TSH) relationship to thyroxine (T4).

Regression analysis of fT4 vs log TSH. Fitting data set 1 with the use of SPSS and cut-off values estimated from Figure 1 indicated three distinct regression lines, which were significantly different from each other and described by the following equations: a (fT4<12): TSH=−0.13×fT4+1.46; b (12≤fT4≥15): TSH=−0.06×fT4+0.05; c (fT4>15): TSH=−0.07×fT4+0.89; a vs b: P<.0001; b vs c: P=.0002; and a vs c: P=.0001.

From Hoermann R, Eckl W, Hoermann C, Larisch R. Complex relationship between free thyroxine and TSH in the regulation of thyroid function. Eur J Endocrinol. Jun 2010;162(6):1123-1129. Reprinted with permission.

suppressed by somatostatin.[211] TSH helps regulate bone density as well.[175,176]

In summary, in the theory of endobiogeny, serum TSH is used to evaluate intra- and extrathyroid activity. Serum TSH is not a sufficient indicator of the efficiency of thyroid regulation of metabolism but can help contextualize thyroid function relative to the demands of the body.

Electrolytes. Potassium and calcium are the only two electrolytes used in the biology of functions.

Potassium. Potassium is the direct IC ion in the body and serves to maintain the resting membrane potential. IC levels are around 140 mmol/L and EC

levels, 4 mmol/L. It is not the quantitative concentration per se but the ratio of IC to EC potassium (35:1) that maintains the resting membrane potential and neuromuscular stability. Serum potassium levels are regulated closely. A quantitative increase of 1 mmol/L can have a significant impact on neuromuscular activity.[215]

One source of EC potassium augmentation is glutamate. The most prominent neurotransmitter in the brain, glutamate is involved in neural plasticity and augments neuronal excitability.[216] The egress of potassium from the cell changes the resting membrane potential, allowing for neurons to be more excitable.

Calcium. While potassium is the element of membrane and cell stability, calcium is the element of action, movement, and variability. Calcium is the most predominant element in the human body because of its role in skeletal formation. Of total body calcium, 99% is in bones and 1% is bioavailable. Of the 1% that is bio-available, 99.99999% is in the EC space, maintaining an EC:IC ratio of 12000:1. Calcium reserves are extremely important to ensuring the proper adaptability of the organism during aggression and programmed changes. Approximately 50% of serum calcium is ionized and bioavailable, and 50% is bound to proteins remaining in reserve. While cytoplasmic calcium levels are kept low, the mitochondrion and endoplasmic reticulum store calcium and make it available to calibrate cell function.

Within the blood, calcium is the essential cofactor in the coagulation cascade. Within the interstitium, it is essential as a second messenger in muscle contraction. Calcium augments the rate of neuronal signal transduction and neurotransmitter secretion through up-regulation of vesicle fusion. Within the IC space, calcium serves as a key signal transducer.

In summary, both potassium and calcium concentrations are finely regulated at the extra- and intracellular levels. Potassium is the direct IC element and maintains membrane stability. Calcium is a key element of adaptation and stimulates excitation, movement, and activity, both extra- and intracellularly. These two elements have opposing actions and overlapping factors that increase or diminish their serum concentration. Our interest in these elements with respect to the biology of functions is how they regulate or are regulated by the adaptation response.

THE DIRECT INDEXES
Direct Indexes Using Red and White Blood Cells
Definition of a Direct Index. A direct index is an index that is a direct multiplication (product) or ratio (division) of biomarkers measured in the blood. The direct indexes are the basis of all the indirect indexes, which are indexes of indexes, direct or indirect in nature. As the direct indexes form the foundation of the indirect ones, the genital ratio (RBC/WBC) is the starting point of the direct indexes.

The Case for Ratios. We believe that when the total RBC count is evaluated relative to other factors, a more nuanced appreciation of androgens in the body can be obtained. Androgens and estrogens have counter-balancing roles. The quantity and quality of action as well as the chronology of action is important with respect to various disorders. Furthermore, the bioavailability of estrogens and androgens is inversely related to each other due to the role of sex hormone binding globulin.[108,217] Quantitative levels can be high, low, or normal, but as circulating androgens increase, the relative proportion of bioavailable estrogens decline due to an increase in sex hormone binding globulin (SHBG), which increases its binding capacity of estrogens. The opposite is true when bioavailable estrogen levels increase in the body. Thus, in the biology of functions, WBC count is also used to evaluate (through an inverse relationship) the relative rate of production and efficacy of androgens.[217]

When evaluating the risk of cardiovascular events, if there is absolute androgen predominance but estrogens are also elevated, the patient may benefit from a quantitative reduction of androgens and estrogens. If there is androgen predominance but quantitative levels are low, the patient may benefit from an increase in testosterone and estrogen, as a number of large clinical trials have suggested. Regardless of the condition, by evaluating the qualitative and quantitative relationship of gonadic hormones, the biology of functions provides guidance as to which clinical intervention may be most beneficial.

In summary, three observations create compelling arguments for reconsidering how androgens are evaluated. The first is the contradictory nature of clinical trials with respect to quantitative androgen levels and risk of disease. The second is the multifactorial nature of disease, requiring that androgen activity be evaluated relative to other factors. Finally, the nongenomic effects of androgens may play a larger role in health and disease than previously appreciated, and these effects cannot be reliably predicted by quantitative measurements.

Direct Index Using Red Blood Cells and Total White Blood Cell Count to Evaluate Androgen and Estrogen Activity
The genital ratio expresses the level of activity of tissue androgens relative to tissue estrogens:

= RBC/WBC

Direct Index Using Neutrophils and Lymphocytes
Genito-thyroid Index. The genito-thyroid index expresses the relative activity of the gonads in relationship to that of the thyroid. When elevated, it reflects an efficient thyroid activity. When low, it reflects an augmentation of TSH demand on the thyroid, regardless of absolute thyroid glandular activity.

= neutrophils/lymphocytes

Neutrophils are a biomarker of the direct role of estrogens in immunologic, inflammatory, and anabolic activity within the body.

Lymphocyte levels are inversely related to the degree of estrogen activity in adaptation and tissue anabolism. Lymphocyte levels are directly related to the degree of appeal to TSH to regulate thyroid function. The higher the lymphocyte count, the greater the appeal to TSH is and often the greater the degree of thyroid insufficiency. Conversely, the lower the lymphocyte count, the more successful TSH has been in modulating thyroid activity regardless of the serum TSH level.

Direct Index Using Monocytes and Eosinophils

Adaptation Ratio. The adaptation ratio reflects the relative activity of ACTH on cortisol in relationship to FSH's activity on estrogen during the adaptation response. When the adaptation ratio is elevated, FSH activity is effectively predominant. When the adaptation ratio is low, ACTH activity is predominant.

= eosinophils/monocytes

Eosinophil count is used in the biology of functions to assess the relative strength of ACTH stimulation on the adrenals (positively correlated) and the relative efficiency of cortisol activity (inversely correlated). Eosinophilia, relative or absolute, is proportional to the degree of adrenal insufficiency in the adaptation response.

FSH stimulates estrogen production and estrogen suppresses monocyte production. The lower the monocyte count, the greater the influence of FSH and estrogen is on the adaptation response. Conversely, monocytosis reflects a relative or absolute insufficiency of estrogen's activity during adaptation.

Direct Index Using Platelets

Platelet Mobilization. The platelet mobilization index expresses the adaptive liberating capacity of platelets sequestered in splanchnic vs splenic reservoirs. When the platelet mobilization index is elevated, the effects of adrenaline are augmented and favor splanchnic demargination, as the splanchnic vasculature has a greater surface area and platelet capacity than the spleen. When it is low, it reflects a relative insufficiency of adrenaline activity in adaptation.

= platelets/6o(RBC)

Of the total mature platelets, some are kept in reserve along the margins of the peripheral vasculature and some in the splenic sinusoids. Because of the role of platelets in serotonin transport and secretion and the role of serotonin in gastrointestinal motility and digestion, platelets are particularly concentrated in the splanchnic vasculature. During times of adaptation, adrenaline liberates—ie, demarginates—platelets in order to achieve an immediate augmentation of plate-

let activity without waiting for megakaryocytes to mature.[207-211,215,217,218]

RBCs are in the denominator of the index for a number of reasons. RBCs, independently of adrenaline, mobilize and activate platelets, stimulating the thrombosis process.[219] In vitro studies suggest adrenaline's activation of platelets (as opposed to its mobilization) may be mediated in part by increasing the metabolic rate of RBCs, which allows them to increase the activation of platelets.[218] Thus, RBCs are in the denominator because they are an activator of platelet activity but not the direct mobilizer. The greater the effects of adrenaline, the more diminished the role of RBCs are as an aid in the aggregation process.

Conversely, in anemia, the lower the hematocrit (RBC ÷ whole blood volume), the greater the compensatory rise in platelets must be in order to maintain a normal rate of thrombosis. The greater the anemia, the greater the cardiac output to compensate for the diminished oxygen-carrying capacity.[219]

Direct Indexes Using Osteocalcin, Alkaline Phosphatase Bone Isoenzyme, Thyroid-stimulating Hormone

Growth Indexes. In these indexes, osteocalcin is in the denominator to reflect the inverse relationship between inactive serum osteocalcin and growth. Because alkaline phophatase bone isoenzyme is associated with growth, it is used in the numerator of indexes evaluating growth and in the denominator of anti-growth indexes. This is in contrast to serum osteocalcin, which has an inverse correlation to growth, hence its role in the denominator.

Estrogen Index. It expresses the endocrino-metabolic activity of estrogens, ie, both the genomic activity of estrogens and the non-genomic metabolic activity within the cells.

= TSH/osteocalcin

TSH levels vary inversely with serum osteocalcin levels.[175-177] Together, they reflect the endocrino-metabolic activity of estrogens.

Estrogen activity is directly correlated to the serum level of TSH.[212,220-222] Estrogens relaunch TSH so that the catabolic activity of thyroid hormones matches the anabolic activity of estrogens.[212,223] The greater the estrogen demand and the less responsive the thyroid, the greater the serum TSH level rises, hence the role of TSH in the numerator of the index.

Estrogens increase the conversion of osteocalcin to its active form to increase bone density; thus, serum osteocalcin levels are inversely related to estrogen activity, hence the role of osteocalcin in the denominator.[172-174]

Growth Index. The growth index expresses the metabolic activity of growth hormone.

= alkaline phosphatase bone isoenzyme (APBi)/osteocalcin

Chronic growth hormone activity increases APBI and reduces serum osteocalcin.[182]

Turnover Index. The turnover index expresses the speed of renewal of tissue; its elevation implies a slowing down of this renewal; conversely, its reduction signifies the acceleration of tissue renewal.

$$= TSH \times APBi$$

Direct Index Using Creatine Phosphokinase and Lactate Dehydrogenase

Thyroid Index. The thyroid index expresses the metabolic activity of the thyroid at the cellular level.

$$= LDH/CPK$$

When assessing the impact of altered creatine phosphokinase (CPK) levels on cellular metabolism, it is important to relate it to the efficiency of long-term energy production, which is reflected in the serum level of LDH. LDH participates in the conversion of glycogen to glucose for de novo production of ATP. When cells cannot keep up with chronic metabolic needs and necrose, the level of LDH rises in the blood. Thus, LDH can be viewed as a marker of chronic metabolic strain.

A person with normal serum levels of LDH and CPK can be, functionally speaking, in one of three states: a relative state of balance between chronic and acute energy management (normal ratio of LDH to CPK); a relative state of metabolic insufficiency (relatively low LDH, relatively elevated CPK); or a relative state of metabolic excess (relatively high LDH, relatively low CPK).

For example, in hypothyroidism, both LDH and CPK levels are elevated compared to normal controls, but the more severe the thyroid disease, the greater the rise in CPK relative to LDH.[224] Conversely, in hyperthyroid states, the ratio of LDH to CPK is increased, but the greater the degree of hyperthyroidism, the larger the ratio becomes (Table 2).

It is interesting to note that in the study by McGrowder et al, the difference in LDH between subclinical and overt hypothyroidism was not found to be statistically significant but the difference in CPK was. The significance of the difference is seen only in evaluating the ratio of LDH to CPK, which decreased by 57% between the subclinical and overt hypothyroid states. [224]

Other studies have shown more dramatic differences in the ratio of LDH to CPK. For example, Burnett et al found LDH levels to be elevated two times above the normal serum values but found CPK levels to be 10 to 15 times above the norm, reflecting from the endobiogenic perspective a greater insufficiency of acute vs chronic metabolic activity.[198] Again, in stable coronary artery disease, LDH levels are elevated to a greater degree than CPK.[203]

During metastasis of cancer, both LDH and CPK

Table 2 Ratio of LDH to CPK in Various Thyroid States

Condition	LDH	CPK	Ratio
Hyperthyroidism	233.80	88.37	2.65
Subclinical hyperthyroidism	227.81	105.98	2.15
Normal controls	202.85	102.19	1.99
Subclinical hypothyroidism	340.38	179.8	1.89
Hypothyroidism	421.00	389.90	1.08

Abbreviations: CPK, creatine phosphokinase; LDH, lactate dehydrogenase. Adapted from McGrowder et al.[304]

can be elevated 10-fold or more, indicating a significant, supra-physiologic demand on the body. The ratio may be normal, but the actual global metabolic demand is elevated. Thus, the absolute values of both LDH and CPK need to be evaluated individually and in relationship to each other, as well as other determinants of cellular energy production.

In summary, the ratio of LDH to CPK evaluates the final functional achievement of thyroid hormones in regulating the rate of metabolic activity of the cell.

Direct Index Using Potassium and Calcium

Adaptogen Index. The adaptogen index expresses the relative level of participation of the pineal gland in the relaunching of non-circular adaptation.

$$= serum\ potassium/(serum\ calcium \times 0.5)$$

THE INDIRECT INDEXES

Direct indexes evaluate specific aspects of basic physiologic relationships, such as the genital ratio (RBC/WBC). Indirect indexes are meta-indexes composed of both direct indexes and indirect indexes—in other words, indexes of indexes. By comparing the activity of numerous factors in relationship to others simultaneously, we believe there are several potential advantages. It allows for a more sophisticated evaluation of an individual's terrain. For example, through these indirect meta-indexes, one can weigh both exacerbating and protective factors related to a disorder. By opening up the meta-index and evaluating the indexes from which it is composed, one can evaluate the particular variables most implicated in the abnormal activity. Finally, one can evaluate the cumulative effect of all variables in toto. Such an approach may allow for a more precise stratification of patients based not on clinical symptoms but on pathophysiology (See part 1 of this article for a discussion of nosology and the concept of the diseasome: Global Adv Health Med. 2013;2(1):64-78.). This, in turn, may allow for a more precise treatment to be devised based on the neuroendocrine factors most responsible for an individual's symptoms as opposed to tissue pathology of clinical symptoms alone. In summary, indirect indexes allow one to model increasingly complex aspects of metabolism based on a systems analysis approach of the terrain.

Some Indirect Indexes Using Red Blood Cells and Other Factors to Evaluate Androgens

Genital Ratio Corrected. The genital ratio corrected expresses the basic level of activity of tissue androgens relative to tissue estrogens during the phenomenon of acute adaptation.

= genital ratio × starter index
 Genital ratio=RBC/WBC
= RBC × starter index/WBC

The starter index evaluates the autonomic vs endocrine, splanchnic vs splenic pathways involved in starting the adaptation response.

Musculotrope Index. The musculotrope index expresses the relative level of endocrine and metabolic (ie, genomic and nongenomic) activity of androgen receptors according to the balance orientation of sex hormones in osteomuscular metabolism.

= genital ratio corrected × (CPK/APBi)

CPK reflects testosterone's role on muscle turnover.[189] APBi reflects the rate of bone turnover.[181] The greater the effects of androgens, the lower the rate of bone turnover, thus the lower the serum level of APBi, thus the greater the musculotropic index.[225,226]

Some Indirect Indexes Using White Blood Cells and Other Factors to Evaluate Estrogen Activity

Genital Ratio Corrected. This index expresses the basic level of activity of tissue androgens outside the phenomenon of acute adaptation.

=genital ratio × starter index

Aromatization of Adrenal Estrogens. This index expresses the relative part of aromatizing activity of adrenal cortex hormones into estrogens relative to the adrenal cortex's other activities.

=permissive cortisol index/Genital ratio corrected
 permissive cortisol index = 1/androgenic index
=1/(genital ratio corrected × androgenic index)

The formula states that the rate of aromatization of adrenal products to estrogens is inversely related to rate of production of androgens in the body. The adrenal gland produces androgens (ie, 17-ketosteroids) that can be converted to testosterone, dihydrotestosterone, or estrogens. The adrenal cortex's contributions to androgens and estrogens are inversely related to each other. The greater the rate of conversion of these products is to estrogens, the less the availability of precursors for peripheral androgen activity. Conversely, the greater the uptake of adrenal androgens by androgen-sensitive tissues, the less the availability of adrenal androgens is to be converted to estrogens.[63,227-229]

Rate of Genital Estrogen Production Index. This index expresses the level of activity of estrogens originating from the gonads.

=estrogen index/(1+aromatization of adrenal estrogens index)

The production of estrogens from the gonads and adrenals is inversely related: the greater the source of estrogens from one gland, the less the relative contribution is from the other.[55]

Some Indirect Indexes Using Neutrophils and Other Factors to Evaluate Estrogen Activity

Throughout the various indexes, estrogen activity is evaluated in relationship to adrenal activity and thyroid activity, as well as its competitive, cooperative, and additive function with respect to anabolic factors such as progesterone, androgens, and somatotropic growth factors.

Catabolism/Anabolism Ratio. The index expresses the relative activity of catabolism in relation to that of anabolism.

= genito-thyroid index/genital ratio

This index evaluates the activity of catabolism relative to anabolism from a gonado-thyroid perspective. As noted above under "direct indexes," the genito-thyroid index evaluates the harmoniousness of thyroid to estrogen activity. The corrected genital ratio evaluates the relative degree of anabolism due to androgens and estrogens during adaptation. An elevated index indicates a relative predominance of catabolic activity due to excessive thyroid activity and/or insufficient anabolic activity. Conversely, a low index indicates a relative anabolic predominance of metabolism for the opposite reasons.

Cortisol Index. This index expresses the secretory activity of cortisol from the adrenal cortex and its excretion during syndromes of adaptation.

= (catabolism/anabolism index)/adaptation index

The numerator, the catabolism/anabolism index, represents the relative response of the body to an aggression. The response to an aggression is represented in the denominator by the adaptation index (See "Direct Index Derived From Eosinophils" for a full discussion).

Proinflammatory Index. This index expresses the dysmetabolic potential of endogenous thyroid dysadaptation and its correction by cortisol. By extension, it witnesses the degree of inflammatory solicitation of the structure in its module of adaptability.
=thyroid relaunching corrected/adaptogenic index
 Thyroid relaunching corrected = genito-thyroid index/thyroid relaunching index
=(Genito-thyroid index/thyroid relaunching index)/adaptogenic index

= Genito-thyroid index/(thyroid relaunching index × adaptogenic index)

Apoptosis Index. This index expresses the general level of apoptotic activity of the organism in its entirety.

= structural expansion (of the cell) index/membrane expansion (of the cell) index

Structural expansion = anabolism × nuclear membrane activity

Anabolism = catabolism/catabolism:anabolism

= (catabolism × nuclear membrane activity)/(catabolism:anabolism × membrane expansion)

Carcinogenesis Index. This index expresses the potential level of carcinogenesis of the organism due to its nucleocytoplasmic instability relative to its insufficiency of physiologic apoptosis.

= nucleocytoplasmic pathogenicity index/apoptosis index

See apoptosis index under "Some Indirect Indexes Using Lymphocytes" for a full discussion.

Some Indirect Indexes Using Monocytes and Other Factors to Evaluate Estrogen Activity

Androgenic Index. This index expresses the relative activity of androgens originating from the gonads in relationship to those originating from the adrenal cortex.

= genital ratio corrected index/adaptation index

Adaptation = eosinophils/monocytes

= genital ratio corrected index/(eosinophils/monocytes)

= (genital ratio corrected index × monocytes)/eosinophils

As noted above, monocytes are inversely related to estrogen activity, which allows for relative androgen predominance, which is why it is in the numerator in the androgenic index.

Rate of Corticoadrenal Androgens. This formula expresses the level of activity of androgens of adrenal origin.

= total androgens/(1 + androgenic index)

Rate of Anabolism. This formula expresses the rate of anabolic activity of the body.

= catabolism index/(catabolism/anabolism index)

catabolism index = thyroid index/corticoadrenal index

corticoadrenal index = catabolism/anabolism/androgenic

androgenic = (genital ratio corrected-monocytes)/eosinophils

= [(thyroid index × androgenic)/(catabolism-anabolism]/catabolism)]/(catabolism/anabolism)

= (thyroid index × genital ratio corrected × monocytes)/[(Catabolism/Anabolism)^2 × eosinophils)]

Some Indirect Indexes Using Eosinophils and Other Factors

Eosinophil count contributes to the evaluation of various aspects of adrenal physiology, such as circulating cortisol, permissive and adaptive cortisol activity,[112,230-233] DHEA production, and adrenal androgen production.[234,235] Due to the extensive role of cortisol in human physiology, the eosinophil count contributes to the assessment of atopic disorders, various aspects of cellular metabolism such as apoptosis, necrosis, and membrane permeability, as well as histamine expression,[116,236-244] inflammation,[245] coagulation,[245] immune function, carcinogenesis, and cancer survival.[246-259] As always, the role of eosinophils needs to be evaluated relative to other factors.

Cortisol Index. This index expresses the secretory activity of cortisol from the adrenal cortex and its excretion during syndromes of adaptation.

= (catabolism/anabolism index)/adaptation index

Adaptation = eosinophils/monocytes

= (catabolism/anabolism index)/(eosinophils/monocytes)

= ([catabolism/anabolism index] × monocytes)/eosinophils

The numerator, "Catabolism/Anabolism" reflects the intensity of the response of the organism. The denominator, "Adaptation index" reflects the intensity of the aggression and the adaptative response at the level of the pituitary (see Adaptation ratio, p 43).

Evoked Histamine Index. This index expresses the circulating rate of active histamine.

= (eosinophils × platelets × adaptation index)/adrenal cortex index

adaptation index = eosinophils/monocytes

= [eosinophils × platelets × (eosinophils/monocytes)]/adrenal cortex index

= (eosinophils^2 × platelets)/(adrenal cortex index × monocytes)

adrenal cortex index = cortisol index/androgenic index

= (eosinophils^2 × platelets × androgenic)/(cortisol index × monocytes)

As noted above, eosinophils are an indirect source of histamine secretion; the greater the relative or absolute percent eosinophils, the lower the rate of circulating cortisol, the greater the rate of circulating histamine. As the formula suggests, other factors modulate the threshold of histamine production, thus eosinophilia alone is not sufficient to account for the total amount of circulating histamine. The greater the estrogen activity (low monocytes), the greater the release of histamine independent of the antihistaminic effects of cortisol.[260] Neither estrogen nor testosterone alone has been sufficient to account for histamine secretion in human models, thus suggesting that a multifactorial assessment of factors related to histamine secretion will be more accurate in assessing the histamine burden in the body.[261]

Some Indirect Indexes Using Lymphocytes and Other Factors

Catabolism-anabolism Index. This index expresses the relative part of activity of catabolism of the organism in relationship to its anabolic activity.

= genito-thyroid index/genital ratio corrected
    genito-thyroid index = neutrophils/lymphocytes
= neutrophils/(genital ratio corrected × lymphocytes)

Cortisol Index. This index expresses the secretory activity of cortisol from the adrenal cortex and its excretion at the time of the syndromes of adaptation.

= catabolism-anabolism index/adaptation index
    adaptation index = eosinophils/monocytes

The greater the degree of adaptation by ACTH (low adaptation index) and the greater the rate of catabolism relative to anabolism (elevated catabolism:anabolism index), the greater the degree of cortisol activity, which corresponds to the classic understanding of the effects of cortisol during the general adaptation syndrome of Selye.

When we open up the formula even further, we find the following relationships:

= (catabolism/anabolism index)/(eosinophils/monocytes)
= ([catabolism/anabolism index] × monocytes)/eosinophils
    catabolism/anabolism index = neutrophils/(genital ratio corrected × lymphocytes)
= (neutrophils × monocytes)/(genital ratio corrected × lymphocytes × eosinophils)

As we have noted above, the lower the lymphocyte count, the greater the cortisol activity; the lower the eosinophil count, the lower the ACTH activity in stimulating the adrenal cortex due to the efficacy of cortisol activity.

Anabolism Index. This index expresses the level of anabolic activity of the organism.

= catabolism index/(catabolism/anabolism index)
    catabolism/anabolism = neutrophils/(genital ratio corrected × lymphocytes)
= catabolism index/[(neutrophils)/(genital ratio corrected × lymphocytes)]
= (catabolism index × genital ratio corrected × lymphocytes)/neutrophils

The anabolism index evaluates the absolute rate of anabolism as a result of corticotropic, gonadotropic, and thyrotropic considerations of relative and absolute activity. (See catabolism-anabolism index under "Indirect Indexes Using Neutrophils" and the catabolism index under "Indirect Indexes Using LDH or CPK" for more information). A low rate of catabolism in and of itself does not mean that the rate of anabolism is low. Each level of activity can be elevated, low, or normal.

The anabolism index seeks to evaluate the quantitative rate of anabolisms. The catabolism index as a quantitative assessment of catabolism is in the numerator. The lower the absolute rate of catabolism, the greater the predominance of anabolism may be. However, the relative rate of catabolism to anabolism rate the greater the predominance of anabolism.

As noted above, the higher the lymphocyte levels, the less well adapted the thyroid is in its catabolic activity, thus the lower the rate of catabolism will be. The greater the genital ratio corrected, the greater the predominance of androgens relative to estrogens in adaptation, which favors the completion of anabolism.

Apoptosis Index. This index expresses the general level of apoptotic activity of the organism in its entirety.

= structural expansion index/membrane expansion index
    Structure expansion index = anabolism index × nucleo-membrane activity index
Membrane expansion = catabolism index × growth index corrected
= (Anabolism × nucleo-membrane activity index)/(catabolism index × growth index corrected)

Apoptosis was first described in 1847. For 140 years (1847-1987), the study of apoptosis was morphologic in nature. From 1988, with the discovery of bcl-2 protein, the genetic mechanisms of apoptosis have been the primary focus of study.[262] From the endobiogenic perspective, because the endocrine system manages the rate of metabolism of the cell, it mediates the life of the cell and the time of apoptosis or necrosis or lack thereof, such as with cancer cells.

The plethora of pro- and anti-apoptotic signaling factors are the means of regulating apoptosis but not the determinant of when and to what degree of intensity apoptosis occurs (or does not). The validity of such an index would allow for a global approach to managing apoptosis that is concordant with the general scheme of factors related to cancer growth and away from the endless search for "silver bullets" in pharmacotherapy—natural or synthetic—that are highly targeted with respect to specific mechanisms of apoptosis but carry the risk of potentially more serious side effects.

The numerator is composed of the anabolism index and the nucleo-membrane index. The greater the numerator, the greater the rate of apoptosis is. Cell growth occurs as a result of represents anabolism, which requires increased activity at the level of the nucleus with respect protein transcription (represented by the nucleo-membrane index). The greater the anabolic activity of the cell, the sooner it will reach the end of its programmed number of division and hence die by apoptosis, which requires a tonic inhibition of apoptosis. Thus, apoptosis is inhibited by anabolic hormones such as cortisol[263] and estrogens.[264-266]

The denominator is composed of the membrane expansion index, which is itself composed of the product

of the catabolism and the growth index corrected indexes. When there is catabolic predominance,[267,268] and/or elevated insulin-like growth factor activity,[269,270] the membrane expands.[224] A greater rate of membrane expansion relative to that of structural activity implies that more energy is devoted to cellular hyperplasia than to cellular divisions, hence the longer it takes for the cell to die due to reaching its programmed time of death.

In summary, the endocrine system is the regulator of apoptosis, while pro-apoptotic proteins are the mechanism of apoptotic cell death. From the endobiogenic perspective, an endocrine approach to the evaluation of the global physiologic rate of apoptosis allows one to evaluate the reason for apoptosis (or its insufficiency) and to pinpoint the causative factors and thus allows for a clinical plan to address these particular imbalances. In contrast, merely enumerating the number of pro- or anti-apoptosis factors active does not at this time offer a path of clinical intervention.

Some Indirect Indexes Using Platelets and Other Factors

Evoked Histamine Index. This index expresses the active circulating level of histamine.

$=$ (eosinophils $\times$ platelets $\times$ adaptation index)/adrenal cortex index

adaptation index = eosinophils/monocytes

$=$ (eosinophils $\times$ platelets $\times$ eosinophils)/(adrenal cortex $\times$ monocytes)

$=$ (eosinophils^2 $\times$ platelets)/(adrenal cortex $\times$ monocytes)

The quantitative amount of histamine in platelets is less than that found in leukocytes.[271] However, because platelets activate neutrophils and monocytes on the endothelial surface of the vasculature and due to their 25-fold numerical superiority to leukocytes, they play an amplifying role in inflammatory disorders[272] well characterized by the actions of eosinophils and basophils.[273]

This is reflected in the formula of the histamine index. The greater the numerator is, the greater the numerical value of the index and thus the greater role of pro-histaminic elements relative to antihistaminic elements. In the numerator is the product of two factors:

eosinophils^2 $\times$ platelets

The normal value of percent eosinophils is 0.1 to 7, square of the norm is 0.1^2 to 7^2, or 0.01 to 49. Conversely, the value of platelets is 100-400 (See Table 1 for conversion factor). Thus, mathematically and it is proposed biologically, the role of platelets in histamine expression is 2-fold to 10 000-fold greater than that of eosinophils, balanced of course by the relative effects of antihistaminic factors expressed in the denominator.

Thrombotic Index. This index expresses the risk of formation of a thrombus. By extension, it permits for the evaluation of the level of blood coagulability.

$=$ 0.1 $\times$ (thrombogenic index $\times$ evoked histamine index $\times$ genital ratio)

See "Precedence of Using Biomarkers in Medicine" for a full discussion of the experimental and clinical basis of the thrombotic index. Platelets are, as noted above, numerically the most significant contributor to the histamine index, which is the most significant contributor to the thrombotic index. In patients admitted for myocardial infarction, elevated platelet counts are independently associated with increased risk of mortality.[193]

Starter Index. This index expresses the relative part of hepatotropic solicitation of the splanchnic system in relation to that of splenotropic solicitation in response to all direct and indirect aggressions on the tissues. By extension, it witnesses the relative functional level of glucagon compared to that of adrenaline in the installation of the general adaptation syndrome and, consequently, of their respective thresholds of response to solicitation be it endogenous or exogenous. By extension, it witnesses the relative level of priority of the adaptive energy response: energo-metabolic compared to neuroendocrine.

$=$ leukocyte mobilization index/platelet mobilization index

Genital Ratio Corrected. See the section on androgens for a discussion.

$=$ genital ratio $\times$ starter index

genital ratio = *RBC/WBC*

starter index = leukocyte mobilization index/platelet mobilization index

$=$ (RBC $\times$ leukocyte mobilization)/(WBC $\times$ platelet mobilization)

Serotonin Index. This index expresses the level of autocoid and metabolic activity of peripheral serotonin. By extension, it allows for an evaluation of the level of neuro-metabolic activity of central serotonin (through inverse association with peripheral serotonin).

$=$ 10 (starter index)/(insulin index $\times$ insulin resistance index)

Some Indirect Indexes Using Hemoglobin

Leukocyte Mobilization Index. This index expresses the adaptive liberating capacity of leukocytes in reserve within splanchnic vs hepatic sequestration. The index features hemoglobin in the numerator (not discussed in this article).

Starter Index. See the section on platelets, above.

$=$ leukocyte mobilization/platelet mobilization

Genital Ratio Corrected. See the section on androgens for a full discussion.

= genital ratio × starter

Genital hormones are the foundation of life. The role of genital hormones in adaptation is corrected by multiplying it by the starter index, which has the leukocyte mobilization index in the numerator, which itself has hemoglobin in its numerator. The genital ratio corrected index is used in more than 50% of indexes in the biology of functions to evaluate the adaptive capacity of the organism. Thus, hemoglobin is, through these three indexes, crucial to evaluating the adaptive capacity of the organism.

Some Indirect Indexes Using Osteocalcin

Proamyloid Index. This index expresses the level of intracellular hypometabolism. By extension, it evaluates the degree of insufficiency of cellular respiration (ie, mitochondrial efficiency in production of ATP by oxidative phosphorylation). By extension, it evaluates the degree of cellular nutritional insufficiency.

= index of reduction × insulin resistance index

The greater the rate of reductive capacity, the less the relative potential of oxidation will be of carbohydrates or fats.[274] The greater the degree of insulin resistance, the less glucose is available for oxidation.[275] Thus, the pro-amyloid index evaluates the degree of cellular nutritional insufficiency (insulin resistance) and insufficiency of material for cellular respiration (index of reduction). It is called the pro-amyloid index because the greater the degree of mitochondrial insufficiency, the more likely the organism will be to rely on proteins such as amyloid proteins as an alternate form of energy.[276]

Anti-growth Indexes

In these indexes, osteocalcin is in the numerator to reflect the relationship between inactive serum osteocalcin and anti-growth activity.

Anti-growth Index. This index expresses the global level of activity of the ensemble of antigrowth factors. (See the section on TSH for a full discussion.)

= 1/growth index corrected
    growth index corrected = growth index/turnover
    growth index = APBi/osteocalcin
    turnover = APBi × TSH
= (APBi/osteocalcin)/(APBi × TSH)
= osteocalcin × TSH

Osteocalcin is as a pro-growth factor at the tissue level. Serum osteocalcin is inversely related to its activity at the tissue level because it measures the inactive form of osteocalcin. The higher the serum osteocalcin level, the less pro-growth activity at the tissue level. Thyroid hormones favor growth by increasing the metabolic rate of the cell. The greater the serum TSH, the less responsive the thyroid is to stimulation, thus

the less well calibrated growth activity is at the cellular level. While this index evaluates the relative insufficiency of pro-growth factors (it is the inverse of the Growth index corrected), it can be considered as an indirect evaluation of anti-growth factors such as leptin, resistin, and other anti-growth factors that are known to directly oppose the effects of alkaline phosphatase and osteocalcin.[277,278]

Somatostatin Index. This index expresses the level of activity of somatostatin; indirectly, it witnesses the relative level of activity of the exocrine pancreas.

= anti-growth index/cortisol index

Somatostatin inhibits growth hormone,[279-282] hence the placement of the anti-growth index in the numerator. Cortisol inhibits somatostatin and stimulates growth. The lower the degree of circulating cortisol, the less inhibition of somatostatin, the greater the relative predominance of somatostatin activity. Hence the circulating cortisol index is in the demoninator.[283-286]

Some Indirect Indexes Using Creatine Phosphokinase and Lactate Dehydrogenase

Catabolism Index. This index expresses the level of catabolic activity of the organism.

= thyroid index/adrenal cortex index
    adrenal cortex = cortisol index/androgenic index
= thyroid index/(cortisol index/androgenic index)
= (thyroid index × androgenic index)/cortisol index
    thyroid index = LDH/CPK
= (LDH × androgenic index)/cortisol index × CPK

Thyroid hormones augment catabolic activity.[287] Cortisol has an initial catabolic effect in liberating glucose from glycogen, but ultimately it has an anabolic predominance through the hyperglycemic stimulation of insulin and the subsequent augmentation of lipogenesis,[288,289] thus its place in the denominator. The catabolism index is evaluating the net catabolic activity of the thyroid and the adrenals. If thyroid activity is greater than the effects of cortisol, the net effect is catabolic.

Anabolism Index. This index expresses the level of anabolic activity of the organism.

= catabolism index/catabolism-anabolism index

Apoptosis Index. This index expresses the general level of apoptotic activity of the organism in its entirety. See the section titled, "Indexes Using Lymphocytes and Other Factors" for a full discussion of the apoptosis index.

= membrane expansion index/structural expansion index
    membrane expansion = catabolism index + growth index corrected
    Structure expansion index = anabolism index × nucleo-membrane activity index

=(catabolism + growth index corrected)/(anabolism × nucleo-membrane activity index)

catabolism = thyroid index/adrenal cortex index
=[(thyroid index/adrenal cortex) + growth index corrected)]/(anabolism × nucleo-membrane activity index)

Apoptosis is programmed cell death and occurs at the end of a cell's life span. The faster the metabolic rate, the greater the number of cell divisions in a given amount of time, the faster a cell will reach its life span and die by apoptosis. Thyroid, as noted above, augments the metabolic rate of the cell, hence the number of mitotic divisions in a given period of time. Thus, the thyroid index is placed in the numerator: the greater the functional thyroid activity, the faster a cell will reach its time of programmed cell death and die by apoptotic mechanisms.

However, apoptosis is more complex than merely the effects of thyroid hormones on the rate of metabolism. Multiple endocrine factors are involved and determine the final state of the global rate of apoptosis. (See the apoptosis index explanation under "Lymphocytes.")

Necrosis Index. This index expresses the relative level of cellular explosion due to necrotic phenomenon in relation to apoptotic cellular destruction.

= membrane fracture/apoptosis

Cell death occurs normally either by apoptosis or necrosis. The lower the rate of apoptosis, the greater the rate of cell death by necrosis, hence the placement of the apoptosis index in the denominator. However, cells can die by necrosis due to other phenomenon besides insufficient apoptosis, such as oxidative stress, infection, and membrane instability due to inflammatory processes.[290] In the face of a low rate of apoptosis, if the cell membrane is very stable, the cell may not die by necrosis either, which is the case with cancer cells.[291]

β-melanocyte-stimulating Hormones (MSH)/α-MSH Index. This index expresses the relative level of participation of the beta- and alpha-MSH in the relaunching of the programmed, integrated adaptation (ie, long loop of adaptation of the pituitary and end-organs) to that of the short loop of adaptation originating from the pineal gland.

=thyroid index/adaptogen index

The MSHs, α-MSH, and β-MSH, as well as ACTH, are derived from a single precursor, pro-opiomelanocortin (POMC) through splicing of various lengths of POMC's amino acid sequence. All three play key roles in adaptation, adaptability and the general adaptation syndrome. Both MSH hormones stimulate ACTH (and ultimately cortisol) but at differing times of the day and year and for various purposes. Thus, this index seeks to evaluate the relative predominance of the two melanocyte-stimulating hormones in stimulating

ACTH and cortisol. In other words, the index evaluates the relative reliance of direct modification of only the corticotropic axis (β-MSH) for adaptation and adaptability in relationship to the stimulation of corticotropic activity as the initial responding axis of the general adaptation syndrome.

The numerator represents the role of the pineal gland. The pineal gland secretes melatonin, which regulates circadian physiology as well as photoperiodicity (ie, seasonal variations in light).[292,293] The numerator is represented by β-MSH, which is related to the pineal gland's regulation of both daily and seasonal modulation of physiology. In the early hours of the morning, a decrease in melatonin levels correlates with a rise in β-MSH. A rise in β-MSH is followed by a nearly commensurate rise in serum ACTH as well as an increase in serum cortisol.[294-296] The degree of increase of all three hormones varies throughout all four seasons, which reflects the role of the pineal gland in modulating corticotropic activity in relationship to variations in the duration of light and dark periods of the day. Thus, the numerator of this index evaluates the role of the pineal gland in adaptation of just the adrenal gland as opposed to all four endocrine axes as occurs during the general adaptation syndrome.

Mathematically, the numerator is derived from the thyroid index, not an adrenal index. β-MSH's actions on the adrenal gland are brief, not prolonged, and therefore not reflected in the indexes of adrenal function discussed above, such as the circulating cortisol index, corticoadrenal index, or the ACTH index. The thyroid index, which reflects the IC metabolic effects of thyroid hormones, is used instead. The thyroid gland expresses β-MSH (and ACTH) receptors. β-MSH in particular stimulates thyroid activity in at least two manners that escape normal TRH-TSH-thyroid hormone feedback loops: (1) long-acting thyroid stimulating effect and (2) augmentation of iodine uptake by the thyroid gland.[297-301] Thus, the thyroid index is used to represent the effects of β-MSH, which represents the pineal gland's role in adaptability and adaptation. α-MSH receptors are present in the pineal gland and exert an inhibitory effect, which is consistent with the designation of α-MSH in the denominator of the index.[293]

The denominator of the index represents α-MSH. -MSH participates in the general adaptation syndrome (GAS), which is the programmed, chronological sequence of alternating activation of catabolic and anabolic hormonal axes that manages adaptation in the face of an unrecognized aggressor. In endobiogeny, it is referred to as the "long route of adaptation" because it involves all the hypothalamic-pituitary–end organ axes as opposed to only ACTH and cortisol. While the GAS is initiated by alpha-sympathetic (αΣ) discharge, the role of α-MSH is to calibrate the adaptation response in three ways: (1) α-MSH is a regulator of energy homeostasis and stimulates secretion of ACTH independent of αΣ, CRH, and other factors; thus, it adapts ACTH's

response to solicitation of the general adaptation syndrome[302]; (2) α-MSH augments cortisol release from the adrenal cortex both directly and indirectly by up-regulating the number of ACTH receptors making the GAS more efficient; and (3) systemic effects OF MSH complement and balance the effects of the general adaptation syndrome: α-MSH is anti-pyretic and antiinflammatory, aids in wound healing and suppresses appetite.[302]

Some Indirect Indexes Using Thyroid-stimulating Hormone and Other Biomarkers

Thyroid Yield. Thyroid yield expresses the relative part of thyroid metabolic activity in relation to its level of solicitation by the pituitary. By extension, it contributes to an evaluation of the threshold of response of the thyroid to pituitary solicitation.

= thyroid index/TSH
    thyroid index = LDH/CPK
= (LDH/CPK)/TSH
= LDH/(TSH × CPK)

The thyroid index evaluates the functional metabolic impact of thyroid hormones on the rate of cell metabolism as discussed under "Creatine Phosphokinase." By assessing this activity relative to the serum TSH level, the thyroid yield index is evaluating how readily the pituitary can adapt the thyroid. For example, a patient with a normal thyroid index (irrespective of serum fT4 and fT3) but a very low TSH (ie, 0.1 mU/L) has a thyroid that is quickly regulated by the pituitary and is at risk of over-adapting thyroid activity relative to the degree of solicitation. This is different than a standard diagnosis of subclinical hyperthyroidism. It relies not on serum levels of T4 of T3 but on this more subtle functional assessment, regardless of the quantitative output of thyroid hormones. For example, in a patient who has a normal thyroid index with an elevated serum TSH (ie, 8 mU/L), your conclusion would not be one of hypothyroidism or subclinical hypothyroidism. Rather it would be that of a euthyroid patient who has a delayed pituitary adaptation of thyroid activity.

Bone-remodeling Index. This index expresses the level of bone remodeling and the degree of alteration of bone and cartilage; it also testifies to the general level of metabolism and, in particular, its activity in adaptation.

= turnover index/osteocalcin
= (TSH × APBi)/osteocalcin

As discussed under "Bone Stroma–derived Enzymes," bone plays a significant role in energy regulation. The rate of bone turnover can be viewed, according to the endobiogenic theory, as a reflection of global rate of cell turnover. The higher the turnover index, the lower the rate of peripheral cell turnover is in the body. Elevated serum TSH implies a lack of thyroid activity at the tissue level and may implicate inefficient thyroid regulation of the metabolic rate of the cell.

Elevated APBi is directly related to the degree of bone turnover from osteoblastic activity.[181] It indirectly implicates, according to the endobiogenic theory, an increased demand on the bone stroma to assist in the regulation of global energetic requirements of the organism.[1-3]

Osteocalcin regulates mitochoncrial activity, estrogen sensitivity, and insulin sensitivity,[2,3,170] which can augment the energetic and anabolic capacity of the cells. Serum osteocalcin is inversely related to these effects of osteocalcin, hence its role in the denominator.

Growth Index Corrected. This expresses the level of activity of IC growth factors.

= growth index/turnover index
    turnover index = TSH × APBi
= growth index/(TSH × APBi)

As noted previously, the lower the turnover index, the greater the rate of cell turnover and renewal is. The growth index corrected corrects the growth index's assessment of potential growth by evaluating it relative to the actual rate of cell renewal, thus creating an assessment of the true impact of growth factors on cellular division and replication.

Bone-remodeling Index. This index expresses the level of bone remodeling and the degree of alteration of bone and cartilage. It also witnesses the general level of metabolism and, in particular, its activity during adaptation.

= TSH × growth index
    growth index = APBi/osteocalcin
= (TSH × APBi)/osteocalcin

Bone remodeling is positively correlated with serum TSH regardless of the serum level of freeT4.[176]

Somatostatin index. This index expresses the level of activity of somatostatin; indirectly, it witnesses the relative level of activity of the exocrine pancreas.

= antigrowth/cortisol

CONCLUSION

There is nothing new in the tendency to take obvious things for granted and to postpone logical thought. . . . For many centuries we were satisfied to accept life itself without questioning and without inquiring as to its beginnings, variations and potentialities. Now we have some desire of understanding how life began, of its continuation and limitations.[303]

—Manfred Sakel, MD, 1938

In this article, the endobiogenic theory of terrain and the development of its biological modeling tool, the Biology of Functions as created by Christian

Duraffourd, MD, were introduced.[304] This was accomplished in five sections: (1) historical review of the philosophy of science, (2) historical review of systems theory and its application to biology, (3) the role of biomarkers and their shortcomings, (4) an introduction to the endobiogenic theory of terrain and the role of the endocrine system as the manager of this terrain, and (5) the development of the biology of functions and discussion of 16 of the 17 biomarkers, their relationship to neuroendocrine activity, and the scientific evidence supporting these relationships.

Contemporary science and medicine is founded on reductionist principles developed more than 500 years ago. The foundations of this approach are based on particular assumptions about the natural laws of the universe, the validity of which has come under question in the last 70 years. Beliefs such as "order arises from predictability and rigid control" and "the whole is the sum of its parts, have been replaced in nearly all fields of academic study, except clinical medicine, with observations such as "order arises from complexity," "the whole is greater than the sum of its parts," and "self-arranging systems allow for complex phenomenon to arise and maintain themselves by self-regulation rather than pyramidal control mechanisms."

Endobiogeny is a theory of terrain, of how the human organism as a system arises and manages itself through basal and adaptive function from internal and external aggressors. Similar to other systems-theory approaches to biology, endobiogeny considers the organism and its various units of activity to be self-regulating, integrated, and interrelated.

Endobiogeny differs from other systems-biology approaches in three key areas. First, it maintains a global vision of the organism in toto, rather than focusing on activity at the cellular level, even when considering subcellular, cellular, tissue, and organ activity. Second, it considers the endocrine system rather than genes to be the manager of the body. Third, it seeks to characterize both the reason and mechanisms of disease, the why and the how, rather than exclusively focusing on the mechanisms.

Considering the endocrine system to be the true manager of the organism, it becomes paramount that this activity be evaluated in a manner that reflects the dynamic functional activity and potential of the organism. Biomarkers hold the advantage of being easily accessible, repeatable, and quantitative. Their disadvantage as currently used is that they are static individual assessments of a dynamic, complex system. If they are to be used to asses the human organism, a dynamic assessment of biomarkers must be undertaken.

Our observations, research, and clinical practice led us to three conclusions. First, quantitative serum measurements of free, unbound hormones are a reliable indicator of neither their individual, cumulative, nor synergistic effects on metabolism. Second, there are relationships between biomarkers and the functional activity of hormones that can serve, indirectly, as indicators of endocrine management of metabolism. Third, because a system functions based on the relative contributions of one unit of activity in relationship to that of others, if the biomarkers related to endocrine activity were applied in a series of ratios, direct and indirect, they may be able to capture and model this activity in a complex and integrated manner, similar to the complexity of the system itself. Thus, from the endobiogenic theory was derived a biological modeling system that evaluates the relative, qualitative functions of the human organism as a dynamic, living, functioning system. This system is called the biology of functions.

It should be noted that the biology of functions does not quantitatively measure or sample the actual level of activity of any biological process or hormone, except TSH, which is a direct biomarker used in the modeling tool. It would not be possible to measure all endocrine and metabolic activity of the entire organism while preserving its dynamic equilibrium and integrity. Instead, the biology of functions simulates biological activity in its qualitative and quantitative functions, as well as in its potential, structural, and functional achievements through an indirect method: the measurement and relationship of various biomarkers that reflect endocrine activity.

From more than 30 years of clinical use and the scientific corpus of more than 120 years of study as presented here, we believe that a convincing argument for the validity of the endobiogenic theory of terrain has been set forth. However, there is much to explore and evaluate.

Because the biology of functions measures relative, not absolute, activity, comparisons to "gold standard" of static biomarkers, biopsies, or quantitative measurements of single serum hormone levels will often be neither accurate nor relevant. Rather than validating each index individually, we propose that groups of indexes be compared against clinical conditions in which particular endocrine or metabolic activity is known to play an important role in the genesis and maintenance of the disorder. For example, in patients with cancer, various endobiogenic indices evaluating necrosis, apoptosis, and DNA fracture and cortisol, estrogen, thyroid, and somatostatin activity can be evaluated clinically in patients based on the activity characterized by in vivo and in vitro and clinical studies. Complex meta-indexes of cancer activity can be applied against survival curves to evaluate risk of mortality. Thus, the clinical application of the biology of functions will serve as its own validation and ultimately the validation of the theory of terrain on which it is based.

Endobiogeny is not a form of alternative medicine. Endobiogeny is the harmonization of clinical practice with scientific principles and the philosophy of science. We believe that the ultimate advantage of an endobiogenic approach is that it contextualizes the relevance of reductionist studies to the dynamism of

the living human. The rational investigative method can be applied in an individualized fashion, preserving both the objectivity of the scientific approach and the humanistic concern for the individual.

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