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THE 'BIOLOGY OF SYSTEMS' OR THE 'SYSTEMS OF BIOLOGY': LOOKING AT DIABETES FROM A SYSTEMIC PERSPECTIVE

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Abstract-

Background- The body is an open dynamic organism which responds to sensory and biological input. It may be studied from the bottom upwards or the top downwards however the biological bottom-up approach invariably ignores that sensory input influences the body's regulatory mechanism and/or that environmental stressors of different nature and/or intensity influence the body's stability, alter the cellular responses, activate or deactivate genes, and result in the onset of pathologies such as diabetes mellitus which affect the body's function and capacity. Accordingly, the major aim of this article is to highlight the fundamental role which the top-down cognitive approach has upon the understanding of the body's function i.e. as a measure of autonomic dysfunction and psychological stress; and to compare such approach with the bottom-up approach so favoured by biomedical researchers which avoids considering and/or largely dismisses the considerable influence of sensory input upon cellular and molecular biology.

The method used in this article is based upon an appreciation that the brain regulates the autonomic nervous system and physiological systems, and that autonomic dysfunction leads to alterations at the cellular and molecular level i.e. to genotype and phenotype. Such understanding, incorporated into a mathematical model and commercialized technology, is highly significant for a number of reasons. In particular that (i) Diabetes is a multi-systemic disorder; (ii) type 1 Diabetes is genotypic and type 2 Diabetes is phenotypic; (iii) most Diabetes is a combination of genotype and phenotype; and (iv) type 2 Diabetes is an issue of acidity which influences the prevailing intracellular levels of essential minerals Magnesium and bioavailability of Zinc.

In conclusion the term top-down systems biology more precisely refers to the role of sensory input which influences the brain's efforts to regulate the autonomic nervous system and physiological systems i.e. the regulation of acidity is a neurally regulated physiological system. The term 'top-down' encompasses the cognitive and/or psychological approach whilst the term 'bottom-up' is solely that of the biological approach. Moreover the most effective way of stimulating the autonomic nervous system and reducing pH (intracellular acidity) is by the top-down approach involving lifestyle interventions e.g. abstaining from acidic drinks, maintaining normal levels of body weight, avoiding stress, and exercise.

Keywords- diabetes, autonomic nervous system, physiological systems, genotype, phenotype, proteins, blood glucose

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Introduction

Diabetes [1] is prevalent as type 1 and type 2. They are considered as two distinct conditions yet patients who are diagnosed with type 2 Diabetes often require injections of insulin to sustain their function i.e. the two conditions are intimately related. These two categories of Diabetes are characteristic of genotype i.e. the level of insulin which has been genetically expressed (initially as pre-pro-insulin and pro-insulin); and non-genetic or phenotype i.e. the rate at which the expressed insulin subsequently reacts or otherwise performs it's cellular function. The fundamental genetic and non-genetic/ environmental aspects of the diabetic pathology which contribute to the emergence of diabetes can be summarized as follows:

Genetic Expression (Genotype)

Genes, either singly or through their genetic conformation and association with other genes, produce proteins. Genes have only one function i.e. to produce proteins. Alterations to genetic conformation influence the rate and extent to which the genes can produce or express a particular protein e.g. insulin. The genetic changes which are typical of type 1 diabetes may be caused by any single factor or combination of factors including viruses, vaccines, genetically modified foods, and stress.

Type 1 diabetes is a polygenic disease in which many different genes contribute to its onset and progression. The spectrum of

genes which contribute to the production of insulin varies between racial groups and gender. Lack of insulin is the essential feature of type 1 diabetes.

Protein Coiling

The conformation of a protein is significant. Proteins such as insulin and leptin may be coiled or uncoiled. If they are uncoiled they do not react. This remains an under- researched topic in diabetes research yet is known to be significant factor in type 2 diabetes [2].

Environmental Factors (Phenotype)

In the context of this article the term phenotype applies to anything which is considered to be non-genetic and of environmental or lifestyle origins. Proteins react with their reactive substrates e.g. the reaction of a substance such as glucose with the enzyme hexokinase. The conditions which govern the rate at which this chemical reaction proceeds are typically the rate at which glucose enters the cell, temperature, pH, levels of essential minerals (which are a function of acidity), and levels of cofactors i.e. levels of vitamins, nucleotides or other materials which otherwise influence the rate at which this reaction proceeds.

Lack of protein reactivity, often referred to as 'insulin resistance', is a feature of type 2 diabetes however the term 'resistance' is not a scientific term. Either chemicals react and perform their biological function or they do not react. Accordingly type 2 diabetes is associated with the inability of insulin to react and/or to perform its cellular function.

Systemic Dysfunction

Organs function in discreet physiological or functional systems [1,3,4]. Physiological dysfunction may affect the stability of more than one system. For example: (a) the occurrence of migraine [4] can be linked to heart function, lowered blood volume, patent foramen ovale and/or /lack of oxygenation of blood, increased blood viscosity, impaired blood flow to the brain, and low blood pressure [5-6]; and (b) lack of sleep [7,8], increased acidity [9,10], osmotic pressure, and perhaps also plasma viscosity [11,12], respiration (exercise) [13,14], and heart function [15], are contributory systemic factors which influence the function of the pancreas and the subsequent onset of type 2 diabetes.

Stress

An estimated 85% of sensory input is visual. Extremes of sensory input, which we experience as stress [16-18]; influence heart function, prevent proper digestive function, contract blood vessels in the lower back, prevent sleep, etc. Stress influences cellular function and alters the spectrum and levels of metabolites. It stimulates the release of hormones by the hypothalamus and endocrines and results in higher levels of blood glucose [19]. Accordingly, the biological response to stress could, in principle, be used as a quantitative measure of psychological stress.

The wider objectives of this article are (i) to illustrate the fundamental role of the top-down cognitive approach upon the body's function i.e. as a measure of autonomic dysfunction and/or psychological stress; (ii) to compare the top-down approach with the bottom-up approach; (iii) to establish whether this presents a need for better medical screening or diagnostic technologies; and (iv) to illustrate how this influences the prevailing understanding of diabetes mellitus.

How does a Systemic Perspective Alter the Prevailing Paradigm?

Consider the implications of such philosophy upon the prevailing understanding e.g. (i) the limitations of existing diagnostic tests and (ii) that diabetes is a complex, multi-systemic condition…….

Current Diabetes Tests: Limitations of

The earlier that the onset of diabetes can be determined the earlier it will be possible to introduce lifestyle modifications and therapies in order to slow the onset of the condition and it's subsequent progression to secondary pathologies e.g. cardiovascular disease(s) [20-23], cancers [24-26], Alzheimer's disease [27], renal disease [28], visual deterioration [29], postural problems, etc; which have significantly greater cost implications.

The tests which are used to determine the onset and progression of diabetes are largely experiential. Although their value has been proven through use over many years the limitations of such tests have become increasingly apparent as researchers seek newer, better, cheaper, safer, and faster ways of diagnosing the onset of diabetes from its earliest presymptomatic origins. Contemporary medical research has established that genotype is the most significant physiological parameter yet the tests that are used in medicine fail to quantify the extent of genotype or phenotype e.g.

Fasting Glucose

(FG) assesses the underlying level of blood glucose following sleep. It assumes, not unreasonably, that this measurement is effectively that of the base state. Nevertheless this remains an unproven scientific assumption because few, if any, tests have been able to prove the concept beyond reasonable doubt. Such measurement encompasses both genotype i.e. the level of insulin expressed from the genes, and phenotype i.e. the rate at which the insulin facilitates the entry of glucose into the cell.

Oral Glucose Tolerance

(OGTT) assesses the extent of the body's ability to handle extremes of blood glucose. It assumes, not unreasonably, that this measurement is effectively that of physiological capacity. Nevertheless this remains an assumption. Such measurement encompasses both genotype and phenotype.

The measurement of FG and OGTT suffer from a number of inherent limitations e.g. (i) that the level of blood glucose will be influenced by the extent of the patient's activity between rising and attending the Diabetes clinic i.e. stimulation of the adrenals and the autonomic nervous system; (ii) that the level of blood glucose is the consequence of the brain's ability to regulate the stability of all physiological systems i.e. a best-fit model of physiological stability; (iii) the results will be influenced by non-diabetic pathologies; (iv) the time of the test; (v) the amount of time between rising and being tested; (vi) genetic/racial/gender differences; (vii) that the normal levels can vary throughout the day including before and after meals, (viii) the influence of medications and/or bioactive substances, (ix) exposure to sunlight, and (x) patient weight and history.

Under normal circumstances a low level of Fasting Glucose should, in principle, be accompanied by a low level of Oral Glucose Tolerance but there will be cases when there is likely to be disagreement between the two tests. For example a viral infection could reduce the genetic expression of insulin however this will only become significant in extremes of demand such as the OGTT, extremes of

exercise, and if the patient exhibits 'insulin-resistance'. Accordingly FG is more typically a measure of genetic 'capacity' whilst OGTT is a measure of phenotypic 'demand'.

The HbA1c test

The HbA1c test has been adopted as the prevailing gold standard however such is the general level of distrust of these tests that clinicians often carry out a series of tests in their efforts to characterise the patient's condition. The HbA1c test provides a measure of the diabetic state. Although haemoglobin plays no part in diabetes etiology it serves as an *indirect marker* for diabetes when glycated. Glycated Albumin has also been proposed as a diagnostic marker for Diabetes [30]. The HbA1c test effectively measures the level of a protein and the level of glycation. Nevertheless this has inherent limitations e.g. the test (i) is influenced by the level of haematocrit; (ii) levels of pH, oxygen, and other biological interferences; (iii) a number of pathologies e.g. anaemia, chronic kidney disease, etc; (iv) the test is increasingly inaccurate at high levels; (v) it assumes that Glycated Haemoglobin does not decay rapidly which is not scientifically sustainable; and (vi) the level of glycation can only be determined if sufficient haemoglobin is available.

HbA1c is significant because it is effectively a measure of both protein and the glycation process. Nevertheless other glycated proteins may be more significant for a number of reasons. Most proteins absorb and emit light. The spectrum and intensity of light emitted is characteristic of the normal and pathological states. Each protein emits a biophoton of light upon reaction with its substrate. Glycated proteins are more bioluminescent than proteins which have not been glycated. The spectrum and intensity of this bioluminescence is characteristic of the diabetic state i.e. of type 1 (genotype) and type 2 (phenotype).

Glycated haemoglobin is just one of a number of glycated proteins which are visually active. Others include the glycated forms of Insulin, Albumin, LDL Cholesterol, etc. Many pathological reactions emit biophotons. Accordingly the measurement of the light emitted from the glycation of a protein e.g. insulin, may be used as a direct measure of the diabetic etiology i.e. of both genotype and phenotype [1].

The simple principle of measuring the level of a biochemical marker which includes FG, OGTT, HbA1c, etc; suffers from a range of inherent limiting factors. The most significant limiting factor is the inability to adequately differentiate between the normally healthy, the pre-diabetic, the diabetic, and to adequately differentiate between the processes which are responsible for type 1 and type 2 Diabetes. Test results are compared with an expected or normal range of values typically in the range 4-8mmol per litre blood glucose. If the results deviate from the norm (normal distribution) this leads to the conclusion that the patient is pre-diabetic or diabetic however such technique often fails to determine the earliest onset of the diabetic because (i) a person's physiology is dynamic and varies according to circumstances throughout each day, (ii) the diagnostic tests are not sufficiently sensitive or robust, (iii) the fundamental principle upon which the test is based has significant limitations, (iv) the condition is related to our age and physical condition, etc.

The ability to screen for the genes which are switched on or off

The ability to screen for the genes which are switched on or off and hence which produce or express a protein is recognised to be of value in the determination of genetically inherited disease states however such a qualitative technique is unable to quantify the extent of protein expression, the rate at which the expressed protein subsequently reacts with its reactive substrates, and/or the stability of other physiological systems which contribute to the onset of diabetes [7-10]. This is a significant limitation of the technique [31].

Diabetes is a Neurally Regulated Multi-Systemic Disorder

Type 2 Diabetes is a multi-systemic disorder [32] which does not have genetic origins. Its origins can often be traced to the lack of good quality sleep, disturbed appetite and/or satiety, consumption of acidic drinks, poor diet, lack of exercise, stress, etc. By contrast Type 1 Diabetes is a genetic disorder which results from anything which has the capacity to alter the genetic and/or epigenetic profile e.g. viruses, vaccines [33], genetically modified foods, stress, heavy metals, etc; and hence the genetic ability to express insulin. Moreover diabetic patients may show the symptoms of both type 1 and type 2 Diabetes. Consequently the idea that a single biochemical can precisely determine the onset of the diabetic condition lacks scientific validity. Every pathology is the consequence of multi-sensory, multi-systemic, and multi-biochemical influences upon the normal regulatory mechanisms. For any such condition to be quantified there must be an assessment of all of the biological deficits which occur throughout the body. See attached example report.

In addition, the onset of any single pathology occurs earlier than can be detected using contemporary diagnostic tests. The earlier that the condition can be diagnosed the earlier that therapies can be allocated to treat the condition and the better the likelihood of recovery however if the condition cannot be accurately diagnosed the doctor may be unable to accurately prescribe an appropriate drug i.e. the wrong drug may be prescribed. Furthermore, the idea that a drug can effectively treat a medical condition must be qualified. Drugs perform a wide range of functions e.g. killing an invading bacterial infection; as biological supplements; assisting the body to be rid of toxins; masking the symptoms of disease; eradicating and/or preventing the growth of tumours. They assist the body to recover a level of homeostasis. Nevertheless diabetes drugs, in common with most other drugs, are ineffective in abt 50% of those treated [34]. They slow the onset of the condition but do not cure the diabetic. The most effective 'cure' or intervention remains diet and exercise which have been shown to have the capacity to almost completely reverse the symptoms of diabetes [35]. There is a need to explain the 50% component which cannot be explained by the prevailing genetic paradigm and to address this fundamental theoretic deficit [36].

The Influence of Acidity upon Metabolic Function

Such a deficit may be addressed by considering how the body regulates its function. The brain seeks to maintain the optimum stability of the body's function during exercise, activity, rest [37] and when confronted by stress [38,39] i.e. blood glucose is a neurally regulated system [40-43]. Acidity is also a neurally regulated physiological system [44]. Changes to the levels of intercellular acidity influence the levels of minerals and their redox states. Such systems are independently regulated by the brain yet are also influenced by the function of other neurally regulated physiological systems e.g. blood pressure, blood cell content, digestion, urination, breathing, sleeping, temperature, etc. The effect of acidity upon the body's function has been widely reported e.g.

- A wide variety of stresses and stressors increase the level of

acidity; lower the levels of vitamins, minerals, and/or cofactors and coenzymes; lead to changes to cellular and molecular biochemistry; and lead to physiological instability and cellular instability e.g. as inflammatory processes [38]. In particular, increased acidity leads to reduced levels of the essential minerals Magnesium, Chromium [47] and Zinc [45,46,48], and contributes to changes of chromatin and protein conformation [49].

- Chromium is an essential dietary component however raised acidity reduces the levels of chromium and influences the function of the GLUT4 glucose transporter protein which requires chromium in order to function at the surface of the muscle cells [47].
- A lack of intracellular magnesium is clearly implicated in diabetic etiology [50].
- Although the role of zinc has not yet been clearly elucidated, it is essential for the production and precipitation of the zinc hexamer, and the subsequent supply of insulin. This is a pH dependent function which is favoured by low levels of acidity i.e. neutral pH. Increased levels of acidity are not favourable for the precipitation of the zinc hexamer which indicates that the problem of diabetes may be associated with acidity, coordination geometry, and bioavailability [10,51,52].
- Magnesium is a cofactor for over 300 enzymes therefore the body cannot function in its absence. Low levels of magnesium influence the onset of diabetes and cardiac dysfunction [53], lipid metabolism [54], the synthesis of triglycerides [54], and the function of a wide range of proteins e.g. it influences the function of chaperonin proteins which often require magnesium – to correct the folding of misfolded proteins and hence, directly or indirectly, influence protein conformation.
- In addition, low levels of zinc slow the metabolism of carbonic anhydrase, the elimination of CO2 from the body, the retention of insulin as the zinc hexamer, and the controlled release of insulin. Some enzymes require both Magnesium and Zinc to function.
- The administration of sodium bicarbonate or calcium carbonate which are alkaline blocks the effect of food upon blood glucose levels [55].

The etiology of most pathologies can only be explained by the laws of chemistry and, in particular, by the physico-chemical factors which govern the genetic expression of proteins; and the subsequent rate at which such proteins react with their reactive substrates i.e. phenotype. No single chemical 'regulates' any chemical reaction. No single biochemical entity 'resists' reaction. Either it reacts-if so, at which rate does it react and what physico-chemical factors influence its ability to react-or it does not react. The idea of insulin 'resistance' lacks scientific rigour. If magnesium or another mineral, vitamin or cofactor is deficient this will influence the rate at which the reaction proceeds and are indicative of an emergent inflammatory response [38] or other morphological change.

The brain is continuously regulating the body's function. It maintains our mechanical stability and it maintains the stability of the autonomic nervous system and the various physiological systems [6,56]. This regulatory mechanism is influenced by (i) the prevailing levels of genotype and phenotype, (ii) multi-sensory input, (iii) physiological damage or dysfunction e.g. due to age. It is an open dynamic system which continuously responds to sensory and biological input [Fig-1].

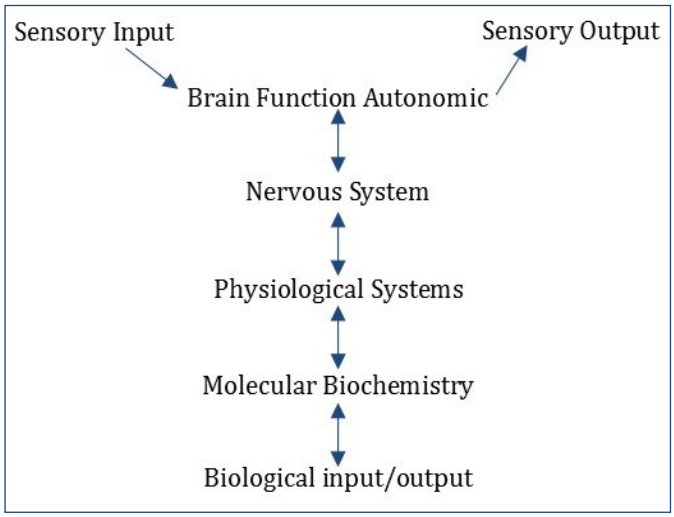

Fig. 1-Linking Sensory Output to Cellular & Molecular Biology

The organs lose up to 75-90% of their capacity by age 70 years. Similarly over 50% of muscle tone is lost by 75-90 years. The capacity to metabolise blood glucose declines with age. If the system was not neurally regulated it is inconceivable that such loss of organ capacity could be accommodated. In diabetes the levels of insulin steadily declines as we age i.e. diabetes is the inevitable consequence of the aging process. The only issue is how well the onset of this condition can be slowed.

As outlined in [Fig-1] the brain continuously regulates the autonomic nervous system and the network of organs commonly known as physiological systems. Autonomic dysfunction leads to changes at the cellular and molecular level i.e. to the level and spectrum of proteins which have been genetically expressed. Such metabolic changes influence brain function. The idea that genes in some thoughtful way control or otherwise regulate our organism is not sustainable [57].

The onset of diabetes is influenced by both genotype and phenotype. It is a medical condition which can be characterised by (i) the level of insulin and (ii) the rate at which insulin reacts and/or performs it's cellular function however it is not possible to entirely differentiate genotype from phenotype e.g. adequate levels of magnesium are necessary to maintain the function of transcriptase enzymes and hence maintain the genetic expression of insulin. Accordingly, in order to properly characterise the diabetic condition (and all other medical conditions), a diagnostic technique must be able to determine such genetic and phenotypic characteristics for the condition and all related secondary effects and/or emergent pathologies. It is an issue of genetic 'capacity' and phenotypic 'demand'. If the phenotypic demand exceeds the genetic capacity (i.e. the amount of insulin, in the case of diabetes) there will be the emergence of physiological symptoms. The system will become stressed e.g.

- In diabetes, type 1 diabetes represents the genetic component and type 2 diabetes represents the environmental or phenotypic component [1].
- In breast cancer, the BRCA1 gene is a contributory factor in circa 20% of breast cancer cases. It requires an environmental 'trigger' to be manifest as the pathology [58] i.e. other biological processes contribute to the onset of the condition e.g. alcohol consumption, age of menarche, first child birth, menopause.

- In angina pectoris, which requires a trigger typically of excessive cardiovascular activity before the symptoms of angina are manifest.
- in migraine whereby the delivery of too little oxygen to the brain leads to the onset of migraineous events [5].
- in skin cancer, caused by excessive exposure to sunshine in fair skinned caucasians whilst being uncommon among dark skinned races [59].

Over 100 medical conditions respond to the therapeutic effect of light. Light is the primary medium which delivers sensory input, influences the autonomic nervous system and alters systemic stability i.e. in cases of autonomic dysfunction the organ networks no longer function in a coherent or synchronised manner. The unique characteristics of light, in particular its colour and intensity, transmits information and influences physiological stability. In the diabetic context the exposure to sunlight has been shown to reduce the extent of diabetic symptoms e.g. by improving the supply of nitric oxide, calcipotriol, the function of the pituitary hormones and endocrines, etc. It illustrates that many proteins [60] cannot perform their biological function of reacting with their substrates unless raised to their activated state. Exposure to light appears to perform this function.

The most significant factors which contribute to better health, at least where type 2 diabetes is concerned, are a balanced diet and adequate levels of regular outdoor exercise [35] i.e. which raise heart rate and metabolic rate; improves plasma viscosity, respiration rate, and intracellular pH; lowers levels of Idl cholesterol; increases the supply of oxygen to the brain, the levels of Magnesium and bioavailability of Zinc, blood circulation through the musculature; and reduces levels of insulin-resistance.

Methods/Biological Computation

It has been for many years a goal of medical researchers to be able to mathematically model the body's function. In their efforts to do so many researchers have sought to mathematically model the function of different organs e.g. Noble developed the first mathematical model of the heart [61]. In order to do so they use the prevailing test methods e.g. measurements of blood pressure or of specific biological components rather than the sum of the neural and biochemical influences which contribute to blood pressure. This led to the development of the Virtual Physiological Human project (VPH) in order to facilitate investigation of the human body as a single complex system [62,63] yet the techniques to achieve VPH focus upon the biological function of individual organs whilst ignoring the coordinated function of organ systems and the influence of sensory input and light. In addition it ignores that the body's function is regulated by the autonomic nervous system, which involves discreet neurally regulated physiological systems [3,6,10,18,32,37, 64-69] although it is increasingly recognised that the physiological systems are significantly under-researched.

The understanding of complex biological systems has been considered in a number of articles by Brenner [70], Noble [63,70], Kohl [63], and other researchers; however this has predominantly looked at biological systems i.e. the bottom-up approach, whilst overlooking the influence of sensory input upon brain function and the autonomic nervous system i.e. the top-down approach.

The nature of modern research to split areas of research into unique specialisms, which can be researched in ever greater levels of detail, is based upon the fundamental assumption that each disease has simplistic origins and can be characterised by single markers however most medical conditions exhibit the characteristics of multi-systemic etiologies. Genetic research has illustrated that most of the common diseases which are prevalent in our societies are polygenomic and often differs between racial subtypes i.e. it is rare that a single disease can be characterised by a single genetic defect. Moreover recent genetic studies have illustrated the extensive range of genetic mutations which are influencing our health and education however an estimated 90% of the common morbidities arise from the complex nature of our lifestyles. They are multisensory, multi-systemic, multi-biological and polygenomic. Consequently, there is recognition that the body's dysfunction, in particular of lifestyle- related morbidities, cannot easily be characterised or diagnosed by the current range of biomarker tests and related technologies. Kandel recognised that there is a fundamental theoretic deficit which is not able to explain how sensory input influences cellular & molecular biology i.e. an understanding of the mechanism by which the brain processes sensory input and regulates the autonomic nervous system and physiological systems appears necessary [36] to advance the current medical paradigm. Such an understanding has been incorporated into the first cognitive technology of its type, Virtual Scanning [71-74] which has been developed by Grakov [73].

Grakov's model is based upon the light-emitting properties of proteins in which changes of bioluminescence can be used to determine the inhibition of normal biological processes and the onset and development of pathological reactions. Accordingly, it lies at the 'level of protein interactions within the context of subcellular, cellular, tissue, organ, and system structures' identified by Noble [75]. It reports in mathematical terms the levels of systemic stability and instability, the level of organ stability, alterations to cellular morphologies, and the nature and level of developing pathologies (typically 5-15 pathologies in each of 30+ organs: determined in terms of both genotype and phenotype). It appears to fit the specification!

A number of mathematical models of blood glucose metabolism have been developed since 1960 [76-84]. These models are invariably based upon the bottom-up approach however such models exclude the very significant role of the brain and the influence which stress has upon the body's function and, in particular, how this influences blood glucose levels and the onset of diabetes. Some of the recent models developed introduce compensatory mechanisms in their efforts to consider the influence of brain and stress [84]. Accordingly such models suffer from inherent limitations:

i. The data employed in the model must be scientifically significant, free from duplicity or misinterpretation, and be scientifically valid e.g. as a measure of the level of the protein which have been genetically expressed or the rate at which such proteins (e.g. insulin), react with their reactive substrates. The prevailing tests used in contemporary diagnostic tests are experiential and often fail to differentiate between genotype and phenotype. In addition all physiologically significant factors should be included.
ii. The role of the sensory input, sense perception and light must be included in any mathematical model.

- Sensory input is the mechanism which we use to experience stress. An estimated 85% of sensory input is visual however

colour perception is altered by the influence of pathologies. In the case of diabetes, glycated proteins are highly bioluminescent. Moreover this bioluminescence influences colour perception. The altered colour perception arising from the emission of biophotons is as significant a metabolite as any chemical metabolite.

- Light acts as an essential photostimulant which catalyses the function of biochemistries which are essential to maintain the supply of calcipotriol, nitric oxide, etc. For example light catalyses the conversion of cholesterol to calcipotriol (vitamin D) i.e. (i) the conversion of ergosterol to ergocalciferol and (ii) in particular, the conversion of of 7- dehydrocholesterol to calcipotriol [85].

iii. The role of the brain and the complex mechanisms which regulate the autonomic nervous system and organ networks must be understood.

In general, the role of the brain and hence the influence of stress is not included in any current mathematical models because:

- of the limitations of existing tests and hence of the current understanding of the diabetic condition which is both genetic and phenotypic;
- the role of acidity in diabetes is not yet recognised. Such understanding may lead to preventative lifestyle modifications;
- insulin supplementation is the only recognised therapeutic modality;
- it is difficult to represent stress in a quantitative manner;
- when designing a research study, researchers are often unable to control all of the variables. They may not understand the full range of variables which need to be studied or they may ignore the variables which are considered to be inconsequential e.g. most research articles routinely ignore the physiological significance of gender [86], sensory input, light, acidity, age, weight and/or physical fitness, altitude and/or gravity.

Discussion

At normal pH, levels of magnesium are sufficient to sustain the normal metabolic processes which are associated with the regulation of blood glucose. The genetic expression of pre-pro- insulin proceeds satisfactorily and produces insulin. The transcriptase enzymes have an adequate supply of magnesium, the transcriptome and/or chaperonin enzymes maintain insulin in the coiled shape, the insulin performs its cellular function, glucose enters the cell and reacts with hexokinase to produce CO2 and energy.

At lower pH

- the levels of magnesium are not satisfactory to sustain the normal metabolic processes. The genetic expression of insulin slows and the supply of insulin declines. This becomes significant at extremes of function. The levels of magnesium are not able to sustain the function of transcriptome and/or chaperonin enzymes and the levels of uncoiled insulin and leptin increase. The levels of magnesium are not adequate to sustain the function of insulin and the insulin is not able to perform its cellular function. Consequently, the flow of glucose to the cells declines.
- The levels of zinc are not sufficient to maintain the supply of insulin from the zinc hexamer.
- The levels of chromium are not sufficient to maintain the function of the GLUT4 transporter protein. The insulin cannot perform its cellular function and is considered to be 'resistant'.
- The levels of intracellular magnesium are not able to sustain normal cell function leading to the classic inflammatory process.
- The levels of magnesium in the bones decline as the body uses magnesium to neutralise excess acidity [10]. This leads to the onset of osteoporosis [87], bone embrittlement, breakages [88], and postural problems.
- The glycolysis pathway is magnesium dependent [50] i.e. the metabolism of glucose to glucose-6-phosphate and the generation of energy through the conversion of ATP- ADP including hexokinase, pyruvate kinase and other enzymes are magnesium dependent reactions.
- Plasma viscosity increases due to hyperglycaemia, and increased levels of glucose, triglycerides and lipids [54].

In extremes of glucose (hyperglycaemia) the normal process of metabolising blood glucose cannot proceed. Glucose is preferentially metabolised into triglycerides [50]. This may lead to the onset of hypoglycaemia, persistent hunger and the inability to control satiety. That the issue is one of acidity is supported by noting that the administration of sodium bicarbonate and sodium carbonate improves metabolic function [55].

Conclusions

As outlined, there are two basic approaches to biomedicine. This article illustrates the limitations of the reductionist or bottom-up systems biology model and highlights the theoretical significance of the top-down systems biology model. The term 'Systems Biology' can be interpreted in two ways i.e. 'the biology of systems' or 'the systems of biology'. Most systems biology appears to be the latter. It uses biology as the means to understand the systems which better explain current biochemical research i.e. seeking to justify yet more drug-based interventions, yet drugs do not cure anyone of morbidities such as diabetes. They only allow the patient to better manage their condition and to slow the onset of the secondary complications. There is an alternative in which changes to systemic stability leads to changes of cellular & molecular biology which can be studied and adapted, for example as Biofeedback technologies, however the reverse is not necessarily so. Changes to molecular biology influence systemic stability but may not have a long-term effect because the brain is continually adjusting its efforts to re-establish optimum physiological stability. The function of the brain is pre-eminent and it explains why symptoms often re-occur when a drug therapy is withdrawn i.e. the drugs interrupt the biochemical processes which contribute to symptoms but they do not interfere with the basic causal mechanisms. It explains why anti-obesity drugs lose only circa 4-6 kgs over a 1-4 year period and when combined with a diet i.e. the initial weight-loss effect is countered by the body's innate regulatory mechanism.

Accordingly what is the actual effectiveness of medicine and what is the extent to which medicine can be expected to be effective? If, as outlined, there is a mechanism which regulates the body's function then (i) to what extent does this mechanism influence the healing process e.g. it may be able to differentiate between autonomic dysfunction and degeneration; and (ii) to what extent does it influence the effectiveness of drug-based medications e.g. drugs may be as little as 12% effective [89] and/or that 90% of drugs may be as little

as 50% effective [34]. Furthermore would this reduce undesirable drug side-effects in those taking drugs and in those who adopt alternative drug-free therapies? Finally, (iii) to what extent does the claimed effectiveness of drugs include the therapeutic effect which is due to the natural healing mechanism [89]? Drugs suppress the symptoms of disease. They cannot be effective unless accompanied by the body's innate regulatory mechanism i.e. the autonomic nervous system. This is hugely significant. It illustrates that drugs often take credit for the body's natural ability to regulate its function but also that the effectiveness of drugs are influenced by the body's innate ability to compensate for biological change e.g. (i) sunlight stimulates the autonomic nervous system and often inactivates immunosuppressive drugs; (ii) the effectiveness of drugs often declines over a period.

In the case of diabetes, drugs slow the progression of pathologies but do not facilitate the recovery from either type 1 or type 2 Diabetes. It may be logical to address the issues which are fundamentally responsible for the onset of the condition i.e. (i) maintaining an activated immune response in order to offer some protection against viral infection and (ii) maintaining an active and balanced lifestyle in order to maintain the body's physiological stability e.g. by limiting the intake of acidity i.e. as highly acidic and/or alcoholic drinks; limiting the intake of high GI foods; maintaining the levels of essential minerals and vitamins; limiting exposure to stress; regular physical exercise of appropriate duration and challenge; and exposure to natural sunlight.

The study of biological systems may be too complex to be explained solely by biochemistry alone [67,68] and should be complemented by research which can explain (i) the nature and structure of the autonomic nervous system and the coordinated function of the organ networks/ physiological systems; (ii) the consequences of stress upon the autonomic nervous system; (iii) the physiological significance of phenotype; (iv) the ability of light to convey information [60,66] and/or to activate biological processes; and (v) the neuroregulatory mechanisms and pathways. Furthermore it should consider adopting a mechanism which can be mathematically modelled. The biological complexity of the bottom-up approach makes it virtually impossible to do so with any degree of precision unless the biological consequences of stress can be incorporated into such a model.

The understanding of the mechanisms which the brain uses to regulate the body's function, if not immediately apparent, has immense significance e.g. to the pharmaceutical industry-leading to combination drug therapies; to the medical device industry-better and less expensive ways of diagnosing and treating disease; to medical researchers-to a more complete understanding of various multisystemic pathologies; to clinicians-leading to the earlier and better diagnosis of the onset of a pathology and conceivably to the earlier introduction of drug treatments, the introduction of preventative lifestyle measures, and non- drug therapies; and perhaps also a reduced need for organ transplants.

The development of a mathematical model of the autonomic nervous system [68]; the recognition of the relationship between sensory input, autonomic nervous system and cellular & molecular biology [69]; and the subsequent development of Virtual Scanning may be one of the most significant successes of Systems Biology. The mathematical model, upon which Virtual Scanning is based, incorporates an understanding of the relationship which exists between the 30 organs which participate in the 13 physiological systems included in this model. It provides a way of quantifying the influence of stress upon the body's function and enables a clinician to monitor the genetic and phenotypic characteristics of over 250 common pathologies from their presymptomatic origins.

Example : Full Report on Health Condition

Sex : Man [Male]

Age: 30 years.

Weight : 64.00 kg.

Diagnostics Date: Jan. 19, 2005 (17:59:27)

Detailed Elaboration on Organs and Systems (Specification of Condition of Organs and Systems).

1. **Brain [Fig-2]**

- Impairment of cerebral circulation: Expressed pathology signal.
- Epilepsy: Weakening of compensatory abilities.
- Verterbral Artery Syndrome: Expressed pathology signal.
- Encephalitis: Expressed compensatory signal.
- Arachnoiditis: Compensatory signal.
- Encephalopathy: Compensatory signal.
- Migraine: Expressed compensatory signal.

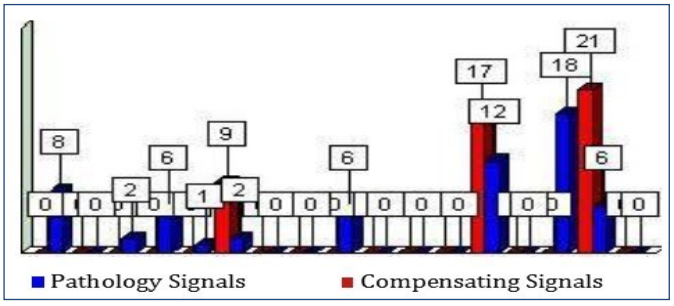

Fig. 2- Detailed Elaboration on Brain

2. **Spinal Cord [Fig-3]**

- Growth of New Cells: Compensatory signal

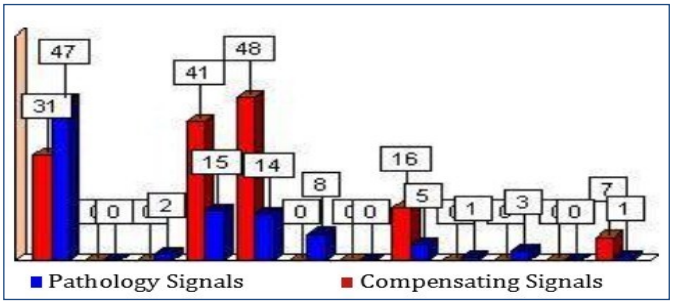

Fig. 3- Detailed Elaboration on Spinal Cord

3. **Peripheral Nervous System [Fig-4]**

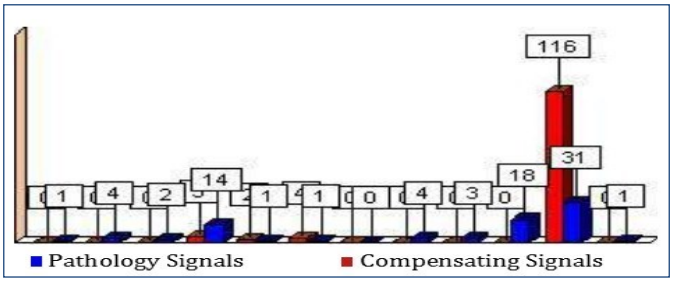

Fig. 4- Detailed Elaboration on Peripheral Nervous System

- Spinal Osteochondrosis with Neurological Effects: Expressed compensatory signal.
- Radiculitis: Expressed compensatory signal.

4. Ear : No changes detected [Fig-5].

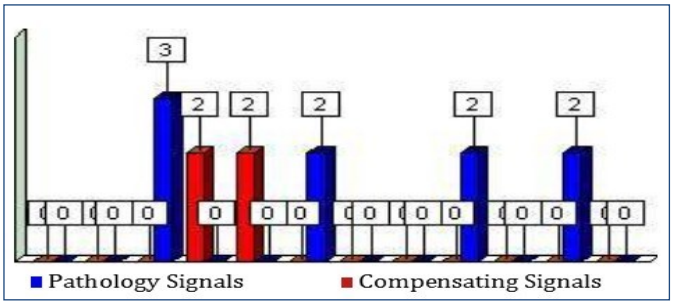

Fig. 5- Detailed Elaboration on Ear

5. Nose : Tension of compensatory abilities [Fig-7]

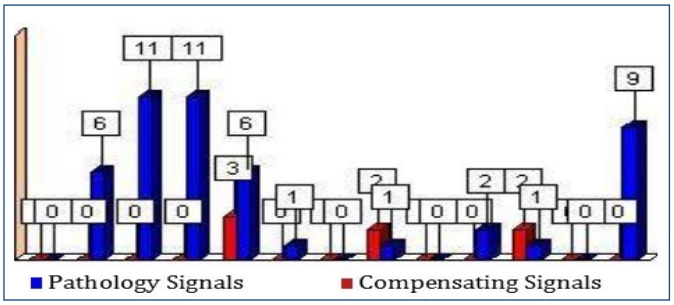

Fig. 6- Detailed Elaboration on Nose

6. Pituitary Gland: Chronic Fatigue: Pathology signal [Fig-7].

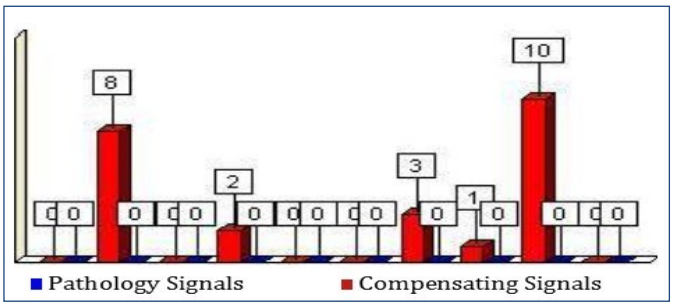

Fig. 7- Detailed Elaboration on Pituitary Gland

7. Thyroid Gland [Fig-8]

- Degenerative Process: Expressed pathology signal.

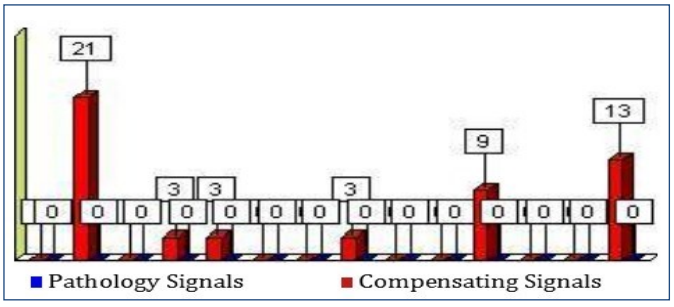

Fig. 8- Detailed Elaboration on Thyroid Gland

8. Adrenal Glands [Fig-9]

- Chronic Fatigue: Expressed pathology signal.
- Insufficiency of Adrenal Cortex: Expressed pathology signal.
- Cushing Syndrome: Compensatory signal.

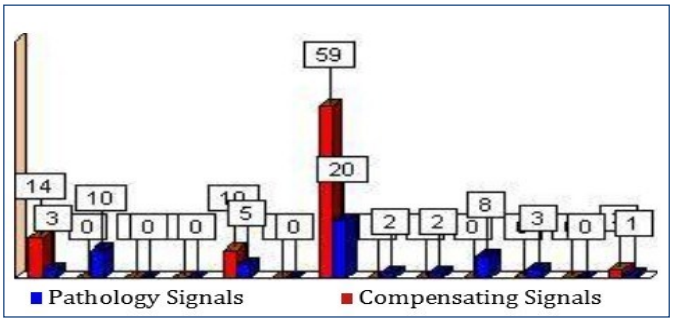

Fig. 9- Detailed Elaboration on Adrenal Gland

9. Prostate Gland [Fig-10]

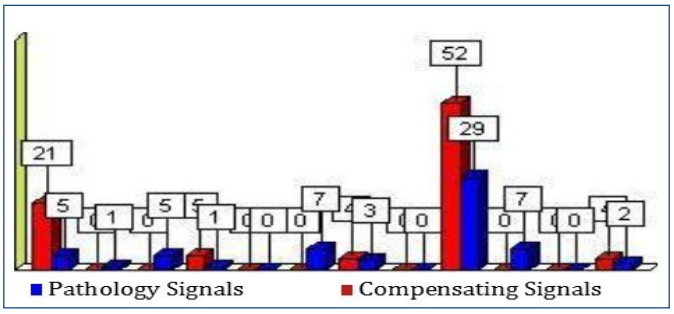

Fig. 10- Detailed Elaboration on Prostate Gland

- Sclerosing Prostatitis: Weakening of compensatory abilities.
- Calculous Prostatitis: Compensatory signal.
- Growth of New Cells: Compensatory signal.

10. Testicles : Post-Stress Effects: Pathology signal [Fig-11].

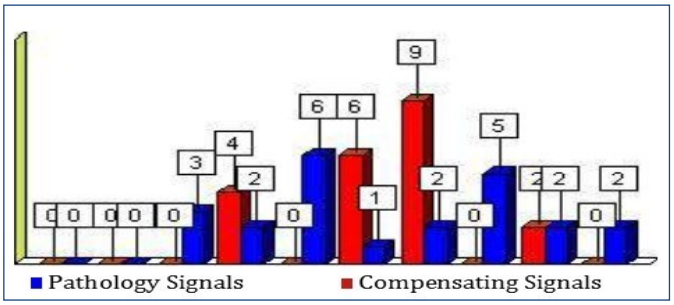

Fig. 11- Detailed Elaboration on Thyroid Gland

11. Liver [Fig-12]

- Chronic Fatigue: Expressed pathology signal.
- Disruption of Bilirubin Metabolism: Expressed pathology signal.

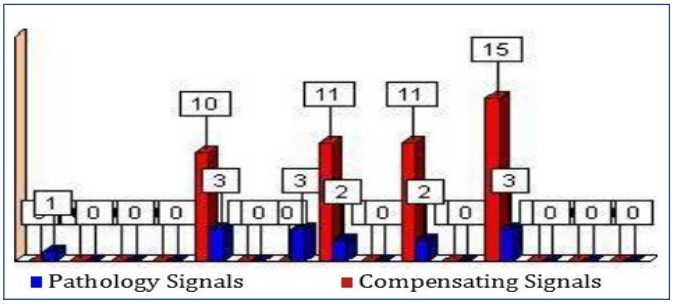

Fig. 12- Detailed Elaboration on Liver

12. Gall Bladder [Fig-13]

- Dyskinesia of Biliary Ducts and Gall Bladder: Expressed pathology signal.

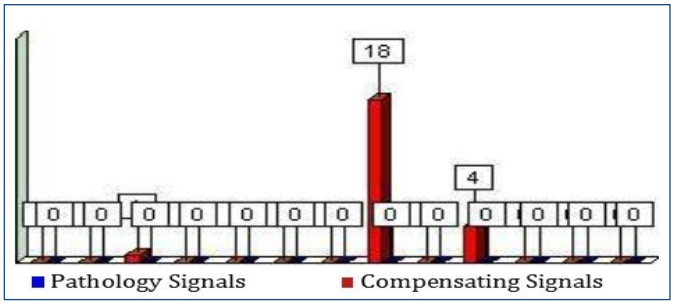

Fig. 13- Detailed Elaboration on Gall Bladder

13. Pancreas [Fig-14]

- Sclerotic Pancreatitis: Expressed compensatory signal.
- Pathology of Islands of Langerhans: Compensatory signal.

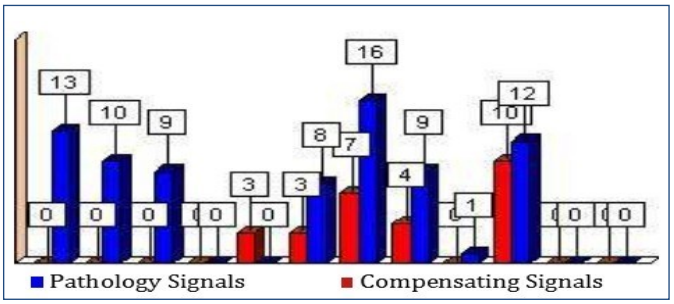

Fig. 14- Detailed Elaboration on Pancreas

14. Heart [Fig-15]

- Chronic Fatigue: Expressed pathology signal.
- Angina Pectoris: Compensatory signal.
- Growth of New Cells: Expressed compensatory signal.
- Myocardial Dystrophy: Compensatory signal.

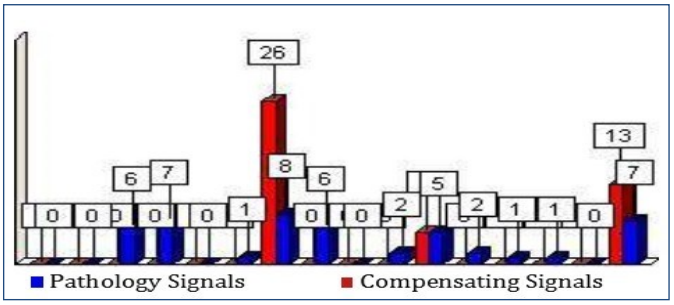

Fig. 15- Detailed Elaboration on Heart

15. Blood and Peripheral Blood Vessels [Fig-16]

- Phlebitis and Thrombophlebitis: Expressed pathology signal.
- Chronic Fatigue: Expressed pathology signal.
- Leukopenia: Expressed compensatory signal.

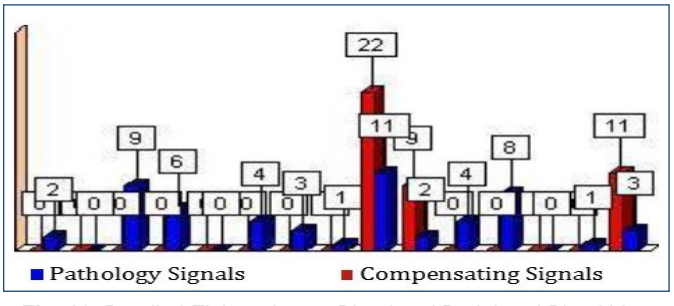

Fig. 16- Detailed Elaboration on Blood and Peripheral Blood Vessels

16. Spleen [Fig-17]

- Functional Changes: Expressed pathology signal.

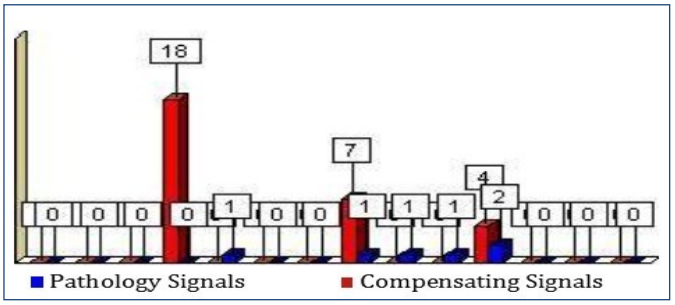

Fig. 17- Detailed Elaboration on Spleen

17. Lungs and Bronchi [Fig-18]

- Bronchiectatic disease: Expressed compensatory signal.
- Age-Related Changes: Compensatory signal.

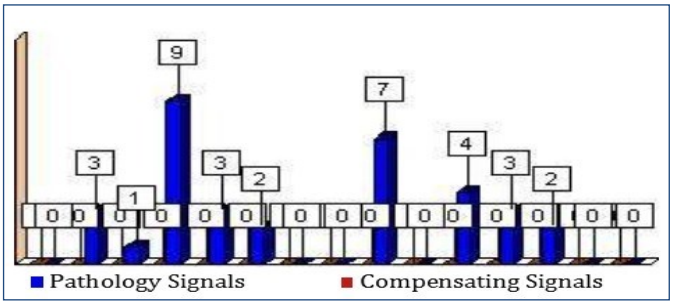

Fig. 18- Detailed Elaboration on Lungs and Bronchi

18. Skin [Fig-19]

- Eczema: Weakening of compensatory abilities.
- Growth of New Cells: Compensatory signal.
- Urticaria: Compensatory signal.
- Dermatitis: Compensatory signal.
- Herpes: Expressed compensatory signal.

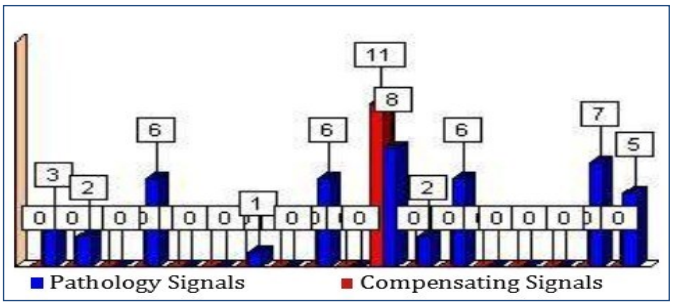

Fig. 19- Detailed Elaboration on Skin

19. Oesophagus [Fig-20]

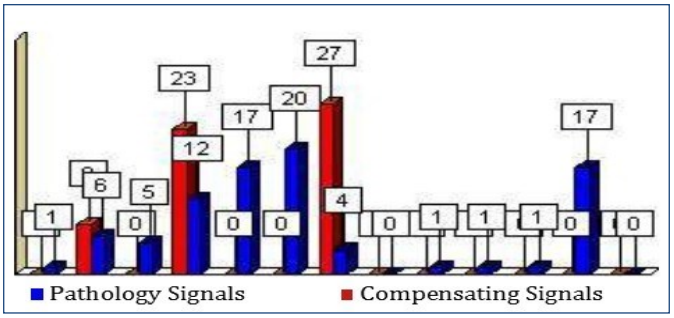

Fig. 20- Detailed Elaboration on Oesophagus

- Chronic Fatigue: Weakening of compensatory abilities.
- Diverticulum: Compensatory signal.
- Oesophagitis: Expressed compensatory signal.
- Abnormalities of Development: Expressed compensatory signal.

20. Stomach [Fig-21]

- Functional Changes: Expressed pathology signal.
- Post-Stress Effects: Expressed pathology signal.
- Gastritis: Compensatory signal.
- Intoxication Effects: Compensatory signal.

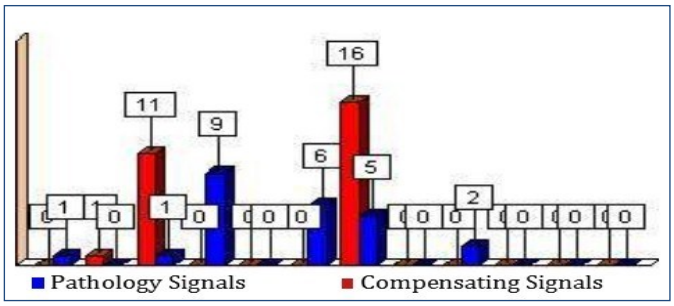

Fig. 21- Detailed Elaboration on Stomach

21. Duodenum [Fig-22]

- Dyskinesia: Compensatory signal.
- Growth of New Cells: Expressed compensatory signal.
- Tissue Growth: Expressed compensatory signal.

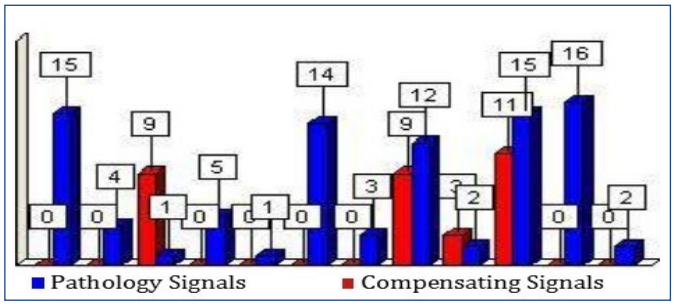

Fig. 22- Detailed Elaboration on Duodenum

22. Small Intestine : Intoxication Effects: Pathology signal [Fig-23]

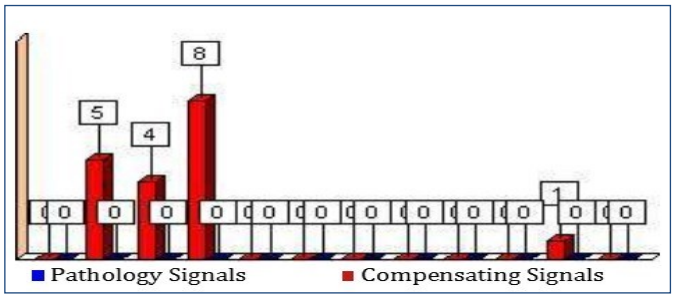

Fig. 23- Detailed Elaboration on Small Intestine

23. Large Intestine [Fig-24]

- Colitis: Expressed pathology signal.
- Post-Stress Effects: Compensatory signal.

24. Kidneys [Fig-25]

- Chronic Fatigue: Expressed pathology signal.
- Post-Stress Effects: Expressed pathology signal.
- Abnormalities of Development: Expressed compensatory signal.
- Tissue Growth: Compensatory signal.

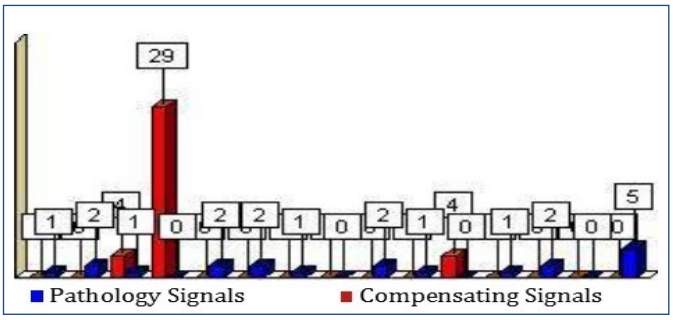

Fig. 24- Detailed Elaboration on Large Intestine

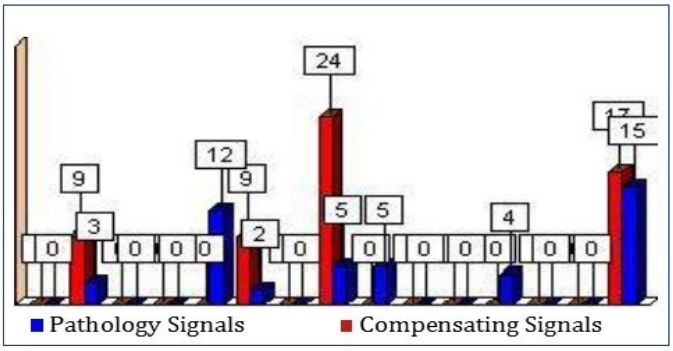

Fig. 25- Detailed Elaboration on Kindeys

25. Urinary Bladder [Fig-26]

- Post-Stress Effects: Expressed pathology signal.
- Urinary Bladder Polyposis: Expressed pathology signal.

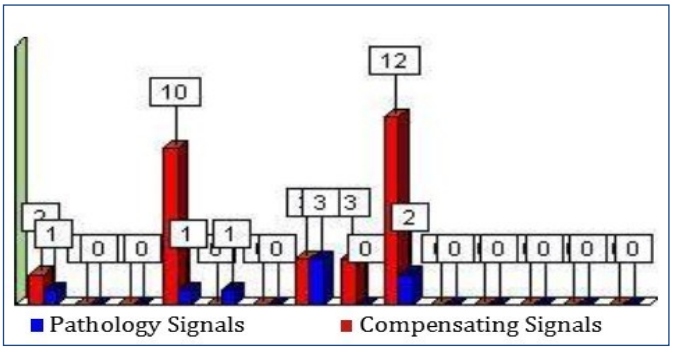

Fig. 26- Detailed Elaboration on Urinary Bladder

26. Penis [Fig-28]

- Post-Stress Effects: Expressed pathology signal.

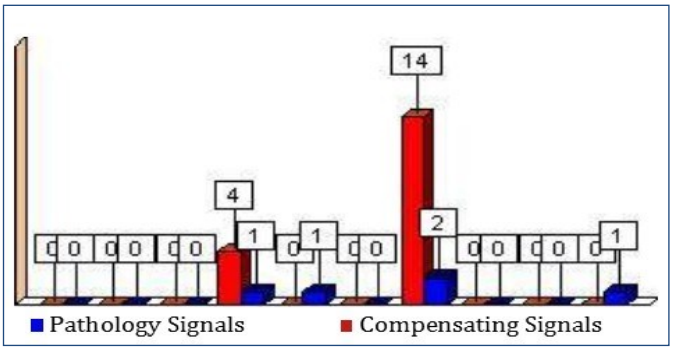

Fig. 27- Detailed Elaboration on Penis

27. Skeletal and Muscular System [Fig-28]

- Myositis: Expressed pathology signal.

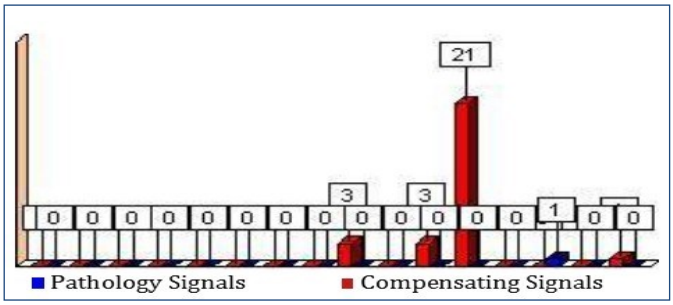

Fig. 28- Detailed Elaboration on Skeletal and Muscular System

Note : *The term compensatory refers to 'genotype' whilst the term pathology refers to 'phenotype'.*

Competing Interests

Graham Ewing is a Director of Montague Healthcare, a company which is solely devoted to the commercialisation of Virtual Scanning technology. Dr Igor Gennadyevich Grakov is the developer of this technology.

Acknowledgements

We thank the many excellent researchers who through their work have indirectly contributed to this article.

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