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# The multi-systemic nature of diabetes mellitus: Genotype or phenotype?

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## Abstract

**Background:** This article discusses factors which materially influence the diagnosis, prevention and treatment of diabetes mellitus but which may be overlooked by the prevailing biomedical paradigm. That cognition can be mathematically linked to the function of the autonomic nervous system and physiological systems casts new light upon the mechanisms responsible for homeostasis and origins of disease. In particular, it highlights the limitations of the reductionist biomedical approach which considers mainly the biochemistry of single pathologies rather than considering the neural mechanisms which regulate the function of physiological systems, and inherent visceral organs; and which are subsequently manifest as biochemistries of varying degrees of complexity and severity. As a consequence, histopathological tests are fraught with inherent limitations and many categories of drugs are significantly ineffective. **Aims:** Such limitations may be explained if disease (in particular diabetes mellitus) has multiple origins, is multi-systemic in nature and, depending upon the characteristics of each pathology, is influenced by genotype and/or phenotype. **Results:** This article highlights the influence of factors which are not yet considered re. the aetiology of diabetes mellitus e.g. the influence of light and sensory input upon the stability of the autonomic nervous system; the influence of raised plasma viscosity upon rates of reaction; the influence of viruses and/or of modified live viruses given in vaccinations; systemic instability, in particular the adverse influence of drinks and lack of exercise upon the body's prevailing pH and its subsequent influence upon levels of magnesium and other essential trace elements. **Conclusions:** This application of the top-down systems biology approach may provide a plausible and inclusive explanation for the nature and occurrence of diabetes mellitus.

**Keywords**: Physiological systems, diabetes mellitus, multi-systemic, mathematical modelling, autonomic nervous system.

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## 1 Introduction

The use of biomarkers to diagnose disease assumes that the measurement of a specific biochemical can be related to a specific disease state however there are inherent limitations with this approach. The most significant and limiting factors are as follows:

- It may not be possible to detect biomarkers for specific diseases because of their low levels [1].

- The unrepresentative nature of blood samples, sampling errors (e.g. due to sample viscosity), sample instability [2], operator errors, test errors, reporting errors, etc.

- There is no currently accepted understanding of the point at which a disease commences. The etiology of DM and related conditions e.g. PCOS, cardiovascular disease(s), etc; are not clearly understood [3, 4] although there are well accepted techniques for their diagnosis and treatment. Most tests are insufficiently sensitive to diagnose the prevalence of disease from its earliest origins. Moreover the fundamental nature of such techniques i.e. how to compare the measured results of pathology with 'what is considered to be normal', may be such that

biomarker-type tests may not be able to overcome this limiting factor.

- The results of biomarker-type tests are compared with an experientially derived range of values. If the patient's results are within the expected or normal range they are considered healthy. This leads to false positives where the patient's results are considered abnormal yet they are healthy, or false negatives where the patient's results are considered normal yet they are in poor health. Often such misdiagnoses are only recognised at autopsy. It is assumed that such limits are stable throughout life however the homeostatic limits are linked to the autonomic nervous system and are continually in a state of flux. In particular, they are dependent upon age, sex and weight.

- There are difficulties when making diagnostic conclusions based upon cut-points identified from the various tests e.g. in diabetes: IFG, IGT (OGTT) and HbA1c [5]. Although there is a clearly established and indisputable value in the differential diagnosis and categorisation of DM by such tests it is nevertheless necessary to recognise their inherent scope and limitations [6-8].

- 90% of drugs are ineffective in 50% of the population [9]. In this review drug treatments for DM are considered to be circa 57% effective.

- Most medical conditions have a multi-systemic nature i.e. pathology irrespective of its origins influences the stability of many of the body's physiological systems, not just single systems and single biochemistries. Moreover the body/physiological system(s) adjust to compensate for the developing pathology [10-12] i.e. a stable 'pathological functional system' is established (the chronic condition). Different physiological systems may exert a compensating influence for the same condition. It is postulated that DM is a multi-systemic disorder influencing the regulation of different physiological systems [13]. Consequently it becomes important to consider the overall level of systemic instability and, in particular, the various biochemical manifestations associated with the dysregulation of PG.

- The measurement of biomarkers considers only the level of the biomarker. In such cases the level of the biomarker may be greater or less than the available substrate i.e. the level of both protein and substrate are equally significant. It may be possible to have a low level of protein yet the overall rate of reaction is normal or to have a high level of protein yet the rate of reaction is low. In addition, the reaction conditions or the toxins produced may inhibit the reaction. A more significant measure is the rate at which the biomarker reacts with substrates (Fig. 2).

- The approach is not person-specific and hence is not able to take into account contextual (racial and environmental) variability [14, 15] i.e. the influence(s) upon a person born in one climatic zone and living in another (perhaps less immunologically compatible) zone.

- The understanding of disease fails to recognise and/or to take into account the influence of sensory input upon organ function i.e. (i) the prevailing level of natural sunlight; (ii) if the patient is given medication but subsequently re-enters the same environment which is the fundamental cause/stress of their condition then the condition will continue (see figure 3); (iii) the release of insulin is triggered by the perception of food intake prior to the digestion of food. This has significance to the management of food intake.

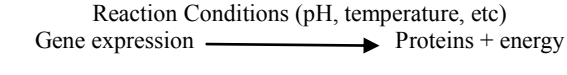
- The environmental factors which influence gene expression (genotype and epigenetics) i.e. the level of proteins expressed, and the factors which influence protein reactivity (phenotype). The factors which influence rate of protein reactions will ultimately be manifest in ways which alter metabolic rate and the onset of pathophysiologies. Circa 25 genetic loci have been associated with NIDDM e.g. a mutation in the beta-3-adrenergic-receptor gene [16], variant of transcription factor 7-like 2 (TCF7L2) gene [17] (n.b. purely as a result of nucleotide variation within TCF7L2), etc.

- Conventional logic assumes that the occurrence of obesity in families justifies the conclusion that this is due to genetic origins however this could be due to habit i.e. that a child brought up by obese parents is unlikely to have an active life or balanced diet. Conventional logic assumes that obesity is the consequence of genetic mutations however there is little work which studies the reverse i.e. influence of obesity upon the genes. It suggests that it is the biochemical consequences of obesity which influence genetic stability, and ultimately lead to genetic mutations. This is supported by noting that reversal of obesity decreases the risk of NIDDM [18] and that diet influences the genetic pathways [19]. It supports the non-genetic argument i.e. that of phenotype, in those with NIDDM. It supports the conclusion that the body is a biodynamic system in which gene and system function influences the body's biochemistry and vice versa [20].

# 2 Physiological Systems

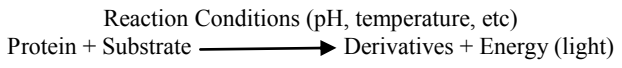
2.1 There are factors (genotype) which influence the rate at which genes express proteins (Fig. 1). In addition, most genes produce proteins which react with their reactive substrates according to the prevailing reaction conditions (Fig. 2). This is fundamental to all biochemical reactions yet is often conveniently overlooked in biomedical research. The rate of reactions (and extractions) in the body, including the rate at which proteins react (phenotype), is limited by various factors e.g. pH, temperature, levels of magnesium, etc.

**Fig. 1** Genotype



The complex nature and structure of DNA including histones and chromatin, interacts with enzymes and subsequently expresses proteins. All enzymes have optimum function within a specific pH range therefore pH may influence gene expression.

**Fig. 2** Phenotype




2.2 pH is influenced by exercise which influences the ratio of CO2/O2 in blood [21]. Apparently minor alterations to pH influence the ability of the blood to absorb nutrients i.e. minerals (e.g. the levels of Fe (II)/Fe (III), the balance of Ca/Mg, Na/K and other apparently minor trace metals) [22] and vitamins. The bioabsorption of differing mineral salts will vary and will be influenced by the prevailing reaction conditions [23]. Severe alterations to pH (e.g. systemic instability during pregnancy and of complications such as pre-eclampsia, or the excessive consumption of acidified soft drinks) induce the reverse effect i.e. a decline in mineral levels (Fe, Na and Mg). This illustrates why nutritional supplements and drugs may be relatively ineffective i.e. the body's prevailing biochemistry influences their absorption and/or reaction. In addition increased PG and levels of fatty acids will increase blood viscosity which in turn will influence the dissociation of reagents, metabolites and toxins to and from reactive sites thereby influencing the rate at which proteins react and alter cell function [24-27].

2.3 The neuroregulation of body temperature influences metabolic rate [28, 29] i.e. it influences the rate at which PG is metabolized. At higher levels, typically above 40C, temperature influences the degree of folding or unwinding of proteins and hence influences their reactivity however body temperature is generally lower than normal in those with NIDDM and obesity [30, 31]. The neuroregulation of temperature and viscosity are interlinked. As outlined above, viscosity influences the rate at which proteins, hormones and their metabolites diffuse to and from reactive sites. Accordingly high blood viscosity lowers heart rate, and/or raises heart rate to compensate thereby increasing BP. This influences the rate at which PG is metabolized and lowers body temperature. Excess PG is preferentially metabolized into triglycerides. This is predominately an anaerobic process. This may explain why (i) short sharp bouts of exercise normalize PG levels; (ii) the effects of exercise are relatively long-lasting; and (iii) why heart drugs which are designed to lower BP (or which have the side-effect of lowering metabolic rate) are invariably linked to increased rates of NIDDM and obesity; and (iv) why inactivity is often accompanied by weight gain. Exercise increases heart rate and the rate at which PG is metabolized. This increases body temperature, increases the rate at which body fats are metabolized, and/or thins the blood.

2.4 pH and temperature are physiological systems (Table 1).

**Table 1** Physiological Systems

| | | | |
|---|---|---|---|
| Sleep | Temperature | Breathing | Digestion |
| Blood pressure | Blood volume | Blood Glucose | Blood Cell Content |
| pH | Posture | Osmotic Pressure | Excretion (Urination) |
| Sexual function | Locomotion | | |

2.5 Exercise through muscle function is required to metabolise PG [32].The neuroregulatory process maintains the intracellular levels of glucose at a stable level/range whilst an estimated 80% of glucose uptake is metabolised in muscle. Exercise regulates pH and subsequently influences the absorption of minerals e.g. the balance of Ca/Mg. Magnesium is essential for muscle function therefore a deficiency of Mg will influence muscle function and the aerobic pathways for metabolism of PG. Magnesium deficits are implicated in the aetiology of DM [33], cardiovascular disease [34], osteoporosis [35], etc. This is especially significant in the elderly. Such observations illustrate that the body's function is that of a neuroregulatory biofeedback system. Whilst the concept of Physiological or Functional Systems [36, 37] is not new to the GP, medical research has steadfastly ignored its significance preferring instead to consider biochemical pre-eminence over system function rather than the alternative i.e. that biochemical dysfunction and pathologies are the consequence of systemic instability.

# 3 Diabetes Mellitus Is Multi Systemic Disorder

3.1 Diabetes Mellitus is a multi-systemic disorder influencing the regulation of blood glucose [13]. It is variously referred to as type 1 (IDDM) or type 2 diabetes (NIDDM) but could equally well be known as hyperglycaemia or hypoglycaemia, or hyperinsulinaemia or hypoinsulinaemia. Its fundamental origins are due to the inability of the pancreas and pancreatic beta cells to function normally either (i) by the lack of insulin due to the influence of the ANS on the pancreatic beta cells and hence of inhibited production of insulin; or (ii) the inability of insulin (and of associated cellular processes) to convert PG into glycogen. Such processes are driven by the prevailing reaction conditions. Although bearing the same or similar identity they are two fundamentally different conditions.

3.2 In IDDM, the pancreas is not able to produce insulin quickly because it is a very large and reactive hormone. In order to overcome this limitation the pancreas stores insulin, as a hexamer, in readiness for its use in the digestive process. This hexamer, a zinc complex, dissociates into its components under the right conditions i.e. (i) zinc is essential for the normal function of this process; (ii) the normal function of pancreatic beta cells are regulated by the ANS.

3.3 Current research has demonstrated that stem cells may be stimulated to restore the function of pancreatic

beta cells in patients with IDDM however as yet the effect is short-lived. Often patients relapse, their pancreatic beta cells fail to sustain the production of insulin, and they require insulin supplementation [38, 39] i.e. the ANS is not able to sustain the existence or function of pancreatic beta cells.

3.4 The body's function is influenced by sensory input (Fig. 3). The colours and intensity of light (and hence of sensory input) have a significant effect upon the regulation of the ANS and physiological systems [37]. Accordingly sensory input is interpreted at different levels e.g. signals processed at the sensory level influence at a cognitive or psychological level i.e. the beta and alpha EEG frequencies; whilst signals processed at a systemic or visceral level influence the body's physiology [20] i.e. the theta and delta EEG frequencies.

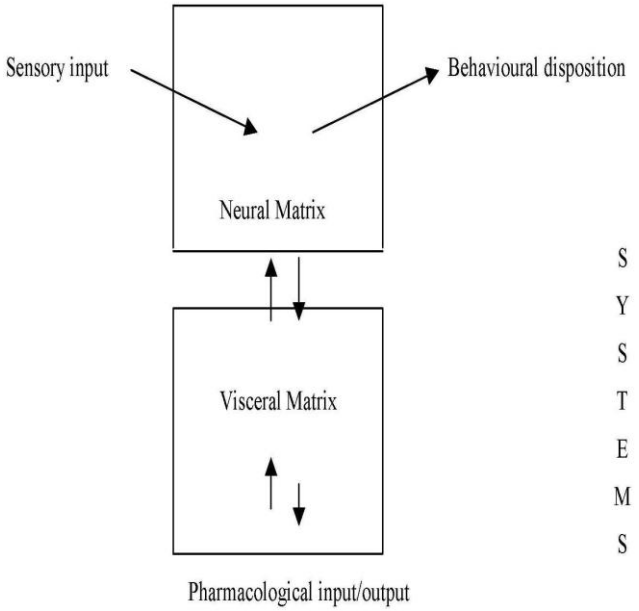



**Fig. 3** The influence of sensory input upon the body's function

3.5. The mechanisms responsible for autoimmunity have not yet been elucidated. Autoimmunity is generally considered to be the failure of an organism to recognize its constituent parts thereby facilitating an immune response against its cells and tissues. There are lower and higher levels of autoimmunity (hyper and hypo function). Autoimmunity is influenced by a number of factors which influence the ANS. e.g. genetic predisposition, suppressed protein expression, suppressed protein reactivity (e.g. insulin and leptin resistance), and the long-term influence of stress [40]. This leads to physiological instability; suppressed immune function; lowered levels of b-cells and t-cells; cognitive dysfunction [41]; etc. Normal immune function requires the activation of b-cells by t-cells before it can produce antibodies in large quantities. The long-term consequences of a maladjusted immune function influence absorption of nutrients, minerals, pH, etc. Consequently the suppressed availability of such cells or their inhibition by the prevailing biochemistry will be manifest as lowered immune function, autonomic instability [42], and/or the manifestation of the condition recognized as autoimmunity.

There is a substantial body of evidence which indicates that vaccines make a significant contribution to the occurrence of autoimmune disease. Prior to the introduction of vaccines IDDM occurred at a rate of circa 1 in 7,000. This has risen steadily to a rate now believed to be more than 1 in 400 [43, 44]. Vaccines influence the balance of viral scavengers [45, 46] i.e, and they suppress the production of b-cells, t-cells, etc. Under such circumstances the lowered concentration of these cells impairs antibody formation which becomes less effective against viral pathogens. This leads to the progressive failure of immune function and the increased incidence of auto-immune disease which we note as allergies [47-49] and immunodeficiency [50]. Furthermore the introduction of many vaccines in the typical vaccination programme introduces a large number of foreign proteins. Under such circumstances immune function may never return to its original base state [51]. There is a suspected relationship between immunizations and the occurrence of auto-immune disease(s) [52] e.g. rheumatoid arthritis [53, 54], multiple sclerosis, diabetes mellitus, lupus erythematosus, lymphoma, leukemia, etc. Some viruses [55-58], and modified live viruses given in vaccines, alter the structure and function of RNA and DNA. Viruses are known to contribute to the occurrence of DM [59, 60]. Each virus is a large molecule therefore its spatial arrangement must influence the stereochemistry of cross-helical structures and linkages within the DNA helix and hence of subsequent protein expression. It is inevitable that the steady accumulation of such foreign proteins arising from an intensive vaccine programme will reach the stage where it influences DNA, gene, and chromosome structure and function. The prevailing reaction conditions - the consequence of protein expression which have been influenced by previous vaccines - may also affect the introduction of each modified live virus. Each is likely to suppress immune function. The greater the number of viruses and foreign proteins: (1) the greater the influence upon immune function and the time required for recovery from each vaccination and; (2) the greater their influence upon DNA, gene and chromosome structure and function, the greater will be their influence upon protein expression, protein mobility [61], system function, etc. The greater the amount of vaccines, introduction of foreign proteins and hence of alterations to the body's most fundamental biochemistry, the greater the risk that the body's immune function no longer recognizes or responds to existing vaccines or diseases [62], and that its immune response has been altered [63]. Genetic mutations, and their influence upon protein/hormone expression and reactivity, influences the regulation of PG and hence the regulation of metabolic rate, metabolism of fat, and ultimately the occurrence of DM and obesity [64]. The spatial structure of genomes and related protein expression [65] alters the stability of the various physiological systems e.g.

- Transition [66] and heavy metals e.g. Nickel [67], Chromium [68, 69], Mercury [69-71], etc; influence gene and chromosome function, contribute to autoimmunity, and increase susceptibility to various behavioural and pathophysiological disorders including cancers.

- The order of addition of metals influences physiological stability [72].

- Spatial orientation influences chromosome 'switching' [73, 74].

- Altered immunoglobulin function, arising from substitution of bound sugars, alters its ability to bind to its receptors [75].

- Abnormal immunoglobulin levels [76-78] have been found in patients with IDDM i.e. IgA, IgD, IgG.

- Infection by viruses may lead to immunoglobulin class-switching [79, 80] e.g. the infection of human B cells with rhinovirus or measles virus could lead to IgE class switching i.e. b lymphocytes typically express IgM but under appropriate conditions can secrete immunoglobulins IgG, IgA, or IgE. IgE in particular may facilitate the release of histamine and leukotrienes which are associated with a hypoallergenic response.

- Protein misfolding [81] has been implicated in the etiology of over a dozen medical conditions including Alzheimer's disease, DM and mad cow disease. Conditions in the cell actively influence the degree of protein folding and influences protein and cellular activity [82, 83].

- Some viruses have a naturally oncolytic activity e.g. Seneca Valley virus [84], Coxsackie virus, Adenovirus, etc; whilst other viruses can be modified to treat cancers [85-87] by suppressing gene mutations and/or or enhancing the genetic processes which regulate protein expression.

- Chemical alterations e.g. thalidomide [88]. Thalidomide inserts itself into the guanine-cytosine regions of DNA. This influences the sections of the genes which participate or control the development of ears, eyes and limbs.

- Ethyl Alcohol in the form of beer or other alcoholic beverages rapidly introduces a high calorific intake which results in a high demand for insulin and a high residual level of insulin. Such drinks typically have a low pH (typical pH 3.5) which influences its metabolism; perhaps favouring different enzymes i.e. pancreatic enzymes amylase and trypsin have optimum function in the pH range 7.0-8.0. The digestive acidity is regulated to optimise the appropriate pH for each enzyme. Ethyl Alcohol is believed to link with DNA and suppress protein expression whilst the formation of acetaldehyde, ethyl acetate and its subsequent metabolism as CO2 contributes to increased blood acidity. Consequences of the metabolism of ethyl alcohol include hypoxia in the liver, the formation of reactive oxygen species [89] and the subsequent development of cardiovascular disease and other side-effects [90]. In addition, Ethyl Alcohol lowers the delta frequency in the brain thereby influencing the quality and quantity, and regenerative properties, of sleep.

- Drug addition has to take into account existing disease states and the possibility of side-effects arising from other biochemical interactions e.g. due to other drugs.

Steroids (Prednisone), antidepressants (Paroxetine, Sertraline), anti-seizure medications (Valproate), antipsychotics (Olanzepine), blood pressure medications (Propranolol, Doxazosin), anti-diabetes medications (Glibenclamide, Chlorpropamide) and heart-burn drugs (esomeprazole, Lansoprazole) interfere with autonomic regulation of system function and often contribute to weight gain.

- The increased occurrence of DM and obesity [91] parallels the worldwide increase in vaccination rates. In particular, an increased occurrence of IDDM appears to parallel the introduction of the vaccines and in particular that of the controversial MMR vaccination. Vaccines contribute to the occurrence of autoimmunity however the issue is complicated by the way in which vaccinations are given [92-94]. In which order are the vaccines administered to each child? Does the vaccination take into account the genetic nature and/or immune status of each child? Could the vaccination have been given when the child was subjected to stress (perhaps in the domestic environment or through poor diet)? Could the vaccination have been given when the child's immune function is compromised e.g. by another viral or bacterial infection? Which other vaccinations have been given in the past? Has the child's immune function recovered (to its base level) following the most recent vaccinations? Which vaccinations are being given simultaneously?

IDDM is an Immune-mediated disease [95] i.e. associated with genotype. By contrast NIDDM is, in most cases, a reversible condition i.e. associated with phenotype.

- Measles and mumps are implicated in the occurrence of IDDM. Various viral infections have been implicated in the aetiology of IDDM [96-99]. A significantly increased rate of occurrence of IDDM followed the introduction of the triple MMR vaccine in the period 1982-7 [100-105]. Under normal circumstances, exposure to a viral pathogen is handled by the immune function which acts at the interface between the body and its environment, typically in the nose, throat, lungs, skin, gut, etc; however vaccination by injection by-passes the body's natural immune mechanism. This is hugely significant and often overlooked. It by-passes the body's signalling mechanisms and the sites at which immunoglobulins are most concentrated and where their viral scavenging activity may be most effective. Immune suppression e.g. by vaccination, infection and stress; is linked to the occurrence of IDDM [106,107]. Accordingly could different degrees of immune suppression, perhaps through combinations of vaccines (given singly or in a single multiple doses) or other factors, lead to genetic mutations, changes in the nature and extent of protein expression, and the subsequent development of autoimmune diseases such as IDDM? For example (i) children of Somali parents vaccinated according to typical

western vaccination schedules have significantly greater rates of regressive autism [108]; (ii) the use of anti-oxidants to enhance immunity appears able to raise the response or immunity to viral infection [109-111]. It appears evident that the nature and extent of epigenetic influences upon gene and chromosome structure alter the body's function and leads to pathophysiologies of varying magnitude and significance.

3.6 Excessive weight has a subtle psychosomatic influence which is initially manifest as fatigue, lethargy, lack of motivation, being hungry or thirsty, eating or drinking to excess, etc. Thereafter its physiological significance increases. The body may not have the musculature to support the increased weight or the available musculature may not be evenly distributed e.g. it may be focussed upon the hips, and the thighs and calves of the legs. Irrespective there is a need for increased energy to move the increased mass. The nature of fat distribution throughout the body determines the extent of the stresses acting upon the various structures, joints, and linkages. Muscles are required to burn glucose and generate energy. Every cell requires energy to maintain its function therefore increased weight requires energy (i) to maintain normal physiological function, (ii) to support and/or transport increased weight, and (iii) to maintain the function of fat cells. Movement becomes slower. Extra weight prevents loss of surplus heat and subsequently influences body temperature. This influences sleeping patterns, rate of metabolism, the function of the endocrine glands, the requirement for insulin, the rate and quality of excrement (solids) and urination (liquid), the ability to inhale (and hence the CO2/O2 ratio in the blood), etc. It influences the function and stability of all of the body's physiological systems and hormones e.g. leptin and insulin resistance are noted consequences of diabetes and are associated with the decreased ability to regulate food intake - leptin and ghrelin being markers of appetite and satiety. The consequences of this physiological instability is expressed as disruption to all physiological systems (see table 1) e.g. influencing the absorption of minerals, vitamins and nutrients; the regulation of hormone levels; the regulation of cholesterol levels; the elimination of toxins; the regulation of water intake and hence the need for salt to maintain osmotic pressure and normal inter-cellular communication, etc.

3.7 It is generally assumed that single biochemical processes can explain single pathologies however there are many cases where single biochemical processes are not able to define the nature of complex pathologies. In such cases, including that of IDDM and NIDDM and subsequent disorders, the body's physiology is of such complexity that single pathological processes do not provide satisfactory explanations for the occurrence of the condition under consideration or of associated side-effects. In such cases the varying origins of the condition initiate differing pathological processes and/or different reaction conditions. This explains why for example DM is often linked to the occurrence of cardiovascular disease and chronic kidney disease but that such conditions may also occur without their manifestation as DM. Similar examples are the occurrence of (i) duodenal ulcer – linked to helicobacter pylori i.e. h. pylori does not indicate that all exposed to this organism will develop a duodenal ulcer. Some without h.pylori develop duodenal ulcers whilst others with h.pylori do not develop duodenal ulcer; and (ii) the metabolism of ethyl alcohol – usually attributed to the principal alcohol metabolising enzymes alcohol dehydrogenase and aldehyde dehydrogenase – but also metabolised by a range of structurally related iso-enzymes [89], catalyse, cytochrome P450, etc. The balance of isozymes being genetically determined.

3.8 There are a number of precedents which illustrate the existence of the body's biofeedback mechanisms e.g. (i) that a severe stroke is usually followed by progressive failure of the various physiological systems, (ii) that there is poor metabolic control following pancreas and kidney transplantation, (iii) in the case of a severe trauma i.e. of 'coma', the biofeedback mechanism may be completely or partially impaired, (iv) in the case of organ transplantation there is a need for immune suppressive drugs and also to reduce exposure to natural or strong sunlight i.e. the body recognises the transplanted organ as a foreign body.

3.9 Age-related physiology: the physiological limits of DM are age-dependent. In general there is an increased progression of DM with age e.g. requiring medication and/or islet transplantation in the over 50's. In recent years the age of onset of DM has become earlier [112,113].

3.10 The physiological limits are weight dependent i.e. significant weight increases lead progressively from pre-diabetes (IFG), to IGT. Morbid obesity influences biofeedback and autonomic regulation.

3.11 A woman's biochemistry is heavily influenced by oestrogen whilst a man's biochemistry is heavily influenced by testosterone. This alters their ability to regulate PG levels. In general women have higher mean PG levels than men.

# 4 Cognitive Evidence And Significance

That altered cognition is associated with the body's regulation and function, and that this is a significant issue, is supported by a number of precedents:

- There is a defined relationship between cognition, the ANS and physiological Systems [114]; and the occurrence of disease [115] which is linked to the occurrence of DM, obesity [13] and metabolic function [114]. This may have value as a diagnostic technology re the screening for DM and diabetic side-effects, including cardiological screening [116].

- Drugs have cognitive side-effects. Cognitive side-effects, in particular those influencing visual perception, are commonly reported as a side-effect of most

drugs e.g. those used in birth-control, and in the treatment of infections, DM, erectile dysfunction, depression, etc.

- Disease has cognitive side-effects. Cognitive side-effects are a commonly reported side-effect of DM, cardiovascular disease(s), migraines, viral and bacterial infections, depression, dyslexia, autism, etc.

- Patients with B or T-cell immunodeficiencies have cognitive side-effects [41].

- Stress influences the balance between the parasympathetic and sympathetic nervous system and suppresses b-cell and t-cell production [117-118]. The function of the ANS is influenced by stress which influences visual perception. In particular the perception of blue and red is linked to the function of the ANS [119].

- Light is both emitted and absorbed by the body. Under normal conditions the absorption and emission of light is in an apparent equilibrium however the development of pathologies alters this balance. Consequently the perception of color and their intensity alters to reflect such physiological changes. This links the influence of light to the body's biochemistry and hence to its systemic regulation and function [20]. This influences sensory input and visual perception. Light has been shown to influence many, if not all, of the body's key physiological functions. The most notable being the generation of Calcitriol, essential for normal immune function, by the epidermis. The epidermis regulates the light received and subsequent generation of Calcitriol according to the intensity of prevailing sunlight.

Light influences the autonomic nervous system and is associated with all aspects of the body's function including the migration of stem cells, the production and metabolism of Nitric Oxide [120-122], the function of the lymphatic system, regulation of intercellular pH balance, improved wound healing [123], modulation of the immune response [124], stimulation of T-cells [125], sexual function [126], etc. The therapeutic use of light has been positively associated with the treatment of over 100 medical conditions including DM [127,128], cardiovascular disease(s), migraine, hyperbilirubinaemia, etc. Significantly reduced exposure to sunlight is recommended in organ transplant patients being given immune-suppressive treatments i.e. to prevent the rejection of organs.

Light, in particular the perception of colors, forms the basis of Virtual Scanning technology [129,116]. It involves mathematical modeling the consequences of cognition, in particular of visual perception and memory, upon the ANS and physiological systems. Such methodology links color perception to pathology and forms the basis of a unique cognitive technique able to diagnose most/all medical conditions (see attached example 1 reports). Furthermore as outlined the technique appears to be free of the fundamental limitations which influence biomarker-type techniques. In addition the understanding of the nature and structure of the physiological systems leads to an understanding of the relationship with brain wave frequencies which have therapeutic significance (claimed to be up to 93.2% effective in a comparative study involving 1678 patients conducted at various Russian medical institutes). The significance of this technology and of its diagnostic and therapeutic applicability are increasingly widely reported [129-131] (Example 1).

# 5 Summary

5.1 The body functions in a biodynamic manner in which neither the brain nor visceral organs function independently, each being dependent upon the other. That the body's function is influenced and/or regulated by sensory input opens the way to an enhanced understanding of the causes of DM and obesity. Light has a multi-level role i.e. (i) it has a diagnostic value, (ii) it has a therapeutic value [20,130], and (iii) appropriate sensory input is required to educate (in the form of behavioural therapy) against dietary transgressions e.g. to limit the consumption of beer (typically pH 3.5) or acidified soft drinks (typically pH 2.5) which influence the digestive system's ability to absorb Magnesium and other necessary trace elements (zinc, chromium, etc). This Mg insufficiency, prevalent in DM and CVD, influences the function of all muscles and hence the function of all visceral organs which are dependent upon rhythmic muscle function.

Increased viscosity, the consequence of poor lifestyle and/or diet, influences the rate at which proteins react. It is linked to impaired metabolic rate and high blood pressure i.e. the heart pumps harder to maintain the flow of oxygenated blood to the brain, and illustrates the need for good diet to ensure adequate levels of viral scavengers and anti-oxidants which are necessary to minimise viral infection and to protect against oxidative stress.

5.2 Of greater controversy is the evidence, viz a viz 'the epigenetic argument', that viruses and vaccinal RNA/DNA influence gene structure and function and that they enhance susceptibility to DM, in particular to IDDM. It is clear that various viruses are linked to the occurrence of autoimmune disease. Accordingly the use of modified live viruses is also likely to be linked to increased predisposition to autoimmune disease. Furthermore the combination of lowered immune function with a schedule of vaccinations e.g. in a child which is living in a different context (perhaps an African origin child now living in Northern regions of America or Europe), leaves such children vulnerable to a spectrum of autoimmune disease(s) and cognitive dysfunction. The sequence of exposure to metals influence gene and chromosome function and contributes to autoimmunity. Similarly the occurrence of IDDM increased following the introduction of the MMR vaccine. Prior to this the vaccines were given singly. This indicates that the sequence in which vaccines are given is likely to influence autoimmunity. Vaccines lower b and t-cell function and contribute to a lowered and less specific immune response. This affects the ability of immunoglobulins to bind to their receptors and hence

influences their effectiveness i.e. it is the effectiveness of antibodies which is significant, not just their existence!

There is a need for greater emphasis upon a balanced diet and the avoidance of factors which lower immune function and contribute to the emergence of autoimmune disease in the case of IDDM or physiological instability in the case of NIDDM.

5.3 Drugs are tested in clinical trials against highly selected patient populations. This can be as little as 1% of those with the condition. It comprises those with a selected profile e.g. similar symptoms, age, weight, sex, genetic/racial origins, etc. On the basis of a satisfactory outcome the drug will be approved for use in the selected population, perhaps more widely. In order to identify the cause of a disease the prevailing medical paradigm requires evidence i.e. it is necessary to find a specific cause. This requires the above process to be reversed however the problem arises if the cause is not associated with a single parameter. If autoimmune disease is caused by a combination of factors as many suspect (e.g. the age (stage of development of the child's ANS) at which a vaccination is administered, the state of the immune system, the order in which vaccinations are given, the time between vaccinations, specific characteristics of each vaccine, etc), it will be almost impossible to identify which vaccine or combination of vaccines were responsible. In such cases the epidemiological evidence will be most significant: (1) how does the occurrence of autoimmune disease compare between those vaccinated and those unvaccinated (ii) did the occurrence of autoimmune disease increase (a) when single vaccinations were introduced, (b) when the schedule was increased and (c) when multiple vaccinations were introduced? As outlined, the occurrence of IDDM and NIDDM is paralleled by an increase in the schedule of vaccinations. The testing of vaccines is conducted on adults however, upon satisfactory outcome of abbreviated clinical evaluation; they are generally approved for use in children. This overlooks the essential physiological differences between the pre-pubertal child and the post-pubertal adult. Such changes to hormonal levels i.e. of oestrogen in the female and testosterone in the male have a significant influence upon the ANS. It is only at puberty that sexual maturity (and hence the maturation of the ANS) is complete. In addition vaccines are given by injection whereas normal exposure to viruses is through the body's environmental interfaces i.e. the clinical evaluation of vaccines is not being tested in comparable situations. Finally, the evidence-based approach requires that drugs are tested for drug-drug interactions however, by contrast, vaccines are not tested for the long-term effect of vaccine-vaccine or vaccine-drug interactions or against other immune suppressing (or raising) influences.

5.4 The understanding of the role played by light conceivably offers a plausible alternative approach to the diagnosis of such conditions and their impact upon the body's function and health. It conceivably opens up the understanding of ways to regulate the body's function, to enhance the effectiveness of drugs, and hence to treat DM and diabetic complications. Stable pathological functional systems, established by altered protein expression, could be treated by such techniques. It highlights the need, as outlined in this article, for a greater understanding of the factors and mechanisms which regulate the body's systemic function. The work by Russian researchers illustrates that light can be adapted with significant diagnostic and therapeutic effect, perhaps more effectively than that used by orthodox medicine. Although medical precedents (verified mainly by medical professionals in Russia) and published work is increasingly available there is not yet a programme of clinical studies which proves beyond reasonable doubt the claims made for such a technology. Nevertheless the published data illustrates how such methodology is consistent with observed phenomena. Of greatest interest is the significance and potential applicability of such technology to the understanding of forms of DM, its diagnosis and treatment.

There is a need to have proper unbiased scientific evaluation of the issues, as outlined, before the long-term cost of managing (i) the epidemic of IDDM and related side-effects exceeds the benefit of vaccinations to society and (ii) the epidemic of NIDDM and related side-effects overwhelms the capacity of healthcare systems throughout the world.

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# 7 Competing interests

Graham Ewing is Director of Montague Healthcare, a company dedicated to the future commercialisation of Virtual Scanning.

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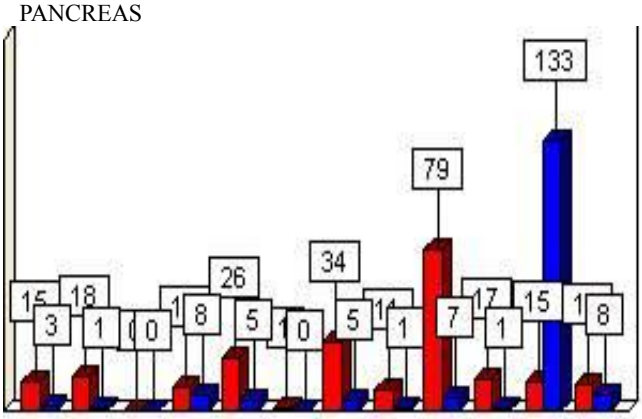
# Example 1 Diagnosis

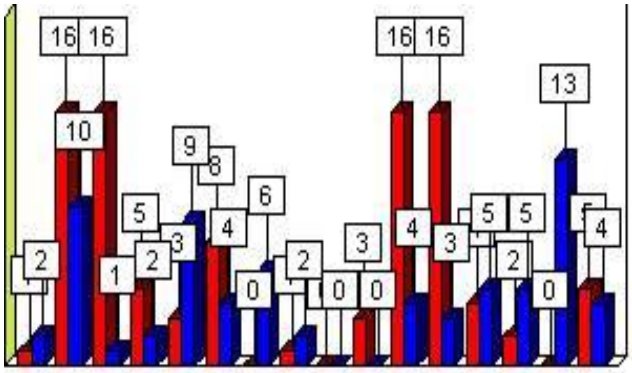
*Female 53 years*

PANCREAS



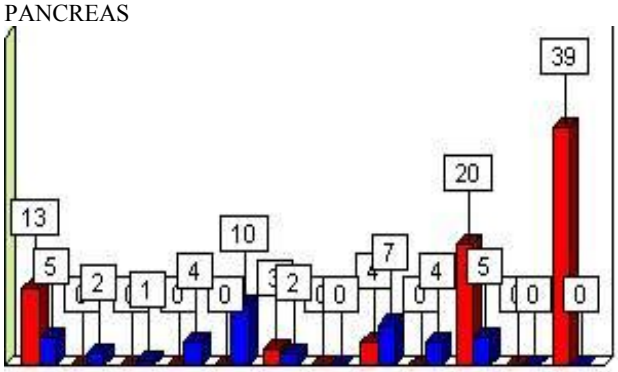

General weakening of compensatory abilities. 15/133 Growth of New Cells: Expressed compensatory signal. 17/1 Pathology of Islands of Langerhans: Expressed pathology signal.

HEART




3/9 Cardiac Infarction: Expressed compensatory signal. 4/5 Cardiac Myopathy: Compensatory signal. 0/13 Impairment of Cardiac Rhythm and Conduction: Expressed compensatory signal. 16/1Angina Pectoris: Expressed pathology signal. 8/4 Cardiosclerosis. 16/3 Cardiac Insufficiency: Expressed pathology signal.

*Male 47 years*
PANCREAS




20/5 Pathology of Islands of Langerhans; Expressed pathology signal.

# Example 2 Therapy

The following case studies illustrate the scope of clinical outcomes arising from Virtual Scanning color therapy. The case studies were reported or observed by GPs.

Female, 16 years old, was diagnosed at endocrinology department with type 1 Diabetes Mellitus (described as heavy form, labile process). There were indications of diabetic encephalopathy, polyneuropathy, and retinopathy. The concentration of blood glucose was up to 28.4 mmol/l. As a consequence she was given 24 units of prolonged insulin and 28 units of simple one. She was given Virtual Scanning color therapy. After 5 sessions of therapy the level of blood glucose lowered to the 7-9 mmol/l.

Male, 23 years old, drug user/narcotic dependent, was diagnosed at endocrinology department with type 1 Diabetes Mellitus (described as heavy form). There were indications of diabetic encephalopathy, polyneuropathy, and microangiopathy. The concentration of blood glucose was between 10-17 mmol/l. He was given up to 40 units' insulin per day. After 5 sessions of Virtual Scanning color therapy the level of blood glucose had lowered to 5 mmol/l and was accompanied by hypoglycemia. It was set at level of 7-8 mmol/l. The insulin dose was lowered and the drug dependency/cravings decreased.

Male, 78 years, with type 2 Diabetes Mellitus, circulatory problems and a swollen foot was dissatisfied with his GP's diagnosis when prescribed antibiotics - presumably as a preventative measure against infection. He was completely immobile, unable to complete the most menial of tasks, lack of social contacts and consequently his quality of life was at a very low level. After a 6 month course of Virtual Scanning color therapy he had stable blood glucose levels, improved circulation, improved mobility, more energy, and dramatically improved quality of life.