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There is a need for an alternative or modified medical paradigm incorporating an understanding of the nature and significance of the physiological systems

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Abstract
Background: There are fundamental limitations associated with the diagnosis of disease and the development of drugs. Drugs are not able to influence the fundamental stress-related and multi-systemic origins of disease. They mitigate only the extent of the symptoms and are often significantly ineffective. They are used to inhibit the progress of specific biochemical sequences associated with pathologies however many diseases are the consequences of impaired neural regulation of the various organ networks commonly referred to as the physiological systems. Very little research is devoted to the study of the physiological systems though extensively used in primary care by the GP. What claims to be systems biology does not take into account the physiological systems. Instead of looking at the systems which regulate the body's function and biochemistry, most systems biology seeks to establish the best-fit ‘systems’ which can best explain the complexity of pathology. This is a significant limitation of orthodox ‘bottom-up’ systems biology. **Aims:** This article reviews the existing biomedical paradigm and emerging alternatives. It takes into account the work of the Russian researcher IG Grakov who has mathematically modeled the consequences of cognition, in particular of visual perception, upon the autonomic nervous system and physiological systems. **Results:** The article illustrates limitations with the bottom-up systems biology approach. In particular it overlooks the significant influence of sensory input upon the autonomic nervous system. **Conclusion:** There is a need for an alternative or modified paradigm, as outlined in the article, to consider the multi-systemic nature of the body’s function and its environmental interface if new and more effective therapies are to be developed.

Keywords: Virtual Scanning, physiological systems, multi-systemic.

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Introduction
The use of drugs to treat disease is limited by their ability to act solely upon individual biochemical sequences. With the possible exception of viral or bacterial infections most disease has multi-systemic origins or consequences. Accordingly some pharmaceutical preparations involve several drugs e.g. the use of a diuretic with a heart drug, the administration of sodium bicarbonate with chemotherapy treatments, etc. It is assumed that upon completion of the course of drug therapy that the patient will recover good health. There is reason to doubt the validity of this assumption.

There is a need to explain many issues which, until they are resolved, contribute to a poor understanding of the mechanisms responsible for disease. For example there is a need to explain why: (i) only 2% of DNA expresses proteins which can be characterised and used in diagnosis or the development of new drug developments. The role of the remaining 98%, considered to be junk DNA, has not yet been determined to any significant extent. (ii) GPCRs play a key role in the link between sense perception and the body's biochemistry yet only a relatively small number lend themselves for use as drug targets. This illustrates that the remaining GPCRs i.e. those which do not lend themselves for use as drug targets, have a more complex function. (iii) The role of the cerebellum, which processes as much data as the rest of the brain, has not yet been clearly determined. It is inconceivable that this organ does not play a significant role in the body's function. (iv) Gene function can be influenced by environmental stressors therefore the value of genetic testing is limited because individual genes cannot be the sole cause of disease. They indicate a contextual predisposition to disease in the event of their suppressed function e.g. by environmental stressors. It is essential to understand the epigenetic factors which influence gene function and protein expression. (v) The value of clinical trials, considered to be the best evidence-based approach, is also under fire due to variations in therapeutic outcomes [1-3] between patients and patient groups i.e. 90% of drugs are ineffective in 50% of the population [4]. In addition, it is increasingly recognised that the results from such studies can be influenced by the careful selection of patient groups.

The Current Biomedical Paradigm

The current paradigm is based primarily upon diagnosis involving biomarker-type (and/or scanning) techniques to determine appropriate remedial action however there are significant limitations with such technique(s) e.g.

- the sampling and testing of biochemical samples e.g. the representative nature of fluid or tissue samples; ensuring their stability, preventing their degradation and suitability for test; the time during the day when the samples were taken; operator and test errors; etc.

- disease has multi-systemic origins and/or consequences. The assumption that the qualitative and quantitative assessment of *biomarkers* can be used as a precise measure of pathology fails to consider the complex nature of disease. Many medical conditions are given a single identity when they are in fact multi-systemic conditions which have multiple origins e.g. migraine, dyslexia, depression, etc.

- the results from biomarker-type tests are compared with experiential norms. Which parameters are used to establish these limits? Such methodology inevitably leads to the false positives and false negatives associated with misdiagnosis e.g. a high level of a protein with low rate of reaction.

- the fallibility of diagnostic techniques. There is a relatively poor level of understanding of many diseases e.g. depression, autoimmune disease(s), epilepsy, cancer(s), etc. This leads to poor diagnosis. If it is not possible to diagnose disease accurately, and/or to have a complete understanding of its influence upon the body, it may not be possible to understand how to use the existing portfolio of drugs or how best to target the development of new drugs.

- the limitations of drugs. An estimated 90% of drugs are considered to be ineffective in 50% of the population [4]. The pharmacological action of most drugs is based upon their action upon GPCRs (G-protein coupled receptors) however their complex function often defies simple logic leading to the failure of new drug developments. Accordingly researchers overlook the complex nature and function of such proteins, preferring instead to look for simpler associations which can be adapted for use as pharmaceuticals.

  It is recognised that GPCRs are intimately involved in the processes of sense perception. Any changes to the levels and reaction of such biochemical components must inevitably influence sense perception.

- the limitations of the doctor i.e. the judgements made by the doctor to correctly diagnose disease and hence to adopt suitable remedial measures. Estimates for the ability of the GP to diagnose disease range from typically 20-80% depending upon the nature of the condition to be diagnosed, the time available for the consultation, the age of the GP, etc.

- the incompatibility of data. The current plethora of diagnostic tests give data which is inherently incompatible e.g. measurements of systemic function: blood pressure, lung function, digestion, excretion, blood volume, sleeping, posture, etc; cannot be inter-related in any significant way. It is only possible to relate biochemical measurements e.g. blood glucose, blood cell content, pH, temperature, osmotic pressure, and of specific pathologies.

Factors Overlooked by Orthodox Biomedical Research

Such limitations may be addressed by considering the innate nature of the body's biochemistry and of its environmental interface e.g.

- understand how the body's biochemistry is influenced by its environment. An estimated 85% of sensory input is visual. Accordingly a substantial element of what we experience as stress is conveyed visually.

- the body's biochemistry is influenced by prevailing memories e.g. of stress-related experiences, severe trauma or of persistent adverse influences. Such memories influence subsequent behaviour and predisposition to further pathologies.

- physiology changes with age. There are specific physiological changes which occur during life e.g. at puberty and menopause. Men and women have significantly differing biology e.g. at the menopause when production of estrogen or progesterone ceases, HGH production declines, etc. This alters our cognition and behaviour.

- chronic disease may be stable [5-7] i.e. the body's physiological stability alters and favours abnormal biochemistries. Most disease, considered by many to be the product of oxidative stress, commences from its presymptomatic origins. Thereafter the body seeks to compensate for pathology; the acute state develops; the body starts to recognise the pathology as the stable chronic state; and/or the body is able to re-establish the natural process of recovery.

- develop an understanding of the relationship between cognition and the body's physiology [8]. Sensory input, in particular light and colour, influences the body's function by modulating biochemical pathways leading to cellular and system level responses i.e. activating enzymes, which catalyse the body's function. [9,10]. Light plays a role in the migration of stem cells [11], the production of Nitric Oxide [12], improved wound healing [13], translocation of proteins to the cell membrane [9], the function of the lymphatic system [14], regulation of intercellular pH balance [15,16], blood flow [17], synapse development [18], etc.

  Light has been shown to be of benefit in over 100 medical conditions. Photostimulation has been linked to the development of ROS species and the occurrence of pathologies [15,19]. Pathologies influence the nature and extent of the light which is absorbed and emitted [20]. This adversely influences sense perception, in particular visual perception.

- instead of considering the level of proteins as biomarkers consider instead the rate at which proteins react and the factors which influence the rate of reactions i.e. the prevailing reaction conditions (pH, temperature, levels of minerals, vitamins, hormones, etc). The rate(s) of protein-substrate reactions are proportional to the light released. Such biochemical changes influence visual perception which can be measured with remarkable precision in a cognitive test.

- consider the nature and structure of the physiological systems and the mechanisms which regulate the function of such organ networks i.e. (i) what are the factors which regulate and/or influence systemic function and stability, and (ii) how do systemic changes influence cellular and molecular biology [21]? (iii)Identify the various systems which are associated with specific diseases e.g. preventing the elimination of toxins from chemotherapy or of heavy metals in a child with regressive autism.

- disease is context dependent e.g. multiple sclerosis and depression are more prevalent at higher latitudes. Biochemistry and genetics is specifically adapted to the local environment i.e. altitude (air quality), latitude, heat, humidity, food supply/diet, water (availability and quality), gravity, sunlight, etc. A person born in one contextual situation may exhibit greater predisposition to disease when living in another context e.g. someone of African origins living in a cold northerly climate.

- use mathematical modelling to develop a cohesive understanding of the inter-relationships which exist between physiological systems [20].

Cognitive Techniques

Such concepts are incorporated into a cognitive technology which has diagnostic and therapeutic significance. The Russian researcher I.G.Grakov has mathematically modelled the consequences of cognition, in particular of visual perception, upon the autonomic nervous system and physiological systems [20].

The cognitive technique, Virtual Scanning [22,23], is able to diagnose the stability of the physiological systems and to provide a health report of unprecedented sophistication. Approved by the Russian Health Authorities in 2001 [24] it can provide an assessment of the health of every organ including the listing of medical conditions of concern. This includes the ability to illustrate the predisposition to future clinical development/pathology and hence the need to undertake suitable remedial measures [25]. Each medical condition includes measurement of pathology and of compensation measures which indicates the influence of genes (genotype), and the systemic factors influencing protein expression and reactivity (phenotype), for each disease state.

Such cognitive technique(s) may have a role monitoring the influence of drugs upon specific disease states.

Virtual Scanning also includes a therapeutic module i.e. a light-based biofeedback technique to treat disease [26]. This adapts an understanding of the computed relationship between light, neural networks, physiological system, and EEG frequencies [24].Such techniques, although empirical, have had success treating migraine [27,28], dyslexia [29], PMS [30-32], etc. I.G. Grakov may be the first researcher to understand the fundamental concepts and to use mathematical modeling to incorporate such concepts into a working technology [22]. It has been able to treat a wide spectrum of disease, often in cases when orthodox medicine has been unsuccessful [24].

The use of mathematical modelling to model the body's function has been considered by many however tests developed to date have assessed organ function by empirical means. As a consequence the results have been relatively imprecise. Nevertheless the possibility to employ mathematical modelling is clearly a possibility i.e. if the reaction kinetics of every biochemical reaction can be calculated it can, in principle, be possible to extend this approach further.

As light emission (i.e. colour perception) is a measure of the rate of reaction from protein-substrate reactions this lends itself as a mechanism for establishing the rate of reaction for all key physiological processes and for developing pathologies. A cognitive test, measuring the full spectrum of colour perception, will provide the core data to diagnose all medical conditions. In addition if the nature and structure of the physiological systems is known this can may be used to create a biomathematical model and compute deviations from the norm, expressed as pathologies, and assess the stability of the various physiological systems.

A Brief History of Light & Systems Research

Since the late 19th and early 20th century the value of light, of a balanced diet, and of the quality of the water supply has largely been recognised.The first significant understanding that light could be used therapeutically was recognised by Finsen [36]. Gurwitsch established that all cells emit light. Adrian & Matthews [37] established the potential of photic stimulation; in particular that a relationship existed between frequency of flickering lights and that of EEG patterns.

Since the1930's, Russian researchers e.g. Speransky, Anokhin [5], Kryzhanovsky [6], Bekhtereva [38], Sudakov [39], etc; have developed an understanding that disturbance of the nervous system disrupts the regulation of the body's functional systems i.e. each disturbance, of specific magnitude or longevity, alters the body's physiological stability, perhaps being manifest as a pathologic functional system.

During the late 20th century laser research established that the body's function responded to laser light of specific colours [22]. More recently, it has been recognised that cell biology must in some way be linked to cognitive function [8].

Light activates the proteins and enzymes i.e. *phenotype*, which subsequent regulate the body's biochemistry and function [33]. The latest evolution of this work i.e. optogenetics, recognises how light of specific wavelengths can be used to activate proteins and stimulate specific biochemistries [10] which appear to influence most aspects of the body's function.

This suggests that the body's function involves a dynamic relationship between that of the physiological systems i.e. of neural networks which synchronise the function of such organ networks; and the body's cellular and molecular biochemistry. This relationship involves sensory input and memory of sensory input i.e. how we determine the extent of stress and of its significance upon the stress limits [34] and its ultimate manifestation as oxidative stress and pathology. The significance of this relationship, the product of Russian research, was recognised and mathematically modelled by IG Grakov (during the period 1985 to 2001) and subsequently incorporated into Virtual Scanning.It illustrates the convergence of different research disciplines i.e. of physiology and pathophysiology, the study of physiological systems, mathematical modelling of organ and system function, cognitive psychology, laser research, EEG research. It recognises the existence of a fundamental relationship involving sensory input, neural function, behaviour, frequency, the neural networks and physiological systems, and that of cellular and molecular biology.

Discussion

The system of medicine i.e. of medical diagnoses and treatment, has evolved over hundreds of years. This article outlines the possibility to consider new techniques which understand the body's regulation and function and hence, by implication, the limitations of current techniques. The techniques currently in use are often based upon the accepted evidence which, in turn, is based upon the prevailing understanding of pathology(s). Such evidence is invariably based upon the prevailing reductionist paradigm in which research considers the function and interaction of the smallest component parts. This overlooks the well accepted, but rarely discussed, understanding that the body's function is multi-systemic and regulated by the brain.

The latest research illustrates that light influences the stability of the autonomic nervous system. It activates the proteins, which are essential for most (if not all) aspects of the body's function, and illustrates the dynamic relationship which exists between the physiological systems and that of cellular and molecular biology. This complements that of the doctor's diagnosis which, in primary care, is mainly based upon an examination of the body's systemic stability.It illustrates the potential benefits which may be associated with sense-based techniques in particular those which seek to adapt the therapeutic influence of light [35]. In combination light and frequency stimulate the resonant frequencies which coordinate the function of organ networks i.e. physiological systems. This offers the potential for better, quicker and significantly cheaper means of diagnosis and treatment.

Orthodox medical research considers mainly the identified pathophysiological processes which have been identified for any disease i.e. the biochemical consequences of disease. Such an approach does not consider the fundamental pathways which have destabilised the body's physiology. This is a fundamental limitation of modern medicine. If the origins of disease i.e. the accumulated memories and experiences of stress [34], are not eradicated then it is likely to re-occur in some form at a later date.

There are processes in the body which under normal circumstances maintain the body's stability, which we experience as good health, and there are also pathophysiological processes which are responsible for disease and its subsequent development. They are not the same. This is significant for the ways we diagnose and treat disease e.g. the treatment of various diseases (i.e. the use of cancer drugs, x-ray contrast media, psychotropic drugs, etc), and overlooks the secondary influences which potentially toxic drugs and vaccines have on the patient's physiology. For the body to recover from toxic influences the body's physiological systems must be sufficiently robust to facilitate their elimination from the body. Accordingly there is scope for expanding the current paradigm to include an in-depth understanding of the physiological systems and of the ways which they are regulated.

Medical research has become fixated upon the reductionist paradigm irrespective of the limitations of the approach, some of the more significant of which have been outlined in this article. Alternative methods of diagnosis and treatment may now exist which address the fundamental stress-related origins of disease and their influence upon the body's multi-systemic stability.

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