The Dynamic Relationship between Cognition, the Physiological Systems, and Cellular and Molecular Biochemistry: a Systems-based Perspective on the Processes of Pathology

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Abstract

The limitations of the reductionist model and hence of the quality of data derived from histopathological tests fail to take into account the multi-systemic and context dependent nature of disease. Biomarker-type tests measure the levels of proteins and other key indicators yet largely disregard the complex phenotype factors which influence their reactivity and subsequent uptake by the body. Sense-based techniques are less susceptible to the factors which adversely influence the accuracy of biomarkers i.e. the understanding of the link between sense perception and biochemistry; in particular between cognition, the physiological systems and autonomic nervous system; may be manifest in a theoretically superior technique which has both diagnostic and therapeutic significance. This article explores the concepts involved.

INTRODUCTION

That the human body is a completely biochemical entity is hugely significant. It means that all aspects of its function can be explained by its biochemistry and by related biochemical phenomenae i.e. that the complex mix of chemicals and related biochemical signals are integral components in the body's self-regulation and the body's ability to resist (or to be corrupted by) disease. This covers issues such as personality, emotions, behaviour, cognition and ultimately the body's function. Furthermore, that the body is a self-regulating entity means that the body's function conforms to set principles (Mesarovic *et al* 2004), follows rules (and is therefore predictable), and that this can be mathematically modelled. This is the consequence of research into system function known variously as digital biology, computational neuroscience/neurobiology, and systems biology. It involves the understanding of how the body's function responds to its environmental interface i.e. in the form of sensory input (light, sound, smell, taste and touch); of its cognitive properties including memory; and the recognition that this is an integral part of the body's self-regulation.

The biochemical reactions in the body adhere to the laws of biochemistry. Those which happen in the body are no different from those in a chemical reactor. The ability of chemicals (proteins) and their reagents (substrates) to react are influenced by the levels of catalysts and reaction conditions which, if optimised, give optimum yields, high purities and low levels of impurities. In the body, biochemical dysfunction alters the reaction conditions and is subsequently manifest as oxidative stress and the release of free radicals i.e. the stress-related reactions which are associated with the occurrence of diabetes (Ewing *et al* 2008), cardiovascular dysfunction (Nwose & Ewing 2009), depression, cancers, etc. The chemical principles are the same although the context differs.

The body can compensate to some degree through the intervention of free radical scavengers, i.e. vitamins, which we routinely consume in our diet from fruit and vegetables although foods such as meat, alcohol and dairy contribute to increase the degree of oxidative stress and levels of free radicals OR to reduce the levels of free radicals. Some vitamins require fats in which to dissolve and to ensure their bioavailability whilst others are stable in the aqueous media. Accordingly the body requires an appropriate balance of such foods in the diet. Conditions such as depression, obesity are the consequence of impaired systemic and biochemical stability i.e. influencing the balance between sense perception, the function of its various organs e.g. the synchronised function of the organs in the digestive system, etc.

The reaction conditions which influence the rate at which proteins react in the body are regulated by the physiological systems which are regulated by neural networks. In good health the physiological systems are stable and are regulated by the function and firing of neural networks however the inhibitory influence of pathology(s) subsequently acts upon the regulation of organ function. Such a principle, of the ‘pathological functional system’ (Anokhin 1975; Sudakov 1987; Khitrov & Saltykov 2003), has been recognised by Russian researchers for many years. By comparison western research has sought to establish how biochemical dysfunction influences systemic stability. This is an important distinction i.e. whether systems regulate the body’s biochemistry or are regulated by its biochemistry. Both instances are correct i.e. the physiological systems and the body’s biochemistry act in a dynamic manner (Misteli 2008; Bruggeman & Westerhoff 2007). The body seeks stability (Cooper 2008). This applies in cases of health and pathology. It is an inherent property of neurons and inter-neural communication i.e. frequency stabilises pathology as ‘chronic’ disease. Long-term exposure to a stressor(s) alters the body’s long-term memory and physiological stability.

The same rationale must also apply to other aspects of biochemistry i.e. to influence the function of Chromosomes, Genes, DNA, and of the nature and quantities of proteins expressed. Indeed if we consider that 99% of human DNA is identical to that of other species then it becomes obvious that the mere existence of the genes and of DNA cannot solely explain the body’s structure or its function. For example (1) oxidative stress is linked to the shortening of telomeres and hence to reduced longevity (De Meyer *et al* 2008); (2) chemical modification of histones (by methylation, acetylation, phosphorylation, etc,) influence the structure of DNA and chromatin (Strahl & Allis 2000) i.e. there must be mechanisms and/or biochemistries which influence the structure, stability and function of chromosomes and genes. This becomes increasingly obvious through epigenetics research which illustrates how significant past events or environmental factors influence which chemical groups or minerals attach to DNA and are associated with behavioural traits, personalities and emotions (Szyf *et al* 2008) i.e. it is part of the human evolutionary process. The epigenetic effect of heavy metals is proven to influence the occurrence of cancers (Costa *et al* 2002; Davidson *et al* 2004; Li *et al* 2006; Kang *et al* 2006) and may contribute to the occurrence of autistic spectrum disorders.

This leads to an understanding of how chromosomes and chromosomal defects influence the body’s structure and function; and hence to an understanding of (1) chromosomal abnormalities and (2) of conditions linked to overuse of vaccines e.g. Gulf War Syndrome and Regressive Autism (Ewing 2009) i.e. that a receptor gene becomes expressed if it comes into contact with a specific part of chromosome 14 (Wenner 2009). This intra and/or inter-chromosomal contact appears to determine which X chromosome gets turned off in female cells. In addition, when chromosomes become too close they create chromosomal translocations, some of which are associated with the development of cancers. This indicates that, far from preventing disease and through their influence upon chromosome stereochemistry, some vaccines may actually be creating pathologies.

Such an understanding of the possible cause of disease illustrates the complex nature of the body’s function i.e. that the normal function of the body can be influenced by the ways which parts of the chromosomes naturally (stereochemically) influence or signal to each other. Biochemical instability disturbs this natural balance to the extent that intra-chromosomal ‘collisions’ create genetic damage and mutations. Various biochemicals, chemicals and minerals (hitherto considered to be of a ‘benign’ nature) can temporarily or permanently influence the structure, degree of folding (coiling and uncoiling) of the chromosome (Lindquist 2008) and hence its function. Such changes will inevitably and ultimately influence the levels of protein expression and of subsequent protein reactivity – which influence sensory function, in particular of visual perception i.e. of colour perception and colour contrast (Martinek & Berezin 1979; Ewing & Ewing 2008).

That miniscule levels of proteins and/or substrates could influence (or be influenced by) cell function and could influence the body's biochemistry and ultimately its function, illustrates the problems faced by biochemical research. Although small concentrations can influence the body's function does biochemistry have the techniques able to distinguish and accurately determine the levels of such components? Is it the reactivity of such components which is significant rather than their levels? Furthermore even if the levels of such components could be determined would their significance be realised bearing in mind the contextual and multi-systemic nature of disease? Would this influence cognition i.e. memory and sense perception?

Such concepts are increasingly proven through research e.g. gene-altered mice have demonstrated the ability to acquire and store information in their long-term memories by comparison with the average mouse (Silva *et al* 1996, 1997). By contrast the reverse i.e. of deteriorated ability to acquire, store and recall memories, is also clearly evident when environmental factors have a degrading influence upon gene function. That genetic alterations and protein expression influence sense perception, in particular visual perception, is discussed later in this article.

Medical research advances at 'the known frontiers of science' however despite the regulatory safeguards which are designed to ensure that there are not major hazards and oversights (e.g. as occured with thalidomide) it is inevitable that the ultimate consequences of biochemical alterations only becomes evident with the benefit of hindsight and through the persistent and often dogged research of those who follow-up the introduction of new technologies. For example the use of Atenolol, considered for many years the main treatment for high blood pressure, is now being replaced by other better therapies with less side-effects i.e. Atenolol is no longer considered fit for purpose. The way such concepts are discussed, developed or commercialised depends upon many factors e.g. the prevailing state of knowledge, resistance to change, commercial necessity, etc.

Orthodox medicine has yet to address such fundamental limitations e.g. (with the possible exception of antibiotics) 90% of drugs are considered to be ineffective in 50% of patients (Spear *et al* 2001). This illustrates a significant deficit in the theoretical understanding which underpins the development of most drugs. If the reductionist approach were correct we could reasonably expect that most drugs would be near 100% effective but this is rarely, if ever, the case. The complex nature of the body's biochemistry (Burbeck & Jordan 2006; Gaasterland 2002; Dinman *et al* 1991; Lopinski *et al* 2000) indicates the need to consider the multi-systemic nature of the body's function. This is not new to those attempting to model the function of the body's organs. It fails to take into account the complex processes and mechanisms which the body employs to regulate its function (Marks 2008). It considers the biochemical consequences of systemic dysfunction rather than taking into account the systems which regulate the body's function and which are ultimately expressed as our biochemistry. Drug research excludes consideration of the single most significant aspects of the body's function i.e. of sensory input. This is not a new observation. The effect of sensory input, of sense perception and of placebo has pre-occupied researchers for decades. Many drugs (abt 50% of known drugs) are based upon their action with G-Protein coupled receptors (GPCRs) however it is also known that GPCRs are involved in the mechanisms responsible for sensory processing e.g. Viagra selectively inhibits the phosphodiesterase PDE5 which alters signal transduction pathways and colour perception. The influence of positive environmental influences is taken into account by health psychologists, neuro-oncologists, etc; who appreciate the influence which a positive attitude can have upon recovery from disease. Similarly the influence of negative environmental influences i.e. of stressors, suppresses immune function and creates the conditions for development of pathology(s) and, importantly, of subsequent developmental disorders which are responsible for the progressive deterioration of health. Consequently, an understanding of the processes which the body uses to regulate its function can complement that of orthodox medicine.

LIMITATIONS OF THE REDUCTIONIST RESEARCH MODEL

Most medical research is based upon the reductionist model however there are significant problems with such an approach e.g.

- the problems of taking representative samples; ensuring their stability, preventing their degradation and suitability for test; and the time during the day when the samples were taken.
- that the results are compared with experiential norms i.e. if the results are within the normative range they are considered normal and if outside this range pathology is considered to be prevalent. Such a philosophy leads to the false positives and false negatives associated with misdiagnosis. Which parameters are used to establish such experiential limits?
- the assumption that the qualitative and quantitative assessment of specific biochemicals (biomarkers) can be used as an accurate measure of disease i.e. the failure to consider that disease has complex, multi-systemic influence(s) upon the body's function.

- there is not yet a recognised explanation for what causes disease. That disease is multi-systemic indicates that the origins of disease cannot be precisely associated with the presence or absence of any single biochemical component.
- the limitations of drugs. The pharmacological action of most drugs is based upon their function upon GPCRs (G-protein coupled receptors) however such mechanisms often ignore the complex nature and function of such proteins, preferring instead to look for the simpler reductionist-style associations.
- age-related influences upon biochemistry e.g. puberty, menopause.
- that sensory input, in particular light and colour, regulates the body's function i.e. it activates the enzymes which catalyse the body's function. (Levskaya *et al* 2009; Shimomura *et al* 2008). These are influenced by pathologies - which subsequently influence sense perception.
- It has been shown to play a role in the migration of stem cells (Gasparyan *et al* 2006), the production of Nitric Oxide (Nagase *et al* 2005), the function of the lymphatic system, regulation of intercellular pH balance, improved wound healing (Horwitz *et al* 1999), translocation of proteins to the cell membrane (Levskaya *et al* 2009), etc.
- the fallibility of the doctor. The medical system is reliant upon the judgements made by the doctor to correctly diagnose disease and hence to adopt suitable remedial measures. It ignores that doctors are human and humans make mistakes.

The reductionist model fails to consider the complex nature of the disease process e.g. in which pathology develops at the presymptomatic level, the body seeks to compensate pathology without symptoms, the acute state develops, the body starts to recognise the pathology as the stable state (the chronic state) and/or the body is naturally able to stimulate the process of recovery (incl. spontaneous regression) and/or subsequent side-effects and physiological deterioration occurs. It may be important to consider the contextual nature of the data derived from biochemical testing e.g. if a person was born in a tropical region but subsequently resided in temperate or frigid zones. This would influence their immune function, and hence their subsequent behaviour and predisposition to disease.

THE MULTI-SYSTEMIC NATURE OF DISEASE

The body's function is regulated by the physiological systems. Although the accepted understanding of physiological systems is of cardiovascular, respiration, digestion, urination, endocrine, sexual, blood, skin, nervous and musculoskeletal systems, the GP's examination appears to assess the stability of the following physiological systems:

Breathing	Sleeping	Digestion	Excretion (Urination)
Blood Pressure	Blood Glucose	Blood Volume	Blood Cell Content
Osmotic Pressure	pH		
Temperature	Sexual Function		
	Posture and Locomotion		

(Origin I.G.Grakov)

Such systems are responsible for the regulation of organ function and of the components required by the autonomic nervous system. Physiological instability (the consequence of stress in its various forms) acts upon the physiological systems and alters the levels of components regulated by the parasympathetic and sympathetic nervous systems e.g. the balance of Ca/Mg, Na/K; the levels of Iron, Chromium, Selenium, Phosphate, vitamins, hormones; pH; temperature; etc. Many medical conditions have multi-systemic origins (Ewing & Parvez 2008) e.g. migraine, diabetes mellitus, cardiovascular disease, cancers, dyslexia, etc.

The Body's Multi-level Function

The body's multi-level function is evident when considering how brain function changes with the onset of sleep. EEG impulses that are evident during the daytime (in particular the gamma, beta and alpha frequencies) become significantly less active; whilst, during sleep, the theta and delta frequencies become dominant. Each EEG range is associated with specific functions e.g. visual input (gamma), reactions (beta), thought (alpha), the processes of pain and of assessment (theta), and the processes of repair and damage (delta). Significant biochemical change is associated with delta wave function i.e. when injury occurs (e.g. in coma). That such frequencies are significant factors in the body's regulation and function are increasingly evident e.g. that photosensitivity in a migraineur can be induced by flashing lights but can also be treated using flashing lights (Noton 1997, 2000; Shealy *et al* 1996). The brain waves are in a dynamic relationship with the body's biochemistry e.g. (1) the use of alcohol induces sleepiness; the influence of severe damage induces coma (delta), (2) the use of stimulants e.g. ephedrine and caffeine, induce activity (beta) at the expense of alpha wave, whilst (3) techniques which adapt the theta wave (meditation and hypnosis) can be used to reduce pain (Zeidan 2009). The link between the autonomic nervous system and neural regulation of the physiological systems becomes clear. There is a link between the brain waves and the multi-level nature of the body's function (Grakov 1985). By understanding the principles responsible for the body's function and regulation it may be possible to influence the body's function at its different (psychosomatic and somatic) levels.

The Link Between Cognition and Cellular & Molecular Biology

Such claims could be considered to be speculative but for the development of a technology which involves the mathematical modelling of the consequences of cognition (and in particular of visual perception) upon the autonomic nervous system and physiological systems (Grakov 1985). Such a technique illustrates that there is a viable alternative to the reductionist model - disease is multi-systemic and is influenced by sensory input. That disease influences the autonomic nervous system and that the autonomic nervous system is linked to visual perception are not new (Kravkov 1941). Both genotype and phenotype are significant factors in the processes of disease. Both influence the autonomic nervous system and visual perception. This is embodied in a commercialised technology. Virtual Scanning is a computer-based, cognitive technology. Its novel approach links visual perception deficits to that of specific pathologies. This is not a fundamentally new concept (Kandel 2006). Visual perception deficits are known to be linked to the autonomic nervous system and to pathologies. Most drugs influence sensory perception. Of greatest significance is the established relationship between visual perception, the physiological systems and the autonomic nervous system. This enables: (1) the understanding of pathologies influencing the stability of each organ system; (2) the expression of pathology in terms of genotype and phenotype (the blue and red signals in reports (see example report 1)); (3) the expression of pathology in terms of (i) disease and (ii) systemic stability and/or instability for every organ; and (4) a conditional assessment of predisposition to further pathologies.

Such a technique avoids the problems listed above which are associated with the reductionist model i.e. (1) it avoids the need for invasive sampling, (2) disease is assessed in terms of its severity i.e. presymptomatic, acute and chronic; (3) disease is expressed in terms of its overall influence upon the body's systems and function; (4) it addresses the observed ways in which disease progresses and/or regresses i.e. it recognises the mechanisms which the body uses (under normal conditions of health and wellbeing) to maintain its stability; and (5) it illustrates the stress-related origins of disease.

Example report 1: male, HEART

<u>*Discussion*</u>

Such developments may have profound implications for the way we understand brain function.

1. It illustrates that sense perception, in particular visual perception, is influenced by altered biochemistry and pathologies.

2. It illustrates that a primary function of the cerebrum is to regulate the body's physiological/systemic stability i.e. that biochemical stability (or instability e.g. in the form of pathologies) influences sense perception, sense coordination and the fixation of memories.

3. Examples of conditions considered to be neurological/neurodegenerative conditions which may be treatable using such techniques include e.g. dysarthria, PMS (Noton 1997), parkinsonism, migraine (Noton 1997, 2000) multiple sclerosis, pain management (Boersma & Gagnon 1992), depression (Lam *et al* 2006), dyslexia (Liddle *et al* 2005), neuroses and psychoses (Vysochin *et al* 2003), autoimmune dysfunction (allergies), improved and/or more rapid wound healing (Monstrey *et al* 1999), etc.

4. Disease and/or injury has multi-level significance i.e. pain or physical injury is manifest in the lower brain wave states (Theta and Delta) and hence of associated biochemistries. Pain and damage (somatic states) are accompanied by psychosomatic influences but the reverse does not apply.

This illustrates the further progress of mathematics into medicine. It illustrates that brain function is hierarchical and systemic; that a major feature of brain function is regulation of the body's function; and that this influences cognition and behaviour i.e. what we have to come to know as psychology. That sense perception is linked to pathology illustrates that disease is context dependent.

The context dependent nature of the body's function has been recognised by athletes who adapt such understanding to improve their athletic performance and by the greater susceptibility to regressive autism of African-origin children living in North America. Phenomena previously considered to be beyond scientific reason are now being understood to be linked to the synchronised function of neuronal networks (Bullock *et al* 2005; Fields 2006) and of the body's systems and organs, and ultimately the function of cells and their molecular biochemistry (Kandel 2006). Physiological dysfunction is characterised as acute or chronic states of disease (Anokhin 1975; Sudakov 1987; Khitrov & Saltykov 2003).

The expression of a single biochemical component or systemic measurement (e.g. blood pressure) is a function of every other biochemical process and systemic interaction at any specific point in time. It is context dependent i.e. it can only be defined by knowing the level of every other chemical or system. It is for this reason that mathematical modelling is an implicit necessity/requirement in the assessment of physiological stability/instability (Brenner 2002).

COMPETING INTERESTS:

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

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