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A Body Divided: Toward Reunification of the Paradigm

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Review Article

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ABSTRACT

Symptoms without obvious physical cause are commonly reported in medical practice; when chronic, they can have a significant influence on patients' well-being. When traditional medicine is unable to provide relief, sufferers of such conditions often turn to alternative therapies. Western medicine has historically viewed the body through a silo model, i.e, a whole consisting of disparate body systems with well-defined boundaries and little relevant interaction. This model ignores the myriad of interactive functions that each system must require and hinders understanding of syndromes for which etiology is not confined to one organ system, particularly those with a strong psychosocial component. In addition, this model is increasingly shown to be antiquated: recent evidence of Pavlovian conditioning of physiological processes (i.e., placebo and nocebo affects, immune system conditioning), physiological distinctions between multiple personalities, and the pervasive effects of psychosocial stress on every body system (down to the level of the genome) demand a new paradigm. As our appreciation expands of the innumerable interactions between body systems as well as those between all body systems and the mind, the human body is revealed to be a complex web of neurological, immunologic and endocrine interactions that in turn modulate a fluid epigenetic base. Firmly planted in the rationalistic viewpoint that is the foundation of Western medicine, but inclusive of the more wholistic (mind and body) view of Eastern medicine, a nexus model which views the body as the series of multi-connected, interacting physiological webs is essential to continued progress in medicine.

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1. INTRODUCTION

Physical symptoms lacking an obvious physiological origin, termed variously *psychosomatic symptoms/diseases, symptom-based conditions, functional somatic syndromes* and *somatization of symptoms*, are not uncommon in medical practice; in fact, for as many as one-third of primary-care patients worldwide, no physiological basis for the patient's symptoms can be confidently established [1]. Ranging from transitory symptoms like tension headaches to enigmatic symptom clusters like fibromyalgia, such inexplicable and often irresolvable conditions can have profound impact on a patient's physical well-being. Chronic symptoms for which identifiable physiological cause is lacking carry a psychosocial burden as well; the term *psychosomatic*, literally meaning "mind/body," grew in common vernacular to mean essentially "imaginary," with origin in a desire on the patient's part to malinger or gain attention. Such patients, stigmatized by traditional medicine despite very real discomfort, neither surprisingly nor infrequently, seek relief outside of traditional medicine. Traditional medicine, when substantial numbers of physicians' patients are driven outside of their physician's offices for effective interventions, has a need to re-examine its paradigm.

The Western model for medicine, with an emphasis on scientific experimentation and analysis, had its genesis in the teachings of Hippocrates, who proposed in 400 BC that the ancient scourge epilepsy (previously treated by rituals meant to appease the evil spirits at fault, [2] had "a natural cause from which it originates," [3] a revolutionary theory that proved to be of incalculable benefit to mankind as physiological origins for disease processes began to be uncovered. Dissection, first made legal in 16th century Brussels, spurred a focus on organ systems and the pathology related to them, an approach that accelerated an understanding of physiology and medicine but one which spawned a gradual, inadvertent dissection and fragmentation of medical science itself into discrete and disconnected functional units [4]. This "silo" model, wherein medical disciplines operate as self-contained, organ system-specific units with high walls and no windows, has hindered recognition of the myriad of interdependent interactions that the functions of each system demand. Current research, however, increasingly recognizes the connections that organ systems share and the integrative functions that they together perform.

The mind/body connection, once akin to shadowy pseudo-spirituality, now by the light of evidence-based science, is being seen as a complex web of neurological, immunological, and endocrine actions which modulate the function of a more basic web of effectors that provide a communication network between body systems. In that respect, the interest in mind/body medicine isn't an assault on the traditional Western medical model, but an appeal to take both a wider view (one which encompasses psychological and social functioning into the disease process and looks at all body systems as integrated whole) [5,6] and a deeper one (one which seeks fundamental causes until the responsible physiological mechanisms are understood). This view recognizes that all body systems (brain and body), together with psychosocial factors (and environmental exposures) act in concert to determine health. While not a topic discussed in this review, the latest research on the effect of the gastrointestinal and vagina microbiome seems to indicate that a truly holistic understanding of health will also need to consider the role and function of the body’s microbial communities.

2. BRAIN IN PAIN AND SYMPTOMS UNEXPLAINED

Neuroscience, and its efforts to understand the mechanisms by which the contents of the skull control all peripheral body processes (particularly neurological and endocrine function), have made tremendous strides over recent decades, spawning sub-disciplines like neuroimmunology, psychoneuroimmunology, psychoneuroendocrinology and cutaneous psychoneuroimmunology. A unified theory, fully explaining the matrix of bi-directional interactions of the mind and the physical body, however, is lacking, as evidenced by consistently observed but still relatively inexplicable biophysiological anomalies which reveal the void and demand a deeper integrative understanding of body function. By these seeming biological paradoxes (e.g., placebo effect), physiological perplexities observed in dissociative identity disorder, Pavlovian conditioning of the immune response, the pathology of stress, and an observed clustering of diseases which affect disparate body systems, the human body is indisputably revealed as a synergistic collection of integrated processes.

2.1 Placebo and Nocebo Effects

Placebo (Latin, "I shall please") effects in medical research, occurring in as many as 65% of individuals and responsible for as much as 80% of treatment effect observed in randomized trials, are well known and widely reported [7]. Part of medical research since the 18th century, the placebo response was akin to "wishful thinking" until studies by Levine, Gordon, and Fields (1978) showed that naloxone, an opioid antagonist, blocked the placebo effect in pain studies [8]. Subsequent positron emission tomography (PET) analyses demonstrated that even placebo anticipation triggered endogenous release of analgesic opioids and cannabinoids and produced subsequent pain relief. Further investigation found the placebo effect to be accompanied by observable changes in the brain, including a decrease in pain-related brain activation in pain centers with parallel simulation of the lateral and medial prefrontal cortex, a sequence initiated in concert with the expectation of pain relief [9]. Interestingly, a 2008 study showed susceptibility to placebo effect to be genetically linked to the Catechol-O-methyltransferase (COMT) gene encoding an enzyme involved in dopamine production [10].

More intriguingly, the placebo effect doesn't appear to require cognitive awareness of the stimulus. In other research, 40 volunteers repeatedly viewed two different human faces simultaneously with an application of thermal heat on the forearm; subjects were told to expect higher heat intensity paired with one face and lower heat intensity with the other. Though in fact, an identical intermediate pain level was delivered with each visualization; subjects (rating their pain on a scale of 1 to 100) reported an average pain level of 53 with the first face and 19 with the second (a result which, due to the power of suggestion, was expected). The experiment was repeated, with one difference--the images the second time were shown at a speed so fast as to be below conscious perception, a methodology demonstrated to activate specific regions of the brain (even though the subjects are unaware of the subliminal stimuli). Pain-perception ratings were again associated with the timing of the subliminal images, despite the subjects being consciously unaware that they had been viewed [11].

An additional contributor to the placebo effect was reported last year. In a randomized clinical trial of 262 patients with irritable bowel syndrome, patients were divided into three treatment groups: one receiving no care, one sham acupuncture with minimal physician contact and one receiving sham acupuncture with at least 20 minutes of physician interaction

accompanied by effusive empathy, reassurance, supportive physical contact (e.g., touching hand, shoulder) and frequent reassurance of success of treatment. The treatment group receiving the best bedside manner showed twice as much improvement in symptoms (based on patient assessments) as did either of the other groups, a treatment effect equal to the best achieved in randomized controlled trials that evaluated actual irritable bowel syndrome (IBS) medications.

Nocebo (Latin, “I shall harm") is placebo's evil twin; nocebo effects are unpleasant symptoms that occur after their possibility is suggested in the absence of an actual trigger. Since disclosure of possible negative side effects is part of nearly every delivery of therapy, the nocebo effect is more widespread than placebo effects. A substantial percentage of subjects drop out of all clinical trials due to the side effects described; for example, more than a quarter of all subjects in the placebo arm of one statin trial dropped out specifically due to the side effects that they had been warned to potentially expect. Naming a specific side effect in the list of possible effects of a test drug, in fact, increases up to six fold the percentage of subjects who experience that effect. The nocebo response, like the placebo effect, has been shown to be genetically predisposed. The efficacy of self-healing techniques is increasingly reported in the medical literature as well. For example, guided imagery in one study in breast cancer patients resulted in altered immune system functioning, including an increase in natural killer (NK) cells as well as lymphokine-activated cells [12].

The apparent efficacy of self-healing therapies such as meditation, the placebo effect, imagery, visualization, spiritual/energy healing, music therapy, hypnosis and yoga may depend on processes similar to those that create the placebo and nocebo effects.

2.2 Physiological Anomalies Associated with Dissociative Identity Disorder

Dissociative identity disorder (DID), formerly termed multiple personality disorder, has been consistently described in the literature; these patients share a history of psychological and physical trauma as children to which, in theory, the mind ostensibly reacts by dissociating, fragmenting the psychological self into multiple distinct alter egos in order to shield the affected person from unbearable psychophysiological pain. Although still a highly controversial psychiatric condition, it is one a *New York Time*s article said "represents a unique experiment of nature that provides opportunities for exploring the intricate web that connects the functions of the central nervous system and the body" [13]. In fact, DID has steadily been documented as having genuine physiological roots [14]. Seemingly inexplicable physiological differences have been observed between the identities of DID patients. The different psychological identities that share a single physiological body have been found to have distinctly disparate psychological and personality structures, different involuntary muscle function, different patterns of brain activity and neural impulses and different concomitant medical issues, including allergies, rates of healing, insulin dependency and medication sensitivities. A list of physiological differences between different identities which share a physiological body, as well as physiological differences between DID patients and normal controls, are in Tables 1 and 2.

Table 1. Physiological differences among dissociated identities with Dissociative Identity Disorder (DID)*: Characteristics that varied among shared personalities

Characteristic	Specific Assessment	Reference
Personality structure	Minnesota Multiphasic Personality Inventory	Larmore et al 1977 [14]
Pain sensitivity	Induced pain	Putnam et al 1986 [15]
Speed of nerve impulses down neural pathways	Average Visual Evoked Response	Larmore et al 1977 [14]
Visual cortex function	Microstrabismus (tiny differences in eye alignment)	Condon et al 1969 [16]
Language-side brain dominance	Handedness	Savitz et al 2004 [17]
Electrical activity produced by skeletal muscles	EMG	Brende 1984 [18]
Skin conductance (an indicator of psychological or physiological arousal (via sympathetic nervous system)	Bilateral galvanic skin resistance	Putnam et al 1986 [15]
Emotional arousal	VER	Putnam1984 [19]a
Insulin dependency	Blood glucose levels	Idan et al 2012 [20]
Immune system function	Differences in allergic responses	Braun 1983 [21]
rCBF	Varied between identities in DID patients	Reinders et al 2012 [22]
Response to medication	Medication administration	Putnam et al 1986 [15]
Activation of brain regions	fMRI	Vermetten et al 2006 [23] Laniu, et al 2002 [24]
Brain activation	PET	Reinders et al 2003 [25]

**Distinct separate psychological identities sharing one physiological body, DID = dissociative identity disorder, EMG = electromyography, fMRI = functional magnetic resonance imaging, PET = positron emission tomography, rCBF = regional cerebral blood flow, VER = vestibulo-emotional reflex*

Table 2. Physiological differences among dissociated identities with Dissociative Identity Disorder (DID)*: Characteristics that differed between DID and normal controls

Characteristic	Specific Assessment	Reference
Increased vigilance in DID as compared to controls	Prepulse inhibition of the startle reflex	Dale et al 2008 [26]
Decreased blood perfusion in orbitofrontal cortex and increased in median and superior frontal regions and occipital regions bilaterally in DID patients	rCBF	Sar et al 2007 [27]
Decreased hippocampal and amygdala volume	Volume measurements of hippocampus and amygdala	Vermetten et al 2006 [23]
Compared to high-fantasy controls	Heart rate	Reinders et al 2012 [22]
Compared to high-fantasy controls	Systolic blood pressure	Reinders et al 2012 [22]
Heart rate variability, normal to normal time intervals	ECG	Reinders et al 2012 [22]
rCBF	Varied with induced trauma in DID patients	Reinders et al 2012 [22]
Brain glucose utilization	PET	Brand et al 2009 [28]

**Distinct separate psychological identities sharing one physiological body, DID = dissociative identity disorder, ECG = electrocardiography, PET = positron emission tomography, rCBF = regional cerebral blood flow*

2.3 Pavlovian Conditioning of the Immune Response

A conditioning of the immune system, similar to the classic conditioning observed with Pavlov and his dogs, has been observed: Ader and Cohen (1982) fed a saccharin-sweetened drink to lupus-prone mice in conjunction with injections of an immunosuppressant drug and found that over time the sweetened drink alone reduced inflammation and lupus symptoms [29]. Similar conditioned immune responses have been observed in humans, such as behavioral conditioning as the mediator of placebo responses in the immune system [30]. Such conditioned responses are clinically meaningful. In a clinical trial of a corticosteroid ointment in psoriasis patients, two treatment groups were evaluated, one which received repeated treatments of the cream and one group which received placebo treatments up to 50% of the time; both groups improved with no statistical difference in outcomes [31].

Immune conditioning has been also observed in humans; for example, allergy attacks were easily provoked by exposure to placebo allergen (e.g., synthetic rose or a picture of a haystack) [32]. Chemotherapy subjects were also observed to experience conditioned increases in NK cell activity as well as plasma concentrations of interferon gamma (IFN-γ) by simply entering the chemotherapy environment [32,33].

2.4 Pathology of Stress

Effects of psychosocial stress on the physiological body were recognized even in ancient texts such as "A merry heart doeth good like a medicine" *(*King James Bible "Authorized Version," Cambridge Edition, Prov 17:22). Only recently, however, has the myriad of physiological changes that stress can induce (particularly in immune function, but affecting nearly every other organ system, even at the level of the deoxyribonucleic acid [DNA]) been revealed. Stress associated with major life events (e.g., bereavement, care-giving), as well as more routine stress (e.g., school exams) are demonstrated to have consistent and clinically consequential effect on multiple immune parameters such as changes in the production of cytokines, cortisol, specific lymphocytes and other immune effectors, and changes in susceptibility to both infectious and noninfectious diseases. Detailed information on the specific physiological effects of stress is in Table 3.

One mind/body interaction in particular, the hypothalamic-pituitary adrenal axis, has been studied at length, providing evidence on the specific mechanisms through which central nervous system (CNS) activity produces seemingly unlikely somatic effects, particularly in the immune and the integumentary systems.

2.5 Clustering of Diseases Affecting Different Organ Systems

Fibromyalgia, chronic fatigue syndrome and interstitial cystitis frequently overlap with IBS [34]. Psoriasis, a skin disease, increases risk for a host of comorbidities related to metabolic syndrome, including chronic pulmonary disease, diabetes, liver disease, cardiovascular disease, peptic ulcer, kidney disease and squamous cell carcinoma [35]. Emergence of an autoimmune disease has also been observed to increase the risk of various others such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Type I diabetes, ankylosing spondylitis (AS), Crohn's disease, celiac disease and ulcerative colitis, which all may show familiar clustering.

Observation of such seemingly inexplicable physiological interdependencies, some long standing, begs a wider and deeper view of human physiology. Specific models of physiological interconnectivity are discussed below.

Table 3. Physiological responses to psychosocial stressors

Psychosocial Factor	Physiological Effect	Reference
Stress (examinations)	Reactivation of latent HSV	Glaser et al. 1985 [36]
Stress (medical school examinations)	Reduction in NK cell activity (≤33%) Increase in total plasma IgA (as compared to prior samples before beginning school)	Kiecolt-Glaser 1984 [37]
Examinations (West Point)	Reactivation of EBV	Glaser et al. 1999 [38]
Examinations (medical school)	Poorer response to hepatitis B-vaccine	Glaser et al. 1998 [39]
	Increase in daytime ACTH levels	Malarkey et al. 1995 [40]
	Increase in cortisol levels	Wolf et al. 2001 [41]
	Decreased memory T-cell response to EBV	Glaser et al. 1993 [42]
	Decreased T-cell response to mitogen stimulation	Glaser et al. 1993 [43]
	Decreased linoleic acid production (precursor omega-6 fatty acid, critical to immune cell membrane function)	Williams et al. 1992 [44]
	Decreased IFN-γ	Glaser 1992 [45]
	Altered expression of the receptor for IL-2	Glaser 1992 [45]
	Increase in infectious illness	Glaser et al. 1987 [46]
	Decrease in total T-cell, helper T-cell and suppressor T-cell counts	Webster Marketon et al. 2008 [47]
Self-report (women) with induced skin blisters	Decreased IL-1α, IL-8 at wound sites	Glaser et al. 1999 [48]
Depression	Delayed wound healing	Gouin & Kiecolt-Glaser 2012 [49]
Caregivers (Alzheimer's disease)	Poorer response to influenza vaccine as compared to matched controls	Glaser et al. 1998 [39]
Caregivers (Dementia)	Decreased immunoglobulin production	Black et al. 2013 [50]
	Increased proinflammatory NF-κB production	Black et al. 2013 [50]
Loneliness	Reduction in natural killer cell activity	Kiecolt-Glaser 1984 [37]
Lack of social support	Poorer response to hepatitis B-vaccine	Glaser et al. 1998 [39]
	Decreased T-cell response to HBsAg	Glaser et al. 1998 [39]

Psychosocial Factor	Physiological Effect	Reference
Bereavement (widows)	Decreased T-cell response to mitogen stimulation	Bartrop et al. 1977 [51]
	Higher levels of inflammatory markers IL-6, IL-1RA	Schultze-Florey et al. 2012 [52]
	Increased mortality (widows)	Boyle et al. 2011 [53]
Bereavement (siblings)	Increased mortality	Rostila et al. 2013 [54-56]
Bereavement (maternal bereavement of children)	Increased cancer risk (children)	Momen et al. 2013 [57]
Motherless monkeys	Suppression of cellular immunity	Laudenslager et al. 1982 [58]
Dysfunctional childhood (Neglect/abuse)	Decreased immune tumor surveillance and Increased risk of skin cancer	Fagundes et al. 2012 [59]
	Erosion of telomere length (associated with advancing chronological age and also increased disease morbidity and mortality)	Shalev et al. 2013 [60,61]
	Increased cancer risk	Morton et al. 2012 [62] Psaty & Siscovick 2010 [63] Tyrka et al. 2010 [64]

ACTH = adrenocorticotropic hormone, AIDS = acquired immunodeficiency syndrome, CREB = cAMP response element-binding protein, EBV = Epstein-Bar virus, HBsAg = hepatitis B surface antigen, HIV = human immunodeficiency virus, HSV = herpes simplex virus, IFN-γ = interferon gamma, IgA = immunoglobulin A, IL = interleukin, IL-1RA = interleukin-1 receptor agonist, NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells, NK = natural killer

3. SPECIFIC MODELS OF INTERCONNECTION

3.1 Vulvodynia

Causes of chronic vulvar pain are many and when not accompanied by obvious physical signs, difficult to unravel. Many common vulvar dermatoses occur without obvious erythema or mucocutaneous lesions, as can some less common disorders of both infectious and allergic origin. In addition, localized and generalized vulvar dysesthesia, recently defined chronic pain syndromes of neurogenic origin, can also occur in the vulvar area [65]. Optimal therapy will recognize the significant psychological distress that accompanies any chronic pain syndrome.

A recent study of vestibular tissue collected from 239 age-matched women with and without localized vulvodynia found a universal presence of mast cells compared to no presence in vestibular tissue among controls. Since histamine is generated by mast cells, and mast cells contribute to the production of cytokines during chronic inflammation, the authors assessed the association between vulvodynia and conditions that elicit a clinically-relevant histamine response and vulvodynia. Women who reported having hives prior to the first report of vulvar pain (or a reference age derived from randomly selected, similar, age-matched controls) were 2.5 times more likely to experience vulvodynia (95% Confidence Interval [1.7, 4.4]); those reporting a history of allergic reactions to insect bites were 2.1 times more likely (95% CI [1.1, 4.0]) and those reporting a history of seasonal allergies were two 2.0 times more likely (95% CI [1.3, 3.2]) to develop vulvodynia than control subjects. Additional analysis in a restricted subset of clinically confirmed cases and matched controls found similar results. It may be that modulation of an immunological-inflammation response to an environmentally induced allergic reaction, spurs development of vulvodynia [66].

Vulvodynia has also been associated with orofacial pain (OFP). In one study (Zolnoun et al 2008), women with vulvar vestibulitis syndrome (VVS) were surveyed for the presence and severity of orofacial pain as well as levels of pain, anxiety, somatization and presence of signs and symptoms suggestive of clinical and sub-clinical OFP and the relationship between the patient's psychological characteristics and their self-reported severity of painful intercourse was evaluated. Orofacial pain was extremely prevalent (78%) among women with VVS. Compared to women with no OFP symptoms (n = 30), those with symptoms (n = 64) had higher levels of anxiety (45.0 vs. 37.8, Bonferroni adjusted $P = 0.017$), somatization (125.2 vs. 96.0, Bonferroni adjusted $P < 0.001$) and psychological distress (62.8 vs. 56.0, Bonferroni adjusted $P = 0.002$) [67]. A similar, but not significant trend was observed for women with subclinical OFP with regard to pain and anxiety; somatization was significantly higher in patients with subclinical pain than in normal controls. Although the severity and duration of pain during intercourse did not differ by OFP classification, the subjects' psychological characteristics did. Interestingly, vulvodynia clusters with other comorbid pain conditions, the most common being IBS and fibromyalgia, two other poorly understood chronic pain syndromes that share comorbidity with a handful of other chronic pain conundrums [68]. Immunological mechanisms, driven by genetic differences in genes coding for immunological messengers like cytokines that modulate the intensity of immunological responses like the inflammatory response have been implicated [69]. Histological samples from women with vulvodynia were observed to be characterized by a universal presence of mast cells, as compared to normal controls, which lacked mast cells completely. Mast cells produce the cytokines associated with chronic inflammation,[66] Vulvodynia, obviously a multifactorial disease with contributions from several body systems,

to be understood, must be looked at as more than a self-contained issue of the vestibular vault.

3.2 Skin Sensitivity

Despite thorough premarket testing of health and beauty products specifically designed to ensure that marketed products are free from potential adverse health effects, in routine postmarket surveillance some consumers report adverse reactions to extensively tested products. These unanticipated reactions are typically itching or pain described as burning, stinging, tingling, or prickling [70]. Common cleaning products and various of environmental irritants (e.g., weather conditions) are also reported to cause similar reactions. This unusual sensitivity to common products or exposures has been termed *sensitive skin.*

Efforts to identify the cause of these symptoms have been frustrating. Subjects who claim sensitive skin often produce no visible irritation in response to irritant testing, while subjects who describe themselves as lacking sensitivity sometimes react strongly [71]. Furthermore, subjects who react strongly to one known irritant may have no sensitivity to another. Long thought to involve only facial skin, it is now known that skin sensitivity occurs at many body sites and is not infrequent in genital skin [72]. Response in one individual, in fact, can differ substantially at different anatomical sites, [73] and even at the same anatomical site on symmetric limbs [74]. Multiple studies investigating the biology of sensitive skin have yet to pinpoint a cause or establish reliable diagnostic criteria. The influence of geographical and cultural influences on sensitive skin is increasingly recognized. A rapid rise in the percentage of men who claim skin sensitivity, for example, has paralleled an increase the number of products (and their associated advertising) for sensitive skin in men, pointing to a cultural component. In fact, dramatic differences observed in skin sensitivity reports across Europe have been attributed to health and beauty product sensitive skin is an area of considerable research interest [75].

As sensitivity varies by anatomical site, a study was performed to determine whether women with prior dermatologist-assessed vulvar erythema exhibited greater irritation to sanitary pads and whether such women considered their skin to be sensitive, based on self-reported reactions to products used on the face or genitalia.

Two groups of women who previously participated in a randomized trial of sanitary pads were administered a questionnaire regarding skin sensitivity to facial cosmetics; women who had pre-existing vulvar erythema upon enrollment to the prior pad study were more likely, in the second study, to report facial redness induced by cosmetics than women without a history of vulvar erythema [76].

As research on sensitive skin has continued, a physiological basis for sensitive skin has started to emerge. Data continue to accumulate which suggest a link between atopy and sensitive skin [77]. In a survey-based assessment of 1039 individuals (83.6% female), subjects who claimed overall to have sensitive skin were 5 times likely to report that they had skin allergies that had been confirmed by a doctor ($P <$ 0.00001), [77] than those without sensitive skin and were also more than 3.5 times more likely to have relatives with sensitive skin [77]. A large early epidemiological study in the UK also observed the incidence of atopy to be higher in subjects with sensitive skin [78]. In a study in older adults with sensitive skin, the percentage of older subjects who responded affirmatively to the question "Do you have any known skin allergies that have been confirmed by a doctor?" was higher than younger

people who claimed sensitive skin [79]. Löffler et al. [80] also observed a link between sensitive skin and self-reported nickel allergy.

A similar study in Greece compared 25 women with medically diagnosed atopic dermatitis with 25 women experiencing dermatological problems unrelated to atopic dermatis. Patients completed a survey which required them to identify whether or not they perceived their skin to be sensitive, the perceived degree of sensitivity and the specific exposures to products or environmental conditions that elicited uncomfortable sensory reactions. A significant association was found between the clinical diagnosis of atopic dermatitis and the self-diagnosis of sensitive skin ($P < 0.001$). All patients in the atopic dermatitis group described themselves as having sensitive skin to at least some degree, with 80% claiming either moderately or very sensitive skin. By contrast, 64% of individuals in the control group described their skin as sensitive to some degree, with only 16% claiming either very or moderately sensitive skin [81]. Patients with atopic dermatitis were also significantly more likely to indicate a family history of sensitive skin than were non-sensitive individuals (68% to 24%, $P = 0.004$); 76% of atopic patients who claimed a family history identified a parent as having sensitive skin [81].

3.3 Autoimmunity

Autoimmune disease (AID), is increasing in prevalence worldwide [82]. A group of at least 80 distinct syndromes, these are mostly a group of relatively rare complaints, together comprise a wide range of genetically complex diseases that afflict as much as 10% of the population [83]. Autoimmune disorders are defined by a dysregulation of immune function that potentiates a breakdown in immune tolerance. The breakdown in immune tolerance in turn permits an over expression of autoantibodies and autoreactive T cells [83] that will if unchecked eventually result in inflammation and tissue destruction [84]. Autoimmune diseases target a variety of tissue types and familial aggregation is modest [85]. For example despite the fact that a family history of systemic lupus erythematosus (SLE) increases risk 25-fold, only 2% of an AID patient's close relatives actually develop the disease [86]. More than 200 genetic loci have now been documented as contributing to various autoimmune diseases [84]. Intriguingly, genetic markers identified for one autoimmune disease prove to be common to several other autoimmune diseases, [84] and the presence of an autoimmune disease in one individual increases risk, in close family members, for a variety of others [87]. Proteins implicated in the pathogenesis of these autoimmune diseases are shared [88]. Such proteins, with genes located in proximity to those implicated in increased risk for multiple autoimmune diseases, may represent an underlying shared mechanism that constitutes the physiological basis for disease risk. This is a theory supported by the observation that autoimmune patients frequently suffer from more than one autoimmune disorder at a time or from different autoimmune diseases during different stages of their lives [83].

Concordance rates among monozygotic (MZ) twins, however, although consistently higher than those in dizygotic (DZ) twins are low, below 50%, (with a few exceptions), a statistic that suggests additional complementary mechanisms in the genesis of AID [89].

The global incidence of autoimmune disease has risen steadily in recent years, worldwide and in all ages, in parallel with steadily increasing global life spans. Autoimmune diseases overwhelmingly affect more women than men, implying a central role for estrogen in their development. Some autoimmune diseases, however, are exacerbated by high estrogen levels, while others experience remission during high estrogen periods. A thorough

understanding of autoimmune disease has been assisted by the recognition of the contribution of a genetic foundation, the senescence of the immune system and environmental exposures. Although autoimmunity is effected largely by autoantibodies, the development of autoimmune disease requires an aberrant yet sophisticated interplay of a multitude of immunoactive genes that results after years of random boosts in risk from genes, estrogen, environmental insults and the inexorable process of aging to a point at which immune tolerance and the onset of autoimmune disease occurs.

3.4 Oral Health

Oral health has been demonstrated to have close association with several aspects of overall health. Bacterial colonization of the mouth, when not kept in check by regular oral care and the body's innate defense mechanisms, can cause tooth decay as well as gum disease, which can in turn result in bacteria leaving the mouth and spreading into the bloodstream [90]. Systemic dissemination of bacteria throughout the body can result in a variety of other infections such as endocarditis (infection of the inner lining of the heart), acquired immunodeficiency syndrome (AIDS) and pneumonia [91]. In addition, immune and inflammatory processes initiated by oral bacteria in the systemic bloodstream are increasingly recognized as contributors to a wide range of other more insidious health effects. Stimulation of the body's immune system by chronic bacterial presence promotes autoimmune diseases such as rheumatoid arthritis as well as a host of other diseases such as diabetes, osteoporosis, erectile dysfunction, gastrointestinal disease, cancer, prostatitis, and kidney disease. Periodontal disease gone systemic has also been implicated in problems with pregnancy such as preeclampsia and low birthweight babies as well as pre-term delivery [92]. Regular oral hygiene and adequate care of oral health is essential to prevent serious impact on overall health.

Conversely the systemic loss of bone density common in older women is also associated with poor oral health [93,94]. Bone loss also occurs in the jaw and is associated with tooth loss; replacing functional dentition as bone is lost becomes difficult to achieve [94]. Severe bone loss can impede nutritional intake enough to affect overall health.

3.5 Back Pain

Back pain is increasingly recognized as a disease not limited to just the skeletal spine, but a widespread multifactorial disorder with significant contributions from psychological and social factors [95]. Psychosocial factors in fact are considered as least as important as the physiological origin of pain in the development, persistence and efficacy of treatment of the disease [96]. Depression particularly is associated with back pain and is believed to be both a contributor and a consequence of the back pain [97]. Back pain highlights the necessity to consider the temporal course of chronic disease over a lifetime, thereby considering a longer course of causal pathways that underlie disease symptoms, with different mediators of the course of disease and different levels of risk at different times [98]. Similarly to considering whole-body influences on organ-specific disease processes, considering the variety of long-term temporal influences on disease processes can benefit understanding of causative factors as well.

4. TOWARD SYNCRETIZATION: UNCOVERING THE FOUNDATIONS OF AN INTEGRATIVE UNDERSTANDING OF HEALTH AND DISEASE

The genetic foundation of the body forms the platform on which body processes proceed, and the effectors of the multidirectional communication between the organ systems and between the genome-level processes in the cell create a complex web of interactions that form the matrix of a merger of the body and the mind. Potential mechanisms for the somatization of psychosocial processes and the integrative function of multiple organ systems are many. Some shared means of action are potentially many and are still being studied, but some means of communication are well established.

4.1 Hormones: Estrogen and Progesterone

Physiological effects of estrogen, with cyclical variations of estrogen levels during a woman's reproductive years as well as various forms with similarly varying levels over the female lifespan, is recognized as a physiological mediator throughout the female body. Estrogen receptors exist in nearly every body tissue of the human female, with a myriad of effects on cognitive and emotional function, immune function, the skin and numerous other physiological processes. The skin has highly sensitive receptors for both estrogen and progesterone, affecting many skin disorders, including autoimmune disorders known as estrogen dermatitis and autoimmune progesterone dermatitis, believed to be cutaneous reactions to the female endogenous sex hormones themselves.

Estrogen is also a modulator of the immune system; high estrogen levels inhibit many autoimmune processes, with high estrogen levels acting to inhibit allergic response. Peak estrogen levels at the time of ovulation are associated with mast cell degranulation, as well as decreases in T-cell numbers, leading to a depression of cellular immune response. B-cell numbers, however, increase in coincidence with ovulation [99]. Cyclically fluctuating levels of estrogen and progesterone influence numerous characteristics of the epidermis, including skin-surface lipid secretion and sebum production, skin thickness, fat deposition, skin hydration and barrier function. Dermal collagen content, which contributes to skin elasticity and resistance to wrinkling, is also influenced. Interestingly, estrogen levels also influence skin pigmentation and ultraviolet (UV) susceptibility, as well as resident microflora on both vaginal and keratinized skin [100,101].

In addition, changing hormone levels across the menstrual cycle produce measurable variations in immune function and disease susceptibility. An understanding of the profound influence that fluctuating estrogen and progesterone levels have on the biological responses of the premenopausal adult woman is critical to optimizing the efficiency of medical therapies in this population [101].

Although the web of physiological effects induced by the complex, interdependent fluctuation of estrogen and progesterone over the course of the female human lifespan has long been recognized as a dominant influence on the female body, the substantial influence that these hormones have on neurological and psychosocial development has only more recently come to light. Estrogen and progesterone impact brain function, cognition, emotional status, sensory processing, appetite and more [101-104]. The ability of reproductive hormones to impact psychoneurological processes involves the interplay of several body systems, lending credibility to the view of premenstrual syndrome (PMS) as a disorder founded in real biochemical disturbances [105].

Autoimmune diseases show a clear predominance in women, implying a central role for estrogen in their development. A thorough elucidation of that role, however, has been challenged by the observation of undeniable contributions to autoimmune disease by genetics, immunosenescence and environmental triggers as well. The global incidence of autoimmune disease has risen steadily in recent years, worldwide and in all ages, in parallel with steadily increasing global lifespans [106].

Interestingly however, some evidence exists which suggests that PMS, a disorder characterized by depressed mood, anxiety, affective lability, irritability, decreased interest in usual activities, difficulty concentrating, low energy, changes in appetite, sleep disturbances, a sense of being overwhelmed or out of control, headaches, joint or muscle pain, breast tenderness and abdominal bloating, may in fact be an autoimmune disease [107]. PMS impacts the majority of adult women on some level, with millions of women affected severely enough to disrupt daily life; nevertheless, it is an under-investigated disorder still lacking a definitive etiology. The pronounced gender discrepancy in the prevalence of autoimmune diseases strongly implicates estrogen and/or progesterone as a culprit. Again, hormonal fluctuations of the menstrual cycle are known to cause exacerbation of the many autoimmune diseases, particularly those with cutaneous manifestations. The demonstration of a dramatic comorbidity of premenstrual exacerbations of cutaneous allergic and autoimmune disorders with PMS, the documentation of hypersensitivity reactions to estrogen and progesterone in PMS patients but not in normal controls and the ability of desensitization therapy to improve symptoms in PMS patients suggests that autoimmunity may play a role in the origin of PMS symptoms [105]. A substantial list of both physiological and psychological effects on the woman's body is in Tables 4, 5 and 6.

Table 4. Physiological changes associated with estrogen level changes over the menstrual cycle

Physiological Factor	Finding	Reference
Spatial orientation (by mental rotation test)	Scores lowest at estrogen peak	Hausmann et al. 2000 [108]
Skin reactivity	Lowest at estrogen peak	Agner et al. 1991 [109]
Patch testing	Nonreactive at high estrogen levels	Alexander 1988 [110]
Atopic dermatitis	Worsens at low estrogen levels (right before menses)	Kemmett et al. 1991 [111]
Asthma	Estrogen levels correlate positively with increase in exhaled nitrous oxide, a marker of airway inflammation, compromised pulmonary function and atopy	Mandhane et al. 2009 [112]
T-cell numbers	Increased CD4+ cells in estrogen-driven follicular phase	Lee et al. 2010 [113]
T reg cells	Increased in estrogen-driven follicular phase	Arruvito et al. 2007 [114]
B-cells	Immunoglobulin levels in cervical mucus peak at estrogen peak, with women an OC added jump in IGA and IgG levels.	Franklin et al. 1999 [115]
Monocyte numbers	Total monocyte numbers peak in estrogen-deficient luteal phase	Willis et al. 2003 [116]
Cholesterol levels	Clinical endocrinology and metabolism	Mumford et al. 2011 [117]

CD4+ = cluster of differentiation 4, Ig = immunoglobulin, OC = oral contraceptive

Table 5. Physiological changes in skin characteristics associated with estrogen level changes over the menstrual cycle

Skin characteristics	Reference
Increased skin thickness	Hall & Phillips 2005 [118]
Decreased collage breakdown	Brincat et al. 2005 [119]
Increased production of collagen fibers	Savvas et al. 1993 [120]
Increased epidermal hyperpigmentation	Manning et al. 2004 [121]
Decreased sebum	Bolognia et al. 1989 [122]
Increased water-binding capacity	Anttinen et al. 1973 [123]
Increased fluid retention	Wilhelm et al. 1991 [124]
Decreased cellular-immune response	Tamer et al. 2003 [125]
Increased vasodilation	Charkoudian et al. 2000 [126]
Increased elasticity	Henry et al. 1997 [127]
Improved wound healing	Ashcroft et al. 1999 [128]
Increase in hair density	Millikan et al. 2006 [129]

4.2 Neurological Interactions among the Endocrine System, the Skin and the Immune System

The nervous system, obviously, interacts with every body system through signals conveyed by sensory nerves and motor nerves; the brain-skin connection particularly is made up of a vast neurosensory web perfused with, in the woman, estrogen and progesterone as well as other hormones. Brain neurotransmitters as well as receptors are also known to exist in the immune system, with interferon and interleukin (IL)-1 effects on the brain [130]. Blalock, a neuroimmunologist, in fact called the immune system a "sixth sense" (in that sense, a branch of the neurological system) that enables us to respond to not only "the universe of things we can see, hear, taste, touch and smell but also the other universe of things we cannot" [131]. The immune system affects regulation in response to stress signals from the nervous and endocrine systems through the production of cytokines; these cytokines, as well, feed back to the CNS and regulate further neurochemical response. This provides an intrinsic system of regulation, through cytokine production that links physiological response to psychosocial and environmental events [132]. Cytokines and the auto-inflammatory reactions they can create, are implicated in the pathology of numerous chronic pain diseases with still dubious etiologies, for example, psoriasis, IBS, vulvodynia and autoimmunity. Even a mild stress like sleep deprivation, for example, is known to activate inflammatory processes (in a gender-specific manner), with cellular markers of inflammation associated with cardiovascular disease, autoimmune diseases, diabetes mellitus and arthritis. Females evidence more cellular immune activation than males, with a functional alteration of monocyte -specific inflammatory cytokine responses [133].

Table 6. Changes in psychosocial function associated with hormone levels in women

Life Stage	Psychosocial Effects	Reference
Menstrual Cycle*	Exacerbation of mood disorders in women coincident with estrogen nadir	Cameron et al. 1988 [134] Cook et al. 1990 [135] Miller & Miller 2001 [136] Sigmon et al. 2000 [137]
	Suicide attempts peak at times of estrogen nadir	Baca-Garcia et al. 1998 [138] Baca-Garcia et al. 2000 [139]
	Spatial orientation (ability to mentally rotate object in space) strongly negatively associated with estrogen levels	Hausmann et al. 2000 [108] Maki et al. 2002 [140] Moody et al. 1997 [141]
	Memory best in mid-luteal phase	Maki et al. 2002 [140]
	Concentration worst pre-menstrual	Lord & Taylor 1991 [142]
	Semantic processing of word tasks best pre-menstrual	Ussher & Wilding 1991 [143]
	Motor skill speed and coordination best at mid-luteal phase.	Hampson & Kimura 1988 [144]
	Fine motor skill worst during premenstrual period	Maki et al. 2002 [140]
	Auditory verbal acuity highest during mid-luteal phase	Sanders & Wenmoth 1998 [145]
	Auditory music acuity highest during menses	Sanders & Wenmoth 1998 [145]
	Hypersensitive to stimuli during premenstrual period	Benedek & Rubenstein 1939 [146]
Menopause	Rapid deterioration of overall mental function	Halbreich et al. 1995 [147]
	Deterioration of memory	Sherwin 2003 [148]
	Decrease in abstract reasoning capability	Sherwin 2003 [148]
	Decreased reaction times	Sherwin 2003 [148]
	Decline in brain volume	Murphy et al 1996 [149]
	Decreased verbalization acuity	Ashman 1999 [150]
	Decreased attention	Stankov et al. 1988 [151]
	Decreased processing speed	Halbreich et al. 1995 [147]
	Increased anxiety	Palmer et al. 2007 [152]
	Increased mood disturbance	Palmer et al. 2007 [152]
	Increased motivation	Palmer et al. 2007 [152]
Estrogen replacement therapy	Better performance on memory testing	Sherwin 2003 [148]
	Better performance on abstract reasoning tests	Jacobs et al. 1998 [153]
	Better performance on general cognitive tests	Kimura et al. 1995 [154]
	Better performance in name recall	Robinson et al. 1994 [155]

** Menstrual Cycle = Follicular Phase: days 1-14 (menses days 1-7, estrogen nadir [lowest point] at day 7, estrogen highest at days 13-14 [ovulation]); Luteal Phase: days 15-28*

5. INTEGRATIVE PHYSIOLOGY: A GENETIC FOUNDATION

Ultimately, the foundation of all body structures and systems in the foundation encoded in the DNA, and that genetic sequence is the determinate factor in body structure as well as many physiological functions; for example, ethnicity influences numerous characteristics of skin structure and function, [156] and many diseases (including autoimmune and skin diseases) have familial affiliations, including psychological function. Nocebo and placebo effects have a genetic basis and DID appears to have genetic basis as well. The genetic sequence which provides the blueprint for the developing child is essentially set in stone; only recently however, has medical science begun to understand that structural changes occur with dramatic effects on health, structural changes that can be influenced by psychosocial events. In addition, it was recently reported that stress acts to shorten telomeres (the protein cap on every chromosome which influences cellular senescence by inducing apoptosis) which in turn accelerates cellular aging in every organ system [157].

Modification of physiological function by non-genomic changes in DNA which act to regulate gene transcription (a regulatory process known as *epigenetics*), is a biological phenomenon which has come to light only over the last couple of decades. Epigenetic actions are cell-specific and stable changes to DNA that act to regulate gene expression but which do not cause mutation. Epigenetic changes do not alter DNA sequence, but instead control gene expression [89]. These epigenetic changes affect real-time control of homeostasis in the body, maintaining normal function of virtually every single body cell and cellular metabolism.

Epigenetic mechanisms confer "phenotypic plasticity" upon the genotypic platform by giving the body, at the cellular level, ability to respond to both internal and external environmental cues [158]. Cells, for example, monitor inventories of necessary compounds and are able to modulate transcription of appropriate genes through epigenetic mechanisms [159]. Epigenetic modifications of DNA are abundant in every cell, changes which are stable because they are heritable during cell division [158].

Epigenetic changes are involved in normal development as well as in disease. Epigenetic variation over time depends on genotype, environment, sex hormone interactions and undoubtedly other undetermined stochastic factors [160]. Such epigenetic changes in fact provide a ready explanation for discordance in MZ twins with regard to epigenetic diseases that clearly have strong genetic foundation, [89] literally serving as the physiological link between the nervous, endocrine and immunological systems; the genome; and the genesis of disease.

Epigenetics provides a mechanism (transcriptional control of cytokines, immune factors, or any gene product) through which psychosocial events can cause physiological distress and disease. The effects of this transcription control can be devastating. Childhood neglect and other early life social adversity causes transcriptional modulation of the developing immune system with patterns of enhanced inflammatory gene expression and inhibited antiviral gene expression; for example, social distress perceived by the CNS influences transcription decision-making in leukocytes [132]. Alterations to immune processing can alter immune function irrevocably, with disturbation of physical function through adulthood [161].

Monkey data, moreover, shows that social adversity can play a role in activating conserved transcriptional response to adversity (CTRA) dynamics during the earliest stages of postnatal immune system development.

Body functions, in conclusion, with input from estrogen levels and environmental impacts, act on the genetic foundation of the individual at both genomic and extra-genomic levels to influence pathways of gene regulation and intra-system communication, with often synergistic effects on disparate organ systems, to influence health and disease.

6. CONCLUSION

The Western paradigm of medicine, which views body systems as distinct entities with limited interaction, has been predominant for more than 2500 years but is increasingly confronted by mounting evidence that the paradigm needs to be revised. A fundamental integration of mind and body, particularly, has been increasingly confirmed. Placebo and nocebo effects are now recognized as significant contributors to the efficacy of treatment. Increased understanding of certain pathogenic processes reveals a fundamental synergy of mind and body: distinct psychological personalities in patients with DID evidence very real physiological differences and immune reactions can be psychologically conditioned to occur in the absence of immune stimulus.

Psychological stress has been demonstrated to induce a myriad of interconnected deleterious alterations in immune function. Integration of all body systems is illuminated by the clustering in certain patients of disorders such as fibromyalgia, chronic fatigue syndrome, and IBS, disorders that affect different body systems. Further, specific disorders, not well understood, are currently being recognized as multi-factorial in origin; for example, vulvodynia (associated with other pain syndromes and which may have both immune and psychosocial components) and skin sensitivity to common products (reported by most surveyed subjects despite intensive product testing) for which cultural factors seemingly play a role.

The body is one integrated system and the genome, which lays down a foundation, is now recognized as a dynamic foundation, continually influenced at the level of expression, by both internal and external factors (i.e., stress) with profound changes to body function. The mechanisms for these apparent disconnects between known physiological processes and seemingly inexplicable physiological events are beginning to be unraveled.

Unexplained medical symptoms in one author's opinion "represent one of most frustrating and intractable puzzles in primary and specialty care" [1]. Accumulating evidence points to a likely basis for the frustration, namely, a neglect of the body as an integrated system with countless bi-directional means of communication between the neural system and body tissues, particularly overlooking the psychosocial context in which the physical body operates. The new paradigm of modern medicine, based on accumulating substantiation of still to be understood communications among all body systems and between all body systems and the DNA will consider all potential factors in disease and thereby, offer patients every potential means to wellness.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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