# Addiction Research

# A New Model for Healing Part II

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My first essay [1] explored the definition of wholeness, for healing involves attaining the experience of the whole. In psychotherapy it is defined as healing the psyche, psyche is defined and the relationship of psyche to the whole is discussed. Two paradigms are presented: the medical model which offers an inadequate model to explain how the psyche and the soma are interrelated, and an older system of healing defined in terms of the archetype of wounded healer. The meaning of wholeness within the archetype of the wounded healeis discussed in terms of the Aggada of the talmud, the shaman and modern therapists.

In part II, I wish to apply and claim that the same mechanisms can be applied to somatic medicine. In order to make this claim I will need to reflect on the cerebral underlying networks that explain psychosomatic disorders then showhow brain imaging reveals structural changes. This will then support my thesis that the intangible interactions found in such encounters with 'wounded healers" may also apply to somatic hard core medical diseases, not just psychotherapeutic encounters. Healing is defined as a return to a state of wholeness, the "restoration through mending of a breach." Wholeness is defined as "not broken off, defective, damaged, injured; or intact; a complete organization'! of the parts, a unity oran entirety.' In most healing systems throughout history, wholeness involved a dynamic interrelationship between body, mind and soul. It has onlybeen in the last four centuries that our current paradigm has changed the concept of the whole. The current medical model relies on an etiological approach which excludes soul, gives partial recognition to the psyche, and concentrates mostly on the body and its physiological and biochemical mechanisms. The body has been thought to be susceptible to invasions by foreign bodies such as germs or antigens. Physicians have adopted an ameliorative stance. Their goal has been to repair the damages rather than prevent the imbalances which cause the body to be susceptible to invasions.

Before proposing my thesis we need to review the current state of

science as it applies to psychosomatic disorders since we need to blur the distinctions bywhich so many of us were schooled in medicine, the split between psyche andsoma. Once we can dismantle the neat distinctions we can then apply many of the categories I outlined in my first paper to actual hard core physical diseases.

#### **Psychosomatic Medicine: concept and history**

D.Yao et al. [2] have described traditional Chinese medicine, "The Emperor's Eighty-One Difficulties" 1900 years ago, as recording four methods for diagnosing various diseases including brain disorders: "looking, listening, asking, and touching." "Looking" refers to observing the patient's complexion,"listening" refers to hearing the sound, coughing, and breathing, "asking" refers to inquiring about their symptoms, and "touching" refers to noting their vital signs (e.g., their heart rate). Thus, even this far in the past, the conceptthat the body and the mind were united was understood and utilized to treatpatients. In 1818, Heinroth introduced the term "psychosomatic," yet the conceptual roots of psychosomatic medicine extend back to ancient Greece. After modern psychosomatic medicine was established as a medical disciplineit rapidly developed, passing through various stages. The central concept of psychosomatic medicine is that the brain and body are integral to all human functions; practitioners assess the psychological factors that affect individual vulnerability as well as the course and outcome of the illness and apply psychological therapies to treat physical illness. Psychosomatic medicine seeks to explain how immaterial events, such as behavioral or psychological responses to psychosocial stimuli, are transformed into physical changes, such as anatomical, enzymatic, autonomic, or endocrine responses. Additionally, this discipline attempts to elucidate the role of the central nervous system (CNS) in the control and regulation of endocrine and neural processes.

The groundwork for psychosomatic medicine was laid in the 1910s–1920s when Cannon investigated bodily changes accompanied by specific emotions [3] and proposed the Cannon– Bard theory. This theory emphasizes the role of the thalamic and hypothalamic centers in organizing the emotional responses to stimuli, marking a shift from the prior James-Lange theory to the study ofcentral brain mechanisms underlying emotions [4] it was an important precursor to the following studies. Based on the Cannon-Bard theory, Papez proposed the mechanism of emotion, and Maclean suggested the presence of a relationship between psychosomatic disease and the "visceral brain" [5] Alexander also identified emotional tension as a significant cause of physical illness [6], and the psychosomatic relationship between personalitycharacteristics and life situations were described [7]. The interaction between stress and physical disease, especially cardiovascular disorders, has been elucidated. Thus, researchers gradually proposed a unified concept of health and disease [8]. Engel further provided a method of interviewing subjects and assessing psychological data, developing a multifactorial model of illness thatwas assumed to result from interactions of the cellular, tissue, organismic, interpersonal, and environmental levels [9]. In this stage (1930s-1960s), the focus shifted from the occurrence of disease to its context.

Representative studies during the development of the field of psychosomatic medicine. In the early twentieth century, Cannon's laboratory studied the physiology of emotions for two decades; with the support and expansion of Bard's studies, they proposed the Cannon-Bard theory that linked emotions and physiological responses. The Cannon-Bard theory was an important precursor for studies, such as Papez's "A proposed mechanism of emotion." In themid-twentieth century (from the 1940s to the 1960s), the psychosomatic perspective identified different kinds of psychological factors in illness, and physiological changes were discussed. After the1960s, researchers in the field proposed and discussed psychiatric connotations, psychosomatic theory, behavioral therapy, and clinicalcriteria. In the past two decades, the psychosomatic medicine framework has broadened to include numerous psychiatric and physical systems, and its measurements and clinical practices for treatment-related care come increasingly to the fore after the 1960s, the development of consultation-liaison (C-L) psychiatry provided an impetus to psychosomatic research worldwide and enhanced thepsychiatric connotation of the field. During this stage, the preliminary application of psychosomatic medicine in consultation psychiatry was established [10]. Additionally, behavioral medicine grew and was increasingly practiced. The risks of certain behaviors for the development of disease wereemphasized [11] as well as the importance of family factors in the development and maintenance of severe psychosomatic problems in children [12]. Stress, trauma, and hostility were also identified as important factors in psychosomatic processes [13]. Moreover, researchers proposed diagnostic criteria for psychosomatic syndromes [14] and outlined the relationships with current psychiatric nosology [15]. In this stage, behavioral therapy was on the rise, as it demonstrated high potential for treatment options [16]. In the past two decades, psychosomatic medicine has continued to advance, providing new effective strategies and measurements for clinical practice. Psychosomatic medicine has linked psychiatric and physical

systems and provided extensions into new areas. Various studies have concluded that immune modulation by psychosocial stressors or interventions is a core mechanism underlying a diverse set of diseases [17]. Inflammatory, oxidative, and nitrosative stress pathways may be the genuine organic cause of chronicfatigue and psychosomatic disorders [18].

How the brain-gut interactions work and the links of the gut microbiome witheurodevelopment and depression suggest another psychosomatic pathway of major importance [19]. Today, the field of psychosomatic medicine is more scientifically rigorous, diverse, and treatment-related than ever before. Regarding depression and anxiety, which are highly prevalent in patients withcardiovascular disease, the effectiveness of cognitive behavioral therapy has been evaluated in internal medicine care [20]. Additionally, clinical practice guidelines have been refined and provided for clinical applications [21]. In the past few years, the use of C-L psychiatry in psychosomatic medicine was recommended. Because C-L psychiatry addresses wider linkages between psychiatry and other medical professions, the integrating care in psychiatry has made the liaison role more important than ever. Currently, the environment and human lifestyle are experiencing profound changes with advances in information science, intelligence science, environmental science, and biological science [22].

Psychosomatic medicine provides a microcosm perspective on mind-body interactions in disease and health; it also provides a basis for maintaining, improving, and enhancing physiological functions in all aspects of human activities.

# **Bio-Psycho-Social Theory**

The interrelationships among mind, body and environment in sickness and health are the central focus of psychosomatic medicine and the essence of George Engel's biopsycho-social model of disease [23]. Engel's clinical approach to the patient Whereas most physicians view the study of disease as a science and the care of the patient as an art, Engel [24] consistently asserted that patient care is as much a matter for science as is the study of disease and also that both are an art. He argued that human behaviour, feelings, transactions, and relationships can be investigated scientifically and that the instruments for data gathering are observation, introspection, and dialogue. Engel [25] had learned many of the methods of scientific research when he and his twin brother worked summers at a marine biological laboratory. When hegot involved in a research project on delirium with John Romano in 1941, he became aware of the important psychological variables in medical illness and liscovered the value of the medical interview and dialogue for gaining accessto this information. It was during his years in Cincinnati, and especially his exposure to the scientific approach of Maurice Levine at weekly psychosomaticrounds, that Engel [26] began to appreciate the value of the psychoanalytic method for accessing personal and psychosocial data, and also for organizingand studying this data systematically.

Engel's subsequent training in psychoanalysis enhanced his skills for accessing psychological data. An openended style of

interviewing, listening to thepatient's verbal communications for hidden meanings, close observation of the patient's non-verbal communications, and looking inward to evaluate the feelings and fantasies evoked by the patient are basic to the psychoanalytic method [27].

In contrast to the interrogative 'yes-no' questioning that occurs in most medical interviews, Engel's emphasis was on permitting patients to speak freely about themselves, their families and other relationships as well as abouttheir symptoms. The physician's task was to observe the patient's gestures, posture, facial expression, and way of speaking, all of which were regarded asraw scientific data. Introspection and dialogue with the patient helped establish meaning to these verbal and non-verbal communications and to thereby clarify the nature of the patient's illness and its interrelationship withhis or her personal life. Also required of the physician was critical scrutiny andanalysis of his/her own behaviour and its impact on the patient [28].

Although not explicitly stated by Engel, the method of listening he advocated was comparable to Reik's [29] exhortation to psychoanalysts to listen with the 'third ear' and to Bion's [30] injunction to suspend memory, desire, and preconceptions so that the mind is open to discovering the unexpected and new. Engel [31] avoided the use of psychoanalytic jargon whenever he wrote about his method of medical interviewing. Indeed, through his style of teaching and writing, he translated basic psychoanalytic principles into formsthat were meaningful and acceptable to most medical students and non- psychiatric physicians. By using the triad of observation, introspection, and dialogue, Engel acquired information that led to a more comprehensiveunderstanding of ways by which mental processes and environmental eventscan influence bodily processes.

Romano has proposed the following formulation: "Health and disease are notstatic entities but are phases of life, dependent at any time on the balance maintained by devices, genetically and experientially determined, intent on fulfilling needs and adapting to and mastering stresses as they may arise from within the organism or from without. Health, in a positive sense, consists in the capacity of the organism to maintain a balance in which it may be reasonably free of undue pain, discomfort, disability or limitation of action, including social capacity." Disease corresponds to failures or disturbances in the growth, development, functions, and adjustments of the organism as a whole or any of its systems. Clearly, such a definition is too broad to be of practical value. Further, it includes value terms "reasonably free," "failures," "disturbances" without defining them. Still, it is useful as a starting point since it does not restrict us to any one parameter. It is to be contrasted, for example, to the cellular concept of disease, which, by focussing primarily on changes within the cell as the basic component of disease, actually restricted attention to only one aspect of disease and one which is not necessarily present.

It tries to get away from the implicit assumption that disease is a thing in itself, unrelated to the patient, the patient's personality,

bodily constitution, and mode of life a concept of antiquity which repeatedly reasserts itself evenin our language, as when we say that a patient has a disease or that we treata disease. The broad definition of disease does not confine our attention to any single system of organization of the body. It permits us to conceptualize disturbances or failures at all levels of organization biochemical, cellular, organ, psychological, interpersonal, or social and to consider their interrelationships.

Further, it does not restrict us to any single etiologic concept but permits theapplication of a multi-factor concept. An important aspect of many concepts of disease has been the tendency to ascribe disease to a "bad" influence, usually something external which gets into the body. This theme characterizes most primitive and prescientific views of disease and has reappeared repeatedly in various guises in the scientific era. To be able to think of disease as an entity, separate from man and caused by an identifiable substance, apparently has great appeal to the human mind.

Perhaps the persistence of such views in medicine reflects the operation of psychological processes to protect the physician from the emotional implications of the material with which he deals. The material of medicine is sick or disturbed man. The physician cannot detach himself from his material as the physicist or the botanist can from his. It should not surprise us, then, that concepts which permit some measure of psychological detachment should have unconscious appeal to both physician and patient. The mechanism of projecting to the outside what is felt or experienced as uncomfortable, painful, or dangerous is universal in every human being and is characteristic of one phase of the psychological development of every child. So too is the idea that what is felt as bad or painful inside got there from the outside. In prescientific medicine such psychological processes achieved expression in the form of demonologic concepts.

# Functional Brain Imaging Results in Traumatic Recall in Trauma Disorders



PET images indicating higher mGluR5 receptor availability in an individual with PTSD vs. a healthy comparison participant. NeuroscienceNews.com image is adapted from the Yale news release.

In a groundbreaking study of FUNCTIONAL BRAIN IMAGING AND THE INDUCTION OF TRAUMATIC RECALL, ERIC VERMETTEN and J. DOUGLAS BREMNER [32] studied the effect of trauma as a hypnotizing effect picturized in the following

Study	Imaging Method		Popula	tion		Trauma Type	Act	ivation	No Activation	Scan Data Acq	Add'l Data Acq	INC PTSD-TC or ACTIV-NO ACTIV	DEC PTSD-TC or ACTIV-NO ACTIV
Rauch et al. (1996)	[ <sup>15</sup> O]H <sub>2</sub> O PET	males	N = 8	PTSD	- 0	combat	lister to tra scrip	uing uuma t	neutral script	during exposure	HR, SUDS	ri limbic, paralimbic and visual	le inferior frontal and middle temporal cortex
Shin et al. (1997)	[ <sup>15</sup> O]H <sub>2</sub> O PET	males	N=14 (7/7)	PTSD	TC d	combat	watc comb relate nega pictu	hing oat ed and tive res	neutral pictures	generating visual mental images	-	ventral anterior cingulate gyrus, ri amvgdala	Broca
Bremner et al. (1999)	[ <sup>15</sup> O]H <sub>2</sub> O PET	males	N = 20 (10/10)	PTSD	TC o	ombat	watc comb relate slide soun	hing pat ed s and ds	neutral slides, nonverbal music	during exposure	HR, SUDS, PTSD symptom scale, PASS, CADDS, VAS fear	ri inf front gyrus, midbrain	prefront cortex (25), le ant cingulate, le thalamus, le vis assoc cortex, sup temp lobe, le mid temp cortex
Bremner et al. (1999)	[ <sup>15</sup> O]H <sub>2</sub> O PET	female	es N=22 (11/11)	PTSD	TC o s a	childhood exual ubuse	lister perso scrip traur	uing to onalized t of na	neutral script	during listening	SUDS, PTSD symptom scale, CADDS, fear VAS	ant prefront cort (6, 9); post cingulate (31), motor cortex, (alt in med prefront cortex)	subcall gyrus (25); ant cingulate (32); ri hipp; inf temp gyrus, sup.marg. gyrus, vis assoc cortex
Osuch et al. (2001)	PET	females, males	N=11	PTSD	no contr	mixed ol		listening t traumatic script plus flashback experience	o no flashback	during listening	HR, SUDS	le inf frontal, le hipp, le ant insula, ri insula, ri putamen, le somatosensory le cerebellum, lingula, brainstem	Bilat dorsolat prefrontal, ri fusiform and ri med temporal v, cortices
Lanius et al. (2002)	fMRI	females, one male TC	N = 17 (7/10)	PTSD (dissociative responses)	тс	sexual, physica emotior abuse	il and nal	listening t traumatic script	o baseline	during reading 30 sec	HR, CADSS	ri sup/mid temp gyri (38), inf frontal gyrus (47), occ lobe (19), ri parietal lobe (7), ri med frontal gyrus (10), ri med prefr cortex (9), ri ant cingulate (24, 32)	-
Pissiota et al. (2002)	[ <sup>15</sup> O]H <sub>2</sub> O PET	males	N=8	PTSD	no contr	combat ol		listening t sounds of combat	o simple tones	during exposure	HR, STAIS, SUDS, panic VAS	ri sensorimotor cortex (4, 6), primary sensorimotor cortex (1, 2, 3), cerebellar vermis, PAG, ri amygdala	ri retrosplenal cortex (26, 29, 30)

#### Table 1 Overview of Designs of Neuroimaging Assessments in PTSD Studies - Up to 2002



Figure 1. Hypothesized similarities between hypnosis and traumatic recall. This diagram may be especially true for high hypnotizable subjects, which is usually the case in patients with PTSD. (Adapted from P. Rainville, personal communication, 2002).

To date, 12 imaging studies that used a symptom provocation paradigm in PTSD have been published. Seven studies used PET, three used fMRI and two used SPECT as imaging technique. The design, patient population, induction method, measure of recall, psychophysiologicalcoregistration, and changes in brain metabolism are tabulated in Table 1 above.

These studies have used various challenge models, exposing the subject atvarying levels of complexity to perceptual stimulations that range from exposing patients to slides and sounds, smells of trauma-related experiences, to reading narrative scripts, to the administration of pharmacologic agents like yohimbine. Reexperiencing of traumatic events typically coincides with heightened attention, lack of awareness for the surroundings, and loss of perception of time. At the same time, emotions of fear, shame, disgust, anger, and sadness, mayoccur and sometimes coincide with dissociation, freezing, and other psychophysiological arousal phenomena.

The first PET studies in traumatic recall used combat slides and sounds and script-driven imagery in PTSD patients. The results suggested that symptoms associated with traumatic recall were mediated by the limbic and paralimbic systems within the right hemisphere. Activation of visual cortex corresponded to the visual component of PTSD reexperiencing phenomena. When generating mental images of combat-related pictures, increased regional cerebral blood flow (rCBF) in the ventral anterior cingulate cortex (ACC) and right amygdala was seen; when viewing combat pictures, subjects with PTSD showed decreased rCBF in Broca's area. These first PET studies of traumatic recall in PTSD have since led to a rapid increase in similar studies modifying the experimental condition and/ or study population.

Current studies support a model of PTSD in which (a) the amygdala is hyperresponsive to threat-related stimuli, and (b) interconnected areas may provide insufficient "top-down" inhibition by mPFC and ACC of amygdala response. This relative dysfunction of mPFC and ACC is thought to lower the threshold of amygdala response to fearful stimuli and is central to symptom mediation. Thus, dysfunction of the mPFC areas may provide a neural correlate of a failure of extinction of fearful stimuli in PTSD.

In a meta-analysis of PET and fMRI studies of general emotional activation reviewing 43 PET and 12 fMRI activation studies

spanning almost a decade ofresearch, Phan, Wager, Taylor, and Liberzon (2002) describe brain areas that are involved in emotion induction with cognitive demand, typical paradigms of the recall of autobiographical elements or visual imagery:

- mPFC
- amygdala
- mPFC/subcallosal gyrus (area 25)
- occipital cortex (OC) and amygdala
- ACC (area 32) and insula

general role in emotional processing specific role in fear processing involved in the processing of sadness activation by emotional induction by visual stimuli induction of emotional recall/imagery and induction of emotional tasks with cognitive demand

In a study with abuse-related PTSD patients, approximately 70% of patients relived their traumatic experience and showed an increase in heart rate whilerecalling the traumatic memory.

The other 30% of patients had a dissociative response with no concomitant increase in heart rate. PTSD patients in a dissociative state showed more activation in the superior and middle temporal gyri (BA 38), the inferior frontalgyrus (BA 47), the occipital lobe (BA 19), the parietal lobe (BA 7), the medialfrontal gyrus (BA 10), the medial cortex (BA 9), and the ACC (BA 24 and 32). Despite a variety in rCBF in application of the traumatic recall paradigm, we now can describe a model of the neural circuitry in traumatic recall. In this model, emotional involvement and memory dysfunction implicate limbic brainregions, including the amygdala, hippocampal formation, and limbic cortex, such as the orbitofrontal and anterior cingulate areas. Additional key brain structures are thalamus (relaying incoming perceptual input), mPFC (planning execution, working memory, attention), and ACC/PCC (attention, affect, and affective control) (see Figure 2).



Figure 2. Schematic working model of the functional neuroanatomy of traumatic recall. Key players are the thalamus (sensory gateway); the hippocampus, which is critically involved in learning and memory; the amygdala, which contributes to information adding emotional significance. The medial PFC (OFC) together with the ACC is involved in the planning and execution, inhibition of responses and in the extinction of fear responsivity. The model is also intended to serve as a working model for hypnotic responsiveness, perhaps with a key role for the ACC. Failure of inhibition by the mPFC, in conjunction with alterations in ACC and amygdale processing is considered the pivotal element in traumatic recall. (Adapted and modified from van der Kolk, 1996).



#### The Psyche-Soma Dichotomy

R. Torta, R. Botto, V. Giorgi and P. Sarzi-Puttini have questioned whether the psyche-soma dichotomy still clinically appropriate? [33].

The debate concerning the relationship between the mind and the body has along medical, philosophical and religious history, with psyche-soma dichotomy and psychosomatics alternating as the dominant clinical approach depending on the prevalence of cultural orientations at different times. The view of the unity or division of the psyche and soma has varied from the holistic medicophilosophical approach of ancient Greece to the "biologisation" of the psychic aspects of scientific medicine. This article proposes a historical re- contextualisation of the mind-body relationship and offers some evidence based reflections on the clinical appropriateness of the different views. Historical background when proposing his humoral theory in ancient Greece, Hippocrates (IV century BC) tried to provide a unitary conception of human beings in which the body, mind and the environment were strictly interconnected. Centuries later, in 1662, Descartes replaced this perspective [33] Clin Exp Rheumatol 2023; 41: 1342-1349. with his reflections on res extensa (the domain of science) and res cogitans (the domain of philosophy and theology) as a means of freeing science from religious influences. However, this was certainly not a real dichotomy as he wrote "Inputs are passed on by the sensory organs to the epiphysis in the brain, and from there to the immaterial spirit" [34].

Unfortunately, posterity misunderstood the difference between res extensa and res cogitans, thus leading to the cultural and medical exclusion of res cogitans that has persisted ever since. The biomedical model, that developedduring the XIV century on the basis of the principles of reductionism and mind-body dualism, is still accepted today. It relates symptoms to pathophysiological mechanisms, which therefore become treatment targets, and attributes less importance to the subjective experiences of the individual.Treatments are not tailored to the patient, and patients are simply required to adhere as closely as possible to what is prescribed. Furthermore, the biomedical model also relates psychiatric symptoms to organic factors, as can be seen in Wilhelm Griesinger's 1868 assertion that "Mental disease is brain disease" [35]. The biomedical model favoured the study of human anatomy and has led to fundamental medical developments, but it runs the risk of ignoring symptoms that cannot be explained by physiological mechanisms and the scientific method, such as some psychological or psychiatric symptoms, or psychosocial factors influencing medical conditions.

This changed with the introduction of psychosomatics [36]. The word "psychosomatic" first appeared in the medical literature in an article published in 1818 by Johann Christian August Heinroth (1773-1843)[37], the first professor of Psychology at the University of Leipzig, Germany. He was the leader of the "Psychiker" school, which suggested that the consideration of the mind was essential when treating illness, unlike the "Somatiker" school, which maintained that mental disorder was caused by bodily disease [38]. At thebeginning of the XX century, there was a rapprochement between the philosophies of phenomenology (Edmund Husserl) and hermeneutics (Martin Heidegger) and the psychology of Wilhelm Wundt (1896), and psychiatrists such as Karl Jaspers and internists such as Viktor von Weizsäcker, also greatlyinfluenced the development of psychosomatic medicine.

It was in this cultural context that Sigmund Freud (1856-1939) pronounced his famous statement: "*The ego is first and foremost a bodily ego. It is not merely a surface entity but is itself the projection of a surface. If we wish to find an anatomical analogy for it, we can best identify it with the 'cortical homunculus' of the anatomists, which stands on itshead in the cortex...*".

These words marked the beginning of the recognition of many clinical and theoretical examples of mind-body interactions and psychoanalysts proposed that people who had difficulty in expressing rage can release their tensions atsomatic level: i.e. unconscious factors may be relevant to the genesis of disease states. Subsequently, disciples of Freud such as Franz Alexander (1891-1964) contributed to the study of somatic diseases that could be related to emotional factors, such as inflammatory bowel disease, peptic ulcer, hypertension, asthma, rheumatoid arthritis, eczema, etc., thus promoting an interdisciplinary scientific approach to the study of the human being and leading to the foundation of scientific journals such as Psychosomatics (Journalof the Academy of Psychosomatic Medicine) in 1939 or Psychosomatics and Medical Psychology in 1948. Finally, Roy Grinker coined the term biopsychosocial in 1954, and used it in his article entitled "A struggle for eclectism" to urge psychiatrists to incorporate advances in biology in their models rather than relying purely onpsychoanalytic dogma [39].

Some years later in 1977, based on the 1907 statement of Ludolf Von Krehl that "We do not treat diseases, but sick people", George Engel advocated the adoption of a new medical model that had a more comprehensive approach topatients: the biopsychosocial model (BPSM). In his opinion, "it is essential to know who the patient is, as well as what disease he has" if we want to avoid treating a disease without considering the peculiarities of the person involved. In this sense, he began to emphasise the psychosocial aspects of illness, whichmust be seen as a result of interacting mechanisms at cellular, tissue, organic, interpersonal, and environmental levels [40].

The BPSM opened the transition from a disease framework that reflects the biomedical perspective of analysing symptoms and signs in order to formulatea diagnosis and prescribe specific treatments, to an illness framework based on the patient's perspective of his disease, which has the purpose of investigating the subjective experience of illness, and which is characterised by beliefs, emotions, perceptions, feelings, expectations, and adaptations. The BPSM integrates the biological and psychosocial aspects of the process of care. Grinker applied it to psychiatry to emphasise "bio" against psychoanalytic orthodoxy; Engel applied it to medicine to emphasise "psychosocial" against the biomedical approach.

The BPSM was partially ostracised by the medical journals that were more susceptible to the biomedical reductionism that simplifies treatments and neglects individual responses, something that was already going against clinical experience [41].

Today's clinical practice: the biomedical or biopsychosocial model?

It is now well established that illness is a complex experience that is not always exclusively somatic or exclusively psychic but can only be understood by considering multiple perspectives. Among the many examples of the psyche-soma overlap, peptic ulcer disease has long been considered a classic psychosomatic illness, but it is often sustained by Helicobacter pylori and can only be cured by a therapeutic approach that addresses both its biological and psychological causes.

The biological effects of psychological interventions It is well known that biological drugs such as anti-depressants, steroids, and immuno-modulators can induce emotional changes, but it is possibly less widely known that psychological interventions can induce a biological response, as severalstudies have shown that psychotherapy enhances cancer survival and improves emotional disorders such as depression, anxiety, and stress [42].

The effect of psychological interventions on the biological mechanisms of disease seems to be due to their capacity to induce neurobiological changes, such as increasing the immune activity of natural killer cells [39,40]. Studieshave found that psychotherapy mediates the immune changes involved in survival by down-regulating the expression of pro-inflammatory genes and up-regulated type I interferon response genes in circulating leukocytes [43].

Shields et al. have also recently shown that psychosocial

interventions (especially CBT) are associated with positive changes in immunity over time, including an increase in beneficial and decrease in harmful immune functions.

The biological activity of psychotherapies is also reflected in the brain changesinduced by anti-pain treatments. A number of recent neuro-imaging studies have shown that psychological interventions such as CBT, meditation, mindfulness, and hypnosis can induce significant modifications in the brain areas and functions involved in modulating pain: for example, CBT favours a cortical control mechanism in patients with chronic pain by increasing the activation of the pre-frontal cortex (PFC), which is associated with executive cognitive control of pain. Moreover, the pain regulation induced by cognitive and meditative therapies can have a positive impact on nociceptive and non-nociceptive brain regions as it increases pre-frontal, orbito-frontal, somatosensory, anterior cingulate, and insula cortical activity, and decreases thalamus activation [44].

The effects of hypnosis on pain are mediated by the activity of the anterior cingulate cortex (ACC), the area involved in the "suffering" component of pain and unpleasant affective reactions. Similarly, other studies have shown that inhibition of afferent nociceptive transmission can be explained by a dramatically decreased activity of the thalamus observed under hypnotic induction, and the hypnotic mediation of executive, salience, and default networks [45].

Mindfulness can also provide pain relief by favouring orbitofrontal and rostralanterior cingulate cortical regulation of the thalamus and primary somatosensory cortex, and de-activating the posterior cingulate cortex. Prolonged mindfulness training is also associated with pre-frontal de-activation and greater activation of the somatosensory cortex, thus moderating the perception of painful sensations [46].

### The Psyche and the Soma in Fibromyalgia

One clinical context that widely expresses the unity of the pathogenetic, clinical and therapeutic aspects of psychosomatics is the fibromyalgia syndrome (FM), about which there is still debate as to whether it should be defined as an illness or a disease.

FM has been called a chronic central sensitization syndrome, a condition thatleads to alterations in a person's sensitivity to pain. It is clinically characterised by allodynia (pain in the absence of painful stimulation) and hyperalgesia (increased pain upon painful stimulation); it is neuro-physiologically characterised by reduced pain thresholds and prolonged electrophysiological responses; and it is psychologically characterised by the unpleasant quality of the perceived pain, a broadening of the pain attentive field, and catastrophism. Early studies of FM focused on its stress-related origin but, although the idea of stress and trauma is still very important it is now clear that its pathogenesis is due to many different biopsychosocial factors such asgenetic neuroendocrine, socio-cultural and, perhaps, even bio-humoral factors [47].

This is confirmed by the fact that the symptoms of FM can be alleviated by treatments that modulate inflammation, and that antidepressants are useful in decreasing the perception of pain even in non-depressed patients. The origin of chronic widespread pain is very complex, and FM is a condition that allows us to reflect on some very important concepts, above all whether the location of the pain is in the brain (psyche) or the body (soma) (Figure 1).

Psyche → Soma	Soma → Psyche				
Catastrophism	Small fiber neuropathy				
Traumas	Inflammatory rheumatic diseases				
Maladaptive stress coping	Any chronic painful disease				
Sleep alterations	Genetic factors				

Fig. 1. The aetiopathogenetic conundrum of fibromyalgia syndrome: reciprocal influences and common psyche-soma pathways.

In most patients, neuro-psycho-pharmacological treatments alone are unsatisfactory in controlling pain, and only an approach that covers all the pathogenic components of the syndrome leads a substantial improvement in symptoms. This underlines the centrality of the psychic dimension in the pathogenesis and treatment of FM pain and confirms the pathogenic unity of the psyche and the soma. From this point of view, within the last few years, patient self-management has been emphasised as essential in the treatment for FM: the unsatisfactory result of a single therapeutic intervention advises the integration of multiple types of care (analgesics, psychoactive drugs, psychotherapies, physical exercise, relaxation techniques, physical care, etc.).

Within this context, patient pro-activity, achieved through a psycho educational approach and a close monitoring of his/ her adherence to treatments, is of paramount relevance [48].

#### **Biomedical Markers of interactions [49]**

In the past two decades, biomedical research has changed our understanding of body systems. It has now come to light that there is a complex network of feedback, mediation, and modulation among the central and autonomicnervous systems, the endocrine system, the immune system, and the stress system.

These systems, which were previously considered pristinely independent, in fact, interact at myriad levels. Psychoneuroimmunology (PNI) is an emerging discipline that focuses on various interactions among these body systems and provides the underpinnings of a scientific explanation for what is commonly referred to as the mind-body connection. One should not construe here that all the phenomena are finally mediated only through immune mechanisms.

# Emergence of PNI [50-54]

In 1964, George Freeman Solomon wrote "Emotions, immunity, and disease: A speculative theoretical integration." In this article, Solomon first used the term '*psychoimmunology*' and introduced

the concept of a medical linkbetween our emotions and immune systems.

In 1975, Ader expanded on Solomon's work and coined the term 'PNI'. During that same year, Ader and his colleagues published the startling results of their research on the conditioned immune response in a rat population. The rats in the experimental group were injected with cyclophosphamide (an immunosuppressive agent), while simultaneously being given drinking water flavored with saccharin. The rats were later given only the saccharinflavored water but no cyclophosphamide. To the researchers' surprise, the rats continued to evidence immunosuppression. This was the first documented example of Pavlovian conditioning of the immune response. In Ader's groundbreaking research, he used a pharmaceutical agent to induce the conditioned immune response. Subsequent studies have expanded on the theory to include investigations of conditioning stimuli that are neither physical nor chemical, but are instead cognitive (e.g, perceptions, thoughts, or emotional states). What has been discovered is that these cognitive stimulican just as easily mediate changes in the immune system. Two noteworthy examples often quoted in the context of PNI are mentioned; one is that lymphocyte activity in men diminishes immediately after the death of a spouse from breast cancer, and second, a study of 75 medical students showed a significant reduction in natural killer-cell activity during the final examinationsas compared to the previous month. Twenty years later, Lancet published a study by Ader and Cohen that concludes with the following statement: "The association between stressful life experiences and changes in immune function do not establish a causal link between stress, immune function, and disease. This chain of events has not been definitively established". Thus, the unifying link remained elusive for a large part of the late twentieth century. Only recently have major breakthroughs occurred that have revolutionized our understanding of PNI. In this article, we will make an attempt to demonstrate the integration among body systems and also the causal link can now be established between these systems based on the available knowledge.

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