Psychosocial Factors, Psychiatric Illness and Functional Gastrointestinal Disorders: A Historical Perspective

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Key Words
Functional gastrointestinal disorders \cdot Psychosocial factors \cdot Psychosomatic research in gastroenterology

Abstract
A new classification of functional gastrointestinal disorders (FGID) became available recently, based on consensus in expert committees (‘Rome III process’). It is widely accepted that these frequent disorders, although their pathophysiology remains incompletely understood, result from a complex reciprocal interaction between biological, psychological and social factors that can be predisposing, precipitating and/or perpetuating. Comorbidity with psychiatric disorders, especially mood and anxiety disorders, is high. Modern epidemiologic, psychophysiological and functional neuroimaging studies have partially elucidated the mechanisms underlying the relation between cognitive-affective processes on the one hand and GI function and symptom reporting on the other. The aim of this article is to provide a noncomprehensive historical review of the literature on FGID up to the mid-20th century, with special emphasis on the role of psychosocial factors and psychiatric comorbidity. We can conclude from this review that a lot of the knowledge that became available recently through modern research methodology can also be found in the historical psychosomatic and neuroscience literature, though obviously less empirically grounded. This provides further support for an integrative, multidisciplinary biopsychosocial approach to FGID.

Introduction
It has been known since long that emotions may robustly influence the sensorimotor function of the gastrointestinal (GI) tract. Most people have experienced changes in GI function during stress or emotional arousal, which may lead to symptoms and medical consultation. This ‘folk psychology’ knowledge is reflected in the medical literature as well as in everyday language (‘butterflies in my stomach’, ‘knot in my bowels’ and the like).

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Twenty-first century medicine and its subspecialties are still frequently confronted with symptoms or syndromes for which no pathophysiologica
explanation can be found, even after extensive technical investigations. In these cases, the term 'functional somatic syndromes' is widely used [1–3]. The modern field of psychosomatic medicine studies complex reciprocal relations between psychological processes, physiological functions and symptom generation. ‘Reciprocal’ implies bidirectional interactions and therefore cannot be reduced to ‘psycho-
somatic’ (from psyche to soma), but also needs to account for ‘somatopsychic’ (from soma to psyche) relationships.

Functional GI disorders (FGID), most notoriously functional dyspepsia (FD) and irritable bowel syndrome (IBS), take a prominent place within these ‘functional somatic syndromes’, together with chronic fatigue syndrome and fibromyalgia, with which they frequently overlap [1, 2, 4]. FGID are frequent disorders of which the pathophysiology is incompletely understood [5]. Expert committees recently published a consensus report on FGID, including an update of the classification system, known as the ‘Rome III criteria’ [5]. Psychosocial factors are believed to influence GI sensorimotor function and/or symptom generation in FGID as predisposing, precipitating or perpetuating factors; comorbidity with psychiatric disorders, mostly mood or anxiety disorders, is frequent (fig. 1) [6–8]. Modern epidemiologi-
cal, psychophysiological and functional brain imaging research has partially clarified the mechanisms through which these psychosocial factors may act on GI function or symptomatology [6, 7, 9, 10], although the exact nature of their relationship remains a matter of contro-
versy. The 'brain-gut axis' can be conceptualized as the bidirectional connection system between the GI tract (with its enteric nervous system) and the brain (central nervous system) through (autonomic) neural, neuroim-
mune and neuroendocrine pathways. Thus, when gut function is disturbed, the cause of this disturbance can be found in the GI tract itself or in the modulatory input from the central nervous system via the brain-gut axis [7, 9–13].

The aim of this article is to provide an overview of the long-standing history of psychosomatic research in gastroenterology from the first half of the 19th until the mid-20th century, including evidence from early viscera-

tal sensory and affective neuroscience. A review of more recent research on this topic falls beyond the scope of this article; recent excellent reviews are available else-
where [6, 11, 12, 14, 15]. However, the historical evidence reviewed here will be linked to modern findings throughout the article when possible. Relevant histori-
cal literature was collected through PubMed, PsycInfo and JSTOR searches (including cross-referencing). Another important source of information on the 19th and

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Fig. 1. Biopsychosocial concept of FGID. Adapted from Drossman [5], with permis-
sion.
early 20th century literature was the textbook on psychosomatics entitled *Emotions and Bodily Changes*, ed. 2 by Flanders Dunbar [16]. More recent books by O. Cameron [17] and G. Adám [18] were valuable sources of evidence from Eastern European psychophysiological research, of which most original sources are not available in English.

Importantly, this historical review does not pretend to be fully comprehensive. For example, we chose not to include a full discussion of the interesting history of parallel research on the role of serotonin in the enteric and central nervous systems (which would require almost a full paper in itself), although this may clearly be relevant for the comorbidity between FGID and psychiatric disorders. Several findings in the 1950s (the effect of the hallucinogen drug LSD on both brain function and peripheral serotonin receptors, the depressogenic properties of the serotonin-depleting antihypertensive agent reserpine, the coincidental discovery of the antidepressant properties of the first monoamine oxidase inhibitors ...) increased interest in the role of serotonin in the regulation of both mood and gut sensorimotor function [19–21]. Since then, this has been the subject of huge research efforts which have taught us a great deal more about the neurophysiology of mood regulation and gut function separately, but unfortunately fairly little about the interaction between both. For example, it remains unclear until today whether (serotonergic) antidepressants alleviate FGID symptoms through their central or peripheral actions.

‘The Father of Gastric Physiology’: William Beaumont

Alexis Saint Martin was a soldier suffering from an epigastric shot wound, through which the gastric mucosa could be observed. He was treated by American army surgeon William Beaumont and recovered fully, but the gastric fistula remained unclosed. The patient remained under Beaumont’s observation for many years, providing him with the first opportunity to study human digestion in vivo, which earned him the title ‘Father of Gastric Physiology’ [22]. Beaumont was primarily interested in physiology per se, but had sporadic opportunities to observe the influence of emotions on gastric function, mostly secretion. He wrote, for example: ‘This experiment shows the effect of violent passion on the digestive apparatus. The presence of bile was believed to be the effect of anger. In a healthy state of the stomach, and an equable frame of mind, this substance has seldom been found in the stomach. When so found, except under peculiar circumstances of diet, it may generally be regarded as an indication of either mental or corporeal disease, and may be seen as a foreign and offending substance in that organ’ [22, p. 149]. This quote is the first reference in the literature towards the idea that a disturbance in gastric function can be the result of either peripheral (GI) or central (emotions) mechanisms. This is in line with the present concept of the brain-gut axis as outlined above. We are not aware of modern research on the influence of emotions on gastric secretion, but anxiety has been recently shown to influence gastric sensorimotor function in health [23] and FD [24].

James-Lange and Cannon-Bard Theories of Emotion and Their Significance for Psychosomatics in Gastroenterology

In the 1880s, the ‘father of American Psychology’, William James (fig. 2), and the Danish physician-psychologist Carl Lange formulated a similar theory of emotion, independent of each other [25, 26]. This theory remains highly influential until today, with (neurobiological) support for it provided by Damasio and others [27–32]. The core idea of the theory is that emotional
stimuli automatically induce bodily changes, and that it is the feedback of these bodily changes to the brain that is constitutive of the feeling of the emotion [25, 26, 28, 33]. This is probably best illustrated by the following classic quote from James: ‘Our natural way of thinking about these standard emotions is that the mental perception of some fact excites the mental affection called the emotion, and that this latter state of mind gives rise to the bodily expression. My thesis on the contrary is that the bodily and that this latter state of mind gives rise to the bodily

The great Harvard physiologist Walter Cannon formulated an influential critical examination of the James-Lange theory in the late 1920s. The importance of bodily feedback in emotional generation and regulation was questioned, based on several lines of experimental evidence obtained by Cannon, mostly in collaboration with Philip Bard [34–36, cited in 28, 33]: decerebrated animals still expressed strong emotions, autonomic nervous system measurements could not differentiate between basic emotions, bodily feedback was considered too slow to be constitutive of emotions and external (chemical) induction of bodily responses was insufficient to evoke emotions. Recent research, however, countered some of Cannon’s arguments against the James-Lange theory of emotion [37–39]. Cannon and Bard provided an influential alternative theory, stating that emotions are generated in subcortical brain regions, especially the hypothalamus. Bodily changes invoked by changes in these regions are seen as the by-product rather than constitutive of emotions. The cortex was believed to inhibit the hypothalamus, based on the observations that decerebrated cats showed uncontrolled rage [34–36].

The relevance of these theories for psychosomatic research on FGID is twofold. First, the conflicting emotion theories were paralleled by equally contrasting ideas about the direction of the relationship between GI and nervous/psychological disturbances (see paragraph below) [16]. Second, the James-Lange theory provided the first theoretical account for an influence of bodily, especially visceral, signals on psychological states like emotions, an idea that has regained influence in the past 20 years, after a decline for a few decades, triggered mainly by Cannon’s criticism. The Cannon-Bard theory, on the other hand, constituted the first attempt to identify brain mechanisms of psychosomatic interactions.

The Link between Psychiatric and GI Disorders in the 19th and Early 20th Century: The Chicken or the Egg?

The belief that there was a close relationship between psychopathology and GI disturbances was widely accepted in the 19th century medical community. There was, however, a considerable amount of debate and confusion about the direction of the relationship. Although modern research is strongly suggesting a bidirectional relationship, this issue has not been fully resolved until today [5, 12].

The first line of thought, represented by, among others, Fleming (1845), van der Kolk (1863), Alt (1892) and Robertson (1902), considered GI disturbance to be the cause of psychopathology (‘somatopsychic’ mechanism). Robertson, for example, offered a theory of melancholia as GI autointoxication (‘intestinal melancholia’) [all cited in 16].

The alternative was to see GI disorders as the effect of psychological disturbances (‘psychosomatic’ mechanism). Leube (1879) was the first to coin the term ‘nervous dyspepsia’, whereas Stillier (1884) favored the term ‘psychogenic dyspepsia’ [both cited in 16]. This idea, including its foundation in ‘folk psychology’, can best be illustrated by the following quote from Stillier: ‘That people develop gastric disturbances after financial losses and suffer from them until their financial conditions turn to the better, is an everyday experience’ [cited in 16]. He estimated that 60–70% of patients consulting for gastric symptoms suffered from ‘nervous/psychogenic dyspepsia’ [16], a figure not far from present estimates (40–60%) [8, 12]. Leyden was the first to demonstrate normal gastric motility and secretion in ‘nervous dyspepsia’ [cited in 16]; this notion of ‘symptoms thought to originate in the gastroduodenal region, in the absence of any organic … findings’ is still the core of the definition of FD today [40]. A number of late 19th to early 20th century authors emphasized and studied the role of psychosocial factors in ‘nervous dyspepsia’, as described in a book by Dreyfus [41, cited in 16]. He concludes his book with a chapter on the putative heterogeneity of ‘nervous dyspepsia’ [41, cited in 16]. This idea of heterogeneity is still very much around today, even if some progress has been made in trying to identify subgroups within the FGID [6, 12, 24, 40]. Rosenbach (1879) described cases of dyspepsia following an emotional shock (‘Emotionsdyspepsie’) [cited in 16], which is remarkably consistent with recent literature on high prevalence of trauma and comorbidity with posttraumatic stress dis-
order in FGID [6, 7, 42–44]. Strümpell (1902) believed that most cases of ‘nervous dyspepsia’ were secondary to psychological changes; therefore, he favored the term ‘psychogene Dyspepsie’. He tried to find evidence for this hypothesis in careful anamnesis and psychiatric examination, mainly stressing the role of anxiety as a primary factor instead of a secondary result of the GI disorder: ‘It is not the gastric trouble that makes the patient a hypochondriac, but hypochondriasis causes the gastric trouble’ [cited in 16]. This is very much in line with recent research on the role of anxiety in FGID [23, 24, 43, 45, 46]. Strümpell also mentioned the effect of psychotherapy in gastric illness as an argument supporting the role of psychological factors, which is remarkably consistent with modern research on the effect of psychotherapy in FGID [6, 8, 46–50].

From these early days on, there was a considerable amount of debate about the concept of ‘nervous dyspepsia’ as a clinical entity, even within the adherents of the ‘psychosomatic’ hypothesis. Ewald (1884), as well as Charcot and Bouveret, considered dyspeptic symptoms as part of the broader syndrome neurasthenia or hysteria, although it may be in some cases the only symptom of such neuroses. This is best illustrated by the following quote from Bouveret: ‘The tendency to localize the point of inception for neurasthenia (i.e. of nervous dyspepsia also) in the sick stomach reminds one of the old error of pathologists who for a long time ascribed hysteria to disturbances in the uterus or ovaries’ [cited in 16]. It should be noted that the issue of comorbidity between FSS, including FGID, and the question whether they are manifestations of common underlying psychological processes remain an unresolved and widely debated issue until today [1, 4, 6, 8, 12, 51].

**The Rise (and the Fall?) of Psychoanalysis in Psychosomatic Medicine**

When psychoanalysis emerged at the end of the 19th century, it rapidly gained influence in psychiatry and psychosomatic medicine; this influence lasted long into the 20th century and, although less pronounced, even until now. One of the important accomplishments of psychoanalytic thought in psychosomatic medicine is its emphasis on (unconscious) psychological processes and their influence on bodily symptoms, emphasizing intrapsychic conflicts or neuroses that are presumed to generate prolonged states of emotional arousal, which in turn produce bodily symptoms or lead to increased disease susceptibility. According to psychoanalytical theory, bodily symptoms have a defensive and expressive meaning and can be interpreted as metaphors through which a patient expresses emotional distress or psychic conflict [52]. This idea is captured in the term ‘organ symbolism’ [53, cited in 16].

Clearly, psychoanalysis stimulated medicine to look at the whole person, rather than at symptoms thought to originate from one isolated organ system. The psychoanalyst Franz Alexander tried to work out a compromise between physiology and Freudian theory and tried to construct specific psychological models for specific diseases. He distinguished between classic conversion hysteria on the one hand, and what he called ‘organ neuroses’, for instance peptic ulcer, on the other. He defined ‘organ neuroses’ as disturbances of organic function controlled physiologically by the autonomic nervous system, and pleaded to take into account the automatic physiological mechanisms that substantially control the expression of emotion as the body responds to stressful stimuli [54, 55]. This reference to stress systems and the autonomic nervous system as mediators of psychosomatic influences remains highly valid today, as evidence in favor of this hypothesis from modern neurobiological research is growing [12, 56].

However, faithful to the psychoanalytic tradition, Alexander also identified specific unconscious wishes and infantile desires (for example, the unconscious wish to be fed) among the ‘psychic stimuli’ that he said precipitated specific chains of physiological response and, ultimately, specific somatic diseases (fig. 3) [55]. This research suffered from two main problems. First, methodological problems hampered the operationalization and assessment of unconscious mechanisms or intrapsychic conflicts. Second, the fragmentary knowledge of the biology of these diseases at that time led to an excessive emphasis on psychological factors in diseases that later proved to be primarily infectious or inflammatory in nature, as for instance peptic ulcer and asthma.

Nevertheless, psychodynamic understanding of functional symptoms may remain clinically useful in conjunction with other models. Exploring expressive and defensive aspects of functional symptoms helps us to talk to and understand our patients, and how they unconsciously deny or avoid development to personal autonomy and responsibility, sexual development or activity (defensive aspects; primary illness gain), or express unconscious wishes to be nurtured and cherished, or to remain dependent.
Walter B. Cannon and Ivan Pavlov: Pioneers of Psychophysiological Research

The influence of Walter B. Cannon (fig. 4, with Pavlov) on psychosomatic medicine can hardly be overestimated. Cannon was, around the same time as Pavlov in Russia, one of the pioneers of methodologically sound psychophysiological research. His importance for the present topic is twofold. First, he was the first to formulate the idea of reciprocal interaction between GI function/symptoms on the one hand and psychological factors on the other, thereby avoiding the contraproductive chicken or the egg discussion outlined above: ‘An emotional disturbance affecting the alimentary canal is capable of starting a vicious circle; the stagnant food, unprotected by abundant juice, naturally undergoes bacterial fermentation, with the formation of gases and irritant decomposition products. These in turn may produce mild inflammation or be absorbed as substances disturbing to metabolism, and thus affect the mental state …’ [57, cited in 16]. This idea of a reciprocal biopsychosocial interaction as constitutive of FGID remains valid until today and is explicitly stated in the Rome III expert consensus reports [5, 6]. The second reason for Cannon’s key role in GI psychosomatics, namely its emphasis on physiological study of the influence of psychological processes (that may be largely unconscious) and the role of autonomic, involuntary responses is best captured in his following quote: ‘The importance of avoiding so far as possible the initial states of worry and anxiety, and of not permitting grief and anger and other violent emotions to prevail unduly, is not commonly understood, for the subtle changes wrought by these emotional disturbances are not brought to consciousness, and are clearly known solely through physiological studies …’ [57, cited in 16]. As early as 1909, Cannon was already convinced of the influence of psychological factors on GI motor function through the autonomic nervous system, a finding confirmed by recent research [23, 58, 59]: ‘… gastric and intestinal peristalsis are stopped in man as they are stopped in the lower animals, by worry and anxiety and the major affective states. Indeed, the feeling of heaviness in the epigastrium commonly complained of by nervous persons may be due to the stagnation of food …’ [57, cited in 16].

In the early 20th century, Ivan Pavlov and coworkers in his laboratory (most notably K.M. Bykov) studied the GI system in their seminal experiments on what became later to be known as classical conditioning. It has since long been known that a GI stimulus can serve as either conditioned or unconditioned stimuli in classical conditioning paradigms, or that the conditioned response may be visceral [60, cited in 17; 61, cited in 17; 62, cited in 17, 18] and [53, cited in 16]. Aversive learning with a visceral
unconditioned stimulus (e.g. nausea) is notoriously fast and robust, as known in ‘folk psychology’ [17, 18]. Interestingly, Pavlov hypothesized the existence of cortical ‘analyzers’ in the brain, processing visceral sensory information. Moreover, he believed that these brain areas played a pivotal role in interoceptive conditioning [17]. Although Pavlov’s own later studies as well as present-day neuroscience research showed that subcortical structures receiving visceral afferent input, including pontine nuclei (nucleus of the solitary tract, parabrachial nucleus), hypothalamus and amygdala, are also involved in interoceptive conditioning [17, 18, 28], recent research confirmed the importance of cortical regions (anterior cingulate cortex, among others) in conditioning of GI sensation [63]. The role of subcortical structures, however, indicates that the majority of interoceptive conditioning processes may occur unconsciously.

‘The Patient as a Whole’

During the 1920s and 1930s, emphasis was put on studying the whole patient rather than the isolated organ system from which the symptoms were thought to originate, an idea that can again be found in the present Rome III reports [5, 6]. The following quote from R.S. Boles, who was also one of the first to use the term ‘functional disorders’, illustrates this point: ‘Unfortunately scientific progress has been so dramatic that the study of the disease overshadows the study of the patient … the clinician of today concentrates his endeavors on the search for something organically wrong; and if their best efforts are not rewarded, interest in the patient lags; he is simply labeled a neurotic …’ [64, cited in 16]. Although quite strong, this sounds undoubtedly familiar to present-day clinicians in both psychiatry and gastroenterology, as absence of a medical explanation still too often is equaled with a ‘psychogenic’ origin of the symptoms, leading to inappropriate referral to mental health professionals.

G.S. Stevenson, however, acknowledges that incorporating this idea of dealing with the patient as a whole in everyday practice faces some serious difficulties: ‘There are two sets of facts about the patient which seem susceptible of isolation and study: the motive of the patient involved in seeking help and the emotional problems of the patient involved in his complaint and disease’ [65, cited in 16]. The discussion on the relationship between psychiatric comorbidity and help-seeking behavior is still ongoing until present times [10, 66].

Psychosomatic Research in Gastroenterology in the Early 20th Century

R. Schindler, besides discussing a number of mechanisms by which psychological processes may influence GI symptoms, gives a definition that is still remarkably relevant to our times: ‘Psychoneuroses of the GI tract are disturbances of its organ function as a result of participation of psychic factors with the absence of anatomical changes’ [53, cited in 16].

Research in the early 20th century focused on psychological states induced by hypnotic suggestion in healthy volunteers as well as study of GI secretion and motor function (mostly using fluoroscopy after barium meals) in patients suffering from psychiatric disorders, including schizophrenia and ‘manic-depressive psychosis’ (corresponding most closely to bipolar I disorder in DSM-IV) [16, 67]. For example, a complete cessation of gastroduodenal peristalsis during suggestion of intake of aversive food was observed, whereas induction of disgust induced reverse contractions of the stomach [68, cited in 16]. Reports on successful treatment of abdominal pain and constipation using hypnotic suggestion were published as early as 1925 [69, cited in 16], and recent research has revived interest in hypnotherapy as treatment of IBS [70].
The Dawn of Visceral Sensory and Affective Neuroscience: P. MacLean and G. Ádám

The late Paul MacLean was the first, after Cannon's seminal efforts outlined above, to articulate a comprehensive theory on brain mechanisms linking emotion and visceral function. In a landmark article [71], MacLean elaborated further on earlier work by James, Cannon and Bard (see above) as well as on the influential theory of emotion formulated by James Papez [72]. The core of its theory is that both the experience and expression of emotion is the resultant of the association and correlation of internal and external stimuli in the phylogenetically old brain (called 'visceral brain' and, later, 'limbic system' by MacLean). This provides the first comprehensive neurobiological framework accounting for the intimate relationship between emotions and visceral function in the brain. The 'visceral brain' was defined by MacLean based on its anatomical location on the interface between interoceptive and exteroceptive systems [71]. It consisted, among others, of the amygdala, hippocampus, cingulate gyrus, brainstem and hypothalamus (fig. 5) [71], regions that have recently been shown to be involved in visceral sensation as well as emotions using functional brain imaging research [11, 27, 28, 33]. The theory of MacLean, therefore, proved to be truly visionary, given the very limited technical possibilities to study brain function at the time it was formulated.

Another ground-breaking, though somewhat forgotten, researcher in the field of visceral perception is the Hungarian physician-physiologist-psychologist György Ádám. His knowledge of Slavic languages as well as English provided him with the unique opportunity to incorporate evidence from both Russian and American psychophysiological traditions in his research. Ádám started his research in the late 1950s, a time when behaviorism flourished. Consequently, visceral perception and the influence of visceral sensory signaling on emotion and cognition were considered too vague and subjective for scientific study, but Ádám did not agree on this point. One of its central points is that visceral afferent signals, besides being firmly rooted in organ homeostasis, also profoundly influence higher human biological and psychological functions, without, however, having to reach conscious awareness [18]. Ádám wrote, as early as 1967: 'Relying on our experimental data we presume that interoceptive impulses constitute an important afferent channel to cortical, limbic and mesencephalic structures governing emotional responses. These visceral signals seem to influence behaviour considerably both in man and animals, even though they become conscious in man only occasionally' [73, reprinted in 18]. He adds in his highly interesting overview published in 1998: ‘... we were already aware of the manifold means by which viscero-sensory input could initiate or modify emotional reactions and even of the possibility that ongoing emotion-
al behaviour could alter the efficiency of visceroceptive signals’ [18]. We can only add here that in the 10 years since then, functional brain imaging has shown that Ádám’s ideas formulated in the 1960s were truly visionary.

Conclusion

It is remarkable how much of the historical evidence from both psychosomatic and neuroscientific research on the reciprocal relationship between psychiatric and GI disorders remains valid in the present era of visceral sensory and affective neuroscience. Although modern investigational techniques including functional brain imaging have elucidated to some extent the mechanisms underlying this relationship, its exact nature remains incompletely understood. We believe, however, that this historical overview provides important evidence in favor of an integrative biopsychosocial approach to FGID. The great Greek philosopher Plato and his teacher Socrates were already convinced of the need of a holistic approach to all disease almost 2,500 years ago: ‘Just as you ought not to attempt to cure eyes without head or head without body, so you should not treat body without soul’ [Socrates, cited in 16]. Twenty-first century medicine may, despite all technical advances, still need to learn from them.

References
