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BOWEL NO 2 - FUNCTIONAL GASTRO-INTESTINAL DISORDERS V DYSFUNCTIONAL HUMAN BEINGS; DEFINING SIZE OF PROBLEM "*MAGNITUDINEM QUAESTIO* (SIZE OF PROBLEM)

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ABSTRACT

Humans are suffering from Nonorganic Gastro-Intestinal Disorders classified as "Functional Gastro-Intestinal Disorders (FGIDs)". This issue critically assesses classification of FGIDs proposed by Rome Group including rumination, Author's first FGID Guru-an illiterate villager, embryological basis of FGIDs and 'Extra Gastro Intestinal Disorders (EGIDs) out of FGIDs' besides 'Possible Organic Disorders' from FGIDs; thenafter defines size of problem (*magnitudinem quaestio*).

KEYWORDS: Functional Gastro-Intestinal Disorders FGIDs, Disorders of Gut-Brain Interactions DGBIs, Gastro Esophageal Reflux Disease GERD, Irritable Bowel Syndrome IBS, Diverticular Disease DD, Functional Dyspepsia (FD).

(1) INTRODUCTION

Humans are suffering Functional Gastro-Intestinal Disorders (FGIDs), sans structural or biochemical abnormalities. This issue critically analyses classification of FGIDs in Gastro-Intestinal Tract (GIT), embryological basis of FGIDs and 'Extra Gastro Intestinal Disorders (EGIDs) out of FGIDs' and 'Possible Organic Disorders' from FGIDs. Drossman and Hasler[1] details the strategy, starting with an overview by Drossman who provides an operational definition and classification system for FGIDs, discusses the process and changes that occurred from Rome III to Rome IV: history, conceptual and scientific understanding of biopsychosocial model in 33 adult and 17 (upgraded 20[10]) pediatric FGIDs.[1] FGIDs are classified into various syndromes, which are symptom clusters! No other school or group than Rome has attempted to classify functional disorders in GIT wholly. Rumination is imprudent in Homo Sapiens *Sapiens*. Montreal (Vakil N[2]) or Lyon (Ghisa *et al*[3]) schools limited themselves to gastroesophageal reflux disease (GERD) only. Drossman and Hasler enlist the FGIDs indicated in Table 1[1] by Rome IV Group.

Table 1:[1] by Rome IV Group; reproduced for ready reference only.

A. Esophageal Disorders	
A1. Functional chest pain	A4. Globus
A2. Functional heartburn	A5. Functional dysphagia
A3. Reflux hypersensitivity	
B. Gastroduodenal Disorders	
B1. Functional dyspepsia	B3. Nausea and vomiting disorders
B1a. Postprandial distress syndrome (PDS)	B3a. Chronic nausea vomiting syndrome (CNVS)
B1b. Epigastric pain syndrome (EPS)	B3b. Cyclic vomiting syndrome (CVS)
B2. Belching disorders	B3c. Cannabinoid hyperemesis syndrome (CHS)
B2a. Excessive supragastric belching	B4. Rumination syndrome
B2b. Excessive gastric belching	
C. Bowel Disorders	
C1. Irritable bowel syndrome (IBS)	C2. Functional constipation
IBS with predominant constipation (IBS-C)	C3. Functional diarrhea
IBS with predominant diarrhea (IBS-D)	C4. Functional abdominal bloating/distension
IBS with mixed bowel habits (IBS-M)	C5. Unspecified functional bowel disorder
IBS unclassified (IBS-U)	C6. Opioid-induced constipation
D. Centrally Mediated Disorders of Gastrointestinal Pain	
D1. Centrally mediated abdominal pain syndrome (CAPS)	
D2. Narcotic bowel syndrome (NBS)/	
Opioid-induced GI hyperalgesia	
E. Gallbladder and Sphincter of Oddi (SO) Disorders	
E1. Biliary pain	
E1a. Functional gallbladder disorder	
E1b. Functional biliary SO disorder	
E2. Functional pancreatic SO disorder	
F. Anorectal Disorders	
F1. Fecal incontinence	F2c. Proctalgia fugax
F2. Functional anorectal pain	F3. Functional defecation disorders
F2a. Levator ani syndrome	F3a. Inadequate defecatory propulsion
F2b. Unspecified functional anorectal pain	F3b. Dyssynergic defecation
G. Childhood Functional GI Disorders: Neonate/Toddler	
G1. Infant regurgitation	G5. Functional diarrhea
G2. Rumination syndrome	G6. Infant dyschezia
G3. Cyclic vomiting syndrome (CVS)	G7. Functional constipation
G4. Infant colic	
H. Childhood Functional GI Disorders: Child/Adolescent	
H1. Functional nausea and vomiting disorders	H2a1. Postprandial distress syndrome
H1a. Cyclic vomiting syndrome (CVS)	H2a2. Epigastric pain syndrome
H1b. Functional nausea and functional vomiting	H2b. Irritable bowel syndrome (IBS) H2c. Abdominal migraine
H1b1. Functional nausea	H2d. Functional abdominal pain – NOS
H1b2. Functional vomiting	H3. Functional defecation disorders
H1c. Rumination syndrome	H3a. Functional constipation
H1d. Aerophagia	H3b. Nonretentive fecal incontinence
H2. Functional abdominal pain disorders	
H2a. Functional dyspepsia	

(2) FGIDs Critical Appraisal: Preceding Table[1] (reproduced for reference) is fairly exhaustive but entire issue of FGIDs appear "*no cause for cause*," a logical fallacy where 'the effect' is mistaken for 'real cause' of an event (*non causa pro causa*) heuristically. Thus guiding principle is the rule against '*subject matter bias*', before accepting FGIDs as a cause vis-à-vis effect (Jindal and Pandey[4]). This led various authors to express views divergently, eg, dyspepsia or indigestion (King and Sachdev[5]) is oldest known term for few centuries, yet it remains a chimera and is rechristianed as Functional Dyspepsia. Jeremy and Amnon[6] exclaim, "We found that dyspepsia was first recorded in hospital statistics at the end of the eighteenth century and

increased markedly thereafter. It remained a common diagnosis throughout nineteenth and twentieth Centuries." Rumination (of food, not thoughts) in humans is not a normal function; is surprise physiopathological phenotype going beyond evolutionary stages in normal *Homo sapiens sapiens*' life inventory. Watkins and Roberts[7] define rumination as multiple negative consequences: (a) exacerbating psychopathology by magnifying and prolonging negative mood states, interfering with problem-solving instrumental behaviour and reducing sensitivity to changing contingencies (b) acting as transdiagnostic mental health vulnerability impacting anxiety, depression, psychosis, insomnia and impulsive behaviours (c) interfering with therapy and limiting the efficacy of psychological interventions (d) exacerbating and maintaining physiological stress responses. On digging more, "Rumination", intrusive thoughts and OCD (obsessive-compulsive disorder) go hand in hand. They feed off each other in an unhealthy way that severely taxes the mind. However, rumination isn't unique to OCD – it can also be part of other mental health concerns, such as depression or anxiety, eg, rumination in depression can lead someone to dwell and stew on disappointment or upsetting things from past. Drossman, a reputed psychiatrist also knows it as psychiatric disorder apart from FGIDs. Michl *et al*[8] define, "Rumination is a well-established risk factor for the onset of major depression and anxiety symptomatology in both adolescents and adults. Despite the robust associations between rumination and internalizing psychopathology, there is a dearth of research examining factors that might lead to a ruminative response style. Unquote." Thus, it appears as psychological aberration beyond FGIDs; apparently against *Natural law (jus naturale*). Most people will be seen plethoric with obesity, who may be habitual gluttons.

The definition of FGIDs has varied based on societal and self-concept of illness and disease over time, on scientific evidence, clinician's training and personal bias. Ray and Ghoshal[9] express, "The attitude toward an illness and expression of pain and bowel habit vary across cultures with variable interpretation based on sociocultural beliefs, which may not tally with the medical definitions. Thus, psychological factors impact DGBI (sic) definitions, their severity and health care utilization Unquote." Thus, behavioral abnormalities were not available for study and mental illness or physical symptoms in absence of pathology were considered less legitimate than structural disease and even stigmatized (Drossman[10]). Holtmann *et al*[11] add, "Another feature of FGID are the highly prevalent psychiatric comorbidities, such as depression and anxiety. It is implied that mood disorders *cause* gastrointestinal symptoms (GIS). In fact, epidemiological data now provide strong evidence that in subsets of cases, GIS arise first and mood disorders occur later, while in other patients the reverse appears to happen. Unquote." Human mind is profoundly intricate faculty, hard to encompass in *cut and dried* framework. Diamond[12] explains, "Executive Functions (also called executive control or cognitive control) are skills essential for mental and physical health; success in school and in life; and cognitive, social, and psychological development. Unquote."

(3) Author's first putative gastrointestinal Guru:
When Author was in his residency training around 1965-66; an innocent middle age villager was admitted in surgical ward whose complaint was, "I can pass *stool* but cannot pass *wind*"? Author made fun of him and chided, "You can pass a bamboo but can't pass air"? Today this Author repents, "How right he was and ignorant of me"? Incidentally, he did not have any GIT organic or obstructive disease. Looking back, his problem may have been one of the 'FGIDs viz, IBS/C, Diverticular Disease (DD), dysbiotic and/or some motility disorder.

Photo – Social Humans Guru.

(4) Extra Gastro-Intestinal Disorders (EGIDs) out of FGIDs – These problems occur outside GIS either due to spill over or due to anatomical contiguity or by ill-understood pathophysiological mechanisms, eg, chronic fatigue syndrome, fibromyalgia, chronic non-gynecological pelvic pain, insomnia, somatisation syndrome, etc. EGIDs can be either proximally or distally or both. **Proximally: (**A) Pharingolaryngeal: hoarseness, dry cough, otitis, (B) Respiratory tract: Tracheo-broncho-pulmonary, new or worsening asthma, feeling of tightness in the throat, bad breath. **Distally: (**A) Both sexes: Urinary tract, e.g. urethral syndrome, interstitial cystitis, petit or irritative bladder syndrome, (B) Females: vaginismus, vulvodynia and dyspareunia, (C) Males: Erectile impotence and/or premature and/or nocturnal ejaculatory issues. In an interesting study, Wilder-Smith *et al*[13] observed that although intensity of GI symptoms might be related to visceral hypersensitivity in FGID, link between the range of GI and extra-GIS and underlying mechanisms remain unclear. Visceral and somatic hypersensitivity and sensitization might be related to inflammatory and cognitive causes, among others. This study piques further research in EGIDs out of box *(ex capsa)* aside the existing concepts of FGIDs; are dealt with hereunder.

(5) Possible Organic disorders linked with FGIDs: Precise etiopathology is still conjectured. **(a) Cranially:**

aphthous ulcers in mouth, dental erosions/caries, angular cheilitis, pathogenesis of rhinosinusitis, pulmonary fibrosis, pharyngitis, asthma, or recurrent otitis media, role in triggering apneic episodes in patients with obstructive sleep apnea. **(b) Caudally:** benign anal lesions, e.g. anal fissures, piles, anal fistulas, ischiorectal abscess, pruritis ani, ano-rectal mucosal prolapse, though it is conjectured. Author has been treating these cohorts as subsets of FGIDs successfully. In an enlightening review, Aziz and Simren[14] express, "Organic conditions that can be mistaken for IBS include coeliac disease, inflammatory bowel disease (IBD), colorectal cancer, and, in those with diarrhoea-predominant symptoms, chronic gastrointestinal infections, microscopic colitis, and primary bile acid diarrhoea. The concept of small intestinal bacterial overgrowth (SIBO) being associated with IBS is shrouded with controversy and uncertainty, mainly because of invalid tests due to poor sensitivity and specificity, potentially leading to incorrect assumptions. There is insufficient evidence to link IBS-type symptoms with exocrine pancreatic deficiency or with symptomatic uncomplicated diverticular disease, since both are hampered by conflicting data. Finally, there is growing appreciation that IBS can present in patients with known but stable organic gastrointestinal diseases, such as quiescent IBD or coeliac disease. Unquote" Author affirms that some patients suffer at both ends, ie, mouth and anus from time to time; its precise etiopathology is obscure. Similarly, globus syndrome and functional noncardiac chest pains (NCCP) classified as esophageal disorders but their etiopathology is not related to esophagus. Proctalgia fugax is another FGID involving painful spasmodic phenotype linked with internal anal sphincter and an incapacitating disorder. Author has been treating these cohorts with these phenotypes successfully with relief in few days by correcting their FGIDs. These issues are evanescent; etiophysiopathology is ill-understood but linked with FGIDs.

(6) Morphological Foundations of GIT: GIT starts from mouth (stomodeum) and ends at anal verge or proctodeum (Bhatia *et al*[15]). Embryologically it develops in several parts, which are described briefly hereunder to help conceive FGIDs fully. The ensuing embryology description is a generally accepted view.

(7) Embryological Foundations of FGIDs related disorders: It is useful to recap embryological development of GIT to understand physiopathology of FGIDs in both sexes (Bhatia *et al*[15]). There are two major steps involved in development of GIT, formation of gut tube and formation of individual organs with their specific cell types. Genes regulating both phases are being identified and well characterized in published comprehensive reviews. The architecture of GIT and its developmental features of different segments are well defined (Rao and Wang[16]). Genes directing initial formation of endoderm and organ specific patterns are beginning to be identified. Signaling pathways regulating overall right-left asymmetry of GIT and epithelial-mesenchymal interactions are clarified. Montgomery et al[17] reviewed the mechanisms of gastrointestinal development, "There are two major steps in development of the gastrointestinal tract: formation of the gut tube and formation of the individual organs with their specialized cell types. Genes regulating both phases are being identified and characterized. Gastrulation, during which the axes of the embryo are determined and formation of the gastrointestinal tract is initiated, is an essential early step in development of all multicellular organisms. Therefore, genes regulating gastrulation and development of the gastrointestinal tract probably arose early in evolution. Unquote." Study of GIT embryology becomes essential to understand GIT pathophysiology phenotypes to evade chaos. Stomodeum, branchial apparatus, frontonasal processes and proctodeum or anal pit are ectodermal; foregut, midgut, hindgut to cloaca are endodermal.

(8) Derivatives of pharyngeal or branchial apparatus and foregut: In 5th week, oropharyngeal membrane degenerates, and development of oral cavity takes place by a complex process of fusion between frontonasal processes, branchial apparatus (develops into head, face, palate, anterior neck) consists of symmetrical paired pharyngeal arches, pouches, grooves, membranes that develop from ectoderm and foregut: (Bhatia *et al*[15]) (1) Primitive pharynx derivatives (oral cavity, pharynx, tongue, palate tonsils, salivary glands, upper respiratory system), (2) Lower respiratory system, (3) Esophagus and stomach, (4) Duodenum proximal to opening of Sphincter of Oddi, (5) Liver, biliary apparatus (gall bladder, hepatic ducts, bile ducts), pancreas.

(8) Respiratory System Embryology: Respiratory diverticulum (laryngotracheal diverticulum) appears between 4th and 6th branchial arches. With continous growth of respiratory diverticulum, at about 22 days, primitive pharynx is visible among branchial arches and pouches. At 28 – 32 days, ventrally situated trachea separates from dorsally situated esophagus and respiratory diverticulum bifurcates in two primary lung buds. Tracheoesophageal septum divides foregut into esophagus and laryngotracheal tube. 'Definitive endoderm' is defined as innermost tissue or germ layer found in all metazoan embryos. It gives rise to vast array of specialized epithelial cell types for respiratory and digestive systems and contributes to organs, viz, thyroid, thymus, lungs, liver, biliary system, pancreas.

(9) Derivatives of Hindgut, cloaca and proctodeum, anal pit: Hindgut forms, distal transverse colon, descending colon, sigmoid colon, rectum, and proximal part of anal canal. Terminal end of hindgut joins cloaca; exists in all human embryos up to 4–6 weeks, which not only forms anorectum (dorsal part cloaca) but also urogenital sinus (ventral part cloaca). Mesoderm-derived *urorectal septum* divides cloaca in ventral urogenital sinus and dorsal anorectal canal (7-8 weeks). At this

point, terminal ends of both urogenital cavity and anorectal canal open at cloacal membrane.

(10)Anorectum: Endoderm of hindgut and dorsal cloaca and ectoderm of proctodeum or anal pit are easily distinguishable. Epithelium of rectum and proximal anal canal is simple columnar. Anal pecten or pectinate line (also known as dentate or Hilton's line) is junction between upper (endodermal) and lower (ectodermal) anal canal. Lower part of anal canal is lined by non-cornified stratified squamous epithelium and perianal skin (anal verge) lined by cornified stratified squamous epithelium with its appendages. Clinical implication lies in proximal anal canal has visceral sensation while distal anal canal has somatic sensations.

(11) Urogenital Sinus: The ventral urogenital sinus develops into parts of urinary and reproductive systems. The cranial part of urethra will form with paraurethral (Skene's) glands located around the lower end of urethral meatus in females, homologous to the male prostate gland, which forms the epithelium of the prostatic urethra in males that penetrated the surrounding mesenchyme. Bartholin's glands, also known as greater vestibular glands, are homologous to the bulbourethral (Cowper's) glands in male, both originating from the urogenital sinus. The bladder begins development during weeks 4 to 7. Initially, bladder is continuous with allantois; involution of cloaca and embryonic allantois form the urachus, whose remnant is median umbilical ligament that connects bladder's apex with umbilicus. **In females**, lower 2/3rd vagina (except fornices), vestibule, urinary bladder except trigone (part of mesonephric ducts), urethra, Skene's glands (prostate gland analog), Bartholin's glands; **In males**, bulbourethral glands (Cowper's glands), spongy urethra, urethral glands (Littre's glands), prostate, urinary bladder except trigone. Embryologically, trigone of bladder is derived from *caudal end of mesonephric ducts*, which are of mesodermal origin (the rest of the bladder is endodermal). In females, mesonephric ducts regress, causing the trigone to be less prominent, but still present. Foregoing embryological knowledge shall aid to understand taxonomy of various FGIDs comprehensively.

(12) FGIDs – Size of the problem: There is no universally agreed definition of FGIDs as there are no such physiopathological disorders *de facto*; different schools have their own interpretations, "*As many pipers, as many tunes".* In absence of objective markers; identification and classification of FGIDs is empirical symptom based phenotype. This makes the issue complex as will be seen in ensuing discourse. Simplistic approach is to define by symptoms but they are neither singular nor are they composite; due to GER or IBS etc but are heterogeneous. Most patients have mixed potpourri of symptoms making the issue more complex. It varies amid different countries, races, region, sex and by different workers, eg, in Rome III and IV (Drossman[10]). Quigley[18] observed, "Overall, 49% of females and 36.6% of males met criteria for at least one FGID - the most common disorders in all regions being functional constipation, functional dyspepsia, proctalgia fugax, functional diarrhea and IBS at prevalence rates of 11.7%, 7.2%, 5.9%, 4.7% and 4.1, respectively. Unquote." About 40% of Western people suffer from it and about 70% of them have multiple symptomatologies that compound the problem further. Fikree and Byrne[19] state, "FGID are very common with worldwide prevalence of 40%, more common in women than men and this decreases with age. They account for 12% of workload in primary care and 30% of gastroenterology outpatient consultations. More than two-thirds of patients with FGID will have seen a doctor in the last 12 months and 40% will use regular medication." Fikree and Byrne[19] go on, "The presence of FGID is often associated with chronic pain (eg fibromyalgia) and other functional syndromes (eg, chronic fatigue syndrome), and two-thirds will have psychopathology including anxiety and depression. It is therefore not surprising that these patients have very poor quality of life, worse than other chronic medical conditions (e.g. grade III congestive cardiac failure and rheumatoid arthritis)" Unquote. Precise pathophysiology is illusory, so is its management. However, it does transpire that FGIDs are a price of our growing civilisation; worst is in Western societies (Burkitt[20]).

(13) Summary: The FGIDs are clinical symptom galaxy transcribed with indeterminate definitions by patients, clinicians and researchers. This has led to their treatment difficulty. The Table of FGIDs described by Drossman and Hasler has been displayed only to portray the various FGIDs syndromes as suggested by the Rome Group. Thenafter its critical analytical appraisal has been done and its logical and heuristical fallacy is discussed. Author has also indicated his first encounter with a patient in his residency, whom he considers his FGIDs first Guru. Extragastrointestinal disorders both proximally and distally are delineated besides possible organic disorders linked with FGIDs with imprecise etiopathology are described both cranially and caudally. Morphological foundations have tried to correlate embryological development of GIT as a basis of FGIDs. At the end, a brief indication of size of FGIDs problem has been indicated.

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