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BOWEL NO 3 - FUNCTIONAL GASTRO-INTESTINAL DISORDERS V DYSFUNCTIONAL HUMAN BEINGS; PATHOPHYSIOLOGICAL ASPECTS – *LIBERANDI CAUSA* – LIBERATING CAUSE

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ABSTRACT

Humans are suffering from some Nonorganic Functional Gastro-Intestinal Disorders (FGIDs). Gastro-Esophageal Reflux (GER) is normal function with some beneficial physiological effects but when it becomes annoying is called "disorder or disease (D), ie, GERD". The anatomical, physiological, pharmacological, neurohormonal, prophylactic as well as offensive factors affecting LES/GER has been analysed. Phenotypes of hiatus hernia and GERD, dyspepsia versus functional dyspepsia alongwith mechanism of LES relaxation in GER and deglutition are described. Lastly heterogeneous nature of FGIDs has been pointed out. Besides, quality, size and nature of FGIDs is attempted to define, though there is no universally agreed definition.

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

(1) INTRODUCTION

Functional Gastro-Intestinal Disorders (FGIDs) are now accepted biophysiopathological entity; still there is no universally agreed definition of FGIDs. De facto, there are no FGIDs but only dysfunctional human beings (DHBs). Gastro-Esophageal Reflux (GER) is normal function with some beneficial physiological effects but when it becomes annoying; is called "disorder or disease (D), ie, GERD". The anatomical, physiological, pharmacological, neurohormonal, prophylactic as well as offensive factors affecting LES/GER has been analysed. Phenotypes of hiatus hernia and GERD, dyspepsia versus functional dyspepsia alongwith mechanism of LES relaxation in GER and deglutition are described. Lastly heterogeneous nature of FGIDs has been pointed out. Besides, quality, size and nature of FGIDs is attempted to define, though there is no universally agreed definition.

(2) Preliminary Prologue: FGIDs have been in the middle of things (*in medias res*) since 1970's when Burkitt[1] drew attention that went unheeded. About 40% of Western people suffer it and about 70% have multiple symptoms (Fikree and Byrne[2a]). Sperber *et al*[2b] stated, "Published studies have involved highly variable diagnostic criteria, study populations, questionnaires, and data collection methods. For irritable bowel syndrome (IBS) and functional dyspepsia (FD), the 2 most researched disorders, reported prevalence estimates are very broad (1.1%–45.0% for IBS, and 1.8%–57.0% for FD). Thus, given the large methodological heterogeneity, it is inappropriate to pool individual prevalence rates, and we are left with an unanswered question as to whether the differences in prevalence rates seen among individual countries in prior surveys reflect genuine differences between populations or are due to methodological differences between studies. Unquote."

Author considers and treats cohorts clinically based on precise history taking and evaluation of phenotypes. History taking is highly diligent observer dependant faculty. Davis and Murray[3] state, "Taking a careful and complete history and performing a thorough physical examination are hallmarks of the good internist and one of the distinguishing characteristics of a master clinician. Unquote."

(3) GERD/FD – Prophylaxis: Despite the odd cohorts of GERD/FD, vast majority of people remain free. This is possible for strong preventive mechanisms in vast majority. Hereunder are few of the prophylactic forces.

(4) Anatomical factors preventing GERD: (1) Rugose mucosal folds in gastric fundus and surrounding GastroEsophageal Junction (GEJ). (2) Intrinsic component of lower esophageal sphincter (LES), (Marchand[4], Mittal and Goyal[5], Zifan *et al*[6], Popowicz *et al*[7] Rosen and Winters[8]), remains closed to prevent reflux in esophagus. Intrathoracic pressure is minus 6 mm Hg and intraabdominal pressure is plus 6 mm Hg making a total of 12 mm Hg pressure gradient in sitting. LES maintains pressure gradient of ±30 mm Hg in sitting position; thus prevents GER. Protective mechanism at GEJ has two components: intrinsic and extrinsic. (3) Intrinsic factors of LES consist of esophageal smooth muscle fibers in neurohormonal control. Marchand[4] stated about importance of anatomy and role of various factors causing hiatus hernia, anatomy of GEJ, diaphragm, (i) Clasp Fibers are Semicircular "C-shaped" smooth muscle fibers on right side of LES and maintain stronger myogenic tone than sling fibers. (ii) Sling Fibers are Oblique gastric muscle fibers found on left side of LES, with weaker resting tone. It maintains Angle of HIS with flap valve mechanism; important in prevention of GER. (4) Extrinsic component of LES consists of: (i) diaphragmatic crura (ii) phrenoesophageal ligament supports LES against GER. Zifan *et al*[6] affirm role of LES, "With advances in manometry techniques over last 50 years, functional existence of smooth muscle lower esophageal sphincter (LES), as an 'intrinsic LES' and skeletal muscle of crural diaphragm (CD) as 'extrinsic LES' at EGJ in humans is well accepted. Esophageal hiatus (EH) formed by two crura was originally thought to be major anti-reflux barrier. However, with invention of water perfused manometry technique by Harris *et al* and a series of publications in 1960's and 1970's proved the significance of smooth muscle LES in reflux disease and esophageal motor disorders. Studies by Boyle et al in early 1980's and later on by our laboratory proved beyond doubt that CD is an important component of sphincter mechanism at EGJ, and it is now called "external LES" analogous to internal smooth muscle and external skeletal muscle of anal sphincters at caudal of gut. Unquote." (5) CD forms "external/extrinsic sphincter" of LES, functions to increase pressure at distal esophagus, crucial during inspiration when intrathoracic pressure (ITP) decreases or during periods of increased intraabdominal pressure (IAP) – both situations predispose to GER. It consists of two crura: (a) Right Crus: Thicker and more extensive, arises from lumbar vertebrae L1, 2, 3 and divides into superficial and deep pats. Superficial part lies to the right of esophageal hiatus. Deep component lies to left of esophageal hiatus, lateral to left crus (b) Left Crus: Smaller, arises from L1, 2 and lies to left of EH (6) Phrenoesophageal Ligament, extension of investing diaphragmatic fascia (part of fascia transversalis and endothoracic fascia) made in two limbs and acts as protective sleeve over intraabdominal esophagus and allows independent movement of esophagus and diaphragm, protecting against gastric reflux and hiatal hernia. (i) Upper limb connects distal esophagus to superior aspect of diaphragm by endothoracic fascia (ii) Lower limb connects cardia of stomach to inferior aspect of diaphragm by extension of fascia transversalis. (7) Abdominal part of esophagus: (a) Normally it varies between 2 and 5 cm; longer length protects better from GER, ie, inversely proportional to GER (b) More oblique esophageal entry in abdomen is better protective against GER, (c) EH in diaphragm is placed away from midline in lower third at left antero-lateral angle from vertebral column prevents GER in sitting or lying posture. (8) Microanatomical configuration of GEJ and intragastric valvular configuration abutting against lesser curvature wall inside gastric lumen prevents GERD. Zifan et al[6] add, "The Most widely quoted publication of LES morphology is based on work of Liebermann-Meffert *et al* in which they described a semicircular clasp (on lesser curvature) and oblique sling fibers (towards greater curvature), with clasp fibers inserted into sling fibers. Unquote." They[6] went on, "We propose that spiral muscle fibers of distal esophagus, crossing at the angle of His (not described by Liebermann-Meffert) are important components of LES because one can easily visualize how such an arrangement will provide circumference squeeze at lower end of esophagus. The LES muscle fibers are actually arranged like a noose (hitch) around esophagus, rather than like a ring or a band of circular muscle fibers. The circular muscle fibers from greater curvature of stomach (similar to lesser curvature) also merge with two oblique muscle bands on anterior and posterior surface of stomach. Unquote."

(5) Physiological factors preventing GER: GER occurs when there is differential intraabdominal pressure (IAP) rise. This IAP is explained by Popowicz *et al*[7], "The World Society (WS) of Abdominal Compartment Syndrome (ACS) was created in 2004. This society standardized definitions and guidelines for evaluating and treating ACS, as this disease process is often underdiagnosed in medical field. The IAP is steady-state pressure within abdomen. Average normal adult IAP ranges from 0 to 5 mm Hg, while IAP can be elevated up to 5 to 7 mm Hg in critically ill patients. Both patient body habitus and chronic medical conditions can influence patient's baseline IAP; thus they must be considered during ACS evaluation. Elevated IAP can

lead to intra-abdominal hypertension (IAH), defined as IAP ≥ 12 mm Hg, but is not synonymous with ACS. ACS can occur when IAP is >20 mm Hg. However, the beginning phases of organ dysfunction can occur before IAP reaches 20 mm Hg. Unquote." Following factors can influence GER pathophysiology: (1) Gravity (2) esophageal motor activity (3) salivation (4) anchoring of distal esophagus in abdomen, helps in prevention of GERD besides others, eg, **(A)** GER is more in awake and sitting posture than in lying down state (i) Transient Relaxation of LES or IAP overcomes LES pressure (ii) During deglutition, transient swallow induced relaxation of LES occurs for food bolus, which are negligible during sleep. (iii) In upright position, there is 12 mm Hg pressure gradient between resting positive IAP of 6 mms measured in stomach and negative ITP measured in esophagus of 6 mms at midthoracic level. It favors flow of gastric contents in esophagus in upright position. This pressure gradient diminishes in supine position, negating GER. Cheatham et al[9] opined, "Head of bed elevation significantly increases IAP compared to supine positioning, especially at higher levels of IAH. Such increases in IAP become significant (increase ≥ 2 mmHg) when patient's head of bed exceeds 20° elevation, well below that currently practiced in many intensive care units. Unquote." Malbrain *et al*[10] echoed, "The upright position significantly increases IAP and lowers Cdyn (dynamic compliance) although not significantly." **(B)** The IAP (0 to 5 mm Hg) in upright position around LES is negative compared to atmospheric pressure (760 mm Hg) and gradually increases caudally. This pressure gradient tends to move gastric contents towards cardia encouraging GER in upright position. In contrast, abdominal hydrostatic pressure under diaphragm in supine position increases causing an increase in sphincter pressure and more competent cardia and LES. **(C)** The LES tonically contracts to an average pressure of 15 to 30 mm Hg under normal conditions. After swallowing, inhibitory signals generated by peristalsis cause a reflex relaxation of LES for approximately 5 seconds, allowing transit of bolus in stomach. During this time, diaphragmatic crura also relax. After bolus flows, LES and crura return to their baseline contracted state. Transient LES Relaxation (TLESR) is another physiologic relaxation of LES that occurs outside of swallowing mechanism. It is believed to be triggered by gastric distention and causes both LES and diaphragmatic crura to relax, allowing belching of excess gas. This is followed by primary peristaltic waves to return any refluxed chyme in stomach. **(D)** Pressure in LES depends on, (a) Myogenic tone of smooth muscles. Myogenic control is intrinsic rhythm of gastrointestinal smooth muscle contraction and relaxation, (b) Neural control through autonomic and enteric nervous systems. Nitrergic nerves are inhibitory, and cholinergic nerves are excitatory, **(E)** Intrinsic Component of LES made of smooth muscle fibres – microanatomical configuration. Clasp Fibers: (i) Not responsive to cholinergic stimulation (ii) Predominantly innervated by inhibitory neurons located in body of esophagus (iii) Utilize L-type calcium channels. Sling Fibers: (i) Contract vigorously to cholinergic agonists (ii) Predominantly innervated by excitatory neurons located in stomach (iii) Responsible for asymmetry of LES pressure (v) Maintains angle of His and flap valve mechanism at EGJ, both are important in prevention of reflux. Rosen and Winters[8] observe, "The pressure in LES depends on three factors: (1) myogenic tone of smooth muscles (2) inhibitory nitrergic nerves (3) excitatory cholinergic nerves. Myogenic tone of smooth muscle is an intrinsic property of cells in LES and is responsible for tonic contraction. LES smooth muscle cells have more depolarized resting membrane potentials, resulting in spontaneous spike-like action potentials and generation of basal tone. Excitatory cholinergic nerves release ACh (acetylcholine) to promote smooth muscle contraction, which enhances tonic, myogenic property of LES and favors contraction. In contrast nitrergic pathway releases NO and favors inhibition, opposing contractile properties of LES. Overall, combination of these forces favors contraction over relaxation. Thus, LES remain contracted even if entirely denervated owing to its myogenic property. Unquote." Myogenic control is intrinsic rhythm of GI smooth muscle contraction and relaxation. Neural control is achieved through autonomic and enteric nervous systems made up of two thin layers of over 100 million nerve cells, including sensory interneuron and motor neurons; is sometimes called 'second brain' **(F)** Salivary bicarbonate helps neutralise acidic refluxed gastric contents in GER **(G)** Altered mucosal defence of 'mucous surface active phospholipids'.

(6) Pharmacological factors affecting LES/GER: Out of long list of agents; briefly: **(A)** Antacids, cholinergics, domperidone (banned in US for serious cardiac issues), metoclopramide, prostaglandin F2 *increase LES pressure*. (NB**:** Alkalinising antacids biophysiopharmacologically are potentially harmful and should be discarded from modern pharmacopeias as there are potent PPIs/H2Blockers/ PCABs (potassium-competitive acid blockers), which block acid formation at source. **(B)** Barbiturates, anticholinergics, calcium channel blockers, caffeine, diazepam, dopamine, meperidine, prostaglandin E1 and E2, theophylline lower LES pressure **(C)** Peppermint, chocolate, coffee, alcohol, fat, lower LES pressure; may worsen GERD symptom/s postprandial.

(7) Neuro-hormonal factors affecting LES/GER: Rosen and Winters[8] described neurohormonal physiology of LES. (1) Alpha-adrenergic neurotransmitters or beta-blockers stimulate LES; conversely alpha blockers and beta decrease LES tone and pressure (2) Cholinergic nerve affect on LES is uncertain (3) Vagus nerves carry both excitatory and inhibitory fibres to esophagus and LES (4) Hormones and LES: (a) Gastrin and motilin increase LES pressure (b) Estrogen, progesterone, cholecystokinin, glucagon, somatostatin, secretin decrease LES pressure (c) Peptides, bombersin, 1-enkephalin, substance-P increase

LES pressure (d) Calcitonin gene-related peptide, gastric inhibitory peptide, neuropeptide Y, vasoactive intestinal peptide decrease LES pressure (5) Excitatory impulses are primarily cholinergic-mediated via ACh with minor contributions by tachykinins (substance P, neurokinin A/Bjv). Inhibitory impulses are primarily nitrergic-mediated (nitric oxide) with smaller contributions by other compounds, including vasoactive inhibitory peptide (VIP), purine structures (particularly ATP) and carbon monoxide. Due to this dual innervation by vagus nerve, bilateral vagotomy or tetrodotoxin (pufferfish toxin which blocks neural transmission via sodium-channel blockade) administration elicits no change in baseline LES tone. Conversely blockade of inhibitory neurons (with NO inhibitors) or excitatory neurons (with atropine – anti-cholinergic) leads to unopposed action of opposite system. While vagus elicits dual effects, there have been suggestions that inhibitory effect is more significant, as studies have demonstrated that vagal stimulation leads to net LES relaxation (6) Motilin, a neurohormonal or neurotransmitter agent released into circulation by specialized cells in wall of intestines is responsible for phasic LES contraction. Phasic contraction of proximal portion of LES also occurs following swallow-induced or esophageal distention-induced LES relaxation. Contraction occurring post relaxation is coordinated with esophageal peristalsis, is atropine sensitive (atropine dose of 15 g/kg reduces LES pressure by 50 to 70% in humans).

(8) MUSE School Physiopathological Classification of GERD: Sonnenberg and El-Serag expressed[11], "In **MUSE** classification of gastroesophageal reflux disease (GERD), esophagitis is assessed by presence of **m**etaplasia, **u**lcer, **s**tricture, or **e**rosion (**MUSE**), each being graded as absent, mild or severe. Daily reflux symptoms affect about 4 to 7 percent population; erosive esophagitis occurs in about 2 percent; prevalence rate of Barrett's metaplasia is 0.4 percent and esophageal adenocarcinoma leads to two deaths per million living population... All forms of GERD affect Caucasians more often than African Americans or Native Americans. Prevalence of GERD is high among developed countries in North America and Europe and relatively low in developing countries in Africa and Asia. Unquote" The statement, "North America and Europe Vs Africa and Asia", eludes the secret of FGIDs lie in lifestyles.

(9) Applied Surgical Anatomy Snippets: (A) Extrinsic innervation: Inferior mesenteric and inferior hypogastric plexuses; both are important for conducting pelvic surgeries and pain management. It has clinical relevance to various urogenital pain syndromes, endometriosis, prostatitis, postherpetic neuralgia, chronic pain of sacral region and rectal pain. Interrupting sympathetic outflow from collateral sympathetic ganglia can result in visceral dysfunction. Bowel motility is controlled by multiple branches of greater thoracic splanchnic nerve. Hence bowel dysfunction is likely complication of greater thoracic splanchnicectomy. Surgeries within pelvis risk injury to pelvic, sacral splanchnic and inferior hypogastric plexuses that can affect bowel, bladder and sexual functions (Sharabi and Carey[12]). (B) Intrinsic innervation: Besides extrinsic nerve supply to gut, there is network of nerve fibers between longitudinal and circular muscle layers (myenteric plexus of Auerbach) and in submucosal layer (Meissner's plexus). In addition to Auerbach's and Meissner's plexuses, there are other intrinsic plexuses that collectively form enteric nervous system. Myenteric plexus (Auerbach) of Colon, though they receive postganglionic inhibitory and preganglionic excitatory fibers, they are autonomous and fully functional without these fibers. This is important in maintaining normal slow wave rhythmic peristalsis that is present even postmortem for few hours. Splenic colon flexure, where parasympathetic efferent innervation shifts from CNX to inferior mesenteric and hypogastric or pelvic (S2-S4) nerve roots; supply from splenic flexure to proximal anal canal. These two regions are clearly innervated and respond to different stimuli. Proximal to pectinate line anal canal receives autonomic innervation from inferior hypogastric plexus. Parasympathetic innervation inhibits tone of internal anal sphincter to evoke rectal peristaltic contraction for defecation. Sympathetic innervation maintains tone of internal anal sphincter and preserves continence. Given the viscerosensory stimuli returning from this region, proximal part of anal canal is viscerosensitive to stretch or distention. Below the pectinate line, anal canal receives innervation by branches of pudendal nerve sensitive to temperature (burn), cuts, touch and stitch; ie, part of somatic stimuli, (Ahmed *et al*[13]). Hence any surgical interference below pectinate line needs some form of anaesthesia to curtail pain.

(10) Physiopathological Offensive factors modulating LES/GER: (1) Gastric emptying mechanism is delayed in: (i) Diabetes Mellitus, (ii) neuromuscular blockade (iii) gastroparesis, (2) Bad lifestyle, interpreted differently by different schools, (3) Obesity, (4) Overeating, eating out, picnicking, (5) Bloating syndrome, (6) Hiatus hernia (HH) and GERD. Apparently and theoretically, HH being upside down funnel shape, may promote GERD but not so in reality. It is detailed later on hereunder, (7) Vast majority of patients investigated for epigastric pain have no evidence of gastric or duodenal ulcer and their symptoms are attributed to reflux disease or non-ulcer dyspepsia, (8) Societal norms, gas formation is normal biophysiological process in intestines with positive role in maintenance of gut health and intestinal motility that ensures proper movements of food during its different stages of digestion, absorption, assimilation, propulsion and defecation. At the same time, some part of gas is exuded out via anus; ruefully called *"fart"*, carrying social stigma. We must realise that 'fart (flatulence or flatus)' is a normal, essential biophysiological function and is part of "involuntary" side of normal gut motility; once interfered with; results in bloating, tightness in tummy, epigastric discomfort, called visceral hypersensitivity

(Sikandar and Dickenson[14]). It may result in secondary megacolon or idiopathic megacolon in chronic stage, (Constantin *et al*[15]). To exemplify it further, in postoperative abdominal surgery, gut loses peristaltic waves temporarily resulting in "postoperative ileus", seen in bloating of tummy (Buchanan and Tuma[16]). Hence 'fart/flatus/flatulence' is an essential physiological process that indicates proper health of GIT. Gut motility is an ill understood biophysiopathological essential gut function and its interference has deleterious effects resulting in FGIDs.

(11) Hiatus Hernia (HH) and GERD: Apparently it looks that hiatus hernia (HH) may either cause or accentuate GERD but this hypothesis does not hold ground. Johnson[17] reviewing Kahrilas commented, "Endoscopic and radiologic studies have demonstrated that 50% to 90% of patients with gastroesophageal reflux disease (GERD) have hiatal hernias. One current hypothesis suggests that hiatal hernia does not cause GERD, but rather impairs esophageal clearance of refluxed gastric acid and increases chance for symptoms, esophagitis, or both. Researchers in this study sought to determine whether a hiatal hernia's effects on transient lower esophageal sphincter relaxation (tLESR) cause GERD. Unquote." Hyun and Bak[18] also observed, "Some propose that instead of hiatal hernia being the cause of reflux esophagitis, reflux esophagitis itself is the primary culprit that initiates and sustains the esophagitis-hernia complex; a study with opossums showed that acidification of the esophageal mucosa induced longitudinal muscle contraction, resulting in shortening of the esophagus. Unquote." Thus mere coincidence of HH and GERD does not hold ground for mutual implication than just a chance in this clinical etiopathology phenotype setting. To further substantiate it, Cohen and Harris[19] concluded in a study, "A hiatus hernia apparently has no effect on gastroesophageal sphincter competence. The rationale for surgical repair of hiatus hernia in patients with gastroesophageal reflux must therefore be questioned. Unquote."

(12) Dyspepsia or Functional Dyspepsia: Dyspepsia was taught ab initio when Author joined medical studies early nineteen sixties but never understood its meaning or relevance to cohort phenotypes. Often physicians label patients with dyspepsia for want of better epistemology. Now a quarter of twenty first century past, it has resurrected as "Functional Dyspepsia" (FD) in her new Avatar. However it still is as vague as centuries ago. Author finds it useful for insurance claims or legal courts more than medical purpose. The term 'dyspepsia' arises from Greek 'δυς-' (dys-) and 'πέψη' (pepse), popularly known as indigestion. It is first recorded in mid-18th century, when dyspepsia was thought as one of the 'nervous disorders' alongwith hypochondria and hysteria; Brun and Kuo.[20] Dyspepsia consists of variety of symptoms that may arise from diverse conditions and refers to pain or discomfort centered in upper abdomen associated with abdominal fullness, early satiety, bloating or nausea (Talley *et al*[21]). This phenotype is remarkably common, with 1-year prevalence rate averaging 25% in the community. Symptoms suggestive of the irritable bowel syndrome and reflux disease frequently overlap; do not form part of definition of dyspepsia, (Bytzer and Talley[22]). FD is defined by Rome IV criteria and subclassified in postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). Despite the Rome IV definition, diagnosis of FD often remains challenging due to inherent heterogeneity in symptoms and overlap of symptoms with other disorders, eg, gastroparesis, IBS and GERD. One study demonstrated that more than 50% of patients of FD with normal pH study reported heartburn and regurgitation. In a study published by National Institutes of Health Gastroparesis Clinical Research Consortium, patients with FD and idiopathic gastroparesis were essentially clinically indistinguishable. Other studies have shown that more than 25% of patients who were diagnosed as FD had delayed gastric emptying and 86% of patients with idiopathic gastroparesis met FD symptom criteria (Harer and Hasler[23]).

Schools like Montreal, Rome, and Lyon groups, yet more, are working independently trying to decode GERD. In one site on internet, it shows up, displaying 22 Clinical Trials.[24] Vakil[25] in 2024 published Montreal group's results, "Developments in Gastroesophageal Reflux Disease over the Last 40 Years." They went beyond symptoms to diagnose and depended on investigative machinery for diagnosis which is in variation to Rome Group that goes with clinical presentation. Drossman *et al*[26] define, "The functional gastrointestinal disorders may be defined as a variable combination of chronic or recurrent gastrointestinal symptoms not explained by structural or biochemical abnormalities... We emphasise the importance of using symptom-based criteria with a minimum of diagnostic studies. Unquote." Montreal Classification was developed and validated to provide endoscopic classification of GERD (Lundell et al[27]). It has become a widely accepted tool that now forms the basis of regulatory studies in Europe and the USA. Additional developments were the development of an endoscopic classification and description of Barrett's esophagus (Sharma *et al*[28]). Montreal qualitative review considers progress that has been made over past 40 years in pathophysiology, diagnostic strategies, pharmacological management, endoscopic and surgical treatment of GERD. Conceptually, the greatest change over this period of time is an evolution of our thinking regarding this disease from an inconvenience to a disease state with a major impact on patients' quality of life. Indications for testing include treatment failure, diagnostic uncertainty and treating (or preventing) complications of GERD. Lyon Consensus evaluated GERD diagnostic tests from a perspective that diagnostic testing may or may not support the initial diagnosis, as the criteria defining GERD are specific to each testing modality, and test results were categorised as being adequate to establish or

refute GERD diagnosis or inconclusive in absence of additional supportive evidence. Gyawali *et al*[29] conclude, "The future approach to phenotyping patients with GERD should focus on assessing important physiological biomarkers and PROs (patient-reported outcome questionnaires) to categorise patients based on severity of refluxate exposure, mechanism of reflux, effectors of clearance and underlying EGJ pathophysiology, while recognising that no single approach is perfect. Unquote"

(13) Mechanism of LES relaxation: GER Vs Deglutition: GER makes up reverse of deglutition and both are essential physiological functions, involving LES relaxation having four aspects: (1) Vagus nerve stimulation-induced (2) Swallow-induced (3) Esophageal distention-induced (4) Spontaneous 'Transient LES Relaxation' (TLESR). In health and disease, transient lower oesophageal sphincter relaxations (TLESRs) are main mechanisms underlying reflux events. TLESR is spontaneous relaxation of LES in absence of swallowing. Typically, TLESR is of longer duration than swallow-induced LES relaxation lasting ±10 to 45 seconds. While TLESR is physiologic mechanism seen in both normal cohorts and cohorts with GERD, TLESR is widely considered primary mechanism of GERD. Boerhaave's syndrome or spontaneous sudden tear in esophagus (Turner *et al*[30]), results in lethal clinical condition of transmural esophageal tear due to forceful emesis causing tear in lower esophagus; possibly results from failure in TLESR.

(14) FGIDs Balloon ruptures or raptures? Mittal[31] laments, "Montreal, Rome, and Lyon Consensus - Will They Resolve the Conundrum of Gastroesophageal Reflux Disease"? He continued[31], "The 1980s was an exciting time for the esophagus because that was when the revolutionary proton pump inhibitors (PPIs) emerged as an effective treatment for erosive esophagitis... I believe what is left are flaws in our understanding of what is being labeled as 'GERD phenotypes' in the year 2021. Unquote." Kahrilas[32] quoting a 33 year old lady observed, "Given that the patient described above presents mainly with a symptom burden, we are faced with task of determining whether or not she is experiencing "impaired quality of life due to reflux-related symptoms." ... From a management viewpoint, the objective is to reduce the patient's symptom burden, irrespective of causality. However, at this point we have only a failed management strategy and no diagnosis. Unquote." He[32] continued on inconsistency and indeterminate nature of different patient phenotypes and stated, "In some cases, individuals are greatly troubled by a lesser symptom burden and in other cases, they trivialize a far greater one. Thus, from a clinical vantage point, it is the patient who decides whether their condition is best described as GER or GERD. Furthermore, there is a multitude of factors, including emotional factors, social circumstances, and support structures,(sic) that dynamically modify whether or not the "D" is appropriate. Given that this patient has sought and pursued medical care for her condition, there is little question about appropriateness of "D"; the bigger question is whether or not "D" is attributable to GER. Unquote" Alt *et al*[33] remarked in face of such inconsistencies, "Science and scientists are not immune to hubris and egocentrism. Unquote." Thus Author observes, "There are no FGIDs but only DHBs" contracting FGIDs.

(15) Summary: As part of FGIDs, GER is normal function with some beneficial physiological effects, when it becomes annoying; is called "disorder or disease (D), ie, GERD". In the preliminary prologue, inconsistent occurrence is indicated in variable incidence of FGIDs in the community. Various prophylactic factors preventing GERD has been delineated, eg, anatomical, physiological, pharmacological, neurohormonal factors have been described. An interesting classification by MUSE School Physiopathological Classification of GERD has been stated. Some clinical syndromes involving neurological innervations have been mentioned. Briefly physiopathological offensive factors modulating LES/GER are described. Some heterogeneous factors about GERD conundrum have been indicated. Observing keenly, one would hardly see a monkey vomiting or retching. Prophylactic and offensive factors about modulating GER(D); relation between HH and GERD, mechanism of TLESR have been discussed. Lastly the opinions of diferent schools have been mentioned under 'FGIDs Balloon ruptures or raptures'?

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