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BOWEL NO 5 - FUNCTIONAL GASTRO-INTESTINAL DISORDERS V DYSFUNCTIONAL HUMAN BEINGS; MICROMANAGEMENT OF MILIEU INTERIOR PART II – *SUBLATA CAUSA, TOLLITUR EFFECTUS* (REMOVING CAUSE, REMOVES EFFECT)

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ABSTRACT

Humans or Homo sapiens sapiens are said to suffer from Nonorganic Gastro-Intestinal Disorders (NGIDs) classed as "Functional Gastro-Intestinal Disorders (FGIDs)". In this issue, subtle issues of clinical history taking, classification of GERD/NERD, role of gastric acidity and its modulation; humans are not ruminants, they are designated omnivores turned opportunistic carnivores, gut fundamental biophysiopathology, eg, gut motility, microbiota, visceral sensitivity, gut mucosal immune system, altered central, autonomic and enteric nervous system processing etc, which are not cause but effects of a subtle cause are discussed.

KEYWORDS: Functional Gastro Intestinal Disorders – FGIDs, Disorders of Gut-Brain Interactions – DGBIs, Functional Dyspepsia – FD, Irritable Bowel Syndrome – IBS; Diverticular Disease – DD; Symptomatic Uncomplicated Diverticular Disease – SUDD.

(1) INTRODUCTION

Humans are afflicted with FGIDs. Factually there are no FGIDs but only 'Dysfunctional Human Beings – DHBs' contracting FGIDs. FGIDs are amorphous heterogeneous gut related indeterminate disorders with putative multiple factors. In this issue, subtle issues of clinical history taking relating to FGIDs, classification of clinical phenotypes of GERD/NERD, merits and demerits of gastric acidity and pharmacological modulation. Humans are not ruminants; they are omnivores turned opportunistic carnivores, fundamental physiopathology, eg, gut motility, microbiota, visceral hyper/sensitivity, gut mucosal immune system, altered central nervous system processing etc, which are not cause but effects of a cause are discussed. GERD and IBS overlap; entire gut acts in unison as one organ.

(2) Preliminary Prologue: FGIDs have aroused vast interest since 1980s. Sperber *et al*[1] put it, "The functional gastrointestinal disorders , or disorders of gut-brain interaction are gastrointestinal disorders related to any combination of motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota and altered central nervous system processing... Published studies have involved highly variable diagnostic criteria... 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). Unquote". It leads to pathophysiological phenotype about micromanagement of milieu interior and intestinal homeostasis. Shi et al[2] explain, "The gut microbiota, largest symbiotic ecosystem with host, is shown to play important roles in maintaining intestinal homeostasis. Dysbiosis of gut microbiome is caused by

imbalance between commensal and pathogenic microbiomes. Unquote"

(3) Deducing FGIDs: Issue of FGIDs is functional symptoms based; hence history of illness is vital to be reliable in reflecting 'Guts' of patient. Daly and Zarate-Lopez[3] stress importance of history taking in patients to arrive at early clinical diagnosis and thereby explore more psychological comorbidities present in FGIDs and relevance of history in identifying predisposing, precipitating, perpetuating and protective factors, which will guide treatment. Mittal[4] resents, "Montreal, Rome, and Lyon Consensus - Will They Resolve the Conundrum of Gastroesophageal Reflux Disease"? Menne[5] felt that FGIDs are possibly a social issue than physiopathological evolution. FGIDs are result of nascent human indulgence drifting away from ancestral dietary traits on plantae based vegetables, plants, fruits.

(4) GERD/NERD – Clarification or Crucifixion: GER shall need strong forces to overcome strong defensive factors. Katzka *et al*[6] briefed, "For more than half a century, gastroesophageal reflux disease (GERD) has been viewed as a continuum of afflictions based on degree of lower esophageal sphincter (LES) dysfunction. With minor dysfunction, perhaps result of transient LES relaxations, patients develop symptomatic but nonerosive gastroesophageal reflux disease (NERD). In contrast, patients with severe dysfunction manifest by marked LES hypotonia, develop erosive esophagitis and/or Barrett's esophagus (BE)... However, it is becoming clear that many presentations of GERD represent distinct phenotypes with unique predisposing cofactors and pathophysiology outside of this paradigm. For example, patients with reflux hypersensitivity may have normal LES function yet abnormalities of peripheral and/or central sensory processing. In contrast, patients with BE may have relative esophageal hyposensitivity alongwith being Caucasian, male, and obese. Furthermore, long-term data have suggested that patients with NERD phenotype show only minimal progression to erosive esophagitis and BE. Given this heterogeneity of what is included under GERD umbrella, it is reasonable that clinical management should target unique pathophysiological features of each syndrome; one size does not fit all. Not every patient benefits from increased potency of acid inhibition and many patients are potentially harmed by surgical intervention. Unquote" On clinical heterogeneity, Fletcher[7] advised, "The interventions are so different that combining them does not make clinical sense. This is an example of clinical heterogeneity. Other circumstances that may give rise to clinical heterogeneity include differences in selection of patients, severity of disease and management. Judgments about clinical heterogeneity are qualitative, do not involve any calculations, and can be made by putting forward a convincing argument about similarities (or differences) between the trials. Unquote" This hypothesis highlights the complex relationship between subjective perception and objective reality.

Kahrilas *et al*[8] observed, "Acid suppression, particularly with proton pump inhibitors (PPIs), is the mainstay of gastroesophageal reflux disease (GERD) therapy. The use of PPIs has accelerated steadily since 1990s with repeated demonstration of remarkable capacity of these drugs to heal reflux esophagitis (RE) and correlation between intensity of acid suppression and clinical efficacy, in both healing and symptom control therapeutic end points. Enthusiasm for pharmacologic acid suppression has led to research into increasingly potent molecules in the hope of eclipsing existing generation of PPIs. One such agent, AZD0865, a potassium-competitive acid blocker, was tested up to phase 2b clinical trials, at which point it was found to be no more efficacious than esomeprazole in healing esophagitis or in resolving heartburn in patients with RE- or nonerosive reflux disease (NERD). Further development of this drug was therefore discontinued. The conclusion from these trials was that a ceiling effect existed, such that beyond a critical level of acid suppression, no further increment in efficacy was observed. Unquote" Such findings on FGIDs show the limitation of acid suppressing agents.

(5) Nature and Role of stomach acid: Hydrochloric acid (HCl) is strong corrosive acid; primary part of gastric acidity in human stomach. Its ability to dissociate in water releasing high hydrogen ions giving a low pH around 1 or even lower defines character of strong acid; essential for activating digestive enzymes, such as pepsin to digest food and protect stomach from bacteria, viruses and other agents. HCl helps in absorption of nutrients from food.

(6) Acid modulating agents – Gastric acidity plays important role in digestive biophysiology. Gastric Acid adjusting agents should be classified in two groups: (A) *Antacids* or alkalinising agents which neutralise acid produced in lumen of stomach, eg, bismuth salts, sucralfate etc, (B) *Anti-acids* suppress production of acid in stomach, eg, H2RAs (histamine H2-receptor antagonists), PPIs (proton pump inhibitors), PCABs (potassium competitive acid blockers). This two-tier classification has practical implication in pharmaceutical as well as clinical practice.

(7) Antacids or alkalinising agents: Days of Lester Dragstedt for vagotomy are over and not applicable in current clinical practice (Modlin and Darr[9]). Secondly antacids have serious pharmacological and clinical effects, but were used for want of better choice. Now, when there are available potent anti-acid agents with safer profile, role of toxic alkalinising agents are over.

(8) Demerits of Antacids (BMJ, Editorial[10]**):** Few antacids or alkalinising agents are bismuth salts, sucralfate is a basic aluminum salt of sucrose octa-sulfate, sodium or calcium alginate, calcium carbonate, magnesium carbonate, magnesium hydroxide or trisilicate, sodibicarb, aluminium hydroxide, etc.

Antacids are sold in different formulations and their effects depend upon actual formula. *Aluminium hydroxide* is converted to aluminium phosphate in intestine and may cause a phosphate deficiency syndrome with anorexia, muscular weakness and osteomalacia. Hypophosphataemia may develop as early as two weeks after starting treatment. Aluminium based antacids increase urinary and fecal excretion of calcium as well as decrease absorption of fluoride resulting in skeletal demineralisation. Aluminium is absorbed from intestine, so that aluminium containing antacids are potentially dangerous in patients with chronic renal failure with risk of aluminium encephalopathy. The signs and symptoms of aluminum toxicity are usually nonspecific. Typical presentations in chronic toxicity may include proximal muscle weakness, bone pain, multiple nonhealing fractures, acute or subacute alteration in mental status and osteoporosis. These patients almost always have some degree of kidney disease; most of them have end-stage kidney disease and are on dialysis. *Magnesium containing antacids* produce diarrhea and over half of patients given 'healing' doses of antacids suffer from this. Magnesium is also readily absorbed and in patients with renal failure may cause bradycardia. *Calcium antacids* are not used in danger of renal damage caused by alkalosis and hypercalcaemia. *Bismuth containing antacids* have been used for many years, especially in France, have achieved notoriety for adverse effects, including encephalopathy and arthropathy occurred even with *insoluble* bismuth salts. Some complications occur irrespective of composition of antacid preparation, eg, most mixtures contain sodium and intake of sodium may exceed minimum adult requirements by a factor of 20. This high content of sodium may be dangerous for patients with sodium retaining diseases. Antacids may predispose to infections by *enteric pathogens* as a result of removal of barrier which gastric acid normally provides against alimentary infection and travellers to tropics are advised to avoid antacids. More important, *antacids alter drug kinetics* by affecting the absorption or excretion of other drugs. Absorption is altered by delayed gastric emptying and by binding of drug in the intestine, while alkalosis produced by antacids may affect excretion of other drugs in urine. Drugs whose absorption is altered include *antibiotics, anticonvulsants, digoxin, warfarin, and anti-inflammatory drugs.* Antacid induced *increase in urinary pH* results in more rapid excretion of salicylates and conversely, retain basic drugs in body, such as quinidines. This is brief list of side effects of treatment with *antacids*, both in short and long terms. Hence their use in modern medical practice needs urgent revaluation or discontinuation when potent anti-acid agents are available.

(9) Anti-acids: Anti-secretary or acid suppressing agents are like H2blockers, PPIs, PCABs that suppress production of HCl in stomach at source. It is mainly HCl that acidifies stomach content to pH of 1 to 2 which helps in chemical digestion for enzymic cleavage of proteins, fats and carbohydrates into tiny amino acids, sugars and fatty acids (Heda *et al*[11]).

(10) Are Humans Ruminants – Myth or Truth? Ruminants (unlike humans) regurgitate and rechew their food (cud) to further break it down into paste to swallow back. Humans differ from ruminant GIT biophysioanatomy totally. Ruminant is an even-toed, hoofed mammal that re-chews cud, has four-chambered stomach: *rumen, reticulum, omasum and abomasum*. Rumen is largest of stomach compartments in ruminant animals like cows, sheep, and goats. It acts as fermentation vat with diverse microbial community that breaks down plant-based food, like cellulose, into energy for the animal. Rumen microbes produce volatile fatty acids that are cow's main energy source; also produce B vitamins, vitamin K and amino acids. There are six genera of ruminants: Bovidae, Cervidae, Giraffidae, Antilocapridae, Moschidae and Tragulidae. Humans are outside these genera and there are more differences in anatomy of GIT starting from mouth. (References[12]; Stover and Collier[13])

(11) Humans Don't Have Typical Carnivorous Features: Humans have short, soft fingernails and small, dull canines. True carnivores have sharp claws, large canines to tear flesh without knives and forks. Real carnivores' jaws move only up and down, enabling them to tear chunks of flesh from their prey and devour. Humans can move their jaws up and down *and side to side* also and have flat molars to chew fruits, vegetables like herbivores that carnivores lack. Humans cannot tear flesh with hand or basic fangs. Human incisors are not suited for cutting flesh and don't have large canines, implying that humans *ab initio* may have been *likely omnivores* but metamorphosed as herbivore. Carnivores have short GIT that allow meat to pass quickly through their digestive tract. Human GIT is longer with bigger cecum and right side colon like plant-eaters and give GIT more time to digest and absorb nutrients from plant-based diet. Some herbivores have specialized structures, ie, large rumen or cecum and contain symbiotic bacteria, protozoa besides fungi in the rumen or cecum that produce enzymes allowing host to gain energy from plantae and help microbial fermentation of cellulose, a major component of plant cell walls.

(12) Human Digestive Physiopathology and Cellulose: Fujimori[14] did excellent study. Cellulose (water insoluble polysaccharide, source of dietary fiber) is not digested by humans as they lack necessary enzymes like *glycosidases* or *cellulases* which hydrolyze beta-1,4-glycosidic linkages in cellulose. Humans cannot extract energy or nutrients from cellulose; it still plays a role in digestive health by providing fiber, regulates digestion and motility. Animals like cows, horses and sheep have evolved to digest cellulose, often with help of symbiotic bacteria in their digestive systems. Herbivores gain energy by degradation of cell wall-derived dietary fiber by microorganisms in digestive tract. Herbivores like

horses have a highly developed cecum and large intestine, and plants are fermented for their efficient use with help of microorganisms. Humans also have an intestinal tract with wide lumen on proximal side of large intestine in which fermentation occurs. Digestive process of horses is similar to humans and many intestinal bacteria found in horses that degrade plants are also found in humans. Thus, it is thought that humans also obtain a certain amount of energy from cell wall-derived dietary fiber, especially in cecum and right side colon with large volume in which fermentation occurs. However intake of dietary fiber by modern humans is low; thus calories derived from indigestible plant fiber are also low. If cell wall can be degraded to some extent by cooking, it is felt that humans can obtain calories from cell wall-derived dietary fiber. Bacteria that are ingested orally in humans are killed by gastric acid pH:1.5-2.0; is more acidic than horses, pH: 4.4. Thus, number of intestinal bacteria is small on oral side; but they increase rapidly to distal end of small intestine. Moreover, gut bacteria progress from aerobic to anaerobic bacteria towards distal small intestine. By ileocecal valve, bacteria increase from 10^7-10^9 to about 10^{10}-10^{12}/mL in colon. It is estimated that this contains 500-1000 different species of bacteria with nearly 80% belong to two bacterial phyla, *Firmicutes and Bacteroidetes.*

(13) Humans Cannot Digest Cellulose and Why it is Important? Humans cannot digest cellulose for several reasons: (1) It is complex hydrophobic polysaccharide carbohydrate. Humans do not produce enzyme *cellulase* to break down these linkages and hydrolyze cellulose into individual glucose molecules. (2) Humans lack specialized digestive structures with monogastric digestive system (single-chambered stomach), but ruminant animals have specialized multi-chambered stomachs. (3) Cellulose is resistant to hydrolysis by human digestive enzymes in stomach and small intestine and forms insoluble plant fiber to alleviate constipation by bulk, assist colon motility, stimulates peristalsis of smooth muscles to propel chyme. (4) Some human colon microbiota leads to partial fermentation of cellulose forming byproducts, eg, short-chain fatty acids (SCFAs: acetate, butyrate, and propionate). SCFAs are absorbed by large intestine and are valuable energy source even for colonocytes. (5) Cellulose is indigestible by humans and increases bulk, promotes feeling of satiety, may help avoid overeating. All these parameters make cellulose vital ingredient for good function of human GIT and valuable source of energy.

(14) Cryptic Evidence on Biodiversity and Modern Industrialised Countries: Cryptic biodiversity of cellulose-degrading gut bacteria in developed nations' urban people are known to contain less microbial biodiversity than those living rurally. Morais *et al*[15] explained, "We have identified ruminococcal species in gut microbiota of humans that assemble functional multienzymatic cellulosome structures capable of degrading plant cell wall polysaccharides. One of these species, which is strongly associated with humans likely originated in ruminant gut and was subsequently transferred to human gut, potentially during domestication where it underwent diversification and diet-related adaptation through acquisition of genes from other gut microbes. Collectively, these species are abundant and widespread among ancient humans, hunter-gatherers and rural populations but are rare in populations from industrialized societies thus indicating potential disappearance in response to westernized lifestyle. Unquote." They[15] concluded, "Our accumulated data indicate that ruminococcal lineages were more widespread in past, evidenced by high prevalence and abundance of these strains in ancient human populations and among hunter gatherer communities and rural societies, combined with their global distribution and low prevalence in industrialized societies. Differences in their prevalence among human populations may reflect dietary variation between industrialized and nonindustrialized societies. Dietary fiber intake appears to be a key factor as high-fiber diets are reported among Hadza hunter-gatherers whereas lower fiber intake is observed in rural people and least consumption of fiber occurs in industrialized societies. These findings collectively imply decline of these species in human gut, likely influenced by shift toward Western lifestyles potentially impacting energy balance and other health-related aspects. Unquote"

(15) Gut Microbiota and Intestinal Motility: GI motility is vital and important function that determines 'HRQOL' of cohort. Gut motility involves synchronized stretching and contractions of muscles in gastrointestinal (GI) tract; called peristalsis. Bai *et al*[16] observed, intestinal motility is essential for effective digestion, nutrient absorption, and timely waste elimination. Recent studies have demonstrated that microbiota play a crucial role not only in maturation of intestinal motility but also in maintenance of established motility patterns. Disruptions in motility can lead to various disorders, eg, chronic constipation, diarrhoea, irritable bowel syndrome and chronic idiopathic pseudo-obstruction. Gut microbiota significantly influence intestinal motility through mechanisms like bile acid metabolism and production of SCFAs. Liu et al[17] put it, "The imbalance of gut microbiota is caused by imbalance between symbiotic microbiota and pathogenic microbiota, called dysbiosis. The commensal microbiome regulates intestinal motility, while pathogenic microbiome causes intestinal motility disorder resulting in disease development. Intestinal motility is general term and its meaning may include intestinal muscle contraction, intestinal wall biomechanics, intestinal compliance, and transmission. The role of intestinal microecology and intestinal motility are interrelated, intestinal flora disorder mediates intestinal motility and abnormal intestinal motility affects colonization of intestinal flora. Unquote." Preceding statement briefly sum-up the

interrelationship between gut microbiomes and intestinal motility.

(16) Biophysiology of GI Motility: GI motility enables food move along digestive tract while ensuring absorption of important nutrients. Sanders *et al*[18] described, "Gastrointestinal smooth muscles are 'autonomous' and generate spontaneous electrical activity (slow waves) that does not depend upon input from nerves. Intrinsic pacemaker activity comes from interstitial cells of Cajal which are electrically coupled to smooth muscle cells. Patterns of contractile activity in gastrointestinal muscles are determined by inputs from enteric motor neurons that innervate smooth muscle cells and interstitial cells. Unquote." Patel and Thavamani[19] described 'Physiology of Peristalsis' is crux of FGIDs. Peristaltic movements enable food to progress along digestive tract ensuring absorption of important nutrients. Microbiota-regulated GI motility is based on unique architecture of GI tract. Zheng et al[20], in their review of gut microbiota-derived signals in the regulation of GI motility present current knowledge on impact of gut microbiota and its products on bowel motility. GI motility is regulated by coordination of various factors, including enteric nervous system (ENS), immune system, gut hormones and gut microbiota. Jyoti and Dey[21] narrate, "Gut microbes play a crucial role in influencing intestinal metabolic homeostasis by affecting nutrient sensing, gut hormones, neurotransmitters, and redox balance, collectively modulating mucosal gene expression and metabolic signaling pathways. These intestinal-level host-microbe metabolic interactions profoundly impact extra-intestinal tissues and organs. Unquote." Regarding control of motility, Dimidi *et al*[22] state, "The hierarchy of neural control of gut motility is as follows: primary regulator is ENS, followed by ANS and then CNS. Simultaneously, immune system, gut secretions, gastrointestinal microbiota and products of fermentation interact and modulate gut motility. Unquote." Waclawiková *et al*[23] credited gut microbiota-motility insights, "Gastrointestinal motility refers to digestive motor function and transit of ingested material throughout gastrointestinal tract. It involves coordination of smooth muscle and nerve function to mix, triturate, and propel products of digestion. Digestion and motility are facilitated by collaborative work of different parts of digestive tract... Gut motility is regulated via a multitude of regulatory elements including enteric neurons, smooth muscle cells, interstitial cells, hormones, and particular stimuli, such as gut bacteria and their metabolites. Unquote." Mukhtar *et al*[24] explained, "The gastrointestinal tract and nervous system are constantly communicating with each other in a bidirectional relationship which is influenced by the autonomic nervous system, immune system, hypothalamic-pituitary axis and gut microbiota. Understanding the molecular and biochemical mechanisms disturbing this complex network of communication is key to our understanding of the pathophysiology of the functional GI diseases. Unquote." Preceding researches are only a glimpse of gut motility and microbiota phenotype interactions showing the importance and complex bidirectional interrelationship towards smooth functioning of GIT.

(17) Types of GI motility (peristalsis) and its applied functions: GIT smooth muscles are autonomous with ENS and generate automatic rhythmic electrical activity (slow waves) independent of CNS input. These movements, ill understood, occur in GIT; peristalsis, haustrations, segmentation and mass movements (giant migrating contractions – GMCs). Peristalsis is involuntary rhythmic contraction and relaxation of smooth longitudinal and circular muscles in GIT resulting in digestion and propulsion of contents upto anus. Segmentation and haustrations mix and help in propulsion of contents. All types of motility play essential role in elimination and absorption of water and nutrients. Slow-wave frequency differs throughout GI tract. The functions of peristalsis within small intestine is three-fold: (1) Mixing of contents with intestinal and exocrine secretions, (2) Uniformly exposing contents to mucosal surface of intestinal cells (3) Propelling contents distally into large intestine that allows for optimal absorption and digestion. Three types of contractions do colonic motility functions (Sarna[25]). (1) Rhythmic phasic contractions (RPCs) cause slow net distal propulsion with extensive mixing, turning over. (2) Tonic contractions (TCs) aid RPCs in their motor function. (3) Giant migrating complexes (GMCs) or Ultrapropulsive Contractions including Mass Contractions produce forward movements randomly 3 to 4 times daily and retrograde giant contractions (RGCs); are several-fold larger in amplitude and longer in duration than RPCs. GMCs rapidly propagate (~1 cm/sec) in anal direction over very long distances. RGCs originate in mid small intestine and rapidly propagate (~10 cm/sec) orally up to antrum, occur during vomiting. Both types of 'giant contractions' produce *mass movements*, ie, rapid propulsion of luminal contents over long segments of gut. Rapid transit caused by GMCs and RGCs does not allow much contact time between digesta and mucosal surface; GMCs remedy constipation and visceral hyper/sensations.

Function of *peristalsis within colon* is to mix, store and slow the transportation of intestinal contents and aid in evacuation of feces (Sarna[25]). Slow-wave frequency differs throughout GI tract, occurring approximately 16 times per minute in small intestine and roughly 3 times per minute in stomach and large intestine. GI sphincters remain under tonic contractions opening in need; e.g, esophageal sphincters during deglutition or GERD; anal sphincter and anal verge opening during defecation. Saunders *et al*[18] defined ICC as pacemaker of GI motility by excitation-contraction coupling stimulating peristalsis. There is neural control of gastric peristalsis, and defecation, hormonal control of gut motility. ENS/Central and Autonomic nervous systems, Brain-Gut Axis, etc, all help modulate GI motility; influenced by microbiota but exact mechanism

is not known. Waclawiková *et al*[23] assert, "Microbial effect on gut motility is often evoked by bioactive molecules from various sources, including microbial break down of carbohydrates, fibers or proteins. In turn, gut motility regulates colonization within microbial ecosystem. However, underlying mechanisms of such regulation remain obscure. Unquote." Commenting on global community dietary and microbial phenotypes, Dey *et al*[26] observed, "Gut motility, a key physiologic parameter governing digestion and absorption of nutrients, is affected by diet, gut microbes, the enteric nervous system (ENS), and host genetics. At present, we lack detailed understanding of complex and dynamic interrelationships between these factors, particularly in the global context of diverse cultural traditions concerning foods, their methods of preparation, and varied human gut microbiota that have evolved under these dietary conditions. Unquote."

(18) Gut microbiota and mucosal immune system. Large number of commensal and pathologic microbiota plays an important role in maintaining normal health. Shi *et al*[2] briefed, "The commensal microbiome regulates maturation of mucosal immune system, while pathogenic microbiome causes immunity dysfunction, resulting in disease development. The gut mucosal immune system, consists of lymph nodes, lamina propria and epithelial cells, constitutes a protective barrier for integrity of intestinal tract. The composition of gut microbiota is under surveillance of normal mucosal immune system. Inflammation, which is caused by abnormal immune responses, influences balance of gut microbiome, resulting in intestinal diseases. Unquote" As Zheng *et al*[20] put it, "The microbiome plays critical roles in training and development of major components of host's innate and adaptive immune system, while immune system orchestrates maintenance of key features of host-microbe symbiosis. Unquote." This is studied broadly by Smith and Garrett[27], "It is intuitive that immune cells in gut may require microbiota-derived cues for their differentiation. The proximity between host and microbe in intestine would seemingly necessitate co-adaptation. However, it has been challenging to determine members and features of gut microbiota that influence immune system development and function. The recent identification of immunomodulatory members of commensal microbiota is providing insight into dependence of select intestinal immune cell subsets on specific microbial species. Unquote."

(19) FGIDs and High Intelligence Parallax: As Gabriel[28] put it, "Thinking about future in a scientific manner is often characterised by an illusion of knowledge, leading to precarious one-sidedness and false conclusions. The reasons for this are misinterpretations of core scientific concepts as well as vested interests in knowledge creation and scientific advice; these misinterpretations and interfering interests can prevail because there is no coherent set of rules on what a scientific enquiry into future could look like. Unquote" We must accept that every human being is not equal in psychomotor acuity. As Karpinski *et al*[29] explained, "High intelligence is touted as being predictive of positive outcomes including educational success and income level. However, little is known about difficulties experienced among this population. Specifically, those with a high intellectual capacity (hyper-brain) possess overexcitabilities in various domains that may predispose them to certain psychological disorders as well as physiological conditions involving elevated sensory, and altered immune and inflammatory responses (hyper-body). Unquote" They[29] further highlight, "Those with high IQ had higher risk for psychological disorders (RR 1.20 - 223.08). High IQ was associated with higher risk for physiological diseases (RR 1.84 - 4.33). Findings lend substantial support to hyper-brain/hyper-body theory. Unquote"

(20) CONCLUSION

FGIDs are functional symptom based phenotypes thus reliable history of illness is vital. GER shall need strong forces to overcome strong defensive factors. Acid suppression, particularly with PPIs is mainstay of GERD therapy. PPIs have remarkable capacity to heal reflux esophagitis but correlation between intensity of acid suppression and clinical efficacy in symptom control is desirable. HCl plays vital role in digestion and absorption of essential nutrients from food in digestive biophysiology. Gastric Acid modulating agents are classified in two groups; *Antacids* or alkalinising agents and *Anti-acids* suppress production of acid by stomach oxyntic cells. This two-tier classification has practical therapeutic implication in pharmaceutical and clinical perspective. Antacids have serious pharmacological and clinical side-effects, but were used for want of better choice. Now, when there are potent anti-acid agents with safer profile, toxic alkalinising agents *must be eliminated*. Humans are not ruminants and basically differ from ruminant GIT biophysioanatomy. Cellulose (source of dietary fiber, water-insoluble polysaccharide,) is not digested by humans due to deficient enzymes like *glycosidases* or *cellulases*. Yet cellulose is vital ingredient for function of human GIT and valuable source of energy and fecal bulking agent. There is cryptic biodiversity of cellulose-degrading gut bacteria in developed nations' urbanized people who are known to contain less microbial biodiversity than those living rurally. Such findings collectively imply decline of these species in human gut, likely influenced by shift toward Westernisation potentially impacting health-related economic aspects. Fundamental physiopathology of gut motility, microbiota, visceral hyper/sensitivity, gut mucosal immune system, altered nervous system processing are not cause but effects of a cause are discussed determining HRQOL. Lastly, thinking about future in a scientific manner is often characterised by an illusion of knowledge, leading to precarious one-sided myopic conclusions.

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