The Gastrointestinal System and Aging

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Introduction

Normal aging is associated with gradual and subtle changes in the morphology and function of most organs and systems [1]. The gastrointestinal (GI) system is no exception; there are suggestions that physiological changes may accelerate in the oldest years. With the increase in life expectancy in the United States and world over, clinicians need awareness of the age-related physiological changes and their consequences, well detailed in a committee report by the American Gastroenterological Association [2]. Demographic changes have led to a disproportionate increase in the oldest segments of the population, many characterized to have several GI disorders including dysphagia, gastroesophageal reflux, gastroparesis, and discomfort due to constipation, stool impaction, and fecal incontinence. True physiologic changes due to aging may be difficult to distinguish from subclinical disease. Data on several age-related alterations have been largely derived from animal studies with implications in humans far from clear. Altered gut physiology, subtle as it might be, may play a role in many manifestations in the aged, including anorexia, constipation, fecal incontinence, and postprandial hypotension [1–4].

Gastrointestinal Motor Function

An increase in the prevalence of gastrointestinal disorders of function and motility occurs with age [5]. Although we recognize an increase in the prevalence of several gastrointestinal motor disorders such as dysphagia and constipation in older people, age per se has minimal direct effects, largely due to the enormous functional reserves. Alterations in motor function more likely result from disease, with clinical implications relating to weight loss or gain, taste disturbances, clinical outcome, and at times even socioeconomic burden [4–8].

The intestinal myenteric and submucosal plexus demonstrate age-related changes which begin in adulthood and worsen with advancing years; changes specifically involve the cholinergic neurons and include concurrent enteric glial cell losses. There appears to be greater losses in the distal GI tract compared to the proximal sites [9–11]. Dystrophic axonal swelling occurs in the sympathetic, vagal, dorsal root, and enteric nitrergic innervation of the gut; these autonomic nervous system changes may in part explain the age-related decline in function [1, 3, 11]. Motor dysfunction in older persons more commonly results from tumor, inflammatory or neurological disease, systemic disorders, and effects of medications. As management will relate to the presence or absence of disease, and not just age, a diagnostic work-up is usually required [11–13].

Oral Changes

Changes in the skin and oral mucosa are known to result from the variable influence of environment, diet, hormonal changes, and medications. Disorders of the oral cavity are detailed in chapter 45 on Oral Health.

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Teeth

With age, the appearance of teeth changes to a yellowish, darker hue from altered composition of the underlying dentin and covering enamel. The vascular supply of the tooth and enamel declines with age, one cause of altered sensitivity to environmental stimuli. There is proneness to caries or trauma, leading to thickening of the cementum (the substance covering the root surface); the total width of the tooth almost triples between ages 10 and 75 years [14–17]. Teeth wear occurs with age, to a large extent as a result of normal chewing; however, the number of edentulous people has declined in the past few decades, with more older people retaining their teeth [15].

The Tongue

The mucous membrane of the tongue accommodates four papillae: filiform, fungiform, circumvallate, and foliate. Although the filiform papillae do not contain taste buds, each circumvallate papilla contains about 250 taste buds, and the foliate papillae (vertical folds in the postero-lateral tongue) contain approximately 1,200 taste buds. Taste buds are found primarily around the tongue margin and dorsum, soft palate, pharynx, and epiglottis. Taste innervation is provided by the chorda tympani branch of the facial nerve and the glossopharyngeal nerve [18–20].

Xerostomia

Xerostomia, the subjective sensation of dry mouth, is the result of a decline in saliva production and affects 29–57% of older persons [21–23]. The functions of saliva include lubrication, promoting dental remineralization, prevention of decay, and protection against fungal and bacterial infections. Manifestations of xerostomia include burning sensation, altered taste, dysphagia, and dysarthria. Age by itself does not cause a decrease in stimulated salivation, but loss of teeth may cause a decline in stimulated salivary flow [22]. Xerostomia results from illness and more commonly as an adverse effect of medications. Examples of medications causing xersotomia include tricyclic antidepressants (amitriptyline, imipramine), serotoin reuptake inhibitors (fluoexitine, sertraline), antipsychotics (thioridazine, olanzapine), and antihistamines (diphenhydramine, cyproheptidine) [21–23].

Clinical Application

Xerstomia calls for a review of medications that decrease salivary flow, and elimination or substitution of the offending agent wherever possible. Patients are encouraged to sip water, avoid alcohol, and minimize consumption of food and drinks that promote xerostomia e.g., caffeinated beverages. Chewing sugarless gum or candy may serve as sialogogues (agents that induce salivation); mechanical foods that serve as stimulants include apples, carrots, and celery. Salivary substitutes may offer temporary relief. Oral moisturizers are an option. Pharmacological stimulants include pilocarpine and cevimeline; they are useful for dry mouth in keratoconjunctvitis sicca (Sjögren syndrome) [18–23]. Decreased salivation and buffering capacity may be associated with low carries risk but high dental erosion progression [22].

Taste Sensation

Taste sensation is appreciated during mastication and deglutition from the contact of food with neuroepithelial cells, the taste buds. The sense of smell contributes much to taste perception. Both taste and smell complement nicely to enhance food palatability. Oral tactile sensation helps determine food texture; flavoring agents and condiments help complete the taste experience. Taste buds in thousands sit atop the papillae. The ovoid taste bud has a life of about 10 days and is constituted by 50–100 taste receptors, essentially taste chemoreceptors. Balding of the tongue or glositis may indicate loss of papillae or malnutrition, among other causes [24–26].

A taste bud has receptors that essentially account for five primary taste sensation: sour, salty, sweet, bitter, and umami. Acids produce a sour taste; ionized salts, mainly cations, stimulate salty taste. Various chemicals, mainly organic, produce sweet and bitter sensations. Monosodium glutamate (MSG), a flavor enhancer, elicits umami taste. Diminishing taste is a consequence of degeneration or reduction in taste buds. In healthy adults, taste buds regenerate approximately every 10 days; the process declines in the old, and in women following menopause or with estrogen deficiency. Protein and zinc deficiency retards taste bud renewal [18, 19, 21]. Although taste perception may change with age, somatic sensations such as touch and burning pain in the tongue are preserved, suggesting that the tongue addresses these stimuli differently [24]. Data now supports an elevation in sensory threshold with age for somato-sensory (warm, cool, two point discrimination) and gustatory senses [26].

Olfaction

The sense of smell is often taken for granted, until it is lost! There is a consistent age-related decline in olfactory function. The loss of smell is gradual along with the ability to discriminate between odors. The decline is significant with the majority of adults over age 80 having olfactory impairment (i.e., elevated olfactory threshold). This is attributed to a decrease in olfactory bulb fibers and olfactory receptors. Olfactory receptors undergo apoptosis at a baseline rate in all; age enhances receptor cell death [19, 21, 25].

Table 5.1 Oral cavity, taste, and smell

Morphology
Teeth
Teeth wear gradually with age from normal chewing
Teeth width increases with age
Teeth loss is not an aging phenomenon, rather from disease
Tongue
Taste buds: several thousand in the tongue and sit on the papillae on the tongue surface
Taste buds house receptor cells; receptors located in the palate, tongue, and upper esophagus
Salivary glands: acinar cells structurally intact, but reduced in number
Functions
Smell: increased threshold in perception, with decline in abilities to perceive smell. Consistent decline with age
Taste, also, known as gestation; basic tastes are salty, sweet, bitter, sour, and umami. Taste sensitivity is located all over the tongue and other locations in the mouth. Taste preferences are altered with age, with a decline in taste discrimination, but alterations less consistent than olfaction
Saliva production: basal <0.5 mL/min and stimulated 1–2 mL/min are intact with age, both quantitative and qualitative, suggesting adequate acinar cell function
Implications
Proper dental care in early life leads to better preservation of teeth in old age
Taste and smell contribute to appetite, an extremely important factor in quality of life
Tastes can benefit or harm and hence stimulates or deteriorates appetite
Most often marked loss in taste and smell is secondary to:
Diseases alter the perception of taste and smell
Adverse effects of medications that alter taste and/or saliva production
Decline in saliva production with xerostomia is a result of disease, medications, or salivary loss (mouth breathing or drooling)

Clinical Application

Olfactory function is also influenced by disorders of liver, cancers, mild cognitive impairment (precursor to dementia), and Alzheimer's disease [19, 21]. Electrophysiological tests have confirmed impaired olfaction in preclinical and clinical Alzheimer's disease.

The human being always has the desire to eat and enjoy food, a process requiring all sensations to be intact. The pleasure of eating the apple comes from the sight of the apple (vision), smell and taste of the fruit, the crunch while eating (dentition and hearing), and intact swallowing function. Aguesia and dysguesia commonly result from nutrient deficiencies or adverse drug effects. Enjoyment of food can be helped by flavor enhancement, use of sugarless candy (to stimulate saliva) and by social dining. Older adults can thus better enjoy their meals [5]. While aging is largely associated with preservation of taste, subtle taste discrimination may be impaired (Table 5.1).

The Esophagus

Clinically significant esophageal dysfunction does not result solely from age although mild manometric changes have been described [27]. Alterations in the old include a decrease in the amplitude of contractions, number of peristaltic waves following a swallow, increase in disorganized contractions in the body of the esophagus and weakening of esophageal smooth muscle. Often, it is the associated neurological disorders that cause secondary esophageal dysfunction; esophageal function is usually well preserved even in advanced age [27–29].

Esophageal Motility

Dysphagia is common in old people. Oropharyngeal dysphagia occurs in 50% of nursing home residents, accounting for frequent aspiration pneumonia. Oropharyngeal (or transfer) dysphagia may result even from subtle changes in upper esophageal sphincter (UES) or pharyngeal function. UES dysfunction results from striated muscle disorders, myasthenia gravis, stroke, Parkinson's disease, and commonly advanced dementia [3, 4, 29]. Zenker's diverticulum and cervical osteophytes are unique mechanical causes of intrinsic and extrinsic obstruction, respectively. Zenker's diverticulum is an out-pouching in the posterior pharyngeal wall immediately above the UES; the diverticulum retains putrified food, with manifestations such as foul breath, cough, neck fullness or gurgling with meals, and the dreaded pulmonary aspiration. The UES, composed of the cricopharyngeus skeletal muscle, is a primary barrier to aspiration of gastric reflux. Subtle alterations in oropharyngeal function are observed through video swallowing studies [30, 31]. UES pressure may decline with age, causing a delay in relaxation after deglutition. Pharyngeal clearance during a swallow may be impaired, partly explaining the risk of aspiration in older age. In addition, a decline in sensory

discrimination in the oral cavity and the pharynx is also a predisposition. Quantitative evidence of age-related changes in tongue movement during natural swallowing is attributed to muscle weakening [30]. The amount of food and liquid required to stimulate a pharyngeal swallow is larger in the old. Secondary esophageal peristalsis in the elderly is either absent or evoked less frequently after esophageal distension; complete lower esophageal sphincter (LES) relaxation in response to esophageal air distension is impaired [32].

Esophageal (transit) dysphagia, as opposed to oropharyngeal dysphagia, may be due to a mechanical cause or a motility disorder. Motility dysfunction infrequently occurs in people over 70 years of age [4, 33]. In symptomatic persons, esophageal abnormalities may be present in 20–30% [2]. A decline in the amplitude of esophageal contractions is explained by a decline in cells of the enteric nervous system with age. The term "presbyesophagus" once popular refers to a constellation of age-associated changes: decreased contractile amplitude, polyphasic waves, incomplete relaxation of the LES, and esophageal dilatation, with frequent simultaneous contractions (symptomatic or asymptomatic diffuse esophageal spasm) [2]. The clinical significance of these findings remains unclear [29, 33].

Age is associated with a reduction in the enteric plexus neurons by 20–60% [6]. The UES and LES act as barriers against reflux. The UES pressure in the old is considerably lower [31]. Age-associated hiatal hernia pushes up the gastroesophageal junction above the diaphragm to decrease LES function. Age is associated with an increase in esophageal acid exposure due to progressive decrease in abdominal LES length and peristaltic activity [34]. Overall, intrinsic changes in esophageal function with age have little impact on function.

Clinical Application

Dysphagia should never be attributed solely to old age. Primary esophageal motility disorders associated with dysphagia would include achalasia, scleroderma, diffuse esophageal spasm, "nutcracker" esophagus, and nonspecific esophageal motor disorders. Achalasia in the elderly may be a manifestation of gastro-esophageal junctional cancer. Medication-induced esophageal injury is a common esophageal disorder in older adults, warranting a medication review, and focused history for substernal pain, odynophagia, and dysphagia. The injuries are generally self-limiting. Swallowing disorders in older adults predispose to aspiration pneumonia and malnutrition [33, 35]. While salivary secretion declines during sleep, the effect of hypnotics decreases secondary peristaltic activity and increases likelihood for esophageal mucosal injury through contact with regurgitated acid.

The Stomach

It is common for asymptomatic individuals over age 60 years to have atrophic gastritis [2–4, 33–37]. Gastric atrophy does not result from normal aging; rather, it is a consequence of other factors. Both basal and peak gastric acid output decrease with age, mostly a result of gastric mucosal atrophy. Yet, most healthy older people maintain normal gastric acid secretion [37]. The role of *Helicobacter pylori* infection in the pathogenesis of gastric atrophy and hypochlorhydria is now well recognized; prior or current *H. pylori* infection is seen in most patients with atrophic gastritis. Serum gastrin concentration increases in *H. pylori* infected subjects but not in older uninfected subjects [36]. Pepsin secretion does not decline, but a decline in gastric bicarbonate, sodium ion and nonparietal fluid secretion occurs with age [2]. In summary, the histological and functional changes in the stomach attributed in the past to aging are now better explained by the presence of *H. pylori* infection, a prevalence that increases with age [36–38].

Gastric mucosal blood flow decreases with age, as does the blood flow to most organs, leading to slower healing of mucosal injury [2]. Gastric prostaglandin synthesis may diminish increasing susceptibility to the adverse effects of NSAIDs on the mucosa. While gastric aging may induce abnormalities of the gastric epithelium, most alterations are a result of chronic insults; these include *H. pylori* infection, adverse effects of medications (NSAID gastritis) and comorbidity [39]. A consequence of gastric frailty with age is the vulnerability to peptic ulcer disease [39]. Mucosal protective mechanisms may be impaired with age [40]. The role for molecules implicated in repair such as trefoil peptides and matrix components is being studied [40].

Clinical Application

Life style factors that impact on gastric filling, distension and emptying, postmeal posture and GERD [41] may favor acid reflux. In large part, the influence of acid-reducing agents, NSAIDs, and *H. pylori* infection cause a variety of gastric disorders including a reduction of defense mechanisms [34, 35].

Gastric and Small Bowel Motility

The major functions of the stomach are to accept ingested food and convert the material to a suspension suitable for emptying into the duodenum and beyond. The presence of comorbidity and drug effects pose difficulties in interpreting motility studies in the elderly. The interstitial cells of Cajal (ICC) decline in the stomach and colon, influencing motility and response to insults from disease and drugs [42].

Isotope studies demonstrate a considerable prolongation of gastric emptying for liquids in healthy older subjects compared to younger controls [43]. However, gastric emptying for solids appears unchanged and the gastric electrical rhythm remains intact [44]. Aging is associated with diminished perception of gastric distension. Age does not alter fasting and postprandial antral motility, believed to play a role in the emptying of solids. Conversely, fundic activity may be affected, which may account for a disturbance in liquid emptying [43]. Gastroparesis is detailed in chapter 33.

Morphological changes in the small intestine include a reduction in number of neurons in myenteric plexus and a reduction in splanchnic blood flow [45]. The surface to volume ratio in the jejunum and enterocyte height remain unchanged, retaining the normal absorptive surface [46]. Mucosal regeneration increases with age [2]. The migrating motor complex (MMC) serves as the gut "housekeeper." MMC occurs in three phases: phase 1, a silent period with small bowel inactivity; phase 2, characterized by irregular patterns; phase 3, with migrating motor activity. Changes in MMC involve velocity and occur only in the eighth or ninth decade of life. Intestinal abnormalities in any age group such as malabsorption cannot be attributed to age-related intestinal motility changes. The control of *phase 3* motor activity is mainly neural; a reduction in propagation velocity may result from age-related alterations in receptors of the enteric nervous system [43, 45, 47].

With age there is little decline in small intestinal function, and malabsorption is uncommon [46]. Overall carbohydrate absorption is unaffected, and the duodenal brush border activity for glucose is maintained [2, 13]. Lipid absorption is maintained in older age, with little decline based on lower splanchnic blood flow [48]. Pancreatic exocrine function is well preserved, since only 10–20% of pancreatic enzyme required for digestion [46]. Fructose, a monosaccharide and a component of fruits and fruit beverages, is increasingly consumed with fructose intolerance (diarrhea) more recognized. The role of transporters will help better understand fructose absorption [49]. Lactase activity that declines during adolescence may become more common with age, as a result of infections and chronic disease, medications (chemotherapeutic agents), and radiation injury. A decline in vitamin D receptor activity lowers the active absorption and transport of calcium, predisposing to osteomalacia [49]. Human studies suggest that although there is little concern for macronutrient absorption, micronutrients such as B12, folic acid, zinc, and copper may be affected with age [2].

Small intestinal motility is a requirement for proper food digestion, nutrient absorption and clearance of cell debris, secretions, and residual undigested materials. Orocecal transit time does not change significantly with age in healthy adults, but is altered in disease; the transit time of facility residents, mean age 82 years, did not differ from younger adult controls [51]. In another study, although age did not affect small intestinal transit time nor gastric emptying time, it did slow colonic transit time [52] (Table 5.2).

Table 5.2 Age-related physiological changes

Esophagus
Decreased upper esophageal sphincter (UES) pressure, increased resistance, and delayed relaxation after deglutition
Decreased amplitude of peristalsis and an increase in synchronous contractions
Progressive decrease in abdominal lower esophageal sphincter (LES) length
Decline in esophageal clearance
Diminished esophageal perception
Stomach
Decline in gastric blood flow with age
Some delay in gastric emptying, noted particularly for liquids, with increase in postprandial antral volume
Little change in pepsin secretion with age
Basal and stimulated gastric acid secretion do not decline in healthy aging; a decline may in fact be due to atrophic gastritis
Decline in interstitial cells of Cajal (ICC) with age
Impaired mucosal protective mechanism; decline in mucosal prostaglandin
Small intestine
Alteration in villous architecture
Reduction in myenteric neuronal plexus
Decline in splanchnic blood flow
Decline in calcium absorption diminishes because of intestinal resistance to action of 1,25-dihydroxyvitamin D
Large intestine
Reduction in rectal wall sensitivity
Decrease in anal canal resting and squeeze pressure with age
Delay in colonic transit may be modest to none
Decline in ICC at 13% per decade
Enteric neurodegeneration (seen in animal models) with age
Higher prevalence of diverticular disease is noted with age
Pancreas
Decline in insulin secretions with age associated with insulin resistance
Exocrine function is largely intact, with no significant impact on absorption
Liver
Blood flow declines with age; decline in phase 1 activity, better preserved phase 2 activity
Liver function relatively preserved, with normal albumin synthesis
Gall bladder
Decrease in hepatic extraction of LDL with higher LDL level
Diminish sensitivity to cholecystokinin (CCK) with age is offset by an increase in endogenous CCK secretion facilitating gall bladder contractions
Increase incidence of cholelithasis, perhaps relating to lithogenic bile

Clinical Application

The delay in gastric emptying noted in pathological states or as a pharmacodynamic effect may allow for longer contact time between harmful medications such as NSAIDs or aspirin and the gastric mucosa, with resultant adverse effects. While small intestinal transit time does not change appreciably with age, diseases such as diabetes and systemic sclerosis may significantly affect prolonged orocecal transit time [53, 54].

Intestinal Microflora

Proximal small intestine in healthy adults usually contains less than 10^4 bacteria/mL, predominantly Gram-positive anerobes [55]. Changes are apparent in the gut bacteria in older persons. An overall decrease in the total number of bifidobacteria is accompanied by an increase in species diversity [56]. Fungi and enterobacteria tend to increase. Overall, no single marker has been identified to denote change in microbiota composition; the impact of age is little, while that from disease and medications modify the composition of the microbial community [57]. In a study of seniors and centenarians, age-related differences in microbiota were related to inflammation and disease processes, and could affect host physiology [58]. Translocation of pathogenic bacteria from the gut into the circulation or lymphatics may lead to release of endotoxins.

Clinical Application

Shifts in composition of microflora may lead to detrimental effects [59], for e.g., increased predisposition to *Clostridium difficile* associated diseases. Therapeutic strategies have been considered and recommended to counter these changes [59]. Aging associated with reduced immune function, coexisting disease, malnutrition, and effect of medications modifies the composition of the microbial community [60]. Small intestinal overgrowth with colonic type bacteria must be considered as a basis for chronic diarrhea, anorexia, or nausea [61]. Based on evidence that the elderly have distinct microbiomes, the healthy old rather than the young may be better donors for probiotics [62]. Probiotics are detailed in chapter 11. With decreased costs of DNA sequencing, it is possible to identify the evolution of microbiota and thereby select probiotics based on patient age [63]. It also appears possible that manipulation of the complex symbiotic ecosystem of gut microbiota may help extend healthy aging and life span [64]. An understanding of the mechanisms of host-gut microbiota cross talk would help design nutritional approaches in targeting immune reactivity [65].

Immune Function

Advanced age associated with breakdown of epithelial barriers of the skin, lung, and genito-urinary tract does not spare the GI system. The gut mucosal immune system is exposed to a large number of antigens [66]. The GI tract surface represents the single largest immunological organ with much of the body's immunoglobulin-producing cells [6]. Aging is accompanied by a decline in the mucosal and secretory immune response, with markedly higher GI infection-related mortality [6]. Changes include decline in regulatory-type cytokine production, T cell compartment, antibody responses to antigens, and the composition of the Peyer's patches lymphoid tissues [66]. Although total T and B cells are generally stable, subset alterations occur. Intrinsic and extrinsic factors dictate macrophage function, with the latter more influential [67]. A better understanding of T cell metabolism, hormones and microbiota may provide insights into immune responses associated with aging. Gut hormones such as leptin, ghrelin, insulin-like growth factor (IGF-1), and cytokines may play a role [68]. Little is known as to how the IgA plasma cells in Peyer's patches and their homing to the lamina propria are affected by age [69]. Intestinal mucosal immunosenescence may be a consequence of reduced homing of IgA plasma cells [69]. Although age does not correlate with surface epithelium and number of intraepithelial lymphocytes, absorption of lipids is somewhat impaired and may result from a decline in blood flow and ischemia [48].

Clinical Application

Gastrointestinal infections are common in older adults and may in part relate to altered immune function. More often, predispositions to infections are contributed by decline in gastric acidity, inappropriate use of antibiotics, presence of blind loops, and other causes.

Colonic Motility

Constipation and colonic motor functional alterations are not solely a consequence of aging. The role of enteric neurodegeneration in constipation has been noted in animal models; whether age affects the intrinsic and extrinsic innervation of colonic smooth muscle or degeneration from neurological disorders (such as Parkinson's disease) deserves study [70]. The number of neurons in human colon declines with age; neuronal nitric oxide synthase-positive neurons are spared and compensation has been noticed in the spared neurons [71]. In both stomach and colon, the number of ICC decrease with age at a rate of 13% per decade; ICC size is affected only in the myenteric plexus of the colon [42]. While the changes do not differ by gender, they may contribute to alteration in motility [42].

In a study of over 3,000 individuals, 26% of women and 16% of men reported recurrent constipation [72, 73]. The variables associated with constipation in the over 65 age group included age, female gender, medication use, and the presence of abdominal pain, diverticular disease, and hemorrhoids. Psychological illness correlated positively with self-reported constipation [73].

Studies on sigmoid function and colonic transit show little evidence of alterations [74]. The most consistent

physiological findings were decreased rectal compliance and an increase in the sensory threshold for the urge to defecate. A large, relatively noncompliant rectum correlates with an infrequent urge to defecate. The presence of stool in the rectum for lengthy periods of time may suggest poor sensation of the urge to defecate.

While there is data to implicate abnormalities in colonic motility in older adults, chronic constipation is associated more frequently with abnormalities of rectal function and afferent sensory mechanisms. Whether the findings are attributable to age-related physiological changes or poor bowel habits is unclear [4, 70, 73].

Anorectal Function

Data suggests a decrease in both resting and squeeze anal canal pressures with age, as noted in healthy volunteers aged 20–89 years and subjects over 50 years [75–77]. The rate of decline in resting anal canal pressures is more apparent in females, and unrelated to parity. While the data is less clear on changes in rectal sensation, the threshold sensation for rectal filling seems to increase with age. Anorectal dysfunction is common in those with fecal incontinence, common in the old and one reason for institutionalization. Fecal incontinence is detailed in chapter 56.

Clinical Application

Constipation is most often the result of disorders seen in the old and influenced by life style and adverse drug effects. Measures must hence address life style, acknowledging the coexistence of disease and adverse effects of medications.

Gastrointestinal Hormones

Neuroendocrine cells regulate homeostasis via neurocrine, endocrine, and paracrine means. Gut neuroendocrine cells demonstrate differential behavior with age and are key to regulatory processes [12]. Gut hormones may be encoded for circadian rhythms of motor and secretory activity, and cell proliferation rhythm [78]. The hormones have been implicated in relaying signals on nutritional status and energy intake to the nervous system; while ghrelin stimulates food intake, cholecystokinin (CCK), peptide YY, pancreatic polypeptide, and glucagon-like peptide-1 (GLP-1) suppress appetite [79].

It is also believed that hormonal interactions occur between gut and brain; hormones circulate in the blood and signal via vagal afferents to communicate with the hypothalamus and brainstem [80]. Circadian biological rhythms account for food intake, hunger, and satiety. Gut hormones such as motilin and ghrelin are responsible for generation of MCC starting in the stomach; gastrin, ghrelin, cholecystokinin, and serotonin are involved in generating contractions in the small and large bowel. Disruption of the gut clock and the circadian rhythm in the GI tract has the potential to cause weight changes [78].

A brief account on gut hormones follows; more information is eloquently detailed in other reviews [81–83].

Gastrin

Gastrin is a peptide hormone released by G cells in the antrum of the stomach, duodenum, and pancreas. The release of gastrin is stimulated by gastric distension, vagal stimulation, peptides in the lumen of the stomach, and hypercalcemia. The actions of gastrin include stimulation of parietal cells to secrete hydrochloric acid. Gastrin plays a role in parietal cell maturation and fundic mucosal cell growth. Further, gastrin increases antral contraction and relaxes the pyloric sphincter to facilitate stomach emptying. Its secretion is inhibited by acidity (negative feedback mechanism) and paracrine secretion of somatostatin. Although gastrin levels were believed to decline with age, it is now believed that basal and stimulated gastric secretion do not significantly decline in healthy aging [13]. Hypergastrinemia occurs in pathologic states e.g., atrophic gastritis, acid suppression from use of histamine receptor antagonists and proton pump inhibitors, and gastrin-producing tumors, a component of the Zollinger–Ellison syndrome [81–82].

Cholecystokinin

CCK is secreted by entero-endocrine I cells in the duodenum and jejunum in response to fat and protein in meals. The actions include gallbladder contraction and promotion of bile entry into the duodenum. CCK stimulates the pancreatic acinar cells to increase enzyme secretion. Other actions include inhibition of food intake and delay gastric emptying. Duodenal mucosal diseases such as celiac disease and surgical procedures that bypass the duodenum (e.g., Billroth II, surgical gastric bypass) decrease CCK production and release, and may be responsible for pancreatic atrophy. Gallbladder sensitivity to CCK is diminished in the elderly, but gallbladder emptying remains unchanged due to an increase in endogenous CCK secretion [81, 82].

Secretin

Secretin, the first hormone, discovered in 1902 (Baylis and Starling) is produced by the S cells of the duodenum and

is released by acid food entering the intestine. Secretin predominantly stimulates the ductal epithelial cells of the pancreas to secrete pancreatic fluid and bicarbonate, facilitating neutralization of acid chyme in the intestine. Secretin is a polypeptide with 27 amino acids; it is present in duodenal mucosa in the inactive prosecretin form. Chyme in the duodenum activates and enhances the release of secretin. Pancreatic alkaline secretion in the duodenum is a protective mechanism against acid mucosal injury. Alkaline pH provides the ideal pH required for action of pancreatic lipase. Age-related effects on secretin are not clear. In pharmacological doses, secretin increases bile flow and GI motility and decreases LES pressure [78–82].

Glucagon

Glucagon, released from pancreatic alpha cells, regulates glucose metabolism through several mechanisms including gluconeogenesis, glycogenolysis, and lipolysis, opposing the actions of insulin. There are no age-related changes. Glucagonoma is a pancreatic cell tumor that causes diabetes, normocytic, normochromic anemia, cheilitis, glossitis, mild diarrhea, psychiatric manifestations, and a predisposition to thromboembolic phenomena. A characteristic erythematous skin reaction (necrolytic migratory erythema) is an association [78–82].

Glucagon Peptide Superfamily

Glucagon Peptide Superfamily is comprised of two peptide hormones: glucagon-like peptide (GLP-1) and glucose-dependent insulin releasing polypeptide (GIP). Incretin hormones (GLP-1 and GIP) are intestinal hormones released following food intake which potentiates glucose-induced insulin response [83, 85–87].

Glucagon-Like Peptide

GLP-1 is produced from the proglucagon gene in L cells of the small intestine. GLP-1 levels are decreased in type 2 diabetes. GLP-1 inhibits gastric acid secretion and gastric emptying [83]. It inhibits food intake through a central nervous system effect and promotes satiety [83]. The incretin effect denotes the phenomenon of oral glucose intake promoting a much greater release of insulin compared to the parenteral isoglycemic glucose infusion. GLP-1 is responsible for incretin effect. Currently GLP-1 analogues are commercially available for the management of diabetes (exenatide, liraglutide, sitagliptin).

Glucose-Dependent Insulin-Releasing Polypeptide

Although not as potent as GLP-1, on a molar basis, GIP also plays a role in incretin effect. Originally termed gastric inhibitory polypeptide (GIP), it is produced by K cells in the small intestine and released in response to ingestion of glucose or fat. Through a complex mechanism, GIP stimulates insulin secretion, in the presence of hyperglycemia. Similar to GLP-1, GIP also inhibits gastric acid secretion and gastric emptying; it also inhibits food intake through a central nervous system effect and promotes satiety [83]. There is experimental evidence that GIP regulates fat metabolism through receptors on adipocytes.

Vasoactive Intestinal Polypeptide

Vasoactive intestinal polypeptide (VIP) is a 28 amino acid peptide with similarities to secretin. VIP is present in brain, spinal cord, lung, and other endocrine organs. The hormone is unresponsive to meals. It is a potent vasodilator that increases GI blood flow and causes smooth muscle relaxation. As a chemical messenger, VIP acts on receptors to stimulate intracellular cAMP generation. It belongs to a family of GI peptides, including secretin and glucagon. The role of VIP is well studied in the syndrome of watery diarrhea, hypokalemia, and achlorhydria. Age-related changes are unclear.

Pancretic Polypeptide (PP)

The PP family of hormones include PP, neuropeptide Y (NPY), and peptide tyrosine tyrosine (termed PYY), each with distinct distribution and function. PP cells are distributed in the pancreatic islets within the parenchyma of the head and uncinate lobe. The secretion of PP correlates with vagal tone and is biphasic. The physiological effects of PP are not clear, but presumed to be inhibitory of pancreatic exocrine secretion. Other roles are inhibitory effects on gallbladder contraction, intestinal motility, and hepatic glucose production. Hospitalized patients may have reduced appetite through excessive release of PP [88]. PP influences several physiological functions including gall bladder contraction and secretion, pancreatic exocrine secretion, intestinal motility, and ileal contractions.

PYY is a 36 amino acid peptide found in the pancreas and in L cells of the distal small intestine and colon. PYY acts an endocrine and paracrine hormone. The stimulants for PYY include fat and products of digestion. PYY in the circulation is reduced by fasting. PYY is a hormone with inhibitory effects on gastric secretion and gastrointestinal motility.

PYY has been termed an "ileal brake" as it increases nutrient–mucosal contact time. Levels are influenced by age and may regulate food intake in the older people, serving as a satiety factor [89]. While PYY cells increase with age in rodents, such change has not been observed in humans [90].

NPY is a 36 amino acid hormone with similarities to PYY, found in the central and peripheral system. NPY stimulates appetite, causes vasoconstriction, and alters circadian rhythm.

Pancreatic endocrine function is altered with age, with a decline in insulin secretion even after adjustment for adiposity and physical activity; this is accompanied with decline in insulin sensitivity and alterations in hepatic glucose production [91]. There appears a significant reduction in PP-positive cells in elderly rats compared to young control rats, suggesting that the distribution of pancreatic hormones is altered to a varying extent during the normal aging process [92].

Somatostatin

Somatostatin is predominantly a paracrine secretion and produced by D cells of gastric and intestinal mucosa and islets of the pancreas. The physiological effects of somatostatin are mostly inhibitory. It regulates gastric, pancreatic, biliary, and salivary secretion and a wide spectrum of GI hormones. The inhibitory effects on secretion have been utilized to treat diarrhea, fluid output from pancreatic fistulas, and to decrease splanchnic and portal blood flow. Radio-labeled somatostatin analogues, such as octreotide, help localize neuroendocrine tumor [93]. Levels of somatostatin increase with aging. The rare clinical syndrome of somatostinoma is characterized by diabetes, diarrhea, and gallstones.

Ghrelin

Ghrelin is a 28 amino acid peptide produced largely in the gastric fundus, with small amounts in the small intestine, pancreas, kidney, testis, placenta, and lung [94]. Ghrelin is the natural ligand growth hormone secretogogue (GHS) receptor; it increases food intake and weight gain [95]. Circulating ghrelin increases during fasting and under conditions associated with negative energy balance, such as starvation or anorexia [96]. In contrast, levels are low following feeds and in obesity. Ghrelin is a central neurohormonal regulator of food intake and energy homeostasis and serves as a signal for initiation of feeding. The usual premeal increase in levels is not observed in gastric bypass patients and may be one of the reasons for the effectiveness of gastric bypass surgery in inducing weight loss [94–97]. In old mice, the release and synthesis of ghrelin seem to be higher compared to that in younger mice, explained by compensation for decline of receptor functions [98]. Ghrelin levels may also decline with aging, and partially explain anorexia in the older adult [99].

Motilin

Motilin is a 22 amino acid peptide produced by endocrine cells of duodenal epithelium and regulates propulsive contractions from the antero-duodenal region to the distal gut. Alterations in gastric motor activity and serum motilin are not related to acid secretory capacity, rather to other alterations in neurohormonal control in the aged [100]. Drugs may serve as motilin agonists to cause abdominal discomfort and diarrhea.

Leptin

Leptin is a protein with 167 amino acids secreted primarily by adipocytes; small amounts are produced by the chief cells of the stomach. Its function is primarily to decrease food intake. Blood leptin levels reflect total body fat stores. Leptin "resistance" in obesity occurs at the level of the blood–brain barrier. Peripherally, leptin acts in synergy with CCK to reduce meal size. Blood levels of leptin increase with obesity, especially in sleep apneic patients and correlate with total fat content; they increase with fasting, stress, and sleep deprivation. *H. pylori* infection in patients over 75 years has been associated with decreased gastric leptin and ghrelin and plasma ghrelin levels [101]. Neuronal nitric acid synthase may be the pathway through which proinflammatory cytokines cause anorexia, and certainly for leptin. Leptin levels remain unchanged with age.

Oxyntomodulin

This is a hormone that has received recent attention. Oxyntomodulin is a 37 amino acid peptide with several actions; these include inhibition of gastric emptying, acid secretion and food intake, and stimulation of intestinal glucose uptake and insulin secretion [83]. It also induces satiety and increases energy expenditure [83]. When administered to humans, it caused weight loss through a reduction in caloric intake and increase in energy expenditure.

Clinical Application

The Baltimore Longitudinal Study of Aging compared healthy "long-lived" individuals (at least 90 years old) with "short-lived" persons (72–76 years), with samples collected between 58 and 70 years. Levels were obtained for ghrelin,

Table 5.3 Aging and gastrointestinal hormones

Hormone	Function	Effect of aging
Gastrin	Stimulates gastric acid secretion	No change with healthy aging
Cholecystokinin	Stimulates gallbladder contraction and pancreatic enzyme secretion	Increase in endogenous CCK, but gall bladder sensitivity is decreased
Secretin	Stimulates pancreatic bicarbonate secretion	Unknown
Vasoactive intestinal polypeptide (VIP)	Stimulates intracellular cAMP	Unknown
Glucagon-like peptide (GLP-1)	Participates in incretin effect. Inhibits gastric emptying, gastric acid secretion and food intake. Promotes satiety	No change
Glucose-dependent insulin-releasing polypeptide (GIP)	Participates in incretin effect. Inhibits gastric emptying, gastric acid secretion and food intake. Promotes satiety	No change
Glucagon	Promotes gluconeogenesis, glycogenolysis, and lipolysis	No change
Pancreatic polypeptide	Inhibits pancreatic exocrine secretion and gut motility	Increase
Somatostatin	Inhibits gut secretion and intestinal motility	Increase
Motilin	Stimulates gastric emptying	Increase
Leptin	Reduces food intake	No change
Ghrelin	Increases food intake, induces weight gain, and stimulates growth hormone	Decline?
Oxyntomodulin	Inhibits gastric emptying, acid secretion, and food intake. Induces satiety and increases glucose uptake and energy expenditure	Unknown

leptin, insulin, interleukin 6, testosterone, and adinopectin. None of the single biomarkers were significantly different, but after combining information from multiple biomarkers, the global score differentiated the two groups [102]. In another study, after weight loss induced by a very low energy diet in overweight or obese patients without diabetes, circulating levels of gut hormones were examined. The levels of ghrlein, GIP, and PP increased, whereas the levels of leptin, peptide YY, CCK, amylin, and insulin declined. This may call for strategies in long-term management to prevent recurrence of weight gain following diet-induced loss [103].

In summary, GI hormone changes in healthy aging result in minimal to no impairment, while the impact may be different in the ill, frail, and homeostenotic states. On the other hand, there may be an emerging role for gut hormones in the management of satiety, gut motility, nutrient absorption, energy handling, and managing disorders involving energy homeostasis [83] (Table 5.3).

Figure 5.1 summarizes the sites and actions of gut hormones.

Hepato-Biliary System

Liver volume decreases with age, with a decline in size but not in the number of hepatocytes. Minor alterations in serum alanine aminotransferase (ALT) are noted. In women, levels continue to increase with age, whereas in men levels increase up to around 50 years [104]. In the frail old, ALT levels demonstrate a bell-shaped curve with lower levels in the old-old [105]. Although liver function is little altered, there is a general decline in the P450 enzyme system in animals [105]. Of note, a greater decline occurs in the activity of rapid metabolism. The fact that age minimally alters liver physiology is supported by the fact that livers from donors over age 80 years are transplanted satisfactorily.

The biliary duct is marginally dilated with age, a result of increased connective tissue; the upper limit for normal is 8.5 mm [106, 107]. Lithogenicity of bile salts increases and leads to a propensity to form gallstones. The prevalence of cholelithiasis increases; however, gall bladder contractions are not affected by age.

Clinical Application

Marked alteration in liver function raises the possibility of diseases including drug-induced liver injury. Evaluation of abnormal liver function must include a medication review to minimize needless evaluation. Alterations in P450 system influence metabolism of numerous medications, additionally influenced by individual variability in enzyme activity with aging; some microsomal enzymes, such as CYP3A are more affected than others [105].

While several physiological changes have been described, one must reiterate that most age-related alterations will have little impact on function. Gastrointestinal dysfunction may be the result of physiological or structural changes in the GI tract or age-related diseases such as tumor, neurological or inflammatory diseases, malnutrition, or the effect of medications [108] (Table 5.4). Often, there is a chronic subclinical inflammation, with the intestine serving as a source of signals that amplify local and systemic inflammation [109]. Several manifestations seldom result solely from aging and

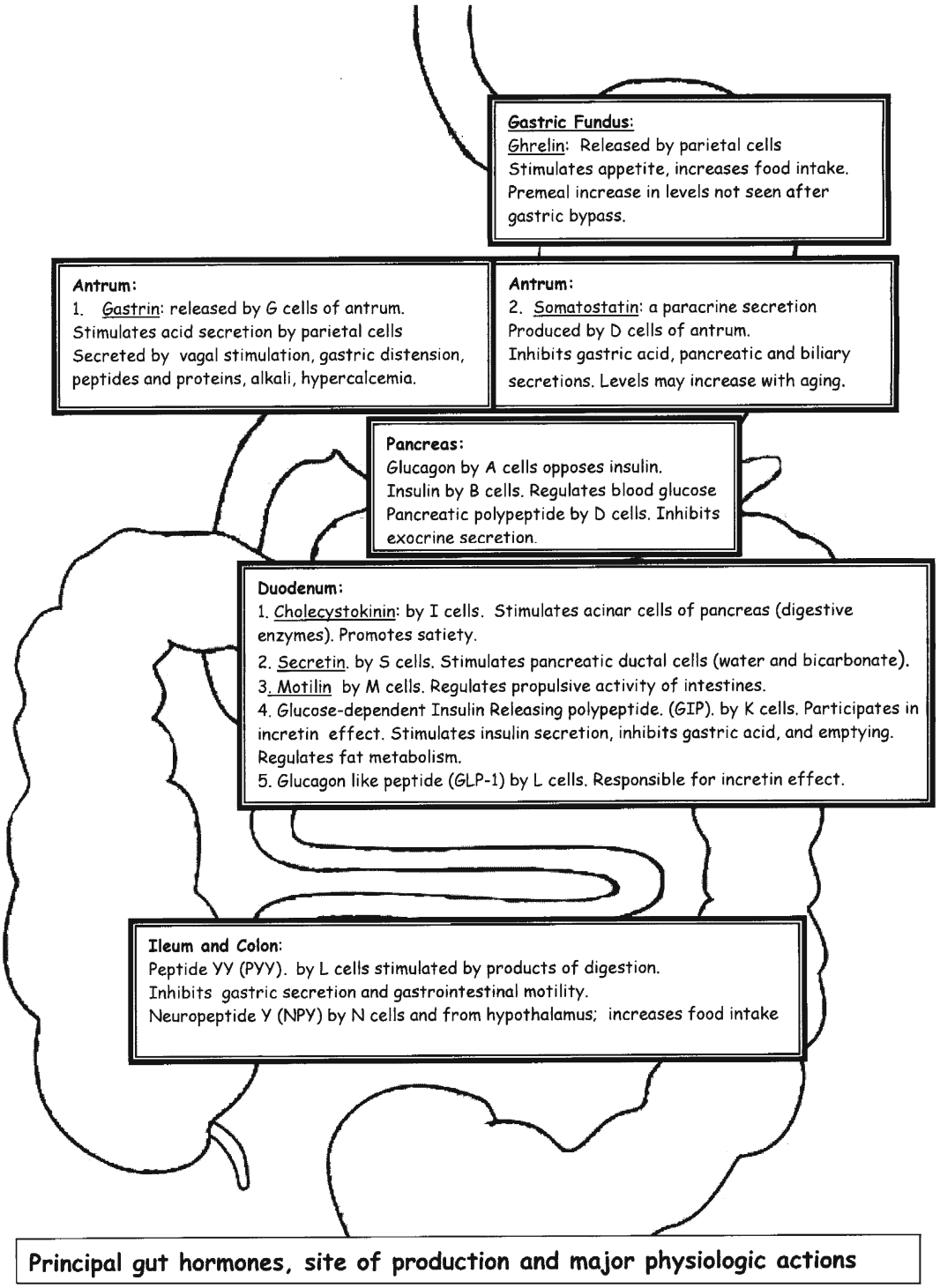

Fig. 5.1 Principal gut hormones, site of production, and major physiological actions

Table 5.4 The impact of medications on gastrointestinal function[a]

Alterations in appetite
Metronidazole
Angioconverting enzyme inhibitors
Iron preparations
Metformin
Dry mouth
Anticholinergics
Clonidine
Diuretics
Alterations in gastric acid secretion and pH
Antacids
H_2 receptor antagonists
Proton pump inhibitors
Constipation
Anticholinergics
Aluminum-containing antacids
Calcium-containing preparations
Calcium channel blockers
Iron preparation
Diarrhea
Antibiotic related (*Clostridium difficile* diarrhea)
Ferrous sulfate or other iron salts
Erythromycin induced
Metformin
Misoprostol
Serotonin reuptake inhibitors
Sorbitol containing preparations
Dysphagia
Large-sized medications (pill esophagitis)
Doxycycline, potassium chloride, ascorbic acid, aspirin, iron salts, bisphosphonates
Candidiasis (following antibiotic use)
Vomiting
Anticholinergic medications

[a]The stated medications are for illustration only and not a complete list

Table 5.5 Gastrointestinal disorders unlikely to result solely from aging

Anorexia
Aguesia, dysguesia
Anemia
Intractable constipation
Diarrhea
Dysphagia
Edentulous state
Fecal incontinence
Iron deficiency
Malnutrition
Malabsorption
Vomiting
Weight loss
Weight gain

are an indication for an evaluation to determine an etiology (Table 5.5).

Key Points

- Age-related physiological changes in the GI tract are minimal and by themselves are not impediments to daily living.
- Gastrointestinal dysfunction is most often the result of age-associated primary disorders of the GI tract or systemic disease.
- Medications often alter gastrointestinal function; adverse drug effects must be addressed before needless testing and evaluation.
- Because of therapeutic options for disease states (as opposed to physiological changes), a differential diagnosis and evaluation is often required in most older persons.
- Several common disorders such as anorexia, dysphagia, constipation, diarrhea, and malabsorption, all common in the old, do not result solely from aging.
- Age has little significant effect on gastric acid secretion, gastric emptying, and small intestinal transit time. Older individuals may have slower colonic transit than the young.
- Most gastrointestinal hormonal changes with age and their effects on body function are subtle; however, gut physiology may play a role in several gut manifestations seen in older age.
- The physiological effects of gut hormones may be utilized in future in the treatment of disorders such as type 2 diabetes mellitus.

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