Esophageal Dysfunction

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The function of the esophagus, the first organ of the digestive tube, appears very simple: it is an anteroposteriorly flattened hollow tube organ that transports material from the mouth into the stomach. However, this requires a very complex swallowing mechanism, lubrication of the swallowed material with saliva and other esophageal secretions, transport into the stomach by peristaltic waves, and prevention of retrograde transport from stomach to mouth. The esophagus is located in the thoracic cavity and enters the abdominal cavity through an opening in the diaphragm. Although short, the intra-abdominal length of the esophagus is important, because the intra-abdominal pressure will cause compression of this part of the esophagus, preventing reflux.

Gastroesophageal reflux (GER), regurgitation, and vomiting are considered to be the most typical, although nonspecific, manifestations of esophageal dysfunction. However, by protecting against excessive postprandial gastric dilatation, GER could also be a feature of normal esophageal function. When GER occurs, nature will try to move any refluxed material that is noxious to the esophageal mucosa out of the esophagus as quickly as possible, both in a downward direction, forcing the refluxed material back into the stomach, and in an upward direction, causing regurgitation and vomiting.

Attempts have been made, although with contradictory conclusions (1,2), to evaluate whether the clinical history or a specific questionnaire may be helpful in selecting infants and children with pathologic GER, as has been considered possible in adults (3).

THE MOUTH: MASTICATION AND SALIVA SECRETION

Mastication is poorly developed in infants. Its importance increases when the food becomes more solid. The major function of mastication is to prepare food mechanically for later transport and the initiation of digestion. No information is available on the influence of mastication on GER, but mastication stimulates the parasympathetic nerves that regulate salivary, gastric, and pancreatic secretion. Chewing gum has been suggested as a treatment for pathologic GER (4).

Saliva has different functions. The larger the volume of saliva, the more the food
is lubricated, and the easier esophageal transport becomes. In adults, the volume secreted daily is 1,000 to 1,500 ml. Saliva is principally composed of water (99.5%), but also contains enzymes and salts, especially bicarbonate. Saliva secretion is decreased during sleep; normal adults swallow 600 times during 24 hours, but only 50 times during sleep.

Acetylcholine stimulates the salivary glands (5). Cisapride, a prokinetic drug stimulating acetylcholine release in the myenteric plexus, results in a 45% increase in salivary volume secreted in basal conditions, a 32% increase during mastication, a 53% increase during mechanical stimulation, and a 51% increase during chemical stimulation (5). Cisapride also changes the composition of saliva, increasing the bicarbonate and nonbicarbonate buffers, and the protein, glucoconjugate, and epidermal growth factor (EGF) content (5,6). Inorganic phosphate is increased in the saliva of patients with esophagitis (7). GER stimulates salivary secretion, so-called waterbrash, although this esophagosalivary reflex is mainly effective only in prolonged episodes of GER (4).

Saliva secretion is determined by mastication, by the state of alertness, and by GER itself. Saliva is important in our understanding of the pathophysiology of GER as it stimulates swallowing, thus increasing primary esophageal peristalsis, and its volume and alkaline composition also help to clear the esophagus of refluxed material. However, the role of saliva should not be overestimated: a 90% reduction in saliva secretion in experimental rat models did not increase the development of esophagitis (8).

ANATOMIC STRUCTURE OF THE ESOPHAGUS

As with all other parts of the alimentary tract, the esophagus consists of four layers; however, because of its special function, structural differences exist between the esophagus and the rest of the gastrointestinal tract. The upper esophagus has a stratified squamous epithelium of the nonkeratinizing type, which continues from the pharynx into the esophagus. This type of epithelium protects against any rough material that may be swallowed, but does not protect against acid reflux. The dense connective tissue of the submucosa layer, together with the muscularis mucosa, forms numerous longitudinal mucosal folds that result in an irregular luminal in cross section. The elasticity of the connective tissue of the submucosal layer allows these folds to be smoothed out when food is swallowed. In contrast with the remainder of the gastrointestinal tract, the outer and inner layers of the muscularis propria in the upper third of the esophagus are composed of striated muscle. It is only in the lower third that the smooth muscle becomes arranged into an outer longitudinal and an inner circular layer, with a myenteric nerve plexus in between. Many spiral or oblique bundles are found in the inner layer. The longitudinal muscularis bundles of the outer layer are irregularly arranged. The extensive system of neural elements in the muscularis externa is known as the "myenteric plexus of Auerbach." In the submucosa, the neural elements form the submucous plexus of Meissner, which
appears at approximately 13 weeks of fetal life. Both plexuses are part of intrinsic neural mechanisms. Extrinsic vagal and sympathetic fibers are also present.

The upper and lower esophageal sphincters are not distinct anatomic structures. The lower esophageal sphincter is an extension of the circular muscle of the esophageal body. In some animals (e.g., the dog and the cat) that spend a great part of their life horizontal, the lower esophageal sphincter is an anatomically discrete sphincter. In humans, the musculature of the sphincter differs from that of the esophageal body, with more impressive length-tension characteristics. The lower esophageal sphincter and the gastric fundus are held in place by a prominent phrenoesophageal membrane—a tough fibroelastic layer attached to the thoracic and abdominal diaphragm and the esophagus within the hiatus. At the junction of the esophagus with the cardia of the stomach is found an abrupt transition from stratified squamous to simple columnar epithelium. Macroscopically, the boundary line between the smooth white mucous membrane of the esophagus and the pink surface of the gastric mucosa appears as a jagged (Z) line.

Connective tissue diseases (e.g., mixed connective tissue disease and scleroderma) often involve the esophagus (9). In patients with familial amyloidosis, it is now thought unlikely that amyloid deposits in the mucosal wall cause increased esophageal stiffness; rather, an autonomic, predominantly vagal, denervation probably best explains the disturbed esophageal function in this disease (10). Similarly, a correlation is seen between esophageal dysmotility and cardiovascular autonomic dysfunction (11). Gastroesophageal dysfunction is a major cause of morbidity and mortality in patients with familial dysautonomia (12).

SWALLOWING

Swallowing is a complex, integrated, continuous act involving somatic and visceral afferent and efferent nerves and their associated striated and smooth muscle (Fig. 1). For simplicity, it can be divided in two distinct phases, oropharyngeal and esophageal. Although the fetus has the ability to swallow by the age of 11 weeks, an effective sucking-swallowing mechanism does not appear before 35 weeks. Non-nutritive sucking develops first; it is characterized by its rapidity, exceeding two sucks per second, which is approximately twice that seen in nutritive sucking. As the change to diversified feeding gradually occurs, the sucking reflexes are repressed, although they can later be reinstalled, as in experienced beer drinkers.

In older children and adults, the initiation of deglutition is under conscious control. However, swallowing also often occurs automatically. Afferent impulses arising from contact between the bolus and the anterior pillars of the pharynx, the base of the tongue, and the soft palate take subsequent events out of conscious control by initiating the swallowing reflex. Dynamic ultrasound techniques can detect tongue incoordination and are especially useful in the objective imaging and identification of tongue thrust in orthodontic patients (13).

Following a swallow, the upper esophageal sphincter relaxes, respiration is inhibited, and the glottis closes as the larynx is drawn forward and upward. The nasopharynx is closed by a combination of elevation of the soft palate and contraction of the
superior pharyngeal constrictor. The epiglottis tips down, deflecting the bolus laterally and posteriorly away from the larynx. The pharyngeal constrictors contract sequentially, propelling the bolus into the esophagus. The muscles of the esophagus relax and respiration resumes as the upper esophageal sphincter contracts to separate the bolus and the esophagus from the pharynx and the airway. The complex neuromuscular reaction pattern of swallowing involves more than 25 muscle groups (Table 1), controlled by the swallowing center in the brain stem. Although the initiation of swallowing is under voluntary control, it appears impossible to swallow if the pharyngeal afferents are blocked by a local anesthetic. Activation of the swallowing center influences the activities of other centers, most notably the respiratory center, as evidenced by a physiologic apneic pause of 0.5 to 3.5 seconds that accompanies every swallow. Apnea occurs also during belching and vomiting. All these phenomena occur with increased frequency in infants with pathologic GER. This may contribute to the irregular, immature breathing pattern in such infants.

The second or esophageal phase of swallowing, which involves the smooth muscle of the esophageal wall, depends on both central coordination and local intramural neural arcs.

Given the complexity of the swallowing mechanism, it is surprising that dysfunction of this phase does not occur more often; an exception is children with certain neurologic disorders such as cerebral palsy. The large reduction in the swallowing
TABLE 1. Factors influencing the incidence and noxious effect of gastroesophageal reflux (GER)

<table>
<thead>
<tr>
<th>Defense mechanism</th>
<th>Adverse factors</th>
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<tbody>
<tr>
<td>Good</td>
<td>Esophageal clearance (gravity ?)</td>
</tr>
<tr>
<td>High</td>
<td>Mucosal resistance</td>
</tr>
<tr>
<td>High</td>
<td>Lower esophageal sphincter pressure</td>
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<tr>
<td>Long</td>
<td>Abdominal esophagus</td>
</tr>
<tr>
<td>Normal</td>
<td>Sphincter position</td>
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<tr>
<td>Acute</td>
<td>Esophagogastric angle</td>
</tr>
<tr>
<td>Small</td>
<td>Gastric volume</td>
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<tr>
<td>Normal</td>
<td>Gastric emptying</td>
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<tr>
<td>Low</td>
<td>Gastric acid output</td>
</tr>
<tr>
<td>Low</td>
<td>Pepsin/trypsin/bile salts</td>
</tr>
<tr>
<td>Low</td>
<td>Intra-abdominal pressure</td>
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<tr>
<td>Low</td>
<td>Gastroesophageal reflux</td>
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rate during sleep can result in delayed esophageal clearance of refluxed material; this would be expected to cause more difficulty for infants than for adults, as they spend more time asleep.

Specific Swallowing Disorders

The Opitz GBBB syndrome is characterized by craniofacial and genitourinary abnormalities, swallowing difficulties, esophageal dysfunction, hypotonia, and moderate development delay (14). Frequently, poor deglutition is one of the most striking phenomena. Patients with globus sensation have frequent abnormalities such as nonspecific esophageal motor disorders, pharyngoesophageal sphincter dysfunction, pharyngeal stasis, achalasia, and laryngeal penetration or aspiration (15). In esophageal dysfunction, contractions can be of low amplitude, incomplete, or uncoordinated.

OROESOPHAGEAL DYSKINESIA

Weight gain during the first year of life is compromised in many infants. Some investigators call these unexplained feeding disorders “nonorganic failure to thrive,” or NOFTT (16,17). The cause of NOFTT is likely to be heterogeneous. Every pediatrician knows infants without any malformations or neurologic deficits but with clearly abnormal sucking, swallowing, and feeding behavior, similar to infants with the Pierre-Robin syndrome. These infants have sucking and swallowing anomalies and esophageal dyskinesia, suggesting that the causative abnormality may be located in the brain stem (18). In most cases, they present with slow feeding (>45 minutes to complete a feed), poor intake, refusal to drink, unexplained and inconsolable crying, and regurgitation and vomiting. During feeding, there may be (micro)aspiration, nasal reflux, and apparent life-threatening events (ALTE). Many infants present
with retrognathia and a deep and ogival palate. Early recognition is associated with improved prognosis, even if the cause remains undetermined (19–21). Esophageal peristalsis in children with the Pierre-Robin syndrome is abnormal. Hypertonia of the lower esophageal sphincter or achalasia (insufficient relaxation) has been described in neurovegetative anomalies such as the Pierre-Robin syndrome, ALTE, or hypervagotonia (22,23). Antroduodenal dysmotility has been suggested as the reason why infants with GER tend to refuse feeds. Stress influences the tone of the vagal nerve and may exacerbate symptoms of GER.

**ESOPHAGEAL SECRETION**

The esophageal glands are irregularly distributed and small, containing only mucous cells. These glands can be detected most often just distal to the upper esophageal sphincter and just proximal to the lower esophageal sphincter. They lubricate the bolus during its passage from the pharynx to the stomach. The bicarbonate-secreting capacity of the human esophagus is small and intrinsic esophageal bicarbonate is unlikely to play an important role in mucosal defense (24). Unlike cisapride, neither omeprazole nor ranitidine affects esophageal bicarbonate secretion (24).

**ESOPHAGEAL PERISTALSIS**

Swallowing induces a contraction wave that begins at the superior constrictor muscle of the pharynx and sweeps through the striated and smooth muscle to the cardia without interruption. This primary peristaltic contraction pushes a solid bolus down the esophagus into the stomach, taking about 12 seconds in a normal adult. Gravity results in fluids taken in the upright position reaching the cardia before the arrival of the primary peristaltic wave. In the head-down position, fluids are propelled by the esophageal contraction wave. In the resting state between two swallows, the esophagus is closed at both ends by the upper and lower esophageal sphincters. Both the upper sphincter and the lower sphincter relax secondary to deglutition. Transient relaxations of the upper esophageal sphincter occur, and when these occur simultaneously with a transient relaxation of the lower esophageal sphincter, a “common cavity phenomenon” is created, resulting in a direct connection between the external world and the stomach. The pressure of the upper esophageal sphincter disappears during sleep, whereas in stress situations and in straining it increases. The activity of the upper esophageal sphincter differs in relation to the kind of material present in the esophagus. It relaxes completely when there is air in the esophagus, as in belching; however, when ingested material or acid reflexes into the esophagus, it normally constricts. Although unproved, it is possible, in patients with chronic aspiration disorders, that the upper esophageal sphincter relaxes instead of constricts secondary to GER.

Secondary peristalsis, which is caused by GER, starts at the highest level in the esophagus reached by the refluxed material. It contributes to clearance of any remnants of the refluxed material that were not cleared by the primary peristaltic wave.
Secondary peristalsis can be produced experimentally by inflation and deflation of an esophageal balloon. Prokinetic agents such as cisapride do not appear to be associated with a greater number or an increased amplitude of secondary peristaltic contractions (25). However, the larger the volume of material refluxed, the greater the amplitude of the secondary waves (25).

Except for their afferent origin, secondary waves are comparable to primary waves. When a subject takes a series of swallows, such as when drinking a glass of water, the upper esophageal sphincter opens and closes at each swallow, whereas the lower esophageal sphincter opens when the first peristaltic wave enters the sphincter, and only closes when the last contraction has passed by. Secondary peristalsis can be inhibited with a swallow. Tertiary peristaltic waves are contractions occurring in the lower smooth muscle segment. These contractions occur spontaneously without any relationship to swallowing or reflux. They do not depend on extrinsic innervation. They can accomplish in quadrupedal animals what gravity or gravitation does in humans (i.e., clearance of the lower end of the esophagus).

Pain delays esophageal clearance. In adults, normal esophageal transit time takes about 12 seconds, but it takes 25 to 102 seconds if the subject's hand is plunged in iced water. Hot substances increase the speed and amplitude of contractions; cold swallows have the opposite effect.

ESOPHAGEAL INNERVATION AND RECEPTORS

Medullary circuits composed of premotor neurons of the nucleus tractus solitarii are intrinsically capable of generating a rhythmic esophageal motor output, but are subject to powerful modulation by peripheral sensory feedback (26). The role of the vagal nerve endings is still poorly understood. Because all kinds of respiratory symptoms (e.g., wheezing) appear to be related to GER suggests that the vagal nerve endings present in the esophagus and the airways develop simultaneous hyperreactivity secondary to GER.

Three kinds of receptors must be present in the esophagus—mechanical, chemical, and temperature sensitive—although these have not all been convincingly identified anatomically. Under pathologic conditions, receptors become nociceptive, resulting in an increased sensitivity; they then respond with a sensation of pain to physiologic stimuli that normally do not cause pain. In Barrett's esophagus, mucosal sensitivity is decreased (27).

The nociceptors inform the patient about the existence of tissue damage. Two types of afferent neurons have been described: unmyelinated C fibers, responsible for deep burning pain; and delta A fibers, responsible for sharp abrupt pain. Repeated noxious stimuli or one very strong stimulus can sensitize both types of fiber so that typical non-noxious stimuli become very painful. This can result in relatively small esophageal distension secondary to belching, minimal regurgitation, or even the passage of a swallowed food bolus being experienced as very painful. The sensation of pain is transported to the brain by calcitonin gene-related peptide (CGRP) and substance P. Substance P has been studied most extensively; it causes smooth muscle
contraction and vasodilatation, with a secondary increase in mucosal permeability. Substance P is released in cases of tissue damage (e.g., with esophagitis), inducing a vicious circle: the more the tissue damage, the more substance P is released and the greater the noxious effect of the refluxed material. Substance P also causes histamine release from the mast cells in the alveoli and, thus, contributes to bronchospasm. The accompanying visceral hyperalgesia will result in disordered motility, again causing more reflux. All this suggests that pain induced by acid reflux is more likely to be caused by motility phenomena than by the chemical composition of the refluxed material, so treatment should focus on motility.

In the ferret, at least three types of esophageal afferent fibers exist, namely mucosal, tension, and tension/mucosal fibers (28). Vagal efferent neurons respond to gastroesophageal mechanical inputs, and also receive convergent inputs from esophageal acid-sensitive and gastrointestinal bradykinin- and capsaicin-sensitive afferents. Sudden rapid stretch of the mechanoreceptors in the proximal esophagus can trigger the hiccup reflex in normal subjects (29). Only rapid distensions above a determined volume threshold will predictably induce hiccups in a particular subject (29).

**ESOPHAGEAL CLEARANCE**

Esophageal clearance is influenced by at least three factors: esophageal peristaltic waves, gravity, and saliva (30,31). Esophageal clearance mechanisms are well developed by at least 31 weeks' postmenstrual age (32). Clearance of acid from the esophagus and decreased pressure of the lower esophageal sphincter are the major mechanisms involved in the development of esophagitis (33). The pH of saliva varies from neutral to alkaline. Swallowed saliva contributes to the neutralization of the refluxed acid. Moreover, the bolus effect of swallowed saliva will help in clearing the esophagus of the refluxed material. It seems logical to suppose that gravity also helps to clear the esophagus. The efficacy of positional treatment may be partially related to gravity. The esophagus tends to function normally in healthy controls when they swallow water without gravitational assistance (34). On the other hand, more abnormal contractions (simultaneous, retrograde, and nontransmitted) occur in the upright position than in the supine position (26% and 12%, respectively; \( p = .013 \)) (34). GER most commonly occurs in the seated position, followed by the supine position; it is least common in the prone position.

**ESOPHAGEAL MUCOSAL RESISTANCE**

The esophageal mucosa has established protective mechanisms that operate within the pre-epithelial, epithelial, and postepithelial compartments. As refluxed acid and pepsin always act from the luminal side of the mucosa, protective factors such as EGF, operating as a part of the pre-epithelial defense, are essential for maintaining the integrity of the esophageal mucosa (35). The resistance of the mucosa to the noxious effects of the refluxed material (e.g., acid, pepsin, chymotrypsin or trypsin,
bile) differs from person to person, and is genetically determined. Prostaglandin E\textsubscript{2} and nitric oxide (NO) are said to be protective (in low concentrations) and detrimental (in high concentrations) for esophageal mucosal integrity (36).

**Prostaglandins**

Prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) is the major arachidonic acid metabolite secreted (37). Esophageal perfusion with saline stimulates the secretion of PGE\textsubscript{2}, whereas perfusion with acid decreases it. HCl or pepsin infusion causes a further increase in PGE\textsubscript{2} secretion in comparison with saline infusion (6,37,38). PGE\textsubscript{2} decreases the duration of esophageal contractions in healthy volunteers (39). An increase in the rate of salivary PGE\textsubscript{2} excretion during mastication or after mechanical or chemical stimulation suggests that it may have a potential therapeutic effect (6,35). Aspirin renders the esophageal mucosa more permeable to acid and pepsin (40). Prostaglandins are only secreted in the presence of esophageal inflammation (37). These effects, in part, are pH dependent and might be partially reversed by PGE\textsubscript{2} cotherapy (40). The decline in luminal PGE\textsubscript{2} release in healed reflux esophagitis indicates that the increased secretion occurring in active esophageal disease may reflect the mucosal damage induced by HCl or pepsin (40). Inhibition of the rate of luminal release of PGE\textsubscript{2} under the influence of HCl and pepsin may play a role in the development or progression of mucosal damage (41).

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the synthesis of prostaglandins. As NSAIDs are also reported to have positive effects in animal models of reflux esophagitis, it has been proposed that prostaglandins have a deleterious effect in esophagitis (42). This hypothesis could explain the relationship between inflammation and dysmotility (42). However, in the rabbit, PGE\textsubscript{2} has no effect on esophageal mucosal repair (43), although HGF (human growth factor), insulin-like growth factor 1 (IGF-I), and EGF (stimulation), and transforming growth factor \( \beta_1 \) (TGF-\( \beta_1 \)) (inhibition) have major effects (43). A study examining PGE\textsubscript{2}, PGF\textsubscript{2a}, PGI\textsubscript{2}, and thromboxane B\textsubscript{2} (TXB\textsubscript{2}) content in esophageal mucosal biopsies from healthy controls and patients with esophagitis showed a difference only for PGI\textsubscript{2} (44). The presence of a murine calcium-sensitive chloride channel in esophageal mucosa suggests the presence of exocrine secretory cells and of transepithelial ion transport (45).

The information presented above can be summarized as follows: PGE\textsubscript{2} (and NO) are protective in low concentrations, whereas in high concentrations they can be harmful (36); in addition, the release of prostaglandins differs in relation to the prostaglandin subtype and according to the composition of the refluxed material (38).

**Sex Differences**

Severe GER disease (e.g., Barrett’s esophagitis) has a male predominance. However, this difference is not found in young infants presenting with uncomplicated
reflux disease. Although it was hypothesized that this sex difference is genetically or hormonally mediated, it is likely that lifestyle is a more important determinant.

THE LOWER ESOPHAGEAL SPHINCTER

The lower esophageal sphincter is a functional barrier and represents a zone where the intraluminal pressure is greater than in the stomach and esophagus. In adults, this high pressure zone has a length of 3 to 6 cm and a pressure of approximately 20 mm Hg, ranging between 10 and 40 mm Hg. In infants, its length is only a few millimeters. The lower esophageal sphincter relaxes 2.5 seconds after the initiation of a swallow, well before the arrival of the bolus, and remains open for 10 to 12 seconds, until the bolus has passed through the region. As a rule, increased abdominal pressure is associated with increased sphincter pressure. However, gastric distension not associated with an increased intragastric pressure is accompanied by a fall in lower esophageal sphincter pressure or by inappropriate transient lower esophageal sphincter relaxations (TLESRs), which can last for 10 to 17 seconds. It is believed that these responses are mediated by vagal reflexes. Stimulation of mechanoreceptors in the gastric fundus, or stretching of the gastric fundus, initiates vagosympathetically mediated reflexes resulting in TLESRs.

The lower esophageal sphincter pressure is one of the most classically reported and relevant defense mechanisms against GER, although only 20% of all reflux episodes are associated with decreased resting pressure (33). The lower esophageal sphincter pressure decreases postprandially, both in normal individuals and in patients with GER. Gastric contractions, gastric alkalinization, and protein meals increase the lower esophageal sphincter pressure, as do gastrin, motilin, and substance P. Cord blood gastrin levels are much higher than adult levels, whereas during the first days and weeks of life, gastrin levels are decreased in comparison with adult levels. The role of gastrin in infant regurgitation has not been determined.

Progesterone, atropine (at least in cats), cholecystokinin, glucagon, vasoactive intestinal peptide (VIP), NO, dopamine, secretin, estrogen, mint, and chocolate decrease the pressure of the lower esophageal sphincter. L-arginine, the endogenous source of NO, prolongs TLESRs (46). The type of meal influences the number of reflux episodes and the severity of heartburn, which are increased by red wine and chilli peppers and decreased by fat and chocolate (47). Circulating glucagon and cholecystokinin, which are increased in renal insufficiency, regulate hunger and satiety.

Esophageal balloon dilatation, the presence of fat in the duodenum, nicotine, and alcohol also decrease the lower esophageal sphincter pressure. VIP and NO both induce TLESRs (48). NO also delays gastric emptying (49) and is increased in infants with pyloric stenosis (50), again suggesting that TLESRs are a protective mechanism against gastric overdistension. NO controls several esophageal neuromuscular functions, including relaxation of the lower esophageal sphincter (36), but NO levels were found to be the same in biopsies of normal and inflamed esophageal
mucosa (51). On the other hand, nitric oxide synthetase (and cyclooxygenase-2) are involved in the neoplastic progression of Barrett’s esophagus (52).

Most reflux episodes occur in relation to TLESRs. TLESRs are also the predominant mechanism of GER in healthy preterm infants (32). TLESRs occur more often in the seated position than in the supine position. Reflux episodes can also occur during periods of prolonged lower esophageal sphincter hypotonia or with pressure drifts, especially in patients with severe esophagitis (53).

Gastric distension and partial or incomplete swallowing induce TLESRs, which are also the normal mechanism for burping and belching. The larger the meal, the more TLESRs occur. Equally, the greater the gastric secretory volume and the higher the intragastric osmolarity, the more TLESRs occur. So TSLERs can be considered protective against overfeeding by enhancing the “up-clearing” of the feeds. And it can also be hypothesized that part of the efficacy of proton pump inhibitors and H2 receptor antagonists is related to a decrease in gastric secretory volume independent of its pH. During sleep, normally no such transient relaxations of the lower esophageal sphincter occur.

All physiologic GER episodes are related to TLESRs, but in patients with severe reflux esophagitis, only 66% of the GER episodes occur in relation to a TLESR. In “chalasia” chronic relaxation of the lower esophageal sphincter occurs. In “achalasia,” a complete absence of TLESRs is seen. GER is related to reduced lower esophageal sphincter pressure, although not particularly in the resting state. Thus, it is not TLESRs that are pathologic per se, but the absence of a control mechanism over this phenomenon. Regurgitation can be considered a natural defense mechanism against overfeeding: when the stomach becomes too distended, TLESRs are induced more frequently, allowing food to flow back into the esophagus.

The major mechanism involved in pathologic GER are TLESRs. However, it is not clear if a decreased resting lower esophageal sphincter pressure should be considered a cause of or a result of GER. It may well be both.

ACHALASIA

Achalasia, which is a complex motor disorder of the entire esophagus, with primary and secondary motility abnormalities of the esophageal body (54), is characterized by a hypertonicity of the sphincter with lack of or incomplete relaxation (55). Achalasia is also associated with extra-esophageal autonomic nervous system dysfunction involving cardiovascular function and the regulation of mesenteric arterial blood flow (56). A lack of NO synthetase in the lower esophageal sphincter, cardia, and gastric fundus is involved in the pathophysiology of cardiac achalasia in children (57). In patients with achalasia, esophageal tonic activity is impaired (58).

INTRA-ABDOMINAL ESOPHAGUS (HIATUS HERNIA)

The crural diaphragm bolsters the lower esophageal sphincter during inspiration, straining, and so on. The intra-abdominal part of the esophagus is very short during
the first weeks of life. No data exist on the prevalence of hiatus hernia in children; in adults more than 50 years of age, however, the incidence is reported to be more than 50%. Only 9% of the adults with a hiatus hernia have complaints suggestive of GER pathology. However, 75% of adults with reflux esophagitis also have a hiatus hernia.

The incidence of reflux symptoms in a population with hiatus hernia is low, however, on the other hand, a high incidence of hiatus hernia occurs in adults with reflux symptoms. The reason for this seems to be that the length of the intra-abdominal esophagus is shortened or nonexistent in patients with a hiatus hernia. Thus, the lower esophageal sphincter region is located in the thorax, where it is exposed to a negative pressure and cannot function as a high pressure zone. As a result, gastric contents are aspirated back into the esophagus because of the pressure differences between the abdomen (positive pressure) and the thoracic cavity (negative pressure during inspiration). During the first year of life, the intra-abdominal esophagus is physiologically very short, which contributes to the increased incidence of regurgitation in this age group.

ANGLE OF INDENTATION

Normally, an acute angle is found between the greater curvature of the stomach and the esophagus. In some patients (e.g., those with a hiatus hernia), this angle is obtuse and favors GER episodes. The function of this acute angle is comparable with the function of a valve. It has been hypothesized that the angle is more obtuse in young infants, and only becomes acute after the age of 1 year.

GASTRIC VOLUME; GASTRIC EMPTYING

It is logical to relate gastric volume to the incidence of GER; if the stomach is empty, no material is available to reflux into the esophagus. Gastric electrical abnormalities underlying delayed gastric emptying have been documented in children with severe GER (59). To accommodate the intake of food or liquid, gastric reservoir functions—adaptive and receptive relaxations—are important reflexes (60). Adaptive relaxation is a reflex in which the fundus of the stomach dilates in response to small increases in intragastric pressure when food enters the stomach. Receptive relaxation is a reflex in which the gastric fundus dilates when food passes down the esophagus. Nitric oxide is involved in both pathways (60). Stretch of the gastric wall activates the mechanoreceptors in the gastric mucosa, inducing the release of NO which causes relaxation of the circular muscle and, thus, of the fundus. Receptive relaxation is mediated by vagal motor fibers. In contrast to the pressure-induced adaptive relaxation, ganglionic nicotinic transmission is essential in the vagally mediated receptive relaxation (60). Phasic relaxations of the lower esophageal sphincter are induced through afferent vagal pathways by stimulation of mechanoreceptors in the fundus of the stomach (61). Children with central nervous system disorders who vomit often have abnormal GER as abnormal gastric motility (62).
In neurologically normal children, gastric dysrhythmias can also play a major role in the pathogenic components of GER (63). Approximately 50% of adults with GER pathology have delayed gastric emptying. Children with untreated delayed gastric emptying have a doubling of reflux frequency (64). However, preoperative selection of these patients seems extremely difficult (65). The role of the vagal nerve endings in the esophagus could be involved in the mechanism: the esophageal nerve endings are very rapidly "irritated" once GER occurs, which increases the local tissue prostaglandin levels, whereas the irritated vagal nerve endings also cause pylorospasm. The NO donor nitroglycerin inhibits pyloric motility, alters the organization but not the number of antral pressure waves, and slows gastric emptying (50). Patients with GER and chronic respiratory disease or GER and failure to thrive present with delayed gastric emptying. The frequency of postprandial GER is related to meal size; gastric bolus feeding causes a greater intragastric pressure increase and more TLESRs. Increasing feed osmolality and volume slows gastric emptying and increases postprandial GER.

Mechanoreceptors are present in the fundus, near to the gastric part of the cardiac region. When these are stimulated because of gastric distension, they induce TLESRs.

GASTRIC ACID OUTPUT

"The more acid is produced, the more acid the gastroesophageal reflux" seems logical (33). Large variation is seen in the secretion of gastric acid during a 24-hour period, and this is regulated by the vagus nerve (66). The volume secreted may be more relevant than the pH; thus, proton pump inhibitors are very potent in the treatment of esophagitis despite the nocturnal breakthrough of acid secretion.

PEPSIN, TRYPsin, AND BILE SALTS

The noxious effect of pepsin on the esophageal mucosa is greater than that of acid (67). The effect of bile salts is influenced by the pH of the refluxed material: at acid pH, it is conjugated bile salts that are noxious, whereas at neutral pH it is deconjugated bile salts and trypsin that are noxious (68). Bile salts increase the permeability of the esophageal mucosa to acid (69). For this reason, "mixed" reflux (as occurs in regurgitation) may be more noxious to the mucosa than pure acid GER. Both endogenous and exogenous cholecystokinin decrease the lower esophageal sphincter pressure and increase the number of TLESRs (67). Cholestyramine increases gall bladder emptying and the number of TLESRs (67).

INTRA-ABDOMINAL PRESSURE

Intra-abdominal pressure is probably an important, although as yet little studied, mechanism favoring GER. In adults, 17% of the GER episodes are related to transient
FIG. 2. Vicious circles of reflux inducing reflux. GERD, gastroesophageal reflux disease; LES, lower esophageal sphincter.

increases in intra-abdominal pressure. The role of increased intra-abdominal pressure in children, as with constipation or a tight diaper, has not been evaluated.

**GER CAUSING GER**

An important mechanism favoring GER is GER itself, because of its effect on the esophageal mucosa, which causes a vicious cycle (Fig. 2): GER contains acid; as a result of the contact of the acid with the esophageal mucosa, regional blood flow increases, which also increases the local tissue content of PGE$_2$; prostaglandins increase the permeability of the mucosa to acid, which enhances the susceptibility of the mucosa to inflammation; inflammation of the mucosa of the lower part of the esophagus causes impairment of the lower esophageal sphincter (favoring GER), dysmotility of the lower esophageal sphincter (favoring GER), and finally esophagitis; NO aggravates the problem by delaying gastric emptying (49).

Contact of acid with the esophageal mucosa causes irritation, dysfunction, and inflammation of the local vagal nerve endings, impairing the lower esophageal sphincter and causing pylorospasm. Both phenomena favor GER. If the refluxed materials also contain bile, local edema and fibrosis presents in the mucosa.

**CONCLUSIONS**

Some individuals may be particularly susceptible to the development of pathologic GER for one or a combination of the following reasons: lack of mucus and bicarbonate secretion by surface epithelial cells; lack of defensive enhancement by prostaglan-
ESOPHAGEAL DYSFUNCTION

Din release; lack of an effective mucous cap after injury; and an apparent failure to heal erosions rapidly by epithelial restitution. A possible mechanism of GER is as follows. The initiating phenomenon may be delayed gastric emptying (e.g., because of overfeeding, overweight, or increased intra-abdominal pressure). Gastric distension then stimulates mechanoreceptors in the gastric wall near the cardia, which has vasovagal effects, resulting in abnormal neural control of the lower esophageal sphincter by the central nervous system. As a consequence, lower esophageal sphincter motility becomes defective, and TLESRs increase. This finally results in defective basal lower esophageal sphincter tone, favoring GER. In the presence of a hiatus hernia, GER will be further facilitated. Ineffective acid clearance (inadequate neutralization of the pH by saliva and inefficient volume clearance by poor motility) enhances the noxious effect of the refluxed material. Finally, poor mucosal resistance, which is partially genetically determined, contributes to the development of reflux esophagitis.

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**DISCUSSION**

*Dr. Zoppi:* In atrophic gastritis, is GER enhanced or diminished?

*Dr. Vandenplas:* I do not think we have any answers regarding the incidence of reflux.
What is probably different is the pH of the refluxed material. This has been seen in adults with *Helicobacter pylori* gastritis and atrophic gastritis: if the *H. pylori* is eradicated and the atrophy disappears, more esophagitis occurs. I think a relationship probably exists between acid secretion and esophagitis.

**Dr. Infante:** In my experience, we often see infants with symptoms that you describe as nonorganic failure to thrive. What kind of treatment do you think is indicated for these infants?

**Dr. Vandenplas:** We do not have any medical treatment at this moment for most of these children. Of course, an anatomic problem such as retrognathia has to be corrected surgically. For those in whom the problem is mainly functional, it seems to disappear after a while, usually about a year. These children may need tube feeding but later on they are able to eat normally. The mechanism is not yet understood, as far as I know.

**Dr. Milla:** I enjoyed your ideas about nociception in the esophagus. I think we all have patients with reflux who we treat with large doses of proton pump inhibitors because the primary complaint is pain. Yet, they steadfastly refuse to stop complaining of the pain. Do you have any insight into how we might deal with that? Should we be looking at their nociception pathways rather than their reflux and esophageal mucosa?

**Dr. Vandenplas:** We are going to start to try to do that. This is a provocative approach, but it should be explored. We all know of regurgitating babies without esophagitis who cry for hours, and it may be that this shows that the volume they regurgitate is painful for them. This is purely speculative.

**Dr. Buller:** We have taught for centuries that babies who regurgitate or vomit should be kept upright and held in that position for a long time. If I interpret your work correctly, you seem to be suggesting that we should not do that. We should put them down immediately because in the upright position transient lower esophageal sphincter relaxation is increased. Is that a fair conclusion?

**Dr. Vandenplas:** I do not think we have the answer to that. People hold infants upright after feeding because that decreases regurgitation, and milk is less frequently ejected from the mouth. But whether that has the same effect lower in the esophagus, I do not know. From the physiologic data, it seems likely that more transient relaxations occur in the upright position.

**Dr. Buller:** As a clinician, what would you advise me to do?

**Dr. Vandenplas:** It depends. If talking about a regurgitating baby, the regurgitation must be taken away. If referring to severe GER—a condition that occurs in a very small number of all regurgitating babies—then in these children it may be that they feel happier when they are lying down after a feed than being held upright. Mothers sometimes do tell you that. But systematic investigation is needed to provide an answer to this question.

**Dr. Jirapinyo:** I once did a study on gastric emptying in infants and was surprised to find that in some infants 20 or 30 minutes after the feed, the gastric volume increased to more than 100% of the milk that was taken in. We found that some infants had 130% of their intake in their stomachs at that time. So, I think the volume of secretions—probably from saliva but also from the stomach—may be a problem and cause pain to the infant, and also cause reflux.

**Dr. Vandenplas:** I agree that this may be one of the possible mechanisms of reflux. Gastric secretion is something we do not consider often enough in infants and children. However, if that viewpoint is taken, then medications (e.g., proton pump inhibitors) would be effective, because they greatly decrease the secretory volume. It would be too easy if only one mechanism was causing reflux or pain in the infant! Likely, a variety of mechanisms are operating, including combinations of the different factors that I discussed. Probably, we will end up
with different therapeutic approaches, because the pathophysiologic mechanism may be very different from patient to patient.

**Dr. Nairn:** My question is regarding sleep patterns in children in relationship to the risk of GER. As you mentioned, infants who show patterns of reduced swallowing and increased sleeping may be at higher risk of GER than others in that age group. It is a normal physiologic process for infants and children to sleep for relatively long periods, but if this normal sleep pattern increases the risk of esophagitis, how are we going to prevent or reduce the risk of GER in this age group?

**Dr. Vandenplas:** It is of course a normal part of life that infants sleep a lot, and it is normal that they sleep in the horizontal position. I would like to be provocative again. We all know that more cases of sudden infant death occur in the prone sleeping position than in the supine position. That is why it is now recommended that infants sleep supine. The arousal threshold in the prone sleeping position is much higher than in supine sleeping position, which means that infants sleeping prone tend to sleep more deeply. If that is translated to reflux, much more reflux occurs in the supine position than in prone position; because of the reflux, apneas and arousals ensue and no sudden infant death occurs. I believe these factors are related, although I am not saying the relationship is causal. However, it does offer another way of looking at the problem. We do not see much severe esophagitis in those young infants; all we see most of the time is a little redness in the distal esophagus. What that means is unclear.

**Dr. Black:** Your statement about the inverse relationship between reflux and sudden infant death syndrome is fairly provocative. Some physicians and pediatricians regularly prescribe antireflux formulas for infants. Are you suggesting that this may not be a good thing to do? If not, we should be very careful about what we prescribe and what we produce as manufacturers.

**Dr. Vandenplas:** I would not like to go that far. One important mistake is found in what you said: I do not consider those formulas to be antireflux formulas, but antiregurgitation formulas. They reduce the symptom of regurgitation but they have no influence on reflux whatsoever. The studies that have been done show that in nearly one third of patients reflux does improve; in one third, no difference is seen, and in one third the reflux worsens (1,2); thus, overall, no change is seen. If such infants do need help, however, then the most physiologic way to do so is probably with dietary treatment, which is better than medication. But the primary recommendation for regurgitating babies is to convince the parents that everything is OK.

**Dr. Brandtzaeg:** I just wonder if you would update me on Barrett’s esophagus. A discussion has occurred to whether these are hypogastric glands, ectopic glands, metaplastic glands, or whatever. Also, what is the relationship to reflux—do these hypoplastic glands affect the tendency to reflux? What is the chicken and what the egg in these cases?

**Dr. Vandenplas:** The only thing I can say about this is that the only patients in whom I still see Barrett’s esophagitis are neurologically impaired children. Those are the ones with the most severe reflux that has been present for the longest time. From a pediatric point of view, I think it is clear a relationship exists between the severity and duration of reflux, and whether the reflux has been treated, and the incidence of Barrett’s esophagitis. It is very rare in children and rather outside my area of interest, so I cannot say anything about the different kinds of glands.

**Dr. Brandtzaeg:** It is not so rare in adults. I am curious about the nature of these glands.

**Dr. Vandenplas:** I think Dr. Wright may have the answer.

**Dr. N. Wright:** Three hypotheses relate to the histogenesis of Barrett’s mucosa. The first one is that the cardiac mucosa extends into the esophagus. The second one is that stem cells...
at the bases of the esophageal rete pegs have the ability to differentiate into glandular epithelium. The third one is that they actually rise from the ducts of the esophageal glands, because when looking at the three-dimensional structure, particularly of regenerating mucosa after omeprazole, the squamous epithelium can be seen in juxtaposition to the esophageal glands. Barrett’s esophagus epithelium is not necessarily unstable until it undergoes metaplasia, and that metaplasia results in so-called specialized mucosa or type 2B, sulphomucin Muc-2, secreting epithelium. That is the epithelium that shows p53 mutations, loss of heterozygocity of APC, and gradually clonal expansion and dysplasia. In a nutshell, that is the histogenesis of Barrett’s esophagus.

**Dr. Goulet:** You pointed out many factors involved in gastric emptying, but what about intrathoracic pressure and the relationship between ventilatory function and esophageal function? In clinical practice, a clear relationship is seen between GER and bronchopulmonary disease. Have you a view on this, and also on the value of investigating upper esophageal sphincter function?

**Dr. Vandenplas:** Regarding respiratory disease, it has been shown that in chronic bronchopulmonary disease giving oxygen by continuous positive airway pressure (CPAP) to those children decreases GER. So, just by changing pressures in the thorax, the reflux is treated. It has also been shown that in infants with wheezing, the greater the respiratory problem and the more negative the intrathoracic pressure, the higher the intra-abdominal pressure becomes and the more the patient will aspirate what is in the stomach.

Investigation of the upper esophageal sphincter is an area on which we need to focus in the coming years. The lower sphincter has been very well studied, but the upper sphincter probably also plays a major role. For instance, it may be that in children with pathologic apneas related to reflux, the response of the upper esophageal sphincter is different from normal. It is difficult to investigate but it needs to be done.

**Dr. Fyderek:** Would you give us your opinion on the role of alkaline reflux in gastroesophageal reflex disease, and what is the best method to investigate this?

**Dr. Vandenplas:** A really a good method is not currently available to investigate alkaline reflux. At least two pH probes are needed and the pH has to be clearly shown rising first in the lower pH probe and then in the higher probe. In theory, this is nice, but when attempting to do it in practice, it is very hard—if not impossible—to demonstrate the phenomenon in a large series of children. I do not know how common it is because it is so difficult to investigate. The question to be answered is whether duodenogastric reflux is an important factor in GER; large amounts of bile are needed in the stomach to neutralize gastric acidity, so even with acid reflux bile can be present in the refluxate. The question of the role of bile reflux is a difficult one, because we have no way of clearly demonstrating the presence of bile in the refluxate, and that is what is of principal interest.

**Dr. Fyderek:** What about the Biletech method?

**Dr. Vandenplas:** I have never used it and I do not know many people who have. Those who did use it do not use it any more as far as I know. Maybe that answers your question.

**Dr. Maki:** Do we have any solid long-term data on reflux disease in infancy? What do we know about its natural history and the consequence of treatment?

**Dr. Vandenplas:** I have no idea. The problem is that long-term follow-up studies of 40 to 50 years, at least, are needed. These have not been done and, in practice, it would be very difficult to do so. The only information I have about this is in relationship to North African immigrant families in western Europe. A lot of these families are seen now and, in this population, we hardly ever see esophageal stenosis in childhood as a complication of GER.
In North Africa, however, they still see a lot of it in children of the same genetic background. This is not evidence that early treatment improves later outcome, but it is suggestive.

*Dr. Steenhout:* I like the concept of an initiating stimulus in the upper part of the esophagus. What might be the role of food at this level? Do you think a food additive or colorant, for example, could trigger the release of a hormone such as substance P, or is this purely a mechanical mechanism?

*Dr. Vandenplas:* That it is a very good question. We really do not know how relevant factors such as substance P are. Studies clearly show that these factors change in concentration, depending on the circumstances, but what initiates those changes and how important they are in clinical practice is unknown as yet.

*Dr. Seidman:* A provocative Italian study (3) suggested that regurgitation caused by reflux can be distinguished from regurgitation caused by cow's milk protein allergy in infants with challenge-proved protein allergy on the basis of their pH probe pattern: the infants proved to have allergy had a progressive and prolonged decrease in esophageal pH after a feed, as opposed to the frequent short-term changes in pH in benign reflux. I would appreciate your comments on that study.

*Dr. Vandenplas:* We were unable to reproduce that. The diagnosis of cow's milk protein allergy is not one that should be made by pH monitoring—challenge tests are needed, which is the only way to diagnose it properly. That reflux should be related to cow's milk protein allergy is logical, because here something is being ingested which is not tolerated and must be gotten rid of. But, on that basis, a lot of short reflux episodes should be expected that provoke vomiting to get rid of what is not being tolerated, rather than prolonged reflux episodes.

**REFERENCES**