INTRODUCTION

Gastroesophageal reflux disease (GERD) is the most common esophageal disorder in children of all ages. Gastroesophageal reflux (GER) signifies the retrograde movement of gastric contents across the lower esophageal sphincter into the esophagus. Although occasional episodes of reflux are physiologic, the phenomenon becomes pathologic (GERD) in children who have episodes that are more frequent or persistent, and thus produce esophagitis or esophageal symptoms, or in those who have respiratory sequelae ***(Behrman et al., 2004)***.

It has been proposed that GER occurs mainly because of weak steady state lower esophageal sphincter pressure, which allows the sphincter to be overcome easily by spikes of increased intragastric pressure ***(Hebra and Hoffman, 1993)***. Recently reported, a prevalent mechanism of pathologic reflux is the presence of inappropriate transient lower esophageal sphincter relaxations ***(Hassal, 2005)***.

Children with certain underlying disorders are at the greatest risk for severe GERD. These include those with neurological impairment, those with repaired esophageal atresia or congenital diaphragmatic hernia, and those with chronic lung disease. Severe GERD may also occur in otherwise healthy children, especially those with a hiatus hernia, or perhaps acid hypersecretion. For GERD that is

severe and/or chronic, the major treatment options are medical treatment with proton pump inhibitors or antireflux surgery ***(Hassal, 2005)***.

Surgical intervention for childhood GERD was not generally considered until the 1950s because the experience with antireflux operations in children was limited and because medical antireflux therapy was felt to be uniformly successful. Since then however, more infants and children with GERD have been identified as having complications severe enough to warrant an antireflux operation. The major complications of childhood GERD that may require surgical intervention include recurrent regurgitation of feedings with or without growth retardation, intractable pain or irritability associated with esophageal mucosal injury, esophageal stricture or columnar cell-lined (Barrett) esophagus, and life-threatening respiratory symptoms ***(Jolley, 2003)***.

Nissen fundoplication is the most common surgical procedure for children with pathological GER. Although its efficacy has been established by clinical picture, endoscopic findings, and by esophageal pH monitoring ***(Turnage et al., 1989)***, yet the mechanism underlying its antireflux effect is not well investigated ***(Mittal, 1994)***.

Although Nissen fundoplication has greater than 90% success in eliminating reflux symptoms, over time, a

proportion of patients develop new or recurrent foregut symptoms. Dysphagia, gas bloating, and mild residual esophagitis are common symptoms in the early postoperative period, but these symptoms generally resolve within 3 months; severe or persistent symptoms may indicate failure and the need for further investigation ***(Minijarez and Jobe, 2006)***.

Evidence-based clinical practice guidelines for pediatric GERD review a number of management alternatives for children with GERD, including lifestyle changes, pharmacotherapeutic agents, and surgical procedures. However, these guidelines also recommend that outcome studies be performed in children with GERD, and in particular those undergoing antireflux surgery ***(Rudolph et al., 2001)***.

AIM OF THE WORK

This thesis aimed to study the antireflux mechanism of Nissen fundoplication by examining its effect on the motor patterns of the lower esophageal sphincter in children with gastroesophageal reflux disease.

GROSS ANATOMY

From mouth to stomach, the food conduit consists of the oral cavity, pharynx, and esophagus. The esophagus serves as a dynamic tube, pushing food toward the stomach, where digestion and absorption can take place. Mucus produced by the esophageal mucosa provides lubrication and eases the passage of food. Active peristaltic contractions propel residual material from the esophagus into the stomach. During vomiting and reflux, the esophagus also serves as a passageway for gastrointestinal contents traveling retrograde from the stomach or small intestine ***(Kuo & Urma, 2006)***.

The esophagus connects the pharynx to the stomach. Beginning in the neck, at the pharyngo-esophageal junction (C5-6 vertebral interspace at the inferior border of the cricoid cartilage), the esophagus descends anterior to the vertebral column through the superior and posterior mediastinum. After traversing the diaphragm at the diaphragmatic hiatus (T10 vertebral level), the esophagus extends through the gastroesophageal (GE) junction to end at the orifice of the cardia of the stomach (T11 vertebral level) ***(Kuo & Urma, 2006)***.

Topographically, there are three distinct regions: *cervical*, *thoracic*, and *abdominal*:

- *The cervical esophagus* extends from the pharyngo-esophageal junction to the suprasternal notch. At this level, the esophagus is bordered anteriorly by the trachea, posteriorly by the vertebral column, and laterally by the carotid sheaths and the thyroid gland.

- *The thoracic esophagus* extends from the suprasternal notch to the diaphragmatic hiatus, passing posterior to the trachea, the tracheal bifurcation, and the left main stem bronchus. The esophagus lies posterior and to the right of the aortic arch at the T4 vertebral level. From the level of T8 until the diaphragmatic hiatus the esophagus lies anteriorly to the aorta.

- *The abdominal esophagus* extends from the diaphragmatic hiatus to the orifice of the cardia of the stomach. Forming a truncated cone, about 1 cm long, the base of the esophagus transitions smoothly into the cardiac orifice of the stomach. The abdominal esophagus lies in the esophageal groove on the posterior surface of the left lobe of the liver ***(Kuo & Urma, 2006)***.

Functionally, the esophagus extends from the lower border of the upper esophageal sphincter (UES) to the lower border of the lower esophageal sphincter (LES).

Thus, although the UES is not a part of the esophagus, the LES is an integral part of it ***(Mashimo & Goyal, 2006)***.

Blood Supply

The rich arterial supply of the esophagus is segmental (Figure 1). The branches of the inferior thyroid artery provide arterial blood supply to the upper esophageal sphincter and cervical esophagus. The paired aortic esophageal arteries or terminal branches of bronchial arteries supply the thoracic esophagus. The left gastric artery and a branch of the left phrenic artery supply the LES and the most distal segment of the esophagus. The arteries supplying the esophagus end in an extensive, dense network in the submucosa. The copious blood supply and network of potentially anastomotic vessels may explain the rarity of the esophageal infarction ***(Kuo & Urma, 2006)***.

The venous supply is also segmental (Figure 2). From the dense submucosal plexus the venous blood drains into the superior vena cava. The veins of the proximal and distal esophagus drain into the azygous system. Collaterals of the left gastric vein, a branch of the portal vein, receive venous drainage from the mid-esophagus ***(Kuo & Urma, 2006)***.

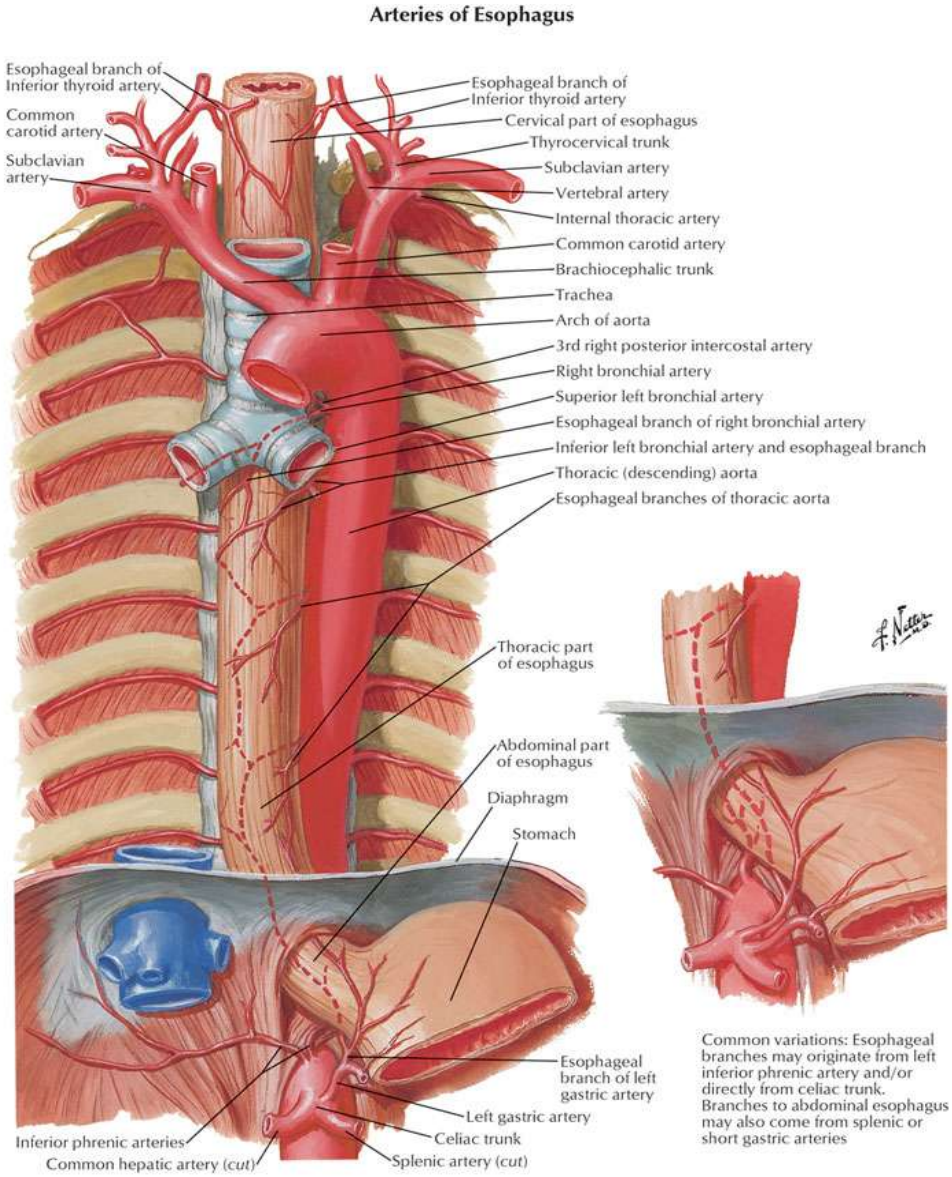

Figure (1): Arterial blood supply of the esophagus (*Source:* Netter medical illustration with permission from Elsevier. All rights reserved).

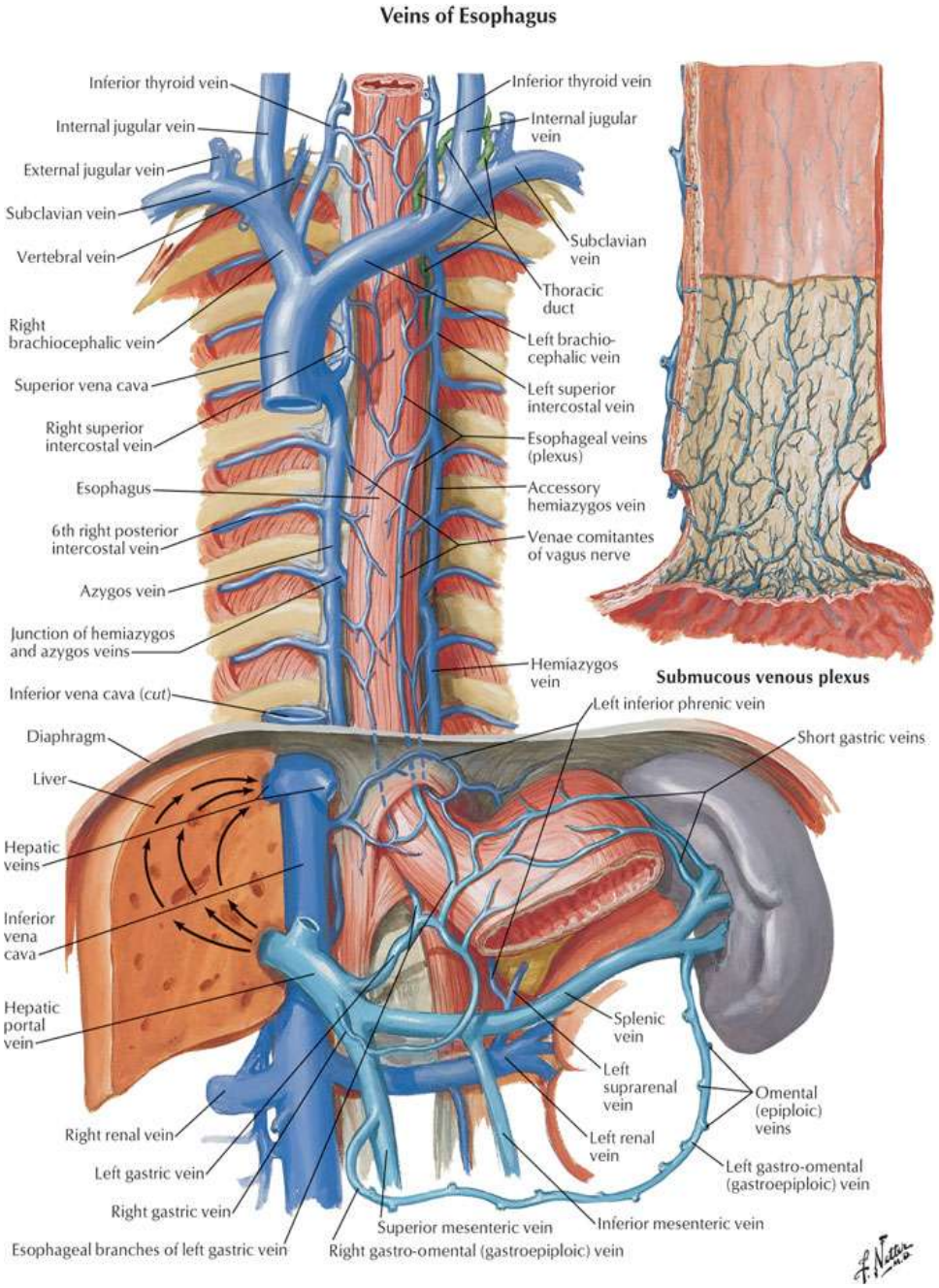

Figure (2): Venous drainage of the esophagus. (*Source:* Netter medical illustration with permission from Elsevier. All rights reserved.)

Innervation

The esophagus, like the rest of the viscera, receives dual sensory innervation, traditionally referred to as parasympathetic and sympathetic, but more properly (based on the actual nerves), vagal, and spinal ***(Goyal & Sivarao, 1999)*** (Figure 3).

The vagal afferents compose 80% of the vagal trunk and have cell bodies in the nodose ganglia and project to the nucleus solitarius. Vagal afferents merging from the esophageal smooth *muscle* layer are sensitive to mechanical distention, whereas polymodal (responding to multiple modalities of stimuli) vagal afferents with receptive fields in the *mucosa* are sensitive to various osmo-, chemo-, thermo-, and mechanical intraluminal stimuli ***(Fass, 2004)***. In general, vagal afferents do not play a direct role in visceral pain transmission, but through mechanoreceptors, vagal afferents transduce pressure into painful sensations ***(Goyal & Sivarao, 1999)***.

The spinal afferents have their cell bodies in the dorsal root ganglia and terminate in the spinal column and in the nucleus gracilis and cuneatus in the brainstem. From there, they project, through the thalamus, to primary sensory and insular cortical areas ***(Aziz & Thompson, 1998)***. The spinal afferents merging from nerve endings in the *muscle* layer and serosa act as nociceptors for perception of discomfort and

pain and are mechanosensitive ***(Mayer & Gebhart, 1994)***. The spinal afferents merging from *intraepithelial* nerve endings are involved in mediating acid-induced pain during topical exposure to intraluminal acid ***(Fass et al., 1998)***. Many of the spinal afferents contain calcitonin gene-related peptide and substance P, which are neurotransmitters that are important in mediating visceral nociception ***(Fass, 2004)***.

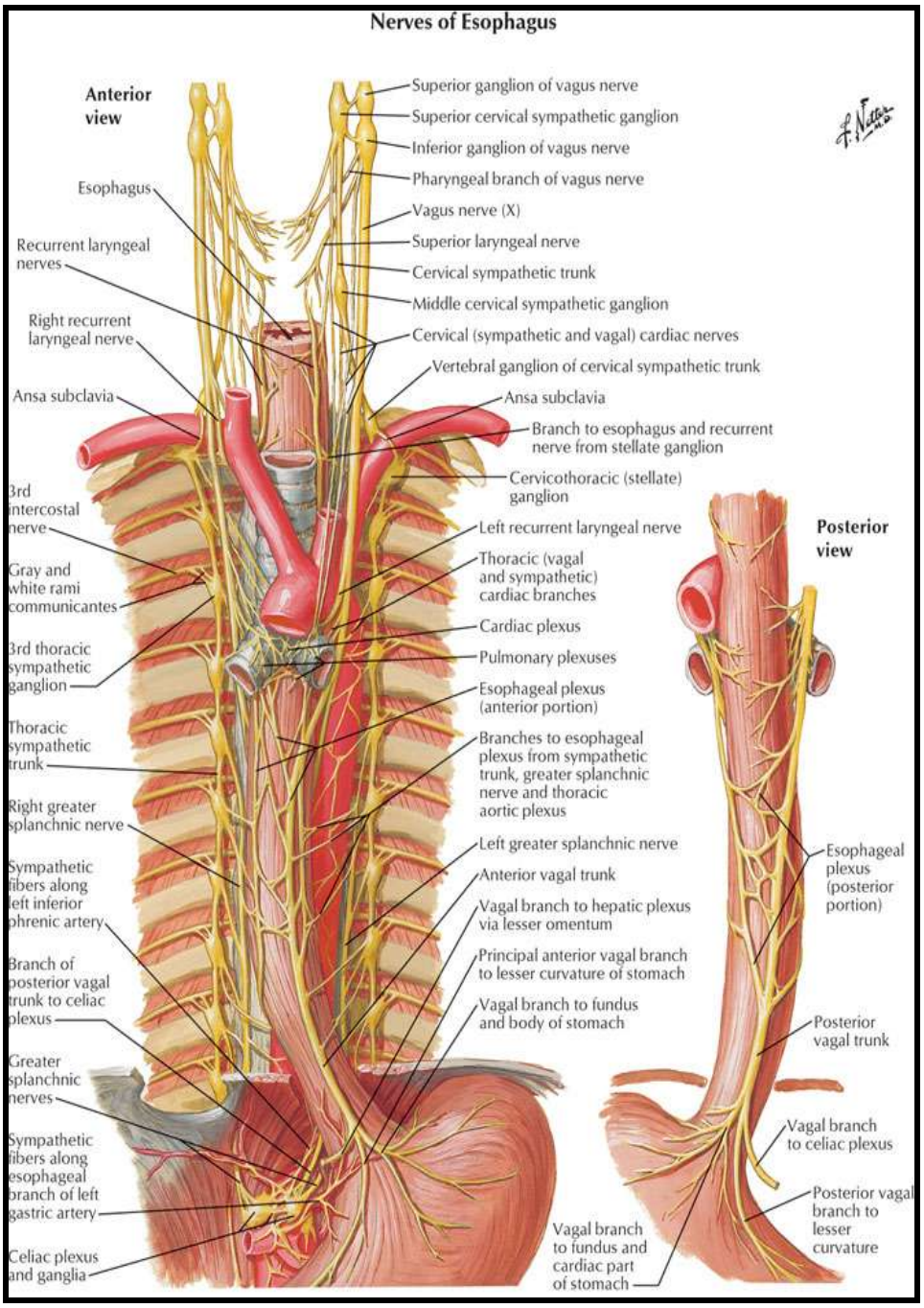

Figure (3): Parasympathetic and sympathetic innervation of the esophagus (*Source:* Netter medical illustration with permission from Elsevier. All rights reserved.)

The motor innervation of the esophagus is predominantly via the *vagus* nerve. The cell bodies of the vagal efferent fibres innervating the UES and the proximal striated muscle esophagus arise in the nucleus ambiguus, whereas fibres destined for the distal smooth-muscle segment and the LES originate in the dorsal motor nucleus of the vagus nerve ***(Kuo & Urma, 2006)***.

The esophagus receives parasympathetic and sympathetic innervation that regulates glandular secretion, blood vessel caliber, and the activity of striated and smooth muscle. The parasympathetic nerve supply comes from the nucleus ambiguus and dorsal motor nucleus of the vagus nerve and provides motor innervation to the esophageal muscular coat and secretomotor innervation to the glands. The sympathetic nerve supply comes from the cervical and the thoracic sympathetic chain (spinal segments T1–T10) and regulates blood vessel constriction, esophageal sphincters contractions, relaxation of the muscular wall, and increases in glandular and peristaltic activity ***(Kuo & Urma, 2006)***.

The thin nerve fibers and numerous ganglia of the intramural myenteric and the submucosal plexi provide the intrinsic innervation of the esophagus. The ganglia that lie between the longitudinal and the circular layers of the tunica muscularis form the myenteric or *Auerbach's plexus*, whereas those that lie in the submucosa form the submucous or *Meissner's plexus*. Auerbach's plexus

regulates contraction of the outer muscle layers, whereas Meissner's plexus regulates secretion and the peristaltic contractions of the muscularis mucosa. The ganglia of the myenteric plexus are more numerous in the smooth muscled esophagus than in the striated muscle esophagus ***(Christensen et al., 1984)***. In the smooth muscled esophagus, the neurons of the myenteric plexus are relay neurons between the vagus and the smooth muscle. In the striated muscle the role of the neurons of the myenteric plexus is largely unknown ***(Aziz et al., 1994)***.

Positron emission tomography (PET) and functional magnetic resonance imaging (MRI) have been used to map the central nervous system projections from the esophagus. Regions that are activated by esophageal stimulation include secondary sensory and motor cortex, parieto-occipital cortex, anterior and posterior cingulated cortex, prefrontal cortex, and the insula ***(Kern et al., 1998)***.

Lymphatic drainage

Lymphatic drainage of the esophagus consists of two systems: the lymph channels and lymph nodules (Figure 4).

The lymph channels begin in the esophageal tissue spaces, namely mucosa & submucosa, as a network of endothelial channels (20–30 microns) or as blind endothelial sacculations (40–60 microns) ***(Long & Orlando, 2002)***. Lymph capillaries drain into collecting lymph channels

(100–200 microns) that continue through the esophageal muscular coat and are distributed parallel to the long axis of the esophagus. Paired semilunar valves within the collecting channels determine the direction of flow. The collecting lymph channels merge into small trunks that open into the regional lymph nodes ***(Kuo & Urma, 2006)***.

As with esophageal innervation, the lymphatic drainage of the esophagus differs in the striated and smooth muscle regions. The lymphatics from the proximal third of the esophagus drain into the *deep cervical* lymph nodes, and subsequently into the thoracic duct. The lymphatics from the middle third of esophagus drain into the *superior* and *posterior mediastinal* nodes, and also to the thoracic duct. Lymphatics of the distal third of the esophageal follow the left gastric artery to the *gastric* and *celiac* lymph nodes. There are considerable interconnections among these three drainage regions primarily owing to the dual embryologic origin of lymphatic pathways from branchiogenic and body mesenchyme ***(Long & Orlando, 2002)***.