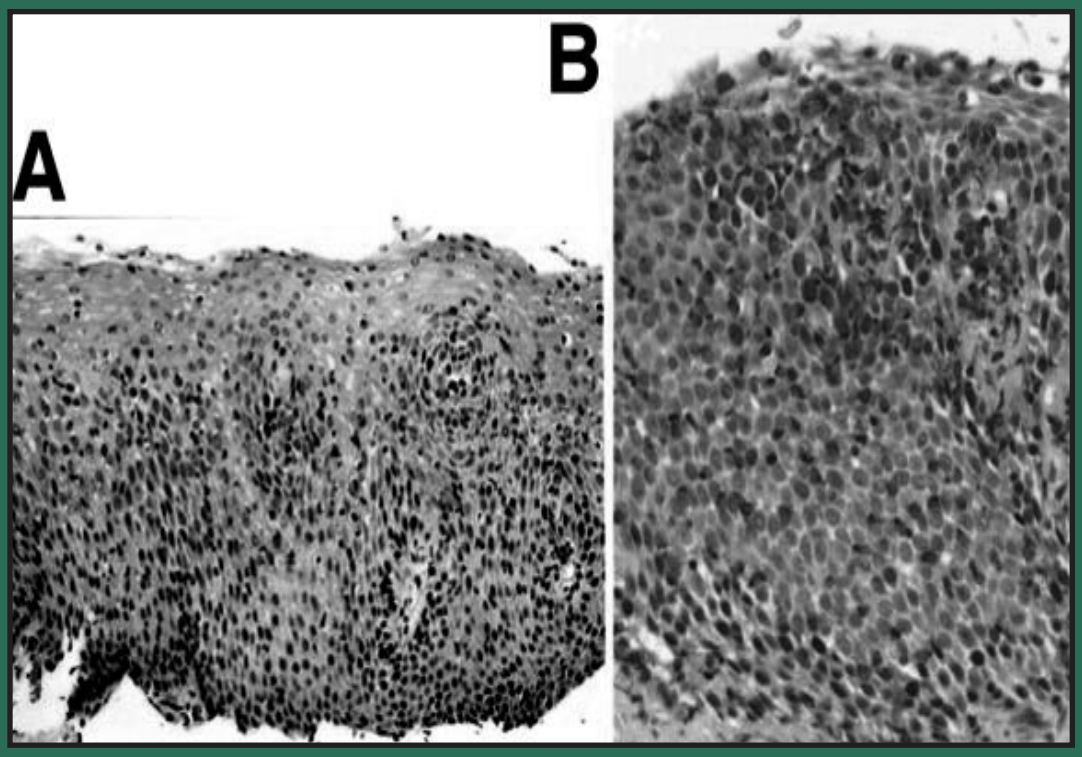

Low (A) and high (B) power microscopic views of the esophageal epithelium in eosinophilic esophagitis, showing distinctive features of this condition, such as increased numbers of immune cells called eosinophils.

Image courtesy of Dr. Glenn Furuta. Reprinted from Gastroenterology, *133, Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, Bonis P, Hassall E, Straumann A, Rothenberg ME. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment, pp. 1342-1363, Copyright 2007, with permission from Elsevier.*

Diseases of the Oropharynx and Esophagus

SUMMARY OF RESEARCH GOALS

Because normal functioning of the oropharynx and esophagus can be compromised by a wide spectrum of diseases, the Commission suggests a number of research goals that address the diverse etiologies and potential treatments for these disorders. Research to understand the neuromuscular biology of the oropharynx and esophagus is critical to developing therapies for conditions like swallowing disorders brought on by stroke, premature birth, non-erosive reflux disease (NERD), and other motility disorders that affect this portion of the gastrointestinal (GI) tract. Similarly, more studies are needed to identify better therapeutic targets for gastroesophageal reflux disease (GERD), among the most common diagnoses for a digestive disorder in the U.S. GERD is also associated with increased risk for Barrett's esophagus and esophageal cancer. Thus, research is needed to uncover the risk factors and mechanisms of disease progression in order to develop more effective prevention and treatment strategies. The emergence of eosinophilic esophagitis and other inflammatory diseases of the esophagus over the last decade highlights the need for research to define the clinical course of these poorly understood diseases and design rational therapies to reverse them. Progress toward these research goals will help to reduce the significant economic toll that these diseases, particularly GERD, take on individuals and the U.S. healthcare system.

INTRODUCTION AND BACKGROUND

The oropharynx and the esophagus can be considered the gateways to the GI tract and, as such, are critical for the digestive processes that follow. Although the two components of the oropharynx (i.e., mouth and pharynx) are relatively distinct anatomically, the oropharynx is usually considered as a unitary functional entity from a gastroenterological perspective, with its overarching purpose being to facilitate safe passage of the ingested bolus of food across the opening to the airways and into the esophagus proper. In accordance with this function, this region is under tight control of the central nervous system (CNS); its nerves and muscles are, therefore, its most critical components, with even subtle dysfunction resulting in considerable morbidity. It is not surprising, therefore, that cerebrovascular accidents (strokes) and subsequent uncoordinated nerve activity account for the vast majority of functional disturbances in this region, with only a minority related to other structural lesions. This is a huge problem: nearly 700,000 strokes per year occur in the U.S. alone, with the incidence of post-stroke dysphagia (difficulty in swallowing) ranging from 37-45 percent, even with cursory screening techniques, and as high as 64-78 percent with formal instrumental testing. Dysphagia not only leads to impairment in food intake, but also puts these patients at a 3-fold or higher risk for pneumonia. Disturbances in oropharyngeal function are also common in the elderly, perhaps independently of overt lesions in the CNS. Swallowing disorders have been reported in 30-40 percent of nursing home residents and 6.9 percent of the surveyed general population. The importance of an abnormal swallowing mechanism in the elderly is reflected by the high incidence of aspiration pneumonia in autopsy studies. A majority of patients with swallowing dysfunction will, therefore, require rehabilitation therapy.

The oropharyngeal musculature is striated, signifying its close control by cranial nerves. This pattern continues for the proximal one-third of the esophagus, after which it is replaced by smooth muscle, which is more characteristic of the rest of the GI tract and indicative of the greater influence of the intrinsic nerve cells found in the wall itself (i.e., the enteric nervous system). Despite its deceptively simple tubular form, the esophagus is in fact a complex organ. Like much of the GI tract, it is organized cross-sectionally into several concentric layers: the epithelium (which is squamous in nature, similar to the skin), the submucosa, and two principal muscle layers, with the myenteric plexus sandwiched in between. In addition, it receives extensive innervation from the vagal (cranial) and spinal nerves. Any one of these components or layers can be the primary or secondary site of a variety of diseases.

The heterogeneous nature of these organs makes them vulnerable to a considerable variety of pathologic processes and a correspondingly broad clinical spectrum that affects patients across all demographic categories. This chapter focuses on some of the diseases in these organs that have large impacts, as defined either by their socioeconomic effects or by the burden of suffering they impose on individual patients. Perhaps the most well-known and most common of these syndromes is GERD, commonly referred to as "heartburn." GERD is common worldwide, but is particularly prevalent in developed countries. The prevalence of heartburn (with or without acid regurgitation) at least once a week ranged from 14-29 percent in the U.S. population and did not differ between Blacks and Whites in a survey from Houston. In a 2004 report, GERD was the leading physician diagnosis for GI disorders, accounting for almost 7 million outpatient clinic visits. This imposes a severe economic cost, estimated to be over $11 billion in 2004. Much of this cost is related

to medications, particularly proton pump inhibitors (PPIs), for which nearly 8 million prescriptions were written per month in 2004—a number that represents more than a doubling compared to the previous 5 years. Beyond economic considerations, the most sinister health threat represented by GERD is the elevated risk for adenocarcinoma of the esophagus. The incidence of esophageal adenocarcinoma has grown dramatically in recent years, and many experts link it to the rise in GERD in the general population. This is based on the current paradigm that chronic GERD leads to Barrett's esophagus, a change in the epithelial lining of the esophagus from a squamous to an intestinal type. In some patients, such a change is associated with dysplasia, an abnormality in the appearance of the lining cells that indicates their instability and tendency to progress to cancer, which occurs in about 0.5 percent of cases per year. Disorders affecting other parts of the body have also been ascribed to GERD, including asthma, dental problems, and ear, nose, and throat disturbances (e.g., erosions, laryngitis, hoarseness, and even laryngeal cancer), but in many cases actual causality has been difficult to establish.

Another common form of esophageal cancer is squamous cell cancer, which arises at a location higher up in the esophagus and is strongly associated with smoking and alcohol intake. GERD does not appear to be a risk factor for this cancer. Unlike Barrett's esophagus, which is predominantly a disease of white males, squamous cell cancer affects African Americans disproportionately, with an incidence that is several times greater, although the incidence appears to be declining.

Another major class of disorders that affects the esophagus arises from disturbances of motility—the coordinated action of nerves and muscles that produces effective propulsion. These disorders include relatively rare conditions, such as achalasia with an incidence of approximately 1 in 100,000 per year, which are nevertheless important because of their chronic and lifelong nature. Other disorders may perhaps be more common, but are less well defined clinically and pathophysiologically. In addition, severe GERD is often associated with significant motility abnormalities of the esophagus, either as a cause or effect, and these may lead to symptoms by themselves in some patients. Abnormal esophageal motility is a consequence of some systemic disorders, notably diabetes and scleroderma or related connective tissue syndromes. Particularly in the latter, an incompetent sphincter and impaired esophageal acid clearance can lead to devastating reflux with serious consequences, such as stricture formation.

Neural changes can not only produce motility disturbances in the esophagus, but can also lead to sensory abnormalities and a hypersensitive esophagus that may account for a significant number of patients with non-cardiac chest pain. This syndrome probably results from multiple etiologies with prominent psychosocial components, akin to what has been described for other painful functional GI disorders, such as functional dyspepsia and irritable bowel syndrome. "Chest pain, not otherwise specified" is the most common inpatient GI diagnosis, with over 320,000 hospital discharges in a recent year.

Esophageal diseases affect children as well as adults. "Reflux" is extremely common in neonates and can assume pathologic proportions requiring treatment in a subset of infants. Such children are more likely to have GERD when they grow up. However, there is a paucity of good data on effective treatment in this age group. Swallowing dysfunction resulting in oral aversion, dysphagia, and regurgitation are also very common problems in neonatal and pediatric intensive care units, often associated with prematurity

and oral/pharyngeal trauma from medical devices such as endotracheal and feeding tubes. Currently, inadequate information is available on the normal development of swallowing function, the mechanisms responsible for its perturbation, and effective means to prevent and treat the same. Finally, a recently described syndrome, eosinophilic esophagitis, has been increasingly recognized in both children and adults. This condition is characterized by esophageal inflammation and infiltration by eosinophils, which are white blood cells that typically are associated with allergies and some infections. Symptoms of eosinophilic esophagitis include vomiting, abdominal pain, poor growth, difficulty with swallowing, and food impaction. This condition is often misdiagnosed as GERD. Although the underlying etiology of eosinophilic esophagitis is often unidentified, foodborne and airborne allergens have been frequently implicated. Currently, effective treatments are limited to steroids and diet restriction.

Finally, a variety of infections can afflict the esophagus, with the most common being fungal (e.g., candida) or viral (e.g., cytomegalovirus or herpes simplex virus); these are typically seen in patients with compromised immune systems, such as those with HIV-AIDS. With modern therapeutic regimens, such cases are becoming less common.

RECENT RESEARCH ADVANCES

Oropharyngeal physiology and pathophysiology

A major advance has been the systematic evaluation of the biomechanical aspects of swallowing function. In addition, recent studies have addressed the effect of bolus volume, consistency, and temperature on the swallowing apparatus. A better understanding of the biomechanical aspect of swallowing has resulted in renewed interest in devising rehabilitative approaches to swallowing disorders. Such an approach would benefit an overwhelming majority of patients with swallowing disorders. The availability of functional imaging should provide a powerful tool for manipulation of brain centers involved in swallowing to either induce or speed recovery.

Gastroesophageal reflux disease

Considerable insight has been obtained into the pathways of acid-induced injury to the esophagus. Luminal acid and pepsin initially damage the esophageal epithelium by attacking the apical junctional complex (APJ), a group of structures that control the permeability of ions and aqueous molecules passing through the intercellular space. The consequence of this is a "leaky" epithelium with dilated intercellular spaces, the latter a clinically identifiable hallmark of early acid injury to the tissue. In turn, protons and other noxious factors (e.g., pepsin) gain access to subepithelial structures, such as nerves and muscle, with several potential consequences. Neural stimulation may result in initiation and/or amplification of inflammation and generate symptoms of heartburn and chest pain. An attractive candidate for mediating these effects of protons is the vanilloid receptor, TRPV1, which is expressed by nociceptive neurons and responds to noxious stimuli, such as acid and heat. Acute, acid-induced esophagitis is reduced in animals lacking TRPV1, suggesting that refluxed acid may induce inflammation through TRPV1, possibly via neurogenic mechanisms. Muscle-produced inflammatory products may also cause dysfunction; for example, in esophageal circular muscle, production of cytokines, hydrogen peroxide, platelet-activating factor, and prostaglandin E2 results in inhibition of acetylcholine release from cholinergic motor neurons without affecting the integrity of the contractile mechanisms.

Thus, in addition to epithelial injury and symptom generation, acid reflux can alter esophageal neuromuscular function in several ways, perpetuating the process by decreasing lower esophageal sphincter (LES) tone and impairing peristalsis and acid clearance. Further, esophageal longitudinal smooth muscle function may also be affected and can contribute to both reflux and delayed clearance by creating a spatial separation of the LES and diaphragm. From the perspective of the mechanics of the esophagogastric junction (EGJ), axial motion attributable to longitudinal muscle contraction is key to the normal opening mechanism, and disordered EGJ mobility and compliance may play a role in the pathogenesis of reflux. Prolonged contraction of this muscular layer may also contribute to generation of symptoms.

Another advance in this area has been the elucidation of the neurophysiology and neuropharmacology of transient LES relaxations, a major mechanism of reflux. This has raised the prospect of mechanistically directed therapy using agents such as the GABAB agonist baclofen in treating symptomatic reflux.

Progress has also been made in understanding and managing childhood GERD, symptoms of which are reported in 8.2 percent of children ages 10-17 years. As in adults, a variety of non-esophageal symptoms have been associated with childhood GERD, including asthma, hoarseness, cough, sinusitis, and otitis media (ear infection). Natural history studies show that while symptoms improve, histopathology may remain abnormal. Initial studies show an excellent safety profile for PPI use in children, although infectious gastroenteritis and pneumonia may be more common among children using PPIs.

Finally, there has been significant clinical research, including randomized, controlled trials, on the safety and efficacy of emerging endoscopic, anti-reflux procedures, as well as surgical procedures, such as prosthetic reinforcement of the hiatus in the repair of giant hiatal hernias.

Barrett's esophagus

Barrett's esophagus can be reversed in some, but not all, patients with endoscopic treatments that either ablate or mucosally resect the epithelium. The neosquamous epithelium may have less malignant potential than the Barrett's-affected tissue it replaces. The ability to effect reversion in the mucosa suggests that there is an underlying "stem" cell, which can either revert to the normal pathway of differentiation to a stratified squamous epithelium or continue to differentiate down the specialized intestinal metaplastic pathway. Continued development of these treatments could result in the ability to prevent the progression of Barrett's esophagus to cancer and may improve healthcare utilization by decreasing expenditures on surveillance endoscopy.

Changes in gene expression likely precede the development of histologic Barrett's esophagus. For instance, the expression of a homeobox gene, *CDX2*, in esophageal epithelium leads to metaplasia and may be an early marker for Barrett's esophagus. Also, epigenetic alterations may be instrumental in the development of malignancy. Hypermethylation of the promoter regions of various tumor suppressor genes are associated with increasing degrees of dysplasia.

The demographic, anthropometric, and symptom-based risk factors for Barrett's esophagus have been better elucidated. Despite reports of the association of Barrett's esophagus with chronic heartburn symptoms, data suggest that Barrett's esophagus is relatively common regardless of whether a patient has a history of heartburn. In fact,

a substantial proportion of patients with adenocarcinoma of the esophagus have no prior symptoms of heartburn. Obesity appears to be a risk factor for Barrett's esophagus and, for any given body mass index, subjects with visceral adiposity may be at higher risk than those with higher hip to waist ratios. Multiple trophic hormones are elevated in subjects with central adiposity, which may explain the increased risk of metaplasia in this group. Preliminary data have been reported showing the influence of heritability on the development of Barrett's esophagus.

A number of novel, high-resolution imaging techniques show promise in identifying high-grade dysplasia and early cancers in Barrett's esophagus patients with moderate sensitivity and specificity. To date, these "optical biopsy" methods do not demonstrate the ability to survey large areas of Barrett's esophagus.

Eosinophilic esophagitis

Eosinophilic esophagitis is an immune-mediated inflammatory disorder that is often triggered in atopic individuals by food products or inhaled allergens. It is characterized by infiltration of the esophageal wall, including the epithelium, with mast cells and eosinophils. Clinically, the inflammatory response by mast cells and eosinophils within the esophagus results in symptoms of chest pain, heartburn, and dysphagia—the latter due either to peristaltic dysfunction or to mechanical narrowing of the lumen by a dense fibrotic reaction within the wall. Notably, infiltration of the esophagus by eosinophils has been shown to result from the release of eotaxin-3 and IL-4, IL-5, and IL-13 by squamous epithelial cells. This observation provides molecular targets for potential treatments for the condition. For instance, intravenous antibodies to IL-5 can reduce both blood and esophageal eosinophilia and improve the quality of life in patients with eosinophilic esophagitis. In 2006, a novel translational study identified the key role of eotaxin-3 in eosinophilic esophagitis. Utilizing a combination of microarray techniques, *in vivo* and *in vitro* studies, eotaxin-3 was shown to be significantly up-regulated compared to controls. Further studies showed mutation of this gene in affected patients, and basic analysis confirmed a significant role in this inflammatory process. In addition to potential molecular targets for treatment, these data add to the growing body of knowledge of the central role of the esophageal epithelium in generation of the inflammatory/allergic cascade that ultimately translates into the clinical manifestations of the disease.

Esophageal motility and "functional" disorders

The pathophysiology of achalasia has been reasonably well characterized and appears to result from a relatively selective loss of nitrergic (inhibitory) neurons supplying the muscle of the LES. However, the etiology of this process remains unknown, although there is growing evidence for a possible autoimmune process associated with antibodies directed against neuronal elements. There have been some advances in the treatment of this disorder. Botulinum toxin injections have been shown to be effective in relieving symptoms in this condition and, although the benefit is short-lived, they are valuable alternatives in patients who are not fit for more invasive forms of therapy. Pneumatic dilation has been shown to be of limited efficacy in younger patients, in whom laparoscopic myotomy appears to be the best option. This surgical approach results in less morbidity and earlier post-operative recovery than traditional, open myotomy. The demonstration that neural stem cells can be injected into the GI tract and result in recovery of nitrergic function raises hope for a true cure for this condition.

The recognition of esophageal hypersensitivity and, in particular, emerging concepts of post-inflammatory neuronal sensitization have been important in understanding the spectrum of pathophysiologic events that lead to esophageal symptom generation in patients. This includes non-cardiac chest pain and "emerging" syndromes, such as NERD.

GOALS FOR RESEARCH [14]

Research Goal 7.1: Understand the neurobiology of oropharyngeal structure and function in health and disease.

Identifying novel molecular, physiologic, and anatomic targets within the oropharynx will accelerate the development of more effective treatments and/or functional rehabilitation of stroke-induced swallowing dysfunction, a major cause of morbidity, particularly in the elderly. Similarly, understanding the processes involved in the development of swallowing function and the mechanisms by which these processes are disturbed in the neonate is very important. Currently, our approach to these problems is empirical and palliative at best, with little ability to prevent permanent disability.

In addition, this region is vulnerable to the effects of gastroesophageal reflux with consequences that potentially affect the airways in the form of laryngitis and asthma. Much needs to be learned about the pathogenesis and treatment of these problems.

Objectives:

- Develop useful animal models of oropharyngeal swallowing disorders to facilitate neuropathologic studies of central and peripheral components and evaluate the effects of interventions directed at specific molecular and/or cellular targets.
- Conduct clinical studies of recovery and plasticity with creative use of functional imaging and novel interventional techniques.
- Understand physiologic and pathologic communication between the functional components of the aerodigestive tract.
- Understand the effects of gastroesophageal reflux on the airways, including the larynx and bronchi.
- Define the effects of sleep abnormalities on upper GI tract physiology.

Research Goal 7.2: Understand the clinico-pathologic mechanisms leading to and/or associated with GERD and identify novel molecular, physiologic, and anatomic targets for more effective and rational treatment.

Although effective in the majority of patients, acid suppression is an indirect method for the treatment of GERD and its complications. Further, treatment is indefinite in duration because of the chronic nature of the disorder. Developing more effective treatments, whether they are pharmacological, endoscopic, or surgical in nature, requires a better understanding of the underlying mechanisms.

Objectives:

- Understand the clinical spectrum, outcomes, and natural history of childhood reflux and its relationship/evolution into adult patterns of disease.

[14] *Research Goals are numbered for ease of reference only; the numbers do not indicate prioritization of scientific topics.*

- Validate and develop more effective and/or less invasive long-term approaches to GERD and identify more precisely the clinical, anatomic, and/or functional predictors of response.
- Understand the biologic basis of gastroesophageal reflux, hiatal hernia, and GERD-associated esophageal dysmotility, including the role of biomechanical factors and longitudinal muscle.

Research Goal 7.3: Define the mechanisms responsible for esophageal injury and repair, with particular emphasis on the interactions among components of the esophageal wall.

Acute and chronic inflammation of the esophagus can lead to serious complications, such as strictures, dysmotility, and pre-malignant or malignant transformation. Esophagitis results from a complex interaction between the inciting factor and the tissue response, which involves many diverse cell types, some of which are harmful and others perhaps beneficial. A full understanding of these pathways will pave the way for more effective methods for treatment and prevention of many esophageal disorders.

Objectives:

- Elucidate mechanisms of increased permeability in the esophageal epithelium.
- Understand the role of neural and muscular elements in modulation or enhancement of esophageal injury.
- Characterize acute and chronic mechanisms responsible for esophageal epithelial squamous cell repair.
- Determine the role of foodborne, airborne, and other environmental allergens in promoting eosinophilic esophagitis and the underlying mechanisms.
- Define basic pathogenic mechanisms by which eosinophils mediate esophageal dysfunction.

Research Goal 7.4: Understand the epidemiology, natural history, and outcomes of eosinophilic esophagitis and identify targets for more rational and effective therapy.

Eosinophilic esophagitis is rapidly emerging as a significant health problem in children and adults. Since it has only been formally recognized in the last decade or so, very little is known about this disease, and much research is needed to answer fundamental questions relating to clinical course and treatment.

Objectives:

- Determine risk factors, natural history, and outcomes of patients with eosinophilic esophagitis and identify biomarkers for disease activity and progression.
- Identify novel targets and interventions for more effective and rational therapeutic approaches to eosinophilic esophagitis and other inflammatory disorders of the esophagus.

Research Goal 7.5: Understand the etiopathogenesis of Barrett's esophagus, determine risk factors associated with its progression, and identify novel targets and/or therapies for chemoprevention and treatment.

Despite several decades of research on Barrett's esophagus, this disorder continues to be a major clinical challenge. Although it is strongly associated with GERD, little is known about the biologic mechanisms by which chronic reflux leads to transformation of the esophageal lining or the particular genetic or acquired factors that predispose a given patient with reflux to this complication.

Objectives:

- Understand the initiation of Barrett's esophagus, with particular emphasis on identifying the putative stem cell involved and studying its biology.

GOALS FOR RESEARCH

- Define the contribution and etiopathogenic role of environmental (e.g., smoking) and genetic/familial factors in the development of Barrett's esophagus.
- Develop biomarkers that reliably predict dysplastic and neoplastic progression.
- Identify novel molecular targets for pharmacological approaches to restoring a stable epithelial phenotype in patients with Barrett's esophagus.
- Conduct chemoprevention studies in subjects with Barrett's based on molecular pathways identified through ongoing studies on human tissue and animal models.
- Develop better and more cost-effective tools for screening and surveillance.

Research Goal 7.6: Understand the etiology and biology of esophageal neuromuscular function in health and disease and develop more effective treatments.

Esophageal dysmotility can be primary in origin or result from several systemic diseases, such as diabetes or connective tissue disorders. In most cases, the pathologic mechanisms responsible for esophageal dysfunction remain largely unknown, leading to therapies that are generally ineffective and palliative at best. Similarly, although chest pain or discomfort of putative esophageal origin is a major drain on healthcare resources, little is known about its underlying neurobiology or potential targets for treatment.

Objectives:

- Understand the neurobiology of normal and abnormal esophageal sensation and identify novel molecular targets for more effective and rational treatment of esophageal hypersensitivity associated with disorders such as non-cardiac chest pain and NERD.
- Understand the etiopathogenesis, genetic predisposition, and risk factors for esophageal motility and functional disorders, including the roles of autoimmunity, environmental factors (e.g., viruses), relationship to GERD, genetic factors, and molecular candidates (e.g., ALADIN).
- Identify novel therapeutic targets for pharmacological, cellular (e.g., stem cell treatment), and physical (e.g., endoscopic) approaches for more effective and rational treatment for esophageal motility disorders.

MAJOR CHALLENGES AND STEPS TO ACHIEVE THE RESEARCH GOALS

Animal models: Many, if not most, disorders of the oropharynx and esophagus lack complete understanding in terms of the underlying pathobiology. This is true even of common problems, such as GERD, and is due in part to a lack of convenient and valid experimental models.

Standards for diagnosis: Challenges in less common or emerging disorders, such as esophageal dysmotility syndromes, eosinophilic esophagitis, and even Barrett's esophagus, include the small number of patients seen by any one center, the absence of uniform diagnostic criteria, the lack of generally available and reliable methods for physiologic testing, and the inaccessibility of tissue for histopathologic correlation. Further, because of variations in practice management, a true epidemiological and clinical picture of these disorders has been difficult to obtain. Such information is necessary for planning studies to elucidate pathogenic mechanisms and improve on current therapeutic strategies.

Interdisciplinary research: A major challenge affecting some disorders in this group is the lack of cross-fertilization among disciplines. This issue is best exemplified by swallowing disorders secondary to CNS pathology, an area that seems

to have "fallen through the cracks" between the neuroscience and GI specialties. In contrast to other areas of CNS, research progress in the neurobiology and pathology of the "swallowing center" and related structures has lagged. Similarly, although emerging disorders, such as eosinophilic esophagitis, initially present to gastroenterologists, research progress in understanding these conditions may require the scientific input of specialists in immunology and allergy.

Disease definitions: In diseases like Barrett's esophagus, enormous variability in disease definitions and histologic grading can be found in the literature. Even among expert centers, one group's low-grade dysplasia is another's non-dysplastic disease. A multinational consensus conference to arrive at standardized disease definitions would strengthen the field.

Validation of novel interventions: Another barrier to the advancement of knowledge in this area is that novel imaging and therapeutic techniques are disseminated prior to rigorous, multicenter testing by conflict-free groups. The result is that multiple "infant" strategies are being developed, with no effort to grade the relative value of the interventions, leading to wasted effort and unnecessary costs, as well as suboptimal patient outcomes. Direct marketing to community gastroenterologists and surgeons is occurring before rigorous testing. Emphasizing rigorous testing of this technology as part of a Request for Applications may improve this situation. Finally, in this context, it is important to point out that past attempts at limiting cancer in the setting of Barrett's esophagus have focused on subjects with chronic GERD symptoms. Increasing evidence suggests that such an approach is, at best, incomplete and flawed and, at worst, largely ineffective and cost-inefficient.

National research resources: The establishment of multicenter consortia with the ability to build large databases and patient registries would promote progress in several ways. Such resources would enable researchers to make a population-based determination of the incidence of these disorders, their etiologies, and risk factors. Researchers could also analyze the natural history of disease, including timing of onset, progression, prognosis, quality of life, cost, and healthcare utilization, and collect annotated tissue and serum specimens to study molecular and cellular mechanisms, as well as to illuminate genetic and environmental influences. Collaborative trial groups that bring together experts from relevant disciplines (e.g., immunology, oncology, and surgery) would be able to validate clinical protocols for the diagnosis and management of these patients and conduct trials of chemopreventive and therapeutic strategies. Multicenter studies could be more effective than single-site trials, which are often restricted by insufficient patient numbers.

Advanced technology: Much progress in this area could be made through technological breakthroughs, and such research and development efforts should be actively encouraged. Examples include endoscopic access for obtaining tissue samples from deeper layers of the esophagus, better physiologic tests, and less invasive and more effective anatomic and physiologic approaches to treatment. Although there is significant overlap between esophageal motility disorders and their counterparts in the rest of the GI tract, the esophagus, because of its limited length and easy access, can be viewed as a model to test hypotheses of a more general nature. An example would include the phenomenon of visceral hypersensitivity, the study of which has best been conducted in the esophagus. Similarly, if a stem cell approach will work at all, it is best tested in the esophagus, which offers a relatively easy site for local (endoscopic) delivery.