

2015 David Y. Graham Lecture: The First Two Decades Of Eosinophilic Esophagitis—From Acid Reflux To Food Allergy

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Collaborative efforts by pediatric and adult gastroenterologists, allergists, dieticians, and pathologists have brought about marked progress in the recognition, understanding, and management of eosinophilic esophagitis (EoE) over the past two decades. Once an esoteric diagnosis, EoE is now increasingly identified as a major cause of morbidity, afflicting both children and adults. The detection of mucosal eosinophils has evolved from a diagnostic feature of acid reflux to a biomarker of food sensitization of the esophagus. Translational studies and murine models have elucidated Th-2 immune pathways in EoE, inspiring the development of targeted biologic therapeutics. At the same time, validation of patient-reported outcomes and endoscopic end points has facilitated the implementation of clinical trials of novel therapeutics. Ongoing investigations have elucidated the importance of “looking beneath the surface” of the epithelium, focusing greater attention on the impact of esophageal remodeling in the clinical consequences of EoE. Elimination diets continue to gain popularity as an intriguing, highly effective, and non-pharmacologic therapy that lends credence to the concept that EoE is a food-driven, immunologic disorder.

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INTRODUCTION: EOSINOPHILIC ESOPHAGITIS: FROM ESOTERICA TO COMMON CONUNDRUM

Eosinophilic esophagitis (EoE) is a relatively recently described disease that relates esophageal symptoms to chronic, eosinophil-predominant inflammation of the esophagus (1). Prior to 1993, EoE had been described in only a handful of case reports and was considered an esoteric entity that a gastroenterologist would likely never encounter (**Figure 1**). The disorder was largely neglected from the curriculum of esophageal diseases and not entertained in the differential diagnosis of dysphagia. Moreover, studies from the 1970s and 1980s had identified the presence of esophageal eosinophils as a biomarker of gastroesophageal reflux disease (GERD) (2,3). The paradigm was based on the demonstration of an association between the presence of esophageal intraepithelial eosinophils and delayed acid clearance on pH testing in a small cohort of children. Of note, the degree of eosinophilia was quite mild (<2 eos/h.p.f.) in the majority of these pediatric cases. In the early 1990s, two groups of investigators independently reported a series of young adult, mostly male, patients with dysphagia and marked esophageal eosinophilia in the absence of clinical evidence of GERD (4,5). As with many important discoveries, the significance of these reports was underappreciated for several years. In fact,

almost a decade later, the tenet associating esophageal eosinophils with GERD was cited as evidence for GERD as the etiology in one of the earliest descriptions of the ringed esophagus in a series of adults with dysphagia and marked esophageal eosinophilia (6).

From 1995 to 2005, both clinical studies and the recognition of EoE increased substantially, largely driven by a handful of dedicated pediatric gastroenterologists and allergists in the United States and an adult gastroenterologist in Switzerland (7). Population-based studies from both countries identified a marked rise in the prevalence of EoE in children and adults. Increased awareness and identification of EoE was greatly facilitated by the publication of diagnostic criteria and consensus recommendations in 2007 (1). Although much of the exponential rise in prevalence has been attributed to increased appreciation of a previously unrecognized condition, studies correcting for increased utilization of endoscopy and biopsies, as well as a review of archived pathology samples, indicated an underlying true increase in disease incidence. The reasons for this rise, although poorly understood, fit well with the worldwide emergence of allergic disease over the past several decades. EoE has now been recognized on every continent, with the exception of sub-Saharan Africa. The prevalence appears highest in Western Europe, Australia, and the United States (8).

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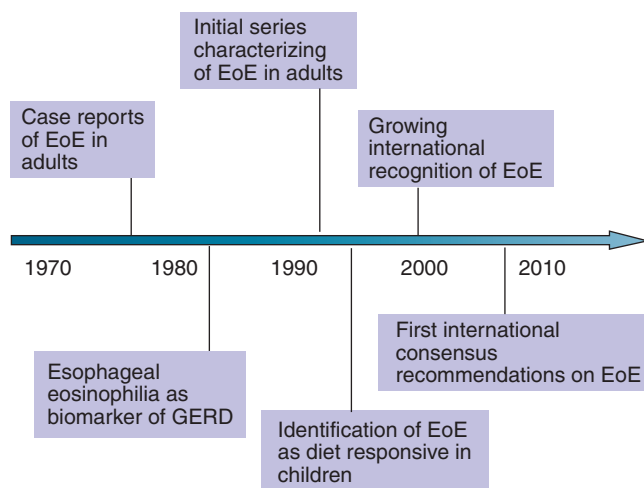


Figure 1. Brief history of the emergence of eosinophilic esophagitis over the past two decades.

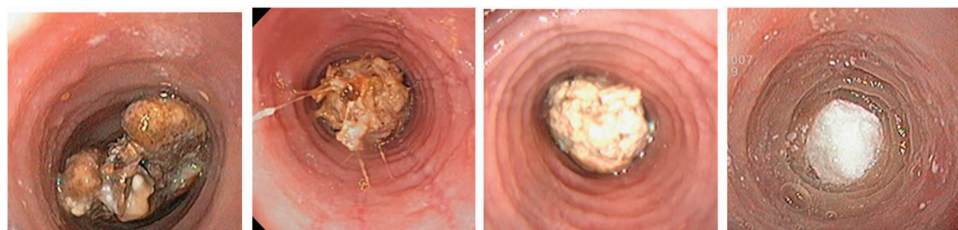


Figure 2. Food impaction is a common consequence of eosinophilic esophagitis that brings patients to medical attention. From left to right, retained substances are a pecan, a piece of beef, a piece of chicken, and a pill. In each case, endoscopic features of remodeling in the form of rings and stricture are evident.

The paucity of cases from Asia, particularly from Japan and Korea, stands out as an intriguing epidemiology aspect of the disease, considering the widespread use of endoscopy and putative environmental influences attributable to the hygiene hypothesis in developed regions of Asia. Current population estimates in the United States were examined in a health insurance database study based on ICD-9 coding for the diagnosis of EoE (530.13) that went into effect in 2008 (8). The prevalence was estimated at 57 cases per 100,000, with most patients being males clustering in the ages between 20 and 50 years. EoE is now recognized as the second leading cause of dysphagia among adults and a leading cause of food impaction in both children and adults (9) (**Figure 2**). The rising prevalence will certainly transition EoE to surpass its current designation as an orphan disease. Clearly, EoE has “come of age” and is now included in textbooks of gastroenterology and internal medicine, as well as medical school curricula.

CLINICAL FEATURES OF EOE: MORE THAN JUST COUNTING EOSINOPHILS

The clinical features of EoE in adults are well recognized by gastroenterologists, allergists, and a growing number of primary care and emergency room physicians (10). The primary symptoms

bringing adult patients to medical attention are dysphagia and food impaction, although secondary symptoms of heartburn and atypical “non-cardiac” type chest pain are also reported. Affected children have a somewhat distinct clinical presentation with symptoms of nausea, vomiting, abdominal pain, food aversion, and growth failure. Interestingly, the presentation shifts to dysphagia in adolescents with EoE. The apparent phenotypic transition from childhood to adult likely results from a combination of improved symptom reporting and progression of remodeling consequences of chronic inflammation (11). In spite of the improved detection of EoE by clinicians, a diagnostic delay of several years remains typical. Contributing to the delayed recognition is the gradual progressive of disease severity over time (i.e., it can take years for a stricture to manifest), as well as coping behaviors adopted by patients to compensate for esophageal dysfunction (e.g., chewing carefully, prolonged meal times, increasing liquid intake during meals). The recent validation of the EoE Activity Index (EEsAI) attempts to account for coping strategies through the use of a visual dysphagia score that queries adaptive behaviors for specific food consistencies (12). The presence of atopy increases the clinicians’ suspicion for EoE, as about 70% of children and adults with EoE have asthma, allergic rhinitis, and/or atopic dermatitis (1).

Histologic features of EoE are important to review not only because histology is critical to the diagnosis but also because of the recognition that features beyond the numerical density of eosinophils may be important aspects of disease activity. Although most clinicians focus on the eosinophil density (eosinophils per high-power field or eos/h.p.f.), other common abnormalities include eosinophilic microabscess formation, surface distribution of eosinophils toward the esophageal lumen, evidence of eosinophil degranulation, and subepithelial fibrosis. Additional features of basal cell hyperplasia, papillary elongation, and dilatation of intercellular spaces are very common but shared with the histopathology of GERD. Interestingly, dilatation of intercellular spaces is getting increased attention in terms of its potential role in the pathogenesis of EoE. Dilatation of intercellular spaces may be an inciting event that allows for antigen penetration through the epithelial barrier for presentation to esophageal dendritic cells (13). Furthermore, the detection of esophageal permeability using esophageal mucosal impedance has been recently examined as a diagnostic test for EoE (14).

The increased practice of obtaining esophageal biopsies in patients with unexplained dysphagia and children with refractory GERD has certainly increased the detection of EoE. Similar to celiac disease and microscopic colitis, the mucosal inflammation in EoE is patchy. Multiple (2–4) biopsies of both the proximal and distal esophagus are recommended to maximize the demonstration of mucosal eosinophilia based on studies examining the predictive value of biopsy sampling. The clinical utility of obtaining these biopsies in separate containers (i.e., proximal, mid and distal bottles) has not been established but sometimes viewed by pathologists as a means of distinguishing GERD (distal predominant inflammation) from EoE (diffuse inflammation).

Recognition of characteristic endoscopic features of EoE has been another significant aspect of the increased disease recognition by gastroenterologists. These features have been adopted into a classification and a grading system known as the EoE Endoscopic Reference Score (EREFS) (15). The EREFS conveniently serves as an acronym for five of the major, endoscopically identified, esophageal features including “Edema” (loss of vascular markings), “Rings” (trachealization), “Exudates” (white plaques), “Furrows” (vertical lines), and “Stricture”. Additional features of mucosal fragility (“crepe paper esophagus”) and narrow caliber esophagus were not included in the EREFS because of very low detection rate and the absence of defined criteria, respectively. The EREFS provides uniform nomenclature for describing the presence and severity of esophageal abnormalities with reasonable inter- and intra-observer agreement based on US and European studies. Importantly, endoscopic severity as measured by the EREFS is a major determinant of physician assessment of overall EoE disease severity (16). EREFS severity has also been associated with food impaction outcomes, as well as symptom severity utilizing validated patient-reported outcome instruments. Of note, these clinical outcomes have shown limited correlation with histologic severity determined by eosinophil density (17). Following the trend in endoscopic mucosal healing as a primary outcome for clinical trials in inflammatory bowel disease, “seeing is believing”.

Improvement in endoscopic features adds credence to the benefits of therapies in EoE that substantiate the current reliance on symptom and histologic measures of disease activity.

PATHOGENESIS OF EOE: FROM ACID REFLUX TO FOOD ALLERGY

Growing evidence supports a dominant role for food sensitization or allergy in EoE. The first study to speculate on the role of food allergy in EoE came from a publication by allergists at Johns Hopkins in 1995, only a few years after the initial characterization of EoE (18). In this landmark study, 10 children with marked esophageal eosinophilia were identified. The children were assumed to have GERD, as eosinophils were considered a highly specific diagnostic feature of acid-related disease at the time. The children, however, failed to respond to acid suppression and/or fundoplication. Following initiation of an elemental diet, symptoms diminished or resolved in all of the patients and recurred with reintroduction of table foods. Moreover, the degree of esophageal eosinophilia substantially improved following the diet. As the elemental formula substitutes amino acids for protein, the study supported the concept that EoE was driven by ingested protein as occurs with other forms of food allergy. This initial observation has been substantiated in further, mostly pediatric, studies reporting an overall over 90% histologic remission rate in hundreds of treated patients with EoE.

Important experimental support for an allergic pathogenesis in EoE comes from the demonstration of a unique gene-expression profile of both upregulated and downregulated genes in EoE. These studies identified eotaxin-3 as the most highly induced gene in EoE and upregulation of a distinct Th-2 and mast cell signature (19). Mechanistic studies using immunohistochemistry and *in vitro* assays have confirmed the increased expression of Th-2 and allergic mediators in EoE. Murine models have induced esophageal eosinophilia upon allergen exposure. Recent GWAS studies have identified a series of candidate gene associations in EoE including thymic stromal lymphopoietin, CAPN14, and XKR6 (20,21). TSLP is noteworthy given earlier studies linking the cytokine to the pathogenesis of both asthma and atopic dermatitis. Indirect epidemiologic clues supporting the concept of EoE as a form of “asthma of the esophagus” come from the high prevalence of atopy among EoE patients and reports of seasonal variation in EoE incidence. Further supporting this concept are studies that identified a subset of EoE patients with increased expression of IL-23, associated with a Th-17 immune response previously linked to the pathogenesis of asthma (22). Therapeutic studies demonstrating the response of EoE to topical steroids, targeted elimination diets, and biologic therapies directed against allergic pathways (anti-IL-5, anti-IL-13) lend further credence to allergic underpinnings of EoE. Finally, although eosinophils are the dominant and most readily identified inflammatory cellular infiltrate, mast cells, basophils, and lymphocytes have important roles in disease pathogenesis that are being increasingly investigated (19,23).

As the presence of esophageal eosinophilic inflammation has evolved from a diagnostic feature of acid reflux to a biomarker of

allergic food reactivity of the esophagus, a commonly asked question is “What accounts for this increase in allergy over the past several decades?” The hygiene hypothesis has had the greatest traction in the search for an environmental cause of increased allergic disease. This concept causally links the rise in allergic disease with the decline in infectious pathogens. An intriguing study identified a significant reduction in *Helicobacter pylori* infection in patients with esophageal eosinophilia (24). Prior studies had identified a similar inverse association between *H. pylori* and asthma, allergic rhinitis, and atopic dermatitis. Although not directly implicating *H. pylori* eradication with the rise in EoE, *H. pylori* may be a marker of the decline in chronic infections in the population, thereby supporting the hygiene hypothesis for EoE. Several ongoing studies examining the role of the microbiome in EoE should further elucidate this fascinating concept.

PPI-RESPONSIVE ESOPHAGEAL EOSINOPHILIA: THERE AND BACK AGAIN?

The controversy surrounding the differentiation of GERD from EoE is better appreciated given the historical context whereby esophageal eosinophilia was initially equated with GERD (2,3,25). Early adult series posited “allergic” EoE as distinct from GERD (3). Substantial overlap in the clinical presentation of the two entities in children, however, is more difficult to tease apart than in adults. A histologic response to proton-pump inhibitor (PPI) therapy was proposed as a diagnostic means to distinguish esophageal eosinophilia related to acid from allergic mechanisms. Recent descriptions, however, of a significant subset (25–50%) of pediatric and adult patients with symptomatic, endoscopic, and histologic findings of EoE that resolved with PPI therapy created both surprise and confusion (2,25). Studies now indicate that patients with PPI-responsive esophageal eosinophilia more closely resemble EoE than GERD from a clinical, genetic, and immunologic perspective. The benefits of PPI therapy in EoE may be due to repair of mucosal permeability defects or direct anti-inflammatory effects. Current views indicate that responsiveness to PPI therapy should not be utilized to rule out EoE (2,3,25). Instead, PPI therapy should be viewed as an effective, safe, and practical initial step in the management of patients with esophageal eosinophilia (2,25). Ongoing studies elucidating the mechanism behind PPI-responsive esophageal eosinophilia will improve our understanding and management of EoE.

COMPLICATIONS OF EOE: IMPORTANCE OF SUBEPITHELIAL REMODELING

A fundamental goal of the therapy of EoE is not only to ameliorate symptoms but also contend with complications that include food impaction, esophageal stricture, esophageal perforation, and malnutrition. Quality of life is another aspect of disease that is adversely affected in both children and adults. Fortunately, to date, progression to generalized eosinophilic gastroenteritis, hyper eosinophilic syndromes, or esophageal cancer has not been reported in EoE. Strictures, on the other hand, are quite

common in EoE and can occur at variable sites along the esophagus. Narrow caliber esophagus with reduced esophageal diameters involving the majority of the esophageal body is a manifestation that is challenging to remedy.

The primary complications of EoE arise as a consequence of esophageal remodeling in the setting of chronic inflammation (11,26). Reduced esophageal caliber is attributable to both inflammation as well as fibrosis. The most consistently identified predictor of risk of stenosis in EoE is duration of disease. In a retrospective study, over 60% of patients with disease duration of over 10 years had clinically significant esophageal strictures (27). Esophageal subepithelial fibrosis and epithelial mesenchymal transition are integral to this remodeling process. The consequence of esophageal remodeling can be demonstrated in patients during endoscopy utilizing the functional luminal imaging probe (Crospon, Galway, Ireland). This catheter-based technique provides quantitative readouts regarding the physical properties of the esophageal wall including muscle function and distensibility. Measurements of esophageal distensibility have been shown to correlate with clinically relevant outcomes of food impaction (17). Additional studies using endoluminal ultrasonography have demonstrated significant expansion of the mucosa, submucosa, and muscularis propria in EoE. Practically speaking, standard esophageal mucosal biopsies may only be “scratching the surface”, as the remodeling in EoE appears to extend beneath the epithelial space.

TREATMENT OF EOE: IS DIET THERAPY A PRACTICAL ALTERNATIVE?

A remarkable amount of progress has been made over the past 20 years in the therapy of EoE. Although no medical therapies have yet been approved by the FDA for the indication of EoE, a number of effective options are available for the management of EoE (10). Esophageal dilation was the first therapy used in adults with EoE but became unpopular because of early reports of perforations in small case series. Subsequent large series have demonstrated both therapeutic effectiveness at alleviating dysphagia, as well as safety of dilation, with reported perforation rates approximating that for benign stricture dilation of any cause (28). Esophageal dilation, however, does not arrest the chronic inflammation in EoE.

Topical corticosteroids have remained a first-line therapeutic option since their initial description. Eight randomized, double blind, placebo-controlled trials have demonstrated significant and consistent reductions in esophageal eosinophilia in the majority of EoE patients. Symptom improvement, on the other hand, has been a more difficult and heterogeneous end point. This difficulty has been attributed to the previous lack of a validated instrument for measurement of symptoms in EoE, as well as a high placebo-response attributed to the ability of patients to minimize dysphagia through changes in food texture selection and eating behavior. The ability of topical steroids to reverse esophageal fibrostenosis also likely contributes to the symptom-pathology dissociation. The most frequently reported side effect of topical steroids has been esophageal Candidiasis but is seldom apparent symptomatically.

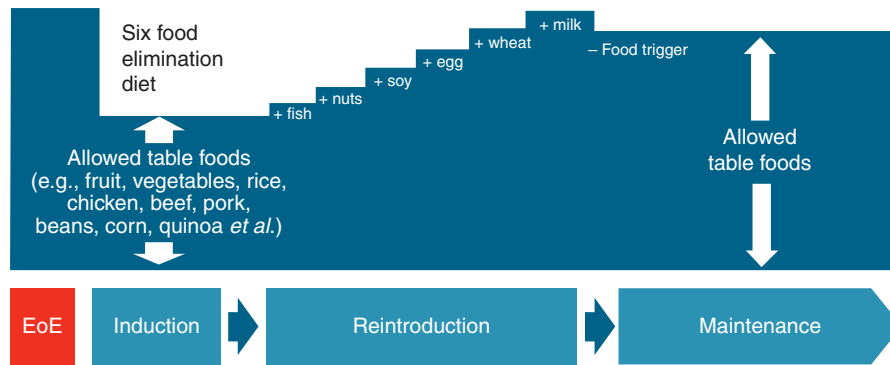


Figure 3. Three phases of the six food-elimination diet (SFED) protocol. From an initial, baseline diet inclusive of all table foods, the six most common food allergens are removed from the patient's diet (induction phase). After documentation of histologic remission, food groups are selectively reintroduced to identify specific food triggers with histologic monitoring of disease activity (reintroduction phase). Once food triggers have been found, the patient resumes a table food diet with elimination of only trigger food(s) (maintenance phase).

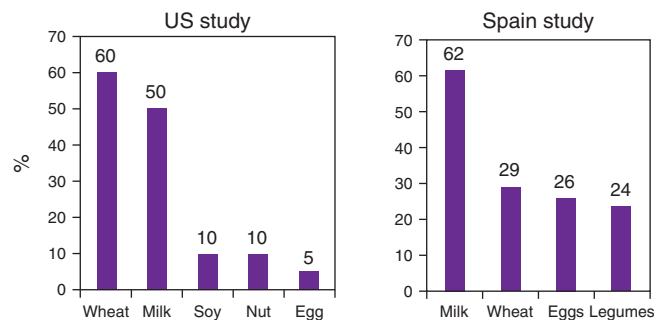


Figure 4. Comparison of specific food triggers identified in prospective, adult series of empiric elimination diets from the United States and Spain. Milk and wheat were the most common triggers (30,31).

Recent studies have raised concerns regarding potential adrenal suppression. Although swallowed administration of topical steroids maximizes first pass hepatic metabolism compared with the inhaled route of delivery, the doses of steroids used for EoE exceed that use for asthma or allergic rhinitis. Another major drawback to the use of topical steroids is the almost universal recurrence of inflammation following treatment cessation.

Diet therapy has emerged as an attractive option for both children and adults with EoE. Three distinct forms of diet therapy exist including the elemental diet, allergy testing-directed elimination diet, and empiric elimination diet. Elemental diets are generally not well tolerated for prolonged periods, resulting in the use of gastric tube feeding for prolonged administration. Allergy testing-directed diet therapy has fallen out of favor at most medical centers owing to limited predictive values for currently available allergy testing.

Because of practical limitations in elemental diet and allergy testing-directed diet approaches, the empiric, six food-elimination diet has emerged as the most popular diet approach in the treatment of EoE. This approach, pioneered by Kagalwalla *et al.* (29), removes the six most common food allergens (milk, wheat, soy, egg, nuts, and seafood) for a period of 6 weeks. The three phases of the SFED protocol include (1) induction during which the six

foods are eliminated, (2) reintroduction during which foods are sequentially reintroduced, and (3) maintenance during which patients avoid specific identified food trigger(s) (**Figure 3**). In patients demonstrating a histologic response, the foods are then individually reintroduced with repeated endoscopies performed to monitor for disease recurrence. The initial pediatric study demonstrated a 74% histologic response (28). Prospective studies in adult cohorts from the US and Spain identified a similar response rate (30,31). An intriguing difference between the US and Spanish study was the identification of a single food trigger in 85% in the US but only 36% in Spain. Milk and wheat were the most common food triggers in both studies (**Figure 4**). Skin prick testing had very limited sensitivity in the prediction of foods identified during the reintroduction process (23–33%).

Involvement of a dedicated dietician is thought to be a factor in the success of the elimination diet and may account for the lower effectiveness reported in smaller, retrospective studies (32). The effectiveness of the elimination diet provides a proof of concept regarding the role of food allergens in the pathogenesis of EoE. The Food Allergen Labeling and Consumer Protection Act was passed by the FDA in 2006. It requires that food manufactured in the US declares the presence of the major food allergens that

include those of the SFED. Major advantages of the diet approach to EoE are the motivation by patients seeking non-pharmacologic, diet alternatives. Diet plans are commonly used by patients for a number of GI-related conditions including lactose intolerance, gluten sensitivity, irritable bowel syndrome, and weight reduction. On the other hand, a major drawback of the diet approach is the cost and inconvenience of repeated endoscopic procedures during diet reintroduction (Figure 3).

THE NEXT DECADE OF EOE: WHAT'S ON THE HORIZON?

Combined efforts by pediatric and adult gastroenterologists, allergists, dieticians, and pathologists have led to marked progress in the recognition, understanding, and management of EoE over the past two decades. Over the next decade, focused efforts will continue to search for epidemiologic factors that have contributed to the emergence of not only EoE but also manifestations of food allergy and atopy in general. Prospective studies are seeking to streamline diet approaches to the management of EoE, as well as develop novel allergy tests to predict causative foods. Translational studies and murine models continue to identify novel disease mechanisms that can be related to phenotypic expression of disease and provide a personalized medicine approach to patient management. On a practical side, office-based tests are coming on-line to obviate the need for repeated endoscopic assessment of disease activity. A multicenter consortium (Consortium for Eosinophilic Gastrointestinal disease Researchers or CEGiR) has been funded by the NIH to foster collaboration between investigators, clinicians, and patient advocacy groups to address several of these initiatives. Finally, the development of validated instruments for EoE activity has been essential to ongoing efforts to advance eagerly awaited, regulatory approval of therapeutics for this important disease that is afflicting a growing number of children and adults worldwide.

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CONFLICT OF INTEREST

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