



The Relationship Between Gastro-Oesophageal Reflux Disease and Chronic Sinusitis

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Declaration

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November 9th, 2006

Abstract

Chronic Sinusitis is a common condition which carries a significant health burden. Despite its prevalence however, its aetiology is still not fully understood. Recently, gastro-oesophageal reflux disease has been implicated as one of the pathogenetic factors in chronic sinusitis. There appears to be a clear association between the two conditions but the mechanism for this relationship is unclear. The prevailing theory in the literature is that reflux of gastric acid to the nasal cavity directly injures the sinus mucosa and leads to chronic inflammation. The evidence to support this is poor and sceptical. We proposed an alternative mechanism to account for the relationship between chronic sinusitis and gastro-oesophageal reflux disease, which is that neurogenic inflammation occurs in the sinuses via a vagal reflex in response to the reflux of acid in the oesophagus. The work presented in this thesis was undertaken in order to reject the hypothesis that the relationship between chronic sinusitis and gastro-oesophageal reflux disease is due to the direct reflux of acid to the sinuses, as well as to document evidence which support a vagal reflex model.

In our first experiment, we aimed to show that acid refluxed from the stomach does not reach as cephalad as the nasopharynx. To achieve this we utilised a specially designed sensor which is able to document pH changes in the nasopharynx without significant artefactual impairments. We studied 40 patients with both chronic sinusitis and gastro-oesophageal reflux. 24-hour pH studies were performed on all these patients using our novel pH probe. We were able to demonstrate that out of the 809 episodes of reflux which we recorded, only 2 of these ever reached as high as the nasopharynx. We were able to conclude from

these results that the inflammation seen in the sinuses in patients with gastro-oesophageal reflux is not attributable to direct acid injury, thereby rejecting the null hypothesis.

The aim of our second experiment was to document an oesophageal-nasal reflex. To achieve this, we infused normal saline, then 0.1N hydrochloric acid into the oesophagus to see if we were able to observe a measurable response in the nasal cavity. We studied 10 healthy volunteers with no past history of sinusitis or gastro-oesophageal reflux disease. We were able to demonstrate an increase in sinonasal symptom score and nasal mucous production in response to the instillation of both normal saline and acid in the oesophagus. Our results therefore confirm a neural reflex between the oesophagus and the paranasal sinuses, and provides strong support for our hypothesis that the chronic sinusitis seen in patients with gastro-oesophageal reflux disease is induced by neurogenic inflammation.

Introduction

Rhinology and Surgery for Sinusitis

The nose and paranasal sinuses have intrigued man for centuries. Being one of the most accessible parts of the human body, the study of rhinology is arguably one of the oldest medical sciences. It is well known that the ancient Egyptians had a working knowledge of the anatomy of the nasal passages, as during the mummification process, the brain is extracted through a transnasal portal.¹ The Egyptians also had instruments for the trephination of the maxillary sinus in the treatment of acute infections.² Hippocrates, born on the island of Cos in 460 BC and often regarded as the father of medicine, documented many rhinological treatments not dissimilar to modern day practice. He described various methods for the removal of nasal polyps as well as nasal cautery for the management of epistaxes.³ Galen (201-131 B.C.) furthered the anatomical understanding of the sinuses through his dissection of animals, as human dissection was illegal for many years. He however believed that the sinuses were filled with fluid and mucous, a *humour* which is purged from the brain and the pituitary gland, leading to nasal catarrh. This humoral theory of the Greeks reasoned that disease resulted from an imbalance or impurities of the humours, and led to practices such as blood letting and other forms of purging which persisted in medical practice until the nineteenth century.⁴

During the middle ages, medical and surgical progress were largely halted throughout Europe, but the works of the Greek philosophers survived through Byzantine compilers in the city of Constantinople.⁵ With the renaissance and

perhaps as the spoils of the crusaders, the writings of the ancient Greek physicians were rediscovered and there was renewed enthusiasm to pursue their scholastic investigations about the human body.

In 1543, Andreas Vesalius (1514 – 1564), lecturer of anatomy in Padua, published his important work “*De Humani Corporis Fabrica*” which reformed anatomy. Through this book Vesalius is often credited to have been the first to describe the human frontal, maxillary and sphenoid sinuses. He also challenged the humoral theories of Galen and declared accurately that the sinuses contain only air.³ In 1978 however, some of Leonardo Da Vinci’s anatomical works were recovered in a casket in Windsor Castle⁶, news which no doubt would have brought hysteria to the legions of author Dan Brown’s fanatics if it occurred today. These drawings, although not published, demonstrate that as early as 1489, Da Vinci had depicted the sinuses as well as the lateral nasal wall. Da Vinci’s drawings also show that his knowledge of the anatomy of the sinuses was probably more detailed and accurate than some of the anatomists who followed in later years.

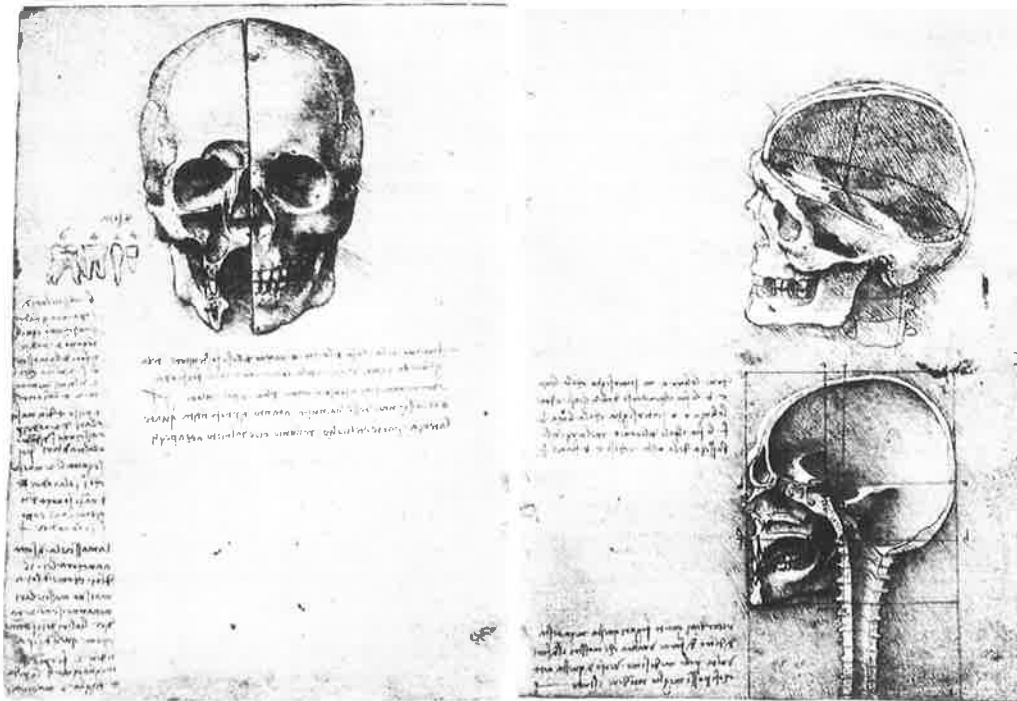


Figure 1. Leonardo Da Vinci's impression of the osteology of the head and neck, demonstrating his knowledge of the sinuses and hiatus semilunaris.⁷

In 1651, Nathaniel Highmore (1613 – 1685) who practiced in Sherborne in Dorset, England, published his book entitled “*Corporis Humani Disquisitio Anatomica*”. This was an important contribution to the understanding of the anatomy of the sinuses, as well as the diseases which afflict them. And because of his work, to this date, the maxillary antrum (of *Highmore*) still bears his name.

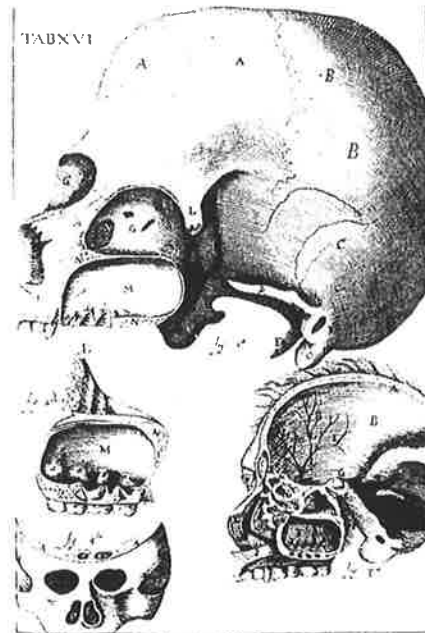


Figure 2. Highmore's depiction of the maxillary sinus⁸

Highmore noted (as did Da Vinci) the intimate relationship between the roots of the upper dentition and the maxillary sinus, and he was first to describe with a case of odontogenic sinusitis in a woman who improved after the extraction of a carious canine tooth. This provided for the first time a pathogenic mechanism for sinusitis, as well as means for relieving the same ailment. This method of creating an oro-antral fistula by dental extraction and perforation through the alveolus was popularised by William Cowper (1666 – 1709), and remained the treatment for sinusitis for centuries.



Figure 3. The extraction of a molar of the upper jaw as engraved by Lucas van Leyden in 1523 (Rijksmuseum Amsterdam)²

Since Cowper described his operation for relieving sinusitis, there has been minimal significant development in its surgical management until the twentieth century. During this period, most of the advances made in surgical technique were based around a central theme – creating an opening into the antrum to provide a route for drainage or irrigation, with the only difference being the site of surgical access. In 1743, French surgeon Louis Lamorier (1696 – 1777) devised an external approach to the maxillary sinus through a space between the

molar tuberosity and the third molar tooth. This method was not utilised however until it was revived by Bordenave a few decades later in 1768.



Figure 4. The method of Lamorier as portrayed by Bordenave⁶

In 1771, Scottish surgeon and anatomist John Hunter (1728 – 1793) published a method of puncturing the antrum through the middle meatus. This procedure was almost identical to the one proposed by Anselme Jourdain (1734 – 1816) a decade earlier in 1761, but the Academie Royale de Chirurgie de Paris however criticised the Frenchman for being too risky. All these procedures for lavaging the sinuses then fell into oblivion and no further advances were made until the latter stages of the nineteenth century.

Johan von Mikulicz-Radecki (1850-1905) and Herman Krause (1848 – 1921) both developed a thick trocar to puncture the antrum from the inferior meatus around 1887. In 1897, American rhinologist Howard Lothrop (1864 – 1928)

published a paper on his method of creating a large opening in the inferior meatus. These more conservative operations were however promptly discarded when the Caldwell-Luc procedure became popularised. George Walter Caldwell (1866 – 1918) from New York and Henry Paul Luc (1855 - ?) from Paris independently published their work in 1893 and 1897 respectively. They described creating a large opening through the canine fossa for complete clearance of diseased antral mucosa. At the same time an inferior meatal antrostomy was made to allow for post-operative irrigation.

A revolution in medical academia emerged in the late nineteenth century and this change in philosophy led to an exponential rise in the accumulation and advancement of medical science. Societies and colleges were formed and their journals allowed free communication and dissemination of information. Some of these journals, such as the *Laryngoscope* (founded in 1896) remain some of the most important literature in otorhinolaryngology today.⁹ With the rapidly advancing surgical technique, surgery became bolder and more radical, and many external approaches not only to the maxillary sinus but also the fronto-ethmoidal complex were described.¹⁰ Frontal empyema, a condition which was prevalent until early twentieth century, is now considered mostly controlled.¹¹

Sir Howard Florey, notably a medical graduate of the University of Adelaide, introduced penicillin to the practice of medicine in 1939. The importance of his work in isolating the active component of Sir Alexander Fleming's discovery was recognised when he received the Nobel Prize for medicine in 1945. Since

then, the use of antibiotics has completely revolutionised all facets of medical practice. In rhinology, the necessity for radical surgery to alleviate sinusitis was remarkably reduced, but remained reserved for those chronic resistant cases.

The diminished interest in rhinology during the middle of the last century since the antibiotic era was revived in the eighties when new technologies were adapted for the practice of the specialty. This new resurgence was heralded by several key factors.¹² Firstly the development of the endoscopic lens system by Hopkins in 1954 provided new means for the modern rhinologist to approach their surgery as well as to assess their patients pre- and post-operatively. Secondly the invention of the computerised tomography (CT) scan by Sir Geoffrey Hounsfield in 1969 brought enlightenment to the understanding of sinus anatomy and disease in the live patient. Together with the new found understanding of mucociliary function, these developments have led to the new “golden era” of functional endoscopic sinus surgery¹³ as introduced by Messerklinger.^{13 14} Over the recent decades, through the work of prominent rhinologists such as Stammberger¹⁵, Kennedy¹⁶ and Wormald¹⁷, endoscopic surgery has largely replaced the traditional open approaches not only for the treatment of sinus disease, but for a host of other sinonasal and even skull base disorders.

Impact of Chronic Sinusitis in the New Millennium

Despite the advent of antibiotics and the success of functional endoscopic sinus surgery, and despite the centuries of investigations into its treatment, chronic sinusitis still remains one of the most prevalent chronic conditions to afflict humankind. It has been described as one of “men’s most democratic ills”.¹⁸ It spares no races and pervades all social classes. Perhaps the most famous patient to have suffered the condition is Franklin D. Roosevelt, American President, and arguably the most influential figure during the second world war. Frank Lucente, ex-president of the American Laryngological, Rhinological and Otological Society, in his entertaining address of the annual meeting of 1972 entitled “The Impact of Otolaryngology On World History”¹⁹, described how Roosevelt received twice daily sinus treatments for much of his 13 years in the Whitehouse. Lucente jests about the possible influence of Ross McIntyre, Roosevelt’s close friend and otolaryngologist on the course of world war II, and labelled Roosevelt as the most over treated sinus patient in history.

Of course sinusitis has greater global impact than just sporadic cases in famous historical figures. Palaeopathological studies of medieval skulls reveal that around 3.6% of these show evidence of sinusitis in the maxillary antrum.²⁰ It seems that with the increase in the density of world population and air pollution following industrialisation, the prevalence of chronic sinusitis has risen to alarming rates. In the National Health Interview Survey of 2004, 14% of adults in the United States had been diagnosed with sinusitis by their doctor.²¹ In the

same series conducted in 1996, the prevalence of chronic sinusitis was estimated to be 12.6%, and was the second most common chronic condition suffered by adults in the US, ranking only below arthritis (12.7%).²² Extrapolating on these statistics, it has been estimated that chronic sinusitis affects approximately 38 million people in the United States.

In Australia, a similar epidemiological pattern has been identified. In the National Health Survey conducted by the Australian Institute of Health and Welfare in 2001, 10.5% of the population reported themselves as having chronic sinusitis.²³ The rate was slightly higher for women (12.4%) compared with that of men (8.9%). In total, these figures translate to about 2 million Australians being affected by chronic sinusitis in our humble country.

With such a high prevalence, it is no surprise that the economical burden of chronic sinusitis is tremendous. In 2000, it has been estimated that chronic sinusitis was responsible for 11.6 million office-based doctor visit in the US.²⁴ This figure did not even include treatments for acute sinusitis, visits to the emergency department or hospital based outpatient services. Patients with chronic sinusitis have been found to make 43% more non-urgent outpatient visits than the general population.²⁵ They also fill 43% more prescriptions than the general population and make 25% more urgent care visits. In 1996, the total health care expenditure attributable to sinusitis was estimated to be a staggering \$5.8 billion in the US alone.

Asking the Important Questions

In the current age, when we have an armamentarium of antibiotics against the bacteria responsible for sinusitis, when we have a newly established surgical technique to correct anatomical obstruction to the drainage of the sinuses, why is it then that chronic sinusitis still carry such a huge burden to the health and finances of every population? Why are there still cases of the disease which persist despite the best efforts of the modern day rhinologist? What is different about those patients who fail treatment when we would have expected them to improve? Kennedy, on his reflections of the controversies in sinus surgery over the past century²⁶, comes to the conclusion that the problem is that we still only have limited understanding of the condition, and that much work needs to be done if we are to make any headway against this age old ailment.

Because of its enormous impact on our society, it can be understood that even small steps made in progress will lead to leaps in terms of benefits. For this reason, over the recent past there has been an explosion of research into chronic sinusitis. We can now appreciate that chronic sinusitis is a multi-factorial disease. Its aetiology and pathogenesis extends beyond the bacterial infection of an anatomically predisposed sinus. It is becoming clearer that other factors such as host immunity, allergy, and impairment of mucociliary function all contribute to the production of disease.²⁷ The role of fungi²⁸, and more recently, the new concept of biofilms²⁹ have caused a shift in paradigm in the way which we view the microbiological basis of chronic sinusitis.

Gastro-oesophageal reflux is one possible aetiological factor which has been raised recently as a cause for chronic sinusitis.³⁰ Interestingly it was also Galen who was first to describe oesophagitis in the second century, but its relationship to acid was not recognised until it was suggested by Rokitansky in the nineteenth century.³¹ Gastro-oesophageal reflux disease is equally prevalent to chronic sinusitis, and studies show that about 19.8% of the adult population in the US experience symptoms at least weekly.³² In Australia, similar figures have been reported, with 15% of adults suffering from heartburn at least weekly.³³ Recently, there has been a fervour of interest in the problems which may be due to acid regurgitation outside of the oesophagus. In fact, there is an enormous amount of literature being generated over the past decades on the supra-oesophageal manifestations of gastro-oesophageal reflux disease.³⁴ This growing list of evils contains many otolaryngological conditions, and has recently included chronic sinusitis amongst them. It is incredible to see that this theory seems to have been readily accepted into the medical literature without question, so much so that it now appears in many review articles in both otolaryngological and gastroenterological journals. However, as we will examine in the next chapter, evidence to support the association between gastro-oesophageal reflux and chronic sinusitis is surprisingly weak. The purpose of the work presented in this thesis is to clarify the relationship between gastro-oesophageal reflux and chronic sinusitis. The importance of such work is obvious as gastro-oesophageal reflux is readily treatable by proton pump inhibition.³¹ Therefore, if we can add

these medications to the regimen of treatment for chronic sinusitis, there may be potential benefits for millions of sufferers.

*Review of the
Literature*

The Aetiology of Chronic Sinusitis

Although there is still much which we do not understand about chronic sinusitis, today we have a wealth of information into its pathogenesis compared with the centuries that have gone before us. We now know, as mentioned in the previous chapter, that chronic sinusitis is a multifactorial disease. There is not a single cause and far from it, a multitude of aetiological factors come into play to produce the clinical manifestations which we identify as chronic sinusitis. We know that anatomical variations in the pneumatisation of the sinuses predispose them to disease. Infection by virulent organisms such as bacteria and fungi may also play a role. More recently, we have gained further insight into the part which allergy and other host factors contribute to chronic sinusitis. We cannot forget, of course about the problems which are produced by other environmental factors such as smoke and pollution. Currently, there is an increasing amount of research into the biofilm model and how this applies to chronic sinusitis. Further to all of this, there is the association of gastro-oesophageal reflux, but the importance of this as a contributing factor in the pathogenesis of chronic sinusitis is debatable, and is the topic of the current research. Thus as outlined, the pathogenesis of chronic sinusitis is extremely complex, and we need to consider the role of each component as well as the disease as a whole in order for our understanding to progress.

Role of Anatomy

The anatomical abnormalities that lead to chronic sinusitis are, in the main, defects which obstruct the ostia of the paranasal sinuses. The paranasal sinuses are hollows in the bones that bound the nasal cavity, with which they communicate by small apertures (ostia). They contribute to warming and humidifying of the inspired air. They may also allow enlargement of certain areas of the skull, thereby determining the position of the eyes and the nose, while minimising the corresponding increase in bone mass. The sinus ostia need to be patent to allow ventilation and passage of mucous, and their obstruction has been associated with sinus disease.³⁵ There are various bony distortions which can impair the natural drainage of the sinus ostia, thereby predisposing an individual to sinusitis. These include concha bullosae (pneumatisation of the middle turbinate), paradoxical curvature of the middle turbinate, Haller's cells, and pneumatisation of the uncinate process.³⁶⁻³⁹ Presence of these anatomical variations are extremely common, and in fact, recent studies have demonstrated that all patients undergoing functional endoscopic sinus surgery carry these abnormalities in one form or another.⁴⁰ The fact that these variations are so widely prevalent have led some authors to place less importance on their role in the pathogenesis of chronic sinusitis.⁴¹ However, correction of such abnormalities form part of the basis for functional endoscopic sinus surgery, a procedure which has been shown to lead to improvement of chronic sinusitis in approximately 90% of cases.⁴² Indeed those patients who have a poor outcome

may be due to more unusual anatomical variants which have not been recognised and addressed.⁴³

Role of Bacteria

Bacterial infection has an undisputed role in the pathogenesis of acute sinusitis, which commonly results from secondary bacterial invasion after viral rhinitis.⁴⁴ However, its significance in the chronic form of the disease is under much debate. The differences in the bacteriology of acute and chronic sinusitis are well documented in the literature. In acute sinusitis the predominant organisms are *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Haemophilus influenzae*,⁴⁴ but the spectrum of bacteria seen in chronic sinusitis is much more variable. In addition to those pathogens encountered in acute sinusitis, *Staphylococcus aureus*, coagulase negative *Staphylococcus*, *Pseudomonas aeruginosa*, and anaerobic bacteria are more commonly cultured.⁴⁶ It is thought that the low oxygen tension generated within an occluded sinus favours the growth of anaerobic species, however, the relative pathogenicity of *any* organism in chronic sinusitis remains speculative – their presence could merely indicate a state of colonisation.⁴⁵

Role of Fungi

Fungi are eukaryotic organisms which are ubiquitous in our environment. They can exist in various forms such as yeasts (unicellular) or moulds (colonies with hyphae). They may also form spores which are potentially air borne and can be disseminated to a wide area. Spores can germinate once favourable conditions are encountered. More than 50,000 species of fungi have been identified but of these only about 300 are associated with human disease.²⁸ Fungal disease in the nose and paranasal sinuses may take various forms. It can range from the fatal invasive fungal sinusitis, seen especially in the immunocompromised, to the less aggressive but yet tenacious chronic form.⁴⁷ It may also rest indolent in the sinuses in a benign condition known as fungal ball. In a recent study, fungi was cultured from 96% of patients with chronic sinusitis using a technique which involved a saline lavage of the nasal cavities.⁴⁸ Interestingly, using the same technique the authors were also able to culture fungi from the majority of their normal controls. This implies the universal presence of fungi in the human nasal cavity, but it is unclear why they are pathogenic in only a certain proportion of the population.

Allergic fungal sinusitis is a special form of chronic sinusitis that deserves special mention. It is thought to occur in 5% - 10% of those patients with chronic sinusitis requiring surgery.⁴⁹ It is characterized by nasal polyposis, eosinophilic allergic mucin, and hypersensitivity to fungi, and its pathogenesis has been suggested to be similar to that of allergic bronchopulmonary aspergillosis.⁵⁰

However, the mechanisms which initiate or perpetuate the disease are still in question and is the subject of ongoing research.⁵¹ There is little doubt though, that fungal protein can stimulate hyper-responsiveness of respiratory mucosa by IgE mediated allergic mechanisms.²⁸

Role of Allergy and Immune Dysfunction

As already alluded to, fungi may contribute to chronic sinusitis by the allergenic nature of its proteins. The potential contribution of allergic mechanisms to the development of chronic sinusitis can be seen in its prevalence in patients undergoing sinus surgery, which could be as high as 84% as demonstrated by a recent study of 200 patients.⁵² Antigen-antibody reactions result in the release of multiple inflammatory mediators, such as histamine which increases vascular permeability leading to mucosal swelling. This may then contribute to the obstruction of sinus ostia with subsequent chronic sinusitis.⁵³ Inflammation may further contribute to chronic sinusitis by increasing mucous production, impairment of ciliary function, and compromising the epithelial barrier which affords protection against invasion by micro-organisms.⁵⁴ Over time, the chronic inflammation is accompanied by eosinophilic tissue infiltrates, and frequently nasal polyps, which may perpetuate ostial obstruction.⁴⁷ At least 50% of patients with chronic hyperplastic sinusitis with nasal polyposis have associated asthma, a condition also characterised by eosinophilic infiltrates and similar to chronic

sinusitis in its pathogenesis.⁴⁵ In stark contrast to hypersensitivity, deficiencies in the immune system have also been associated with chronic sinusitis. An unexpectedly high incidence of T-cell dysfunction as well as quantitatively low immunoglobulin levels were found in patients with refractory sinusitis.⁵⁵

Role of Ciliary Dysfunction

Defects in the mucociliary apparatus lead to mucous stasis and predisposition to bacterial infection. Accordingly, prolonged nasal mucous transport time has been demonstrated in patients with chronic sinusitis.^{56 57} Reduced mucociliary clearance may occur with changes in the rheological properties of mucous, abnormal ciliary activity, increased infectious cells, histopathological changes of the nasal lining, defective secretory pressure, or anatomical obstruction.⁵⁸ Cilia obtained from sites of purulent infection has been shown to beat more slowly than those obtained from normal controls, and this may be due to both toxins released by bacteria as well as the host inflammatory response.⁵⁹ There is some controversy however in these situations as to which is the preceding and causative event – the inflammation or the abnormal mucociliary function. There is strong evidence though that in certain situations mucociliary dysfunction does produce chronic sinusitis, as can be seen in patients with cystic fibrosis and Young's disease where in both conditions there is primary dysfunction of ciliated tissue.²⁷

Role of Environmental Factors

Many exogenous substances, such as cigarette smoke influence the beating frequency of cilia. It has been well documented that the toxic fumes from cigarette smoke inhibit the beating of cilia in respiratory mucosa.⁶⁰ It is not surprising then that pollutants and environmental factors predispose an individual to the development of chronic sinusitis.⁶¹ Studies into the outcome following functional endoscopic sinus surgery show that cigarette smoking is one of the most important prognostic factors in predicting the need for revision surgery.⁶² Other interesting evidence for the role of environmental pollution can be derived from the analysis of skulls from antiquity. It has been demonstrated that skulls from the Anglo-Saxon period show a higher prevalence of sinusitis than that of the preceding periods such as the bronze or iron ages.²⁰ This difference has been attributed to the smoky hearths and the poor ventilation of the Anglo-Saxon homes. It was also Saxon custom that much of the cooking was done indoors as opposed to outside in the preceding periods. Other environmental factors, such as a cold, damp climate have also been implicated in the pathogenesis of sinonasal disease.²⁷

Role of Osteitis

Functional endoscopic sinus surgery, as mentioned previously, is a highly successful procedure in the treatment of chronic sinusitis. In this scientific era,

since its introduction, rhinologists have pondered why some patients fail to improve after endoscopic sinus surgery despite seemingly equivocal conditions pre-operatively. As in the case of other illnesses, research has turned to animal models in an attempt to gain deeper understanding of the diseases which affect mankind. Some interesting observations have been made when animal sinuses have been deliberately inoculated with virulent bacteria. Infection of rabbit sinuses with *Pseudomonas* and *Staphylococcus aureus* have demonstrated that the inflammation is not limited to the mucosa of the sinuses but rather, extends to the underlying bony architecture.⁶³ This underlying *osteitis* can in fact spread to the adjacent bony structures as well as that of the contralateral side through Haversian canals.⁶³ In human studies, such bony changes have also been observed. The resected ethmoid bone in patients undergoing surgery for chronic sinusitis show increased physiological activities.⁶⁴ These histomorphometric changes include periosteal osteoid and new bone formation, increased osteoclastic activity, and bony sclerosis as a reparative response to the weakened bone. These changes are similar to that seen in osteomyelitis of long bones and have been identified underlying diseased as well as healthy mucosa.⁶⁴ Because of this, osteitis has been proposed as one of the mechanisms which propagate recalcitrant chronic sinusitis. Mystery however still remains as to how exactly the presence of bacteria in the sinuses lead to inflammation of the underlying bone. Although bacteria are often identified histologically in osteomyelitis of long bones, thus far no study have been able to demonstrate this in the bones of the paranasal sinuses. It has been suggested that osteitis of the sinus bone may be compared with the situation seen in periodontal disease, where bacterial biofilms

have been demonstrated subgingivally, and have been implicated in the remodelling of alveolar bone.⁶³

Biofilms in Chronic Sinusitis

Biofilms are structured communities of cells enclosed in a self-produced polymeric matrix and adherent to an inert or living surface. It may be composed of bacterial or fungal cells that communicate with one another in a cooperative manner. This self-produced matrix, which is slime-like, may include polysaccharides, nucleic acids, and proteins.²⁹ Pond scum and biofouling of water intake pipes are examples of biofilms in nature. The study of biofilms was born of science in the water and engineering industries, but its application to the *in-vivo* clinical scenario has resulted in a paradigm shift in the way which medical science view infective diseases. Since its inception, microbiology has been concerned with the free-floating, planktonic form of bacteria which we now know constitutes only a very small proportion of the bacteria in the actual living situation. The vast majority of bacteria organise themselves into biofilms and it is clear that the bacteria in these colonies differ from those of the planktonic form.⁶⁵ Lurking within the matrix and the structure of the biofilms, bacteria can evade host defence systems and resist antibiotics which would have been detrimental to those in the exposed, planktonic form. Investigators are now only just beginning to learn about the various forms and morphology of biofilms, but it is clear that

some bacteria, such as *Pseudomonas*, are better formers of biofilms than others. The existence of bacteria in such biofilms provides a model of understanding for the reason why infections persist and treatments relapse in chronic sinusitis.²⁹

Gastro-Oesophageal Reflux and Chronic Sinusitis

In this brief overview of the available literature on chronic sinusitis thus far, we have demonstrated that its aetiology is indeed extremely complex. How then, does gastro-oesophageal reflux disease weave into this intricate and complicated tapestry? What evidence exists for the association between these two commonly prevalent conditions? And can we convincingly lay causative blame on gastro-oesophageal reflux disease as a contributing factor for chronic sinusitis? Furthermore, if this is indeed the case, what is that pathogenic mechanism that leads to mucosal inflammation in the sinuses? Can it be as simple as direct acid contact?

Perhaps the strongest evidence for the association between gastro-oesophageal disease and chronic sinusitis comes from a study of military veterans in the United States. El-Serag and Sonnenberg⁶⁶ reported their audit of the comorbid occurrence of extra-oesophageal conditions in 101,366 patients with oesophagitis. This data is derived from a computerised record of all inpatients treated at the 172 Veteran Affairs hospitals over a 14 year period. The authors compared these patients with an identical number of unmatched controls

randomly chosen from the remainder of the database. They found a significantly higher prevalence of sinusitis amongst the patients with oesophagitis when compared with the control group. Using multivariate regression analysis, the authors were able to calculate the strength of this association, which yielded an odds ratio of 1.6 (95% confidence interval 1.5 – 1.7). Interestingly, other respiratory problems such as bronchial asthma were also more prevalent in those patients with oesophagitis. The importance of this association will be highlighted later in this review.

Other evidence in support of the association between gastro-oesophageal reflux and chronic sinusitis can be found in the outcome analysis of functional endoscopic sinus surgery. Chambers et al⁶⁷ examined the long term outcome of functional endoscopic sinus surgery and attempted to identify factors which would predict a poor prognosis. They evaluated one hundred and eighty-two patients who had undergone endoscopic sinus surgery with a mean follow-up period of 42.5 months. Out of all the possible prognostic indicators which they evaluated, and this included smoking, allergy, asthma and polyposis, *gastro-oesophageal reflux disease* was the only significant factor which was associated with a poor outcome.

The first study investigating the relationship between chronic sinusitis and gastro-oesophageal reflux disease was reported in 1991 by Contencin and Narcy.⁶⁸ Here, the Parisian otolaryngologists examined 31 infants and children, thirteen of which were known to suffer from chronic sinonasal symptoms as well

as gastro-oesophageal disease. The other eighteen were healthy controls who were free from both of these conditions. All subjects underwent pH monitoring for approximately 24 hours using a single glass probe located in the nasopharynx. The authors found that a significantly greater number of acid episodes were observed in the patient group in comparison with the control group. They offered this finding as evidence in support for the role of gastro-oesophageal reflux in the pathogenesis of chronic sinonasal diseases, but then essentially concluded that their study was fundamentally flawed and that more research is required. However, despite the weakness of the evidence presented in this paper, it is frequently quoted by many authors subsequently in substantiation for the pathogenic mechanism of gastro-oesophageal reflux leading to chronic sinusitis.

Phipps et al⁶⁹ also explored the possible role of gastro-oesophageal reflux disease in children with chronic sinus disease. Their study sample consisted of 30 children referred to their unit for evaluation of chronic sinusitis. All these patients were investigated with 24 hour dual pH probe monitoring, with one probe situated at the lower oesophagus and the other placed in the nasopharynx. Their results showed a high prevalence (nineteen children, 63%) of gastro-oesophageal reflux disease in these children, and nasopharyngeal acid events were demonstrated in 6 of these patients. The investigators went on to treat these patients for their gastro-oesophageal reflux disease and found that fifteen of the nineteen children with demonstrated gastro-oesophageal reflux improved to

parental satisfaction, though it is unclear from the paper exactly what this treatment consisted of.

Other authors have also examined the effects of treating patients with chronic sinusitis with anti-reflux treatment. DiBaise et al⁷⁰ reported on nineteen patients with chronic sinusitis and found that fourteen of them (78%) had abnormal pH studies on dual probe 24 hour testing. They administered treatment for reflux which included proton pump inhibition, prokinetic agents or Nissen's fundoplication and found that twelve patients (67%) noticed improvement in their sinus symptoms. The same group of authors again reported further experience with treating chronic sinusitis using proton pump inhibitors a few years later in 2002.⁷¹ This time DiBaise et al evaluated eleven patients with chronic sinusitis and found that nine of these had abnormal pH studies. They treated all eleven patients with a 3 month course of omeprazole and found that about 90% of the patients experienced improvements in their sinus symptoms as well as global satisfaction.

Ulualp et al⁷² realised the paucity of studies in literature in regards to the role of gastro-oesophageal reflux in the pathogenesis of chronic sinusitis, especially in the adult population and attempted to address this deficiency. They evaluated 11 patients with CT documented chronic sinusitis and subjected them to 24 hour pH monitoring using a three channel probe with sensors in the upper and lower oesophagus as well as one in the pharynx, situated 2 cm above the upper oesophageal sphincter. They compared this group to a group of 11 healthy

volunteers. They were able to demonstrate in this study that pharyngeal acid events occurred in 7 of the eleven patients with chronic sinusitis. A total of 34 pharyngeal acid events were recorded in these eleven patients. In comparison, only 2 of the eleven healthy volunteers exhibited gastro-oesophagopharyngeal reflux events. The results of this study support the notion that direct contact of refluxed gastric acid may contribute to the pathogenesis of chronic sinusitis in adult patients.

Perhaps the largest study to date analysing 24 hour pH monitoring in patients with chronic sinusitis was conducted by DelGaudio⁷³, who in 2005 published his thesis on the direct nasopharyngeal reflux of acid as a contributing factor in refractory chronic sinusitis. He studied 38 patients with persistent symptoms following endoscopic sinus surgery in comparison with 30 controls who either did not have chronic sinusitis, or had improved after endoscopic sinus surgery. He was able to demonstrate nasopharyngeal reflux events in 15 of the thirty-eight patients with persistent chronic sinusitis, which were significantly more frequent when compared with the controls. Interestingly, in this study the subject who demonstrated the second highest number of nasopharyngeal reflux events was one of the controls without chronic sinusitis. Overall, 3 of the thirty subjects in the control group also exhibited nasopharyngeal reflux.

In a recent study published in 2006, Pincus et al from the New York Otolaryngology Group investigated 30 patients in a large private practice with recalcitrant chronic sinusitis. They investigated these patients with 24 hour pH

monitoring, using a 3 channel catheter in 23 of these patients. For this study the probes were placed 5 cm above the lower oesophageal sphincter, above the cricopharyngeus and also in the nasopharynx. Of these 23 patients, nasopharyngeal reflux was demonstrated in 2 patients. The patients were then treated with proton pump inhibitors and out of the fifteen patients which the authors were able to follow-up, fourteen of these reported improvements in their sinonasal symptoms. The authors concluded that their study demonstrated the ability of gastric acid refluxate to reach as cephalad as the nasopharynx, but offered no explanation as to why nasopharyngeal reflux was observed in only two patients even though almost every single patient responded to anti-reflux treatment.

Indirect evidence for gastric refluxate reaching the nasopharynx can be found in the studies of *Helicobacter pylori*. This bacterium was discovered by two Australian pathologists Robin Warren and Barry Marshall, who won the Nobel prize for medicine or physiology in 2005 for their work in identifying *Helicobacter*, as well as demonstrating its role in the pathogenesis in peptic ulcer disease.⁷⁴ Because of their work, the treatment and diagnosis of gastritis and other peptic conditions has been completely revolutionised. Acid suppression alone is now no longer the standard treatment for peptic ulcer disease, but rather, the main aim of treatment is currently focused on the eradication of *H. pylori*. It has been estimated that in 50% of the population, *H. pylori* colonises the gastric mucosa, which is thought to be the only reservoir to harbour this bacteria in the human body. Ozdek et al⁷⁵ studied the nasal mucosa of 12 patients with chronic

sinusitis and was able to demonstrate the presence of *H. pylori* in 4 of these patients by polymerase chain reaction. Three of these four patients were symptomatic of gastro-oesophageal disease. In comparison, the authors studied the mucosa of 13 patients who presented with nasal obstruction only resulting from concha bullosa of the middle turbinate. None of these nasal mucosa biopsies tested positive for *H. pylori*.

Further indirect evidence of nasopharyngeal reflux can be extrapolated from the analysis of middle ear effusions. Tasker et al⁷⁶ found that 59 of the sixty five samples of middle ear effusions analysed tested positive for either pepsin or pepsinogen. The concentration of this was much higher than that of serum, and it therefore lead the authors to make the conclusion that gastro-oesophageal reflux is responsible for the presence of pepsin in middle ear effusion. This provides good support that, at least in children less than two years of age, gastric refluxate does indeed commonly reach the nasopharynx.

In a recent Portuguese study, Dinis and Subtil⁷⁷ also tried to locate *H. pylori* and pepsin/pepsinogen in the nasal mucosa of patients with chronic sinusitis. They investigated 15 patients who required endoscopic sinus surgery for medically recalcitrant chronic sinusitis and compared these to 5 patients who required anatomical correction only and did not have sinus disease. Interestingly, the authors were able to demonstrate the presence of *H. pylori* in both groups of patients with no statistical difference between their prevalence. The tissue pepsin and pepsinogen levels never rose above that of serum in either group of patients.

This study lends credibility to the theory that sinonasal tissue may merely be a reservoir for the transmission of *H. pylori*, rather than a pathogenic presence of the bacteria in this area.

Recently in 2005, a Brazilian group assessed 24 hour oesophageal pH measurements in children with chronic sinusitis. In this study, Monteiro et al⁷⁸ examined 10 paediatric patients with radiologically documented chronic rhinosinusitis. Although this is only a small study, the authors found that only one of these 10 patients tested positive for gastro-oesophageal disease. This is in fact, as discussed in the previous chapter, a lower rate than the general population. Despite this result, the authors came to the conclusion that their study supports the role of gastro-oesophageal reflux in the pathogenesis of chronic sinusitis, and that potentially 10% of sinus surgery may be avoided.

Such a study draws attention to the inadequacy and the conflicting data which exists in the literature at the present time. It also highlights the current entrenched philosophy that the association between gastro-oesophageal reflux and chronic sinusitis is due to inflammation as a result of direct acid contact. All the available literature on the topic have now been presented in this review and it can be stated that the evidence from which these conclusions are derived are either weak or flawed. Although alternate theories are often suggested by many authors, these only seem to be mentioned *en passant* for completeness sake without any serious devotion to their plausibility. One of these theories is that, in contrast to direct acid contact, the inflammation in the sinonasal mucosa could possibly be

neurogenic, being mediated by a vagal reflex in response to the presence of acid in the oesophagus. The purpose of the research presented in the current thesis is to test this hypothesis of a vagally mediated reflex.

Rationale for a Vagally Mediated Nasal Reflex

The mucosa of the nasal cavity is under the constant influence of the autonomic nervous system, and this neural control is important both in the normal function of the nose as well as in the pathogenesis of sinonasal disease. The neuroregulation of the nose has been intensively studied and perhaps the most vocal in the literature on this topic is John Widdicombe⁷⁹⁻⁸², Professor of Physiology at the St George's Hospital Medical School in London. Amongst his numerous publications on the physiology of the nose, Widdicombe credits Florian Kratschmer (1843-1922), a Viennese physician, as one of the pioneers in the study of nasal reflexes. Widdicombe in fact reprinted in 2001 an English translation of Kratschmer's original 1870 article entitled "reflexes from the nasal mucous membrane on respiration and circulation"⁸³. In this paper Kratschmer described the reduction in heart rate and respiration when the nasal mucosa is stimulated by various noxious stimuli, such as mechanical pressure and cigarette smoke. Through animal studies he was also able to demonstrate that these reflexes are abolished when the vagi and trigeminal nerves are sectioned, indicating their involvement in this reflex. Thus even as early as 1870 a reflex

arc for respiratory mucosa involving both the vagus and trigeminal nerves had already been demonstrated.

Since Kratschmer's time there has been a vast amount of studies on the autonomic control of the nasal mucosa. The autonomic nervous supply of the nasal mucosa is derived from the pterygopalatine ganglion (the ganglion of hay fever) which is situated in the pterygopalatine fossa immediately in front of the pterygoid canal. It receives the Vidian nerve (nerve of the pterygoid canal) which is formed by the union of the deep petrosal and the greater superficial petrosal nerves. The deep petrosal nerve carries sympathetic fibres from the internal carotid sympathetic plexus which originate in the superior cervical ganglion. The greater superficial petrosal nerve carries parasympathetic fibres from the superior salivary nucleus via nervus intermedius. A branch of the maxillary nerve provides the sensory root for the pterygopalatine ganglion, with the cell bodies in the trigeminal ganglion.⁸⁴

Under this autonomic influence a number of physiological reflexes that occur in the nasal mucosa have been elucidated. Within itself, the nasal mucosa undergoes a regular cycle of congestion and decongestion, such that most animals and humans breathe through only one side of the nose at a time.⁸⁵ With exercise the nose improves its efficiency, and it can be demonstrated that nasal patency is increased due to an increase in sympathetic outflow.⁸⁰ The nasal mucosa also responds to various stimuli from around the body through reflexive mechanisms. It is well documented that nasal patency is reduced on the nostril of

the ipsilateral side when pressure is applied on the face or the axilla.⁸⁵ The physiological advantage for such a reflex is unclear but it has been postulated that breathing through the upper most nostril whilst lying on one side may permit breathing of less polluted air. Interestingly, further away on the body from the nose, a cutaneous-nasal reflex has also been elucidated. Assanasen and colleagues⁸⁶ were able to demonstrate elevation of the nasal mucosal surface temperature when subjects' feet are submersed in water of 42°C. They attributed this finding to a reduction in baseline sympathetic tone.

Another well documented reflex, the *diving reflex*⁸⁷, is exhibited in all mammals and birds. Here contact of the nose with water or contact of the face with a cold wet cloth induces apnoea with cessation of breathing held in expiration. In addition to this there are cardiovascular changes including bradycardia and cutaneous vasoconstriction, with resultant reduction in cardiac output but preservation of the cerebral and coronary circuits. At the same time there is glottic closure, and in those species capable of it, the external nares is also closed. It is clear that this reflex allows animals to submerge and survive underwater with prevention of water entering the airway. The diving reflex clearly demonstrates neural connections between the trigeminal and the vagus nerves.

The nose, as can be expected of a natural defence mechanism, reflexively congests and increases nasal secretion when it is presented with various noxious stimuli, such as smoke or even cold air.⁸⁸⁻⁹⁰ This reflexive response is mediated

by the parasympathetic system, through the pathways outlined above. The postganglionic fibres, like those for the parasympathetic system elsewhere in the body, act through cholinergic terminals.⁹¹ In recent times, research has shown the importance of neuropeptides such as vasoactive intestinal peptide (VIP), substance P and other tachykinins as mediators in the generation of this *neurogenic inflammation*.⁹²⁻⁹⁴

We have demonstrated thus far that the nose as an organ initiates reflexes which act on itself as well as the rest of the body. It is also a target organ of control by reflexes through the autonomic nervous system. The time has now come to examine the oesophagus, to see what evidence there is that it may participate in the complex array of nasal reflexes described.

The literature is in fact already splashed with an abundance of evidence that the reflux of acid into the oesophagus induces reflexive changes in the upper respiratory tract. Stimulation of the lower oesophagus by acid contact or by distension has been shown to produce glottic closure.⁹⁵⁻⁹⁸ Such a reflex is obviously protective and serves to prevent aspiration of gastric contents into the airways. It has an afferent pathway through the vagus nerve, with efferents via its recurrent laryngeal branch.

Other evidence for the effect of gastro-oesophageal reflux on the respiratory system can be seen in the studies of asthma. The association between asthma and gastro-oesophageal reflux is well documented.⁹⁹⁻¹⁰⁴ Similar to chronic sinusitis, there is an unusually high prevalence of gastro-oesophageal reflux in patients

with asthma.¹⁰⁵ Furthermore, just as in chronic sinusitis, treatment of the gastro-oesophageal reflux disease in asthmatic patients, whether by medical or surgical means, leads to improvement of their respiratory symptoms.¹⁰⁶⁻¹¹¹ And like the situation in chronic sinusitis that the current study is attempting to address, there had been much debate in the literature during the eighties and nineties as to whether the association between reflux and asthma is due to direct acid aspiration or a neural reflex mechanism. There is no doubt that acid is irritant in the airway and that instillation of a low pH solution in the airway will lead to an asthma like condition.¹¹² Because of this there was pervasive believe in the seventies amongst the respiratory physicians that aspiration of acid content from the stomach is the causal link between asthma and gastro-oesophageal reflux. Further support for this theory came from studies that pulmonary contamination can be detected after ingestion of a radio-labelled solid meal.¹¹³ However, most respiratory physicians no longer consider this micro-aspiration theory to be responsible for the pulmonary changes due to reflux, but rather prefer the neural reflex mechanism. The rationale for this change in philosophy was derived from a multitude of studies whereby acid is instilled into the oesophagus, a procedure known as the Bernstein test for oesophagitis.¹¹⁴⁻¹²³ These studies demonstrate changes in airway function with the application of acid in the distal oesophagus, and these changes can be abolished by section of the vagi nerves or with atropine. Further more, protective reflexes in the larynx have also been demonstrated during the Bernstein test.¹²⁴ Given that the nasal cavities are lined with respiratory mucosa, exactly the same as that in the airway, we can

reasonably expect a similar oesophago-nasal reflex which would account for the association between gastro-oesophageal reflux and chronic sinusitis.

Aims

Aims of the Current Study

Through the review of the literature, we have demonstrated that the aetiology of chronic sinusitis is extremely complex, but there appears to be good evidence for an association between gastro-oesophageal reflux disease and chronic sinusitis. There is also good evidence for causality in this relationship as treating gastro-oesophageal disease in patients with chronic sinusitis improves their sinonasal symptoms. The prevailing theory to explain the pathogenic mechanism for this association at the present time is that direct contact of gastric refluxate causes inflammation in the nose and the sinuses. The lack of good evidence to support this theory has already been outlined in the previous chapter. We have also presented our rationale for an alternative pathogenic mechanism, that is, that the sinonasal inflammation seen in patients with gastro-oesophageal reflux is neurogenic, and is mediated by a vagal reflex when acid comes into contact with the oesophagus. It follows then that the aims of the current study is to test the null hypothesis that the relationship between chronic sinusitis and gastro-oesophageal reflux is due to direct reflux of gastric acid. Once this has been rejected our secondary aim is to document evidence to support a vagally mediated reflex. We hope to achieve this by a series of experiments.

Firstly, we aim to demonstrate that refluxed acid from the stomach does not reach the nasopharynx. To demonstrate this, our plan is to utilise a specially developed pH sensor which can be used above the oesophagus, without

significant artefacts corrupting the results. Further details about this sensor will be described in the following chapter.

Secondly, we aim to demonstrate that a vagally mediated reflex exists, when acid comes into contact with the oesophagus, which leads to inflammation in the respiratory mucosa of the nasal cavity. To demonstrate this, our plan is to follow the methods utilise by the respiratory physicians to elucidate a similar reflex in the lower airways. This will involve a Bernstein challenge test which, as already described, involves instilling acid into the oesophagus to simulate the situation in gastro-oesophageal disease. We will aim to detect any changes in the nasal cavities by measuring nasal inspiratory peak flow, nasal secretion production, as well as any subjective changes in sinonasal symptoms.

*Materials
& Methods*

Experiment 1

Hypothesis:

“Acid from the stomach in patients with gastro-oesophageal reflux disease reaches the nasopharynx and directly induces inflammation”

To test this null hypothesis, we decided to study patients with both chronic sinusitis and gastro-oesophageal reflux. The patients who suffered from chronic sinusitis were selected from a specialist rhinology practice. Chronic sinusitis was defined as two or more symptoms of facial pain/pressure, nasal congestion/fullness, nasal obstruction/blockage, nasal discharge or postnasal drainage, or hyposmia/anosmia which persists for more than twelve weeks despite adequate medical therapy. This is in accordance with the definition proposed by Kennedy which is widely accepted in the literature.¹²⁵ These patients with chronic sinusitis were recruited into the study if they also suffered the classical symptoms of gastro-oesophageal reflux disease, namely, epigastric burning or regurgitation. Those patients who showed clinical evidence of gastro-oesophageal reflux on clinical examination were also recruited into the study. The signs of gastro-oesophageal reflux include erythema and oedema of the post-cricoid region, arytenoids or the pharynx.¹²⁶ All patients who were recruited into the study underwent 24 hour pH monitoring at the Oesophageal Function Laboratory of the Royal Adelaide Hospital. 24-hour ambulatory pH monitoring

is considered the gold standard for the diagnosis of gastro-oesophageal reflux disease.¹²⁷ However, attempts using conventional pH sensors which are unidirectional to measure acid events above the oesophagus had been complicated by technical difficulties, with loss of mucosal contact leading to artefacts known as “pseudoreflux”.¹²⁸ An example of the unidirectional pH probe and pseudoreflux is demonstrated in figures 5 and 6 respectively.



Figure 5. Typical unidirectional antimony pH sensor

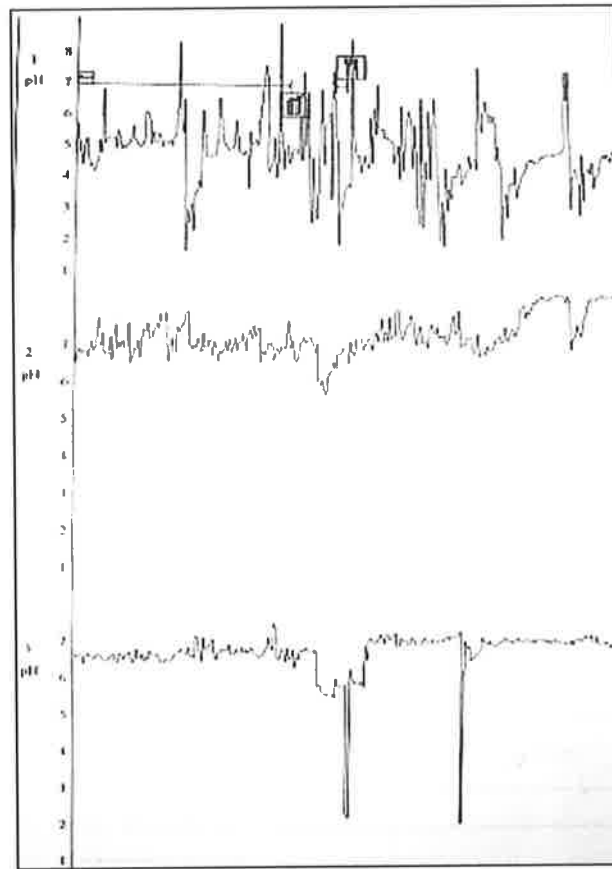


Figure 6. Typical recording of a unidirectional pH sensor showing artefacts and pseudoreflux in the supra-oesophageal sites (See channels 1 and 2 cf figure 7)

To overcome this problem of pseudoreflux, a specially developed pH probe was designed with sensors which were circumferential such that they are able to maintain constant mucosal contact even in the hypopharynx and nasopharynx. An example of the circumferential pH probe and a recording made using this novel sensor is given in figures 7 and 8 respectively. Note the lack of artefacts in the tracing compared with figure 6.

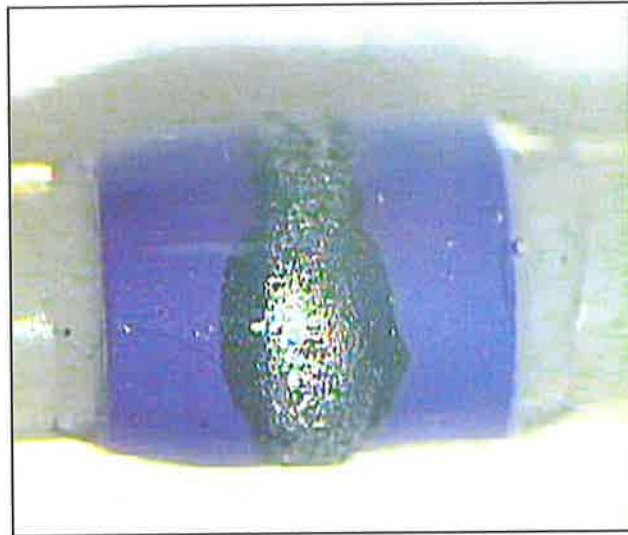


Figure 6. Novel circumferential antimony pH sensor from GastroTech

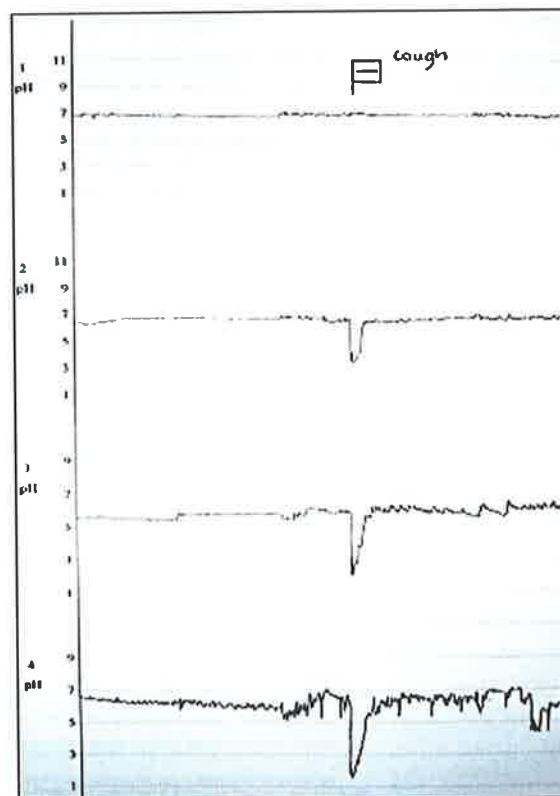


Figure 8. pH monitoring trace recorded using the novel circumferential sensor

All patients recruited in this experiment underwent 24-hour ambulatory pH testing using a 4-channel pH probe which contained these specially designed antimony pH sensors (GastroTech Pty Ltd, North Adelaide, Australia). This probe is adjustable to the patients' oesophageal length because of its bifurcated catheter design. It utilises two conventional unidirectional sensors for the distal and proximal oesophagus and two of the novel circumferential sensors for the hypo- and naso-pharynx. The design of this bifurcated catheter is illustrated in figure 9.

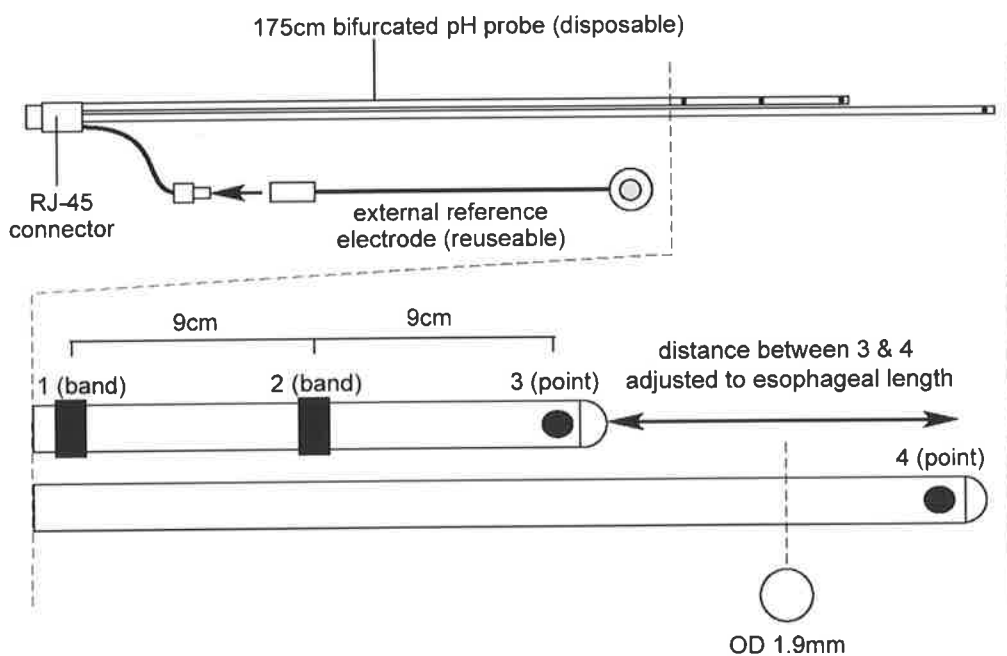


Figure 9. Schematic diagram of GastroTech[®] 4 Channel ENT monitoring catheter

Patients who were taking proton pump inhibitors were instructed to cease their medical therapy for 5 days before testing. Those taking H₂-antagonists were similarly stopped 2 days prior to the test. Antacid treatments were withheld on the day of testing. Patients were fasted for at least 6 hours prior to commencement of the test. In all patients a standard manometric study was performed prior to insertion of the catheter to determine the position of the upper and lower oesophageal sphincters. After standard calibration of the pH probe in reference solutions of pH 1 & 7, the catheter was then introduced via the nostril, with the sensors positioned accordingly as shown in figure 10. The external reference was then adhered to the chest wall.

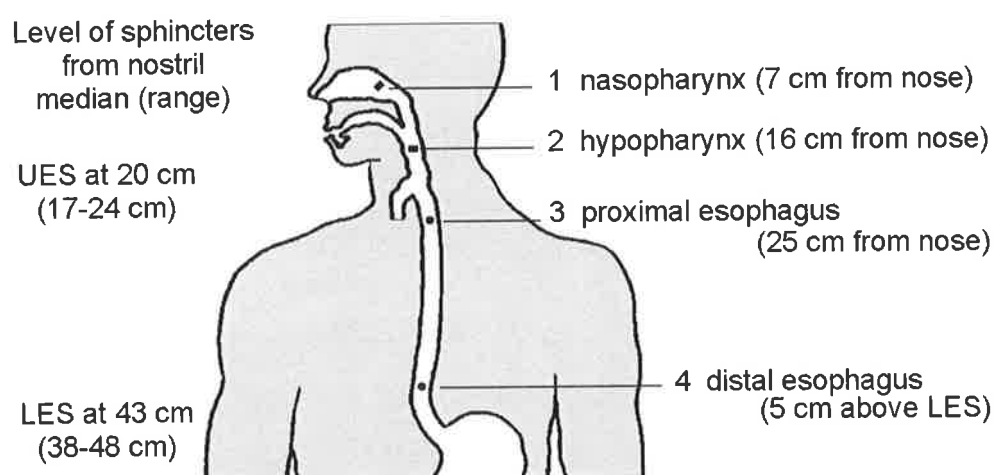


Figure 10. Sensor positioning in relation to the nose and upper and lower oesophageal sphincters (UES, LES)

The pH probe was then attached to a portable pH data logger (Mk III Digitrapper, Medtronic Inc., Salt Lake City, Utah). This unit is shown in figure 11 attached to the pH probe.



Figure 11. Photograph showing the 4 channel pH probe connected to the Digitrapper Data Logger

The patients were requested to keep a diary of all oral intake, as well as any symptoms and change in posture (upright or recumbent). The patients were instructed to refrain from acidic food and beverages, but to carry out their usual activities as normally as possible. Recordings were downloaded to a computer for analysis using a dedicated software (EsopHogram v2.01, Medtronic Inc). A reflux episode was defined as a fall in pH from above to below 4.0 for > 4 secs in the distal oesophagus and the proximal extent of each GER was indicated by a

sequential pH drop of >1 pH unit in the proximal channels. A diagnosis of gastro-oesophageal disease was made in patients with a reflux index (percentage of time at pH < 4 at the distal oesophagus) of greater than 7.0%. Those with a reflux index less than 4.0% were regarded as normal. The diagnosis was considered inconclusive for those with a reflux index between 4.0% and 7.0%.

This study was performed with approval from the ethics committee of the Royal Adelaide Hospital. Statistical analyses were performed using the software *SPSS v 11.0* (Chicago, Illinois). Proportion of patients diagnosed with GER was compared using the Chi-square test. Reflux indices and number of reflux episodes were compared using the Mann-Whitney-U test. Significance level was set at $p < 0.05$.

Experiment 2

Hypothesis:

“There is no neural reflex relating the oesophagus and the mucosa of the nasal cavity which is triggered as acid is refluxed into the oesophagus”

To reject this null hypothesis and to demonstrate that a reflex does in fact exist, we decided to determine if there is any measurable nasal response when the oesophagus is challenged with a Bernstein test. This is in accordance with similar studies which had been performed demonstrating a vagally mediated response in the lower respiratory tract when acid is instilled into the oesophagus. For the purpose of this experiment, we decided to use healthy volunteers as the subjects for our study. These volunteers were recruited from students of a number of university campuses. Advertisements were placed on student notice boards of various academic departments with permission of each department as well as the universities.

Subjects who responded to the advertisements were given information about the study by telephone with opportunities to ask questions about any aspect of the procedure which they failed to understand. Those subjects who remained interested in the study after this initial discussion were then given appointments for a screening interview. During this interview a medical history was obtained

from the subjects and particular attention was given to any history of sinusitis, reflux, asthma, eczema or allergic rhinitis. These subjects were excluded from the study. Smokers and patients with previous sinonasal surgery were also excluded from the study. Those subjects who had not met any of these exclusion criteria were then examined for any abnormalities of their nasal airway. Anterior rhinoscopy and nasendoscopy was performed in these subjects. Those subjects with a rhinitic appearance of their nasal mucosa or a grossly deviated nasal septum were excluded from the study. Subjects with nasal polyposis or with presence of mucopus in the nasal cavities were also excluded. A RAST test was organised for the subject and this screened for specific IgE to respiratory allergens including, grasses, moulds, animals, and house dust mite. Patients with a positive RAST test indicative of allergy were excluded.

Volunteers who were deemed to be appropriate for the study after the screening clinical evaluation were then given a trial run of the experimental procedure. The purpose of this was to allow the subjects to familiarise themselves with the sampling technique in order to prevent any inadvertent loss of critical samples during the actual study. It also provided a true impression of the experimental procedure for the volunteers so that informed consent could be obtained prior to progressing with the study. Adjustments could also be made so that the instruments and equipment utilised during the experiment could be tailored to suit the individual subject.

All subjects were fasted for 6 hours prior to the commencement of the experiment on the day of testing. All subjects were tested at the same time in the afternoon. After arriving at the oesophageal function laboratory all subjects underwent routine manometry using a multichannel catheter. Figure 12 is a photograph of the catheter used in this experiment.

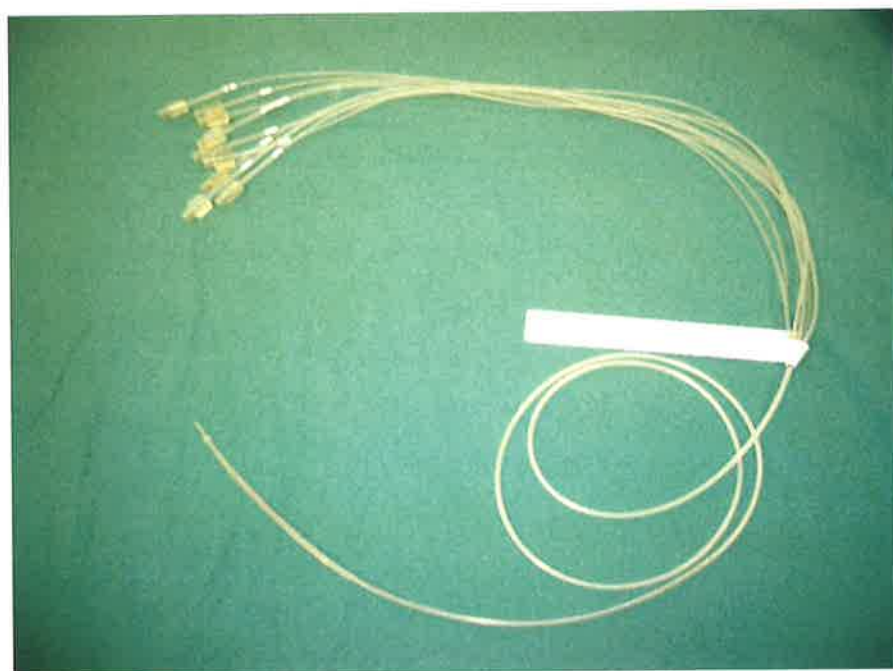


Figure 12. Photograph of the multichannel manometry catheter

This manometry catheter has 8 channels which are connected to pressure sensors and an infusion channel which expels infused solutions at 10 cm above the distal tip. The location of the lower and upper oesophageal sphincters were identified through the manometry study.



Figure 13. Study subject undergoing manometry study. The pressure transducers and the recording tracing can be seen in the background.

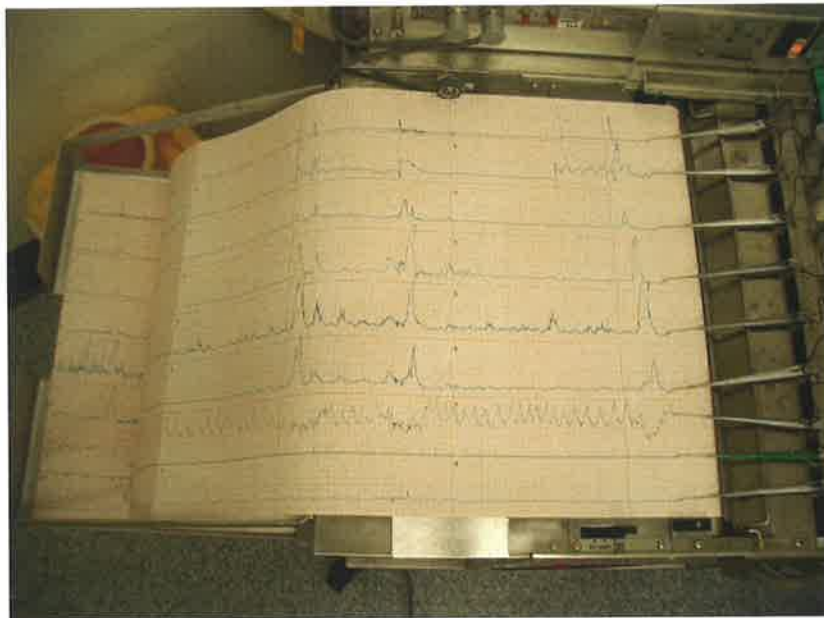


Figure 14. An example of the manometry trace recording showing sequential pressure changes during a normal swallow.

Once the location of the lower oesophageal sphincter was identified the catheter was then positioned such that the tip of the catheter was just proximal to the gastro-oesophageal junction. This was to standardise the site of solution infusion in all study subjects relative to the lower oesophageal sphincter. The catheter was then secured in place with adhesive tapes. A pre-baseline nasal lavage was then performed using the nasal pool device.¹²⁹ The nasal pool device, designed in Lund, Sweden as pictured in figure 15 is a squeeze bottle with a nasal adaptor which fits snugly within the alar rim of the subjects. It can be filled with various solutions which will then bathe the nasal cavity for as long as the subjects maintain compression of the device. When the device is released, the lavage fluid is then recollected into its chamber and the sample can then be analysed for various biochemical markers.



Figure 15. "Nasal Pool Device"



Figure 16a. Subject performing a nasal lavage using the nasal pool device



Figure 16b. Subject performing a nasal lavage using the nasal pool device. The manometry catheter can be seen in the alternate nasal cavity

The purpose of the pre-baseline lavage was to remove any secretions already on the mucosa of the nasal cavity. It also allowed the subjects to have further practice of the sampling procedure. 15 mls of normal saline was utilised in the pool device for each lavage during this experiment. The initial pre-baseline lavage was of 5 minutes duration. This sample was collected and stored for analysis. To ensure that the nasal cavity was devoid of pre-existing secretion, two further lavages of 2½ minutes duration was also performed in series as a “wash-down”. These samples were discarded. The subject then spent a period of 30 mins in quiescence completing a standard questionnaire. The questionnaire enquired about gastro-oesophageal as well as sinonasal symptoms and a copy is attached in the appendices.



Figure 17. Subject completes a questionnaire after pre-baseline lavages

After this time period has passed, the true baseline lavage is then collected using the described technique. The duration of this lavage was once again 5 minutes. A baseline nasal inspiratory peak flow was also recorded at this time using the In-Check Nasal Device (Clemente Clarke International, London). Three measurements were taken with instruction from the investigator to ensure correct technique and maximal effort was achieved. The subjects were asked to expel all air from their lungs, then place the peak flow meter on their face, and to ensure complete seal with the mask before maximally inspiring through their nose. The best of the three readings was then recorded and utilised for analysis



Figure 18. Subject undergoing nasal inspiratory peak flow measurement.

At this point of the experiment, the subject was also asked to rate their overall sinonasal symptoms and to give a score between 0-10. After this the infusion channel of the manometry catheter is connected to a Gemini pump via a giving set. The purpose of using a Gemini pump is so that 2 different solutions can be infused with minimal disturbance to the subject and the manometry catheter.



Figure 19. Gemini pump used in the experiment for infusion of the solutions via the manometry catheter.

The Gemini pump has two separate channels for infusion and both can be individually controlled for flow of solution at a precisely specified rate. The subject then undergoes an infusion of normal saline solution. 100 mls of solution was infused over 15 mins.



Figure 20. Infusion of normal saline solution through the infusion port of the manometry catheter.

After this infusion was complete, the subject was once again asked to rate their sinonasal symptoms as a score between 0-10. A five minute nasal lavage was collected at this point, after which a measurement of nasal inspiratory peak flow was taken by the described technique.

Once all this data were recorded the Gemini pump was then switched over to the other channel which contained 100 mls of 0.1N hydrochloric acid. This was once again infused over 15 mins. After the infusion of acid was complete the same

measurements were once again collected, namely, a 5 minute nasal lavage, nasal inspiratory peak flow, and a sinonasal symptom score out of 10.

At 30 minutes after the commencement of acid infusion, the subject was once again asked to provide a sinonasal symptom score. Another measurement of nasal inspiratory peak flow was also recorded.

At 45 minutes after the commencement of acid infusion, a full set of measurements were once again made. This of course involved a 5 minute nasal lavage, sinonasal symptom score and a nasal inspiratory peak flow.

Once all these measurements are complete, the manometry catheter was then removed. A specially developed 4 channel antimony pH probe, as used in experiment 1 was then inserted. The sensors were once again positioned at 5 cm above the lower oesophageal sphincter, at the upper oesophagus, and also in the hypo- and nasopharynx. As in experiment 1, this catheter was first calibrated in solutions of pH 1 and 7, and was then connected to the datalogger shown in the previous experiment. The subject then undergoes 24 hour ambulatory pH monitoring according the protocol already described previously. A diary of symptoms and diet was collected by the subject during this study.



Figure 21. Once the nasal measurements are complete the subject then spends the next 24 hours with the 4 channel probe and datalogger attached as shown.

The nasal lavage fluids collected during the experiment was rushed to the clinical biochemistry laboratory of the institute of medical and veterinary science (IMVS) adjacent to the Royal Adelaide Hospital. The fluid was then centrifuged at 105g for 10 mins at a temperature of 4°C.



Figure 22. The Collected nasal lavage specimens are centrifuged

The purpose of centrifuging the specimens was to separate all cellular material from the dissolved mucous. The supernatant was then pipetted away and separated into 2 identical 5 mls sample tubes with a screw lock cap.



Figure 23. The samples are split into two identical specimens and labelled with only a number and designation.

Both samples are marked with an identical reference number. One specimen from each patient was labelled “Adelaide” and stored at IMVS. The second sample was labelled “Lund” and again stored at -20°C . Once sample collection was complete, the specimens designated for Lund were sent there frozen via a medical courier for biochemical analysis. The fucose levels of each specimen was then determined, as it is a marker of nasal secretion.¹³⁰ The laboratory in Sweden was blinded as to the details of the samples as they were labelled by only a number. The results were then returned to Adelaide, where interpretation and statistical analyses were carried out. These were performed using the software SPSS v 11.0 (Chicago, Illinois).

The protocol for this study was approved by the ethics committee of the Royal Adelaide Hospital. Photographs of the subject illustrating the experimental

procedure are printed with written permission from the subject. For clarity, figure 24 is a summary of the timing of the nasal lavages collected during this experiment.

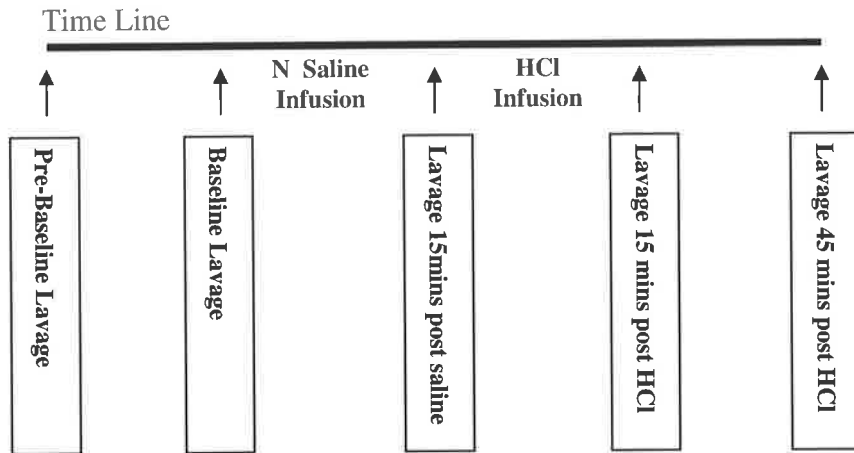


Figure 24. Timing of the nasal lavages collected during this experiment.

Results

Experiment 1

Subjects

In total, forty patients underwent 24-hour pH testing. Twenty five (62.5%) of the subjects were female and fifteen (37.5%) were male. The mean age of the subjects was 56.3 years (range 17 – 76). Nineteen of the forty patients were on anti-reflux regimens prior to the test. Of these, two failed to cease their medication according to their instructions. One further recording was judged to be technically inadequate. Therefore, a total of thirty seven meaningful studies were obtained from the forty patients.

Diagnosis of Gastro-Oesophageal Reflux

Seventeen of the thirty seven patients reported symptoms of gastro-oesophageal reflux at the time of testing. The median reflux index was 4.2% (IQR 1.0 – 7.9). In 19 of the patients, which represented 51.4% of the study sample, the 24 hour pH study was regarded as normal. Abnormal 24 hour pH monitoring recordings were then returned from the other 18 patients, which amounted to 48.6% of the subjects in experiment 1.

Profile of Reflux Episodes

A total of 809 reflux episodes were recorded from the thirty seven studies. Figure 25 shows the distribution of these episodes in terms of their proximal extent. Of

the 809 recorded episodes, only 2 episodes (0.2%) reached the nasopharynx. These were seen in 2 separate patients. Both of these patients were females aged in their sixties. In both of these patients the 24 hour pH study was considered abnormal with reflux indices of 14.6% and 6.3% respectively.

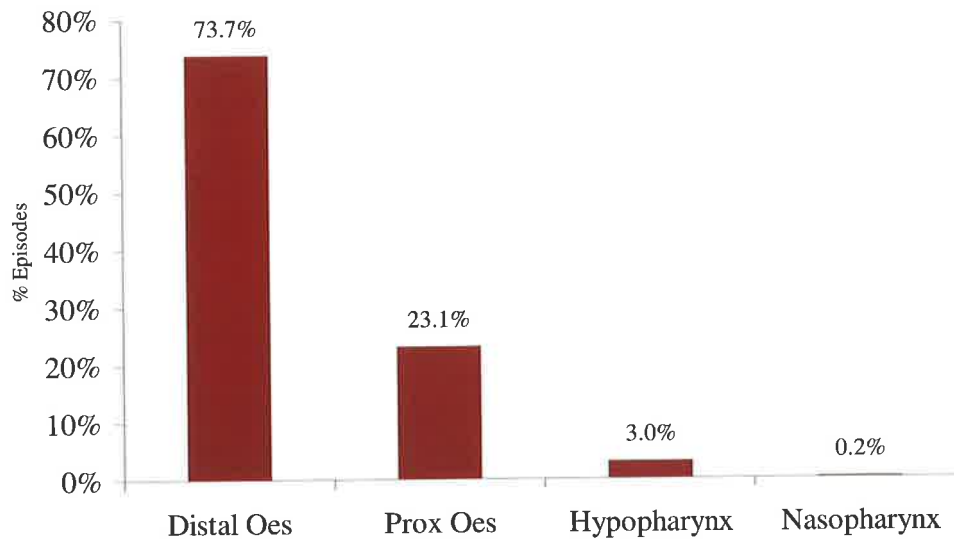


Figure 25. Proximal extent of the 809 recorded episodes of reflux. Only 2 episodes reached as cephalad as the nasopharynx

In addition to these two, another ten patients recorded acid reflux episodes reaching the hypopharynx. Only one acid episode was recorded in the majority (55%) of these patients. A total of 24 episodes were recorded at this site, representing only 3% of all the recorded episodes. Nearly all (95.8%) of the supra-oesophageal reflux episodes were recorded in the upright position. There was no significant relationship between the number of reflux episodes or reflux index and any patient characteristic.

The median percentage of time at pH less than 4 was 3.9% (IQR 1.1 – 6.4), 0.2% (IQR 0 – 0.7), 0.0% (0 – 0), and 0.0% (0 – 0) at the distal oesophagus, proximal oesophagus, hypopharynx and nasopharynx respectively. The profile of pH recorded at each sensor is shown in figure 26.

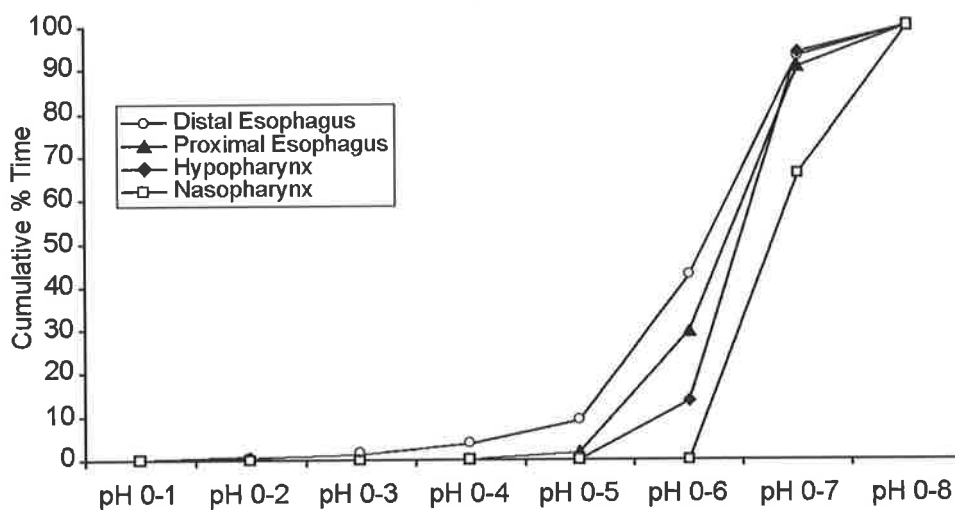


Figure 26. Profile of pH recorded at each sensor

It can be seen from this graph that during the total recorded time through every 24 hour ambulatory monitoring, the nasopharyngeal probe (represented by the square dots) almost never ventured below pH of 6. All pH recording tracings were meticulously reviewed by our laboratory technician and the circumferential sensor used in the hypo- and nasopharynx exhibited a stable baseline largely free of artefact.

Experiment 2

Subjects

The first ten volunteers to meet the inclusion and exclusion criteria were entered in the study. All subjects were therefore devoid of any sinonasal pathology or symptoms of gastro-oesophageal reflux. RAST testing on all subjects were negative. Out of the ten subjects, nine were female and one was male. The mean age of the subjects was 27.4 years (range 18 – 52).

Diagnosis of Gastro-Oesophageal Reflux

The median reflux index was 1.6% (Interquartile range 0.4% - 4.4%). One of the ten studies was judged abnormal with a reflux index of 8.9%. Therefore 10% of the study sample returned a 24 hour pH study which is consistent with a diagnosis of gastro-oesophageal reflux.

Profile of Reflux Episode

A total of 267 reflux episodes were recorded during the ten studies. Of these, 67.3% was detected only in the distal oesophageal probe, whereas 23.4% reached as high as the proximal oesophagus. Only 3.9% of all the recorded reflux episodes were registered in the supra-oesophageal probes. All of these 11 episodes climbed as cephalad as the hypopharyngeal probe, with none of the reflux episodes reaching the nasopharynx at all. Figure 27 is a graphic

representation of the distribution of the reflux episodes in terms of their proximity of extension.

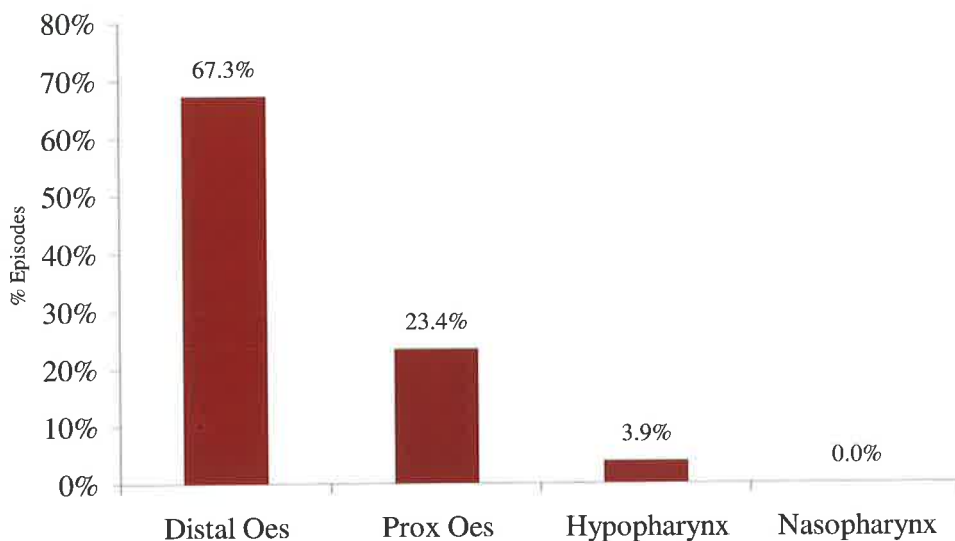


Figure 27. Proximal extent of all recorded reflux episodes.

Comparison with Chronic Sinusitis Patients

The profile of the reflux episodes in terms of their proximal extension were compared with that of patients with chronic sinusitis as gathered in experiment one. There was no statistical difference in the distribution of the reflux episodes in their proximal extent between these two groups of patients. ($p = 0.60$; $\chi^2 = 1.874$; $df = 3$)

Sinonasal Symptom Profile

Table one represents the nasal symptom profile of all the subjects prior to the study. The subjects rated a score on a visual analogue scale between 0-10, with 10 being the maximum.

Subject	Nasal Congestion	Head-ache	Facial pain	Alteration in smell	Nasal Discharge	Sneezing	Overall Score
1	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0
4	2	0	0	0	4	0	1
5	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0
7	1	0	0	0	2	0	1
8	0	0	0	0	0	0	0
9	0	0	0	0	0	1	0
10	3	0	0	0	3	0	3

Table 1. Profile of sinonasal symptoms of the study subjects as represented by visual analogue scores (0-10)

Effect on Sinonasal Symptoms

The subjects were asked to rate their overall sinonasal symptoms as a score between 0-10 at various points during the study. These points were at baseline; at 15 mins post infusion of normal saline; at 15 mins, 30 mins and 45 mins following the infusion of 0.1N hydrochloric acid. Most subjects did not notice any significant change in their sinonasal symptomatology during the study. These results are presented in table 2 and figure 28.

Subject	Symptoms Baseline	Post Saline	15 mins Post HCl	30 mins Post HCl	45 mins Post HCl
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
4	1	3	3	1	1
5	0	0	0	0	0
6	0	0	0	0	0
7	1	2	2	4	2
8	0	0	2	2	2
9	0	0	1	1	0
10	3	3	2	2	2

Table 2. Effects of oesophageal saline and acid infusion on sinonasal symptom scores (0-10)

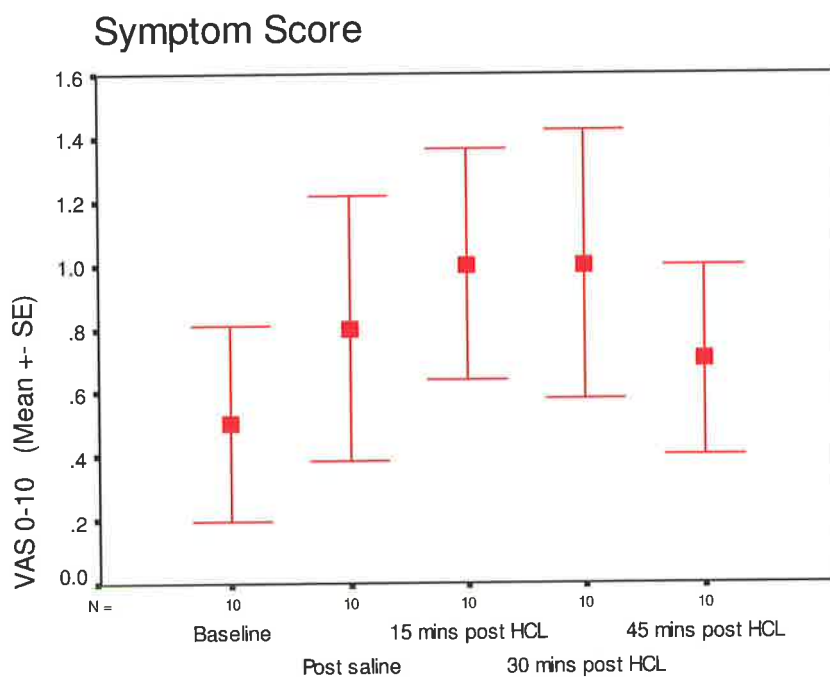


Figure 28. Effect of oesophageal infusion of normal saline and acid on mean sinonasal symptom score

Although the mean symptom score was higher following oesophageal infusion of saline and acid, this difference was not statistically significant. (Friedman test; $p = 0.443$). There was a trend for the symptom scores to return to baseline levels at 45 mins following the infusion of HCl.

Effect on Gastro-Intestinal Symptoms

The Bernstein test were negative for all ten subjects and none of them reported any heartburn during the infusion of either saline or acid. However, a significant proportion of the subjects reported that they could detect a sensation of a fluid being infused into their oesophagus. Most subjects reported this sensation as a “cold feeling”.

Effect on Nasal Inspiratory Peak Flow

Nasal inspiratory peak flow was measured for each subject at the same point in time during the study as the symptom scores were collected. The results are presented in figure 29.

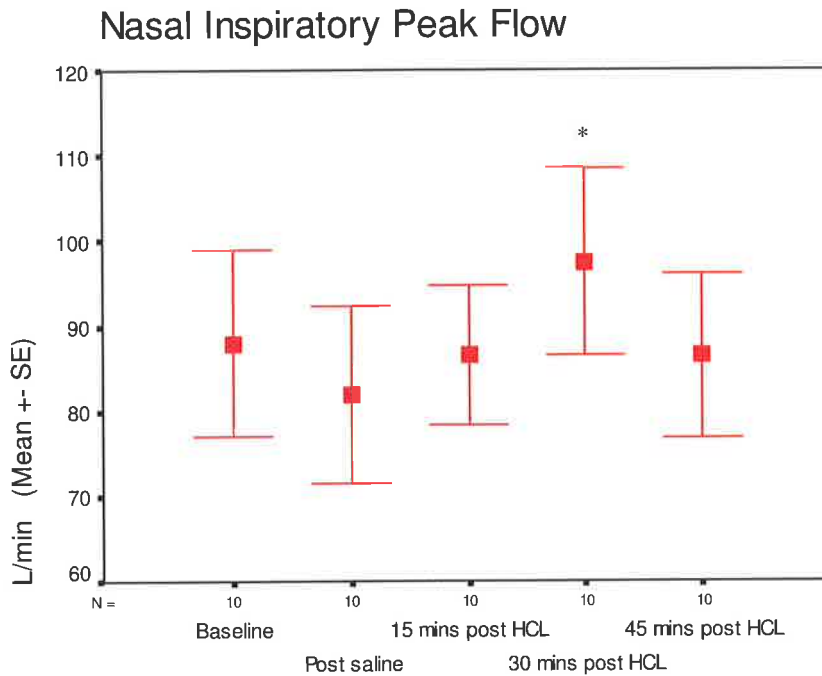


Figure 29. Nasal inspiratory peak flow measurements.

* $p = 0.036$ when compared with post saline measurements and $p = 0.024$ when compared with 15 mins post HCl (Wilcoxon signed ranks test)

A clear trend can be seen in the graphic representation of the nasal inspiratory measurements in figure 29. There appeared to be a reduction in nasal patency following infusion of saline in the oesophagus when compared with baseline also this difference was not statistically significant. A smaller reduction was detected 15 mins following the infusion of HCl. There was significant improvement of nasal patency at 30 mins following HCl infusion. At 45 mins post HCl infusion, nasal inspiratory peak flow measurements appeared to return to baseline levels.

Effect on Nasal Lavage Fucose Levels

Nasal lavages were collected from each subject prior to the commence of the study; after a “wash-down” to achieve a uniform baseline; then at 15 mins following saline infusion and at 15 and 45 mins following HCl infusion. The fucose concentrations of the nasal lavages are presented in figure 30.

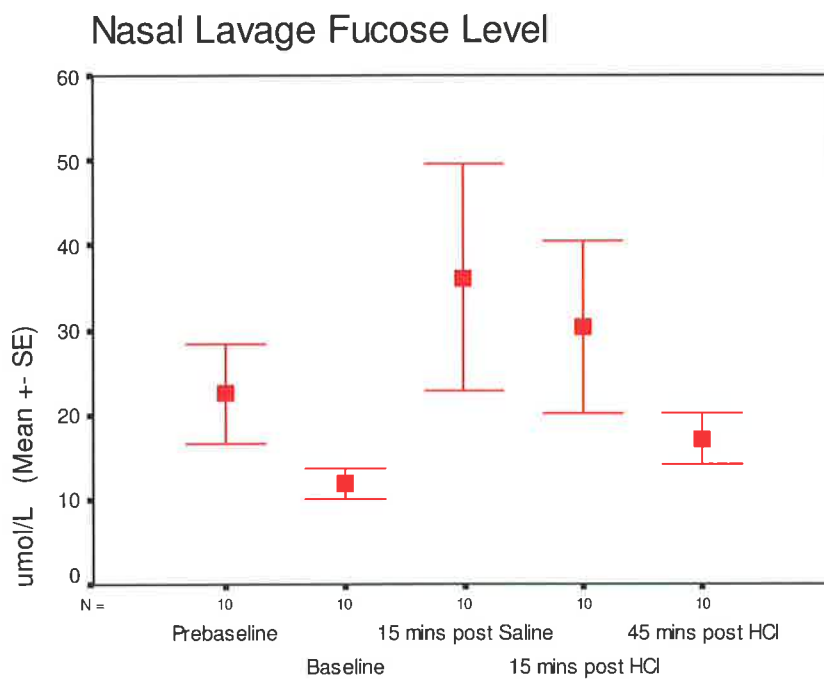


Figure 30. Nasal lavage fucose levels

A similar trend which reflects the nasal inspiratory peak flow measurements can be seen in the nasal lavage fucose levels. There appeared to be a parasympathetic response in the nasal cavities when saline was infused into the oesophagus. This effect seemed to fade at 15 mins following the infusion of HCl into the oesophagus. By 45 mins after the infusion of HCl, the fucose levels appeared to

return to baseline levels. Although this trend is clearly evident from the graphic representation of the results, the differences measured in this parameter did not quite reach statistical significance (Lowest p -value = 0.11 between baseline and 15 mins post saline; wilcoxon signed ranks test). Figure 31 demonstrates the progression of nasal lavage fucose levels for each individual subject.

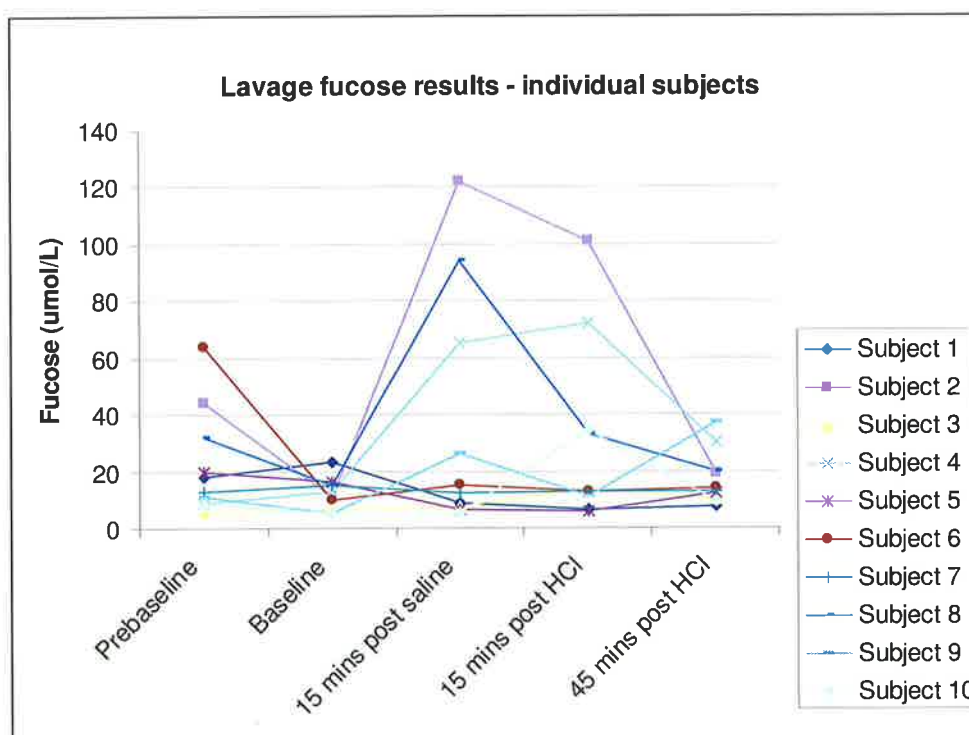


Figure 31. Trend of nasal lavage fucose concentration for each of the ten subjects

Discussion

Gastro-Oesophageal Reflux Disease

Mankind has suffered from gastro-oesophageal reflux disease since prehistoric times. Over 4000 years ago, Chinese herbalists had been reported to have treated dyspeptic symptoms with alkali substances such as extracts of seminal fluid and baby urine. Caius Pliny effectively relieved symptoms of reflux with coral powder and milk in the first century. However, it was not until the late nineteenth century that Rokitansky suggested gastric acid could be responsible for pathology in the oesophagus. The pathophysiology of this condition continued to baffle clinicians for half a century, when in 1946, Phillip Allison of Leeds proposed hiatal herniation as a possible mechanism for “reflux oesophagitis”, a term introduced by Norman Barrett in 1950.³¹ Since that time, the prevalence of gastro-oesophageal reflux had been steadily rising, so much so that it is now the most common gastrointestinal disorder in the western world. As reported in the review of the literature previously, some 20% of the adult population regularly suffers dyspeptic complaints.

The reason for the rising prevalence of gastro-oesophageal disease is unclear, and it stems from the fact that even today, there is still ongoing debate amongst gastroenterologists and gastrointestinal surgeons about the pathogenesis of the disease. Prevention of gastric contents refluxing into the oesophagus is afforded by the lower oesophageal sphincter. The lower oesophageal sphincter is a 3 – 4 cm long segment of tonically contracted smooth muscle at the distal end of the oesophagus. The maintenance of its contraction is a function of both the

surrounding musculature as well as extrinsic innervation via the vagus nerve. As a swallowed bolus is propelled distally by peristalsis, the lower oesophageal sphincter relaxes to permit the entrance of the bolus into the stomach. One assumes that at other times, the contraction of the lower oesophageal sphincter is maintained, but it is clear now that this is not the case. The lower oesophageal sphincter in fact periodically relaxes in what has been termed “transient lower oesophageal sphincter relaxations” (TLSR’s).¹³¹ It is well documented that patients with gastro-oesophageal reflux disease have reduced lower oesophageal sphincter pressures and that increasing this pressure, which is the surgical basis of Nissen’s fundoplication, ameliorates the symptoms of reflux. Recent research shows that in up to 80% of patients with gastro-oesophageal reflux, the acid reflux episodes are associated with TLRS’s. Little is known about physiological regulation of TLRS’s and less about its pathological significance, but it seems that hiatal herniation increases the frequency of TLRS’s. This would support the postulates proposed by Allison back in the forties.

It is with this hiatal hernia theory in mind that Stephen Sontag, a gastroenterologist from Chicago, proposes several intriguing theories why gastro-oesophageal reflux is becoming more prevalent.¹³² It would appear that the rise of gastro-oesophageal reflux is associated with the western diet and lifestyle. There is a wide geographical distribution of gastro-oesophageal reflux disease and in third world countries such as Senegal, its rate remains as low as 1%. Sontag offers three hypotheses for the development of hiatal hernias and why “*after 1.5 million years of standing erect, we have evolved into a species*

that is destined to live with the scourge of gastro-oesophageal reflux disease”.

His first hypothesis is that the hiatal hernias may be congenital, and this is supported by prospective studies that hiatal hernias in infancy persist into adult life. His second hypothesis is that an acute traumatic event to the abdomen or chest permanently disrupts the antireflux barrier. Although there are no studies to demonstrate this effect, Sontag based this speculation on several case reports where this has occurred.

The third hypothesis which Sontag proposes is that instead of a single traumatic event, the anti-reflux barrier is weakened over time through chronic trauma as a result of years of straining to defaecate. Two aetiological factors for this are alleged by Sontag and these are firstly, eating a low fibre diet and secondly, living on the high-seated toilet. Insufficient dietary fibre results in small calibre stools which can only be expelled by generating and maintaining very high abdominal pressures. The high-seated toilet promotes a physiologically unsound position during defaecation which during straining, directs abdominal forces upwards through the oesophageal hiatus. Sontag concluded that the low fibre diet and *“abandoning the popular and worldwide practice of squatting to defaecate”* may be responsible for up to 90 percent of the gastro-oesophageal reflux disease seen in western civilisations. However, regardless of the underlying reason, the fact that gastro-oesophageal reflux disease is increasing compels us an impetus to further understand its pathophysiology and its relation to the plethora of complications with which it has been associated. Chronic sinusitis is, but one of the many sequaelae which has been linked to this ailment.

Relationship to Chronic Sinusitis

We had already outlined in the review of the literature that there appears to be support for a relationship between gastro-oesophageal reflux disease and chronic sinusitis. It is difficult to delineate the exact mechanism by which the two conditions are related because both chronic sinusitis and gastro-oesophageal reflux are such highly prevalent diseases, thereby providing a great opportunity for confounding variables to lurk. As discussed previously, the current prevailing theory is that direct reflux of acid into the nasal cavity produces injury and inflammation. The evidence for this in the literature is however extremely poor. We hypothesised that an alternative mechanism exists which involves a vagally mediated neural reflex between the oesophagus and the respiratory mucosa of the nose and the paranasal sinuses. A similar reflex has already been established between the oesophagus and the respiratory epithelium of the bronchopulmonary system. It was the aim of the current project to show that such a reflex also exists between the nasal cavity and the oesophagus.

Experiment 1

In order to show that the inflammation in the nasal cavity responsible for chronic sinusitis results from a neural reflex and not from direct acid exposure we necessarily needed to demonstrate in the first instance that refluxed gastric acid

did not reach the nasopharynx. This was the main objective of experiment 1. We chose patients with both chronic sinusitis and gastro-oesophageal reflux as subjects for this study because this is the group of patients that we would possibly expect to find refluxed acid from the stomach in the nasopharynx if such an event did occur. And indeed, the results of experiment 1 confirms the association of chronic sinusitis and gastro-oesophageal reflux disease as 51.4% of the subjects had abnormal 24 hour pH studies, a figure more than double what we would expect in the general population.

Through the use of the innovative circumferential pH sensors, we were able to detect only 2 episodes of gastro-oesophageal reflux that reached as high up as the nasopharynx. This result clearly contradicts the theory that direct exposure of acid on nasal mucosa induces the inflammation and hence promotes the sinusitis that is seen in patients with gastro-oesophageal reflux disease. Previous support for direct acid contact with the nasal mucosa came from Contencin and Narcy⁶⁸, who demonstrated a greater number of acid episodes at the nasopharynx in children with chronic rhinopharyngitis compared with controls. This study differs from ours as they utilised a single glass electrode positioned at the nasopharynx, hence the origin of the acid episodes could not be attributed to gastro-oesophageal reflux with any certainty. There is also some evidence to suggest that results from glass and antimony pH electrodes are not comparable, with glass electrodes being more sensitive and responding faster than their metal counterparts.¹³³ Furthermore, an acid episode was defined as pH < 6 in this study, which may have over estimated the number of events.

Phipps and colleagues⁶⁹ also investigated nasopharyngeal reflux, this time using dual probe pH monitoring. In their study, nine of the 30 children with chronic sinus disease recorded reflux episodes that reached the nasopharyngeal probe. There were no controls in their study for comparison (because of ethical constraints). This study also differs from our study as, like the French study of Contencin and Narcy, Phipps and co-authors studied patients in the paediatric population and the findings may not necessarily be extrapolative to the adult situation. As already discussed, the pathophysiology of gastro-oesophageal reflux disease is complicated and not completely understood, but many differences between the paediatric and adult patient have been identified. The most important of which being the fact that gastro-oesophageal reflux is more likely to extend higher in infants, due a shorter oesophagus and lower oesophageal lumen volume relative to gastric volume.¹³⁴ Recent intraluminal impedance studies in infants have observed that over 80% of liquid gastro-oesophageal reflux episodes reach the hypopharynx. This is much higher than that observed in adults (33%) using the same technique.¹³⁵ These observations indicate that the potential for supra-oesophageal penetration of refluxate may be much greater in infants and children compared to adults.

The role of gastro-oesophageal reflux in adult patients with chronic sinusitis was examined by Ulualp and associates⁷² using a 3 site oesophago-pharyngeal pH monitoring technique. The highest probe was placed 2cm above the upper oesophageal sphincter in this study, where an increased prevalence of pharyngeal acid reflux events was found in patients compared with controls (7/11, 64% vs.

2/11, 18%). The authors raised this result as support for the role of gastric acid in the pathogenesis of chronic sinusitis. Ulualp's study differs from the present study as we found a much lower rate of hypopharyngeal reflux in patients with chronic sinusitis (11/37, 29.7%). In addition, our data suggest that reflux to the hypopharynx does not necessarily correlate with acid in the nasopharynx, as only two of the twelve patients who recorded reflux reaching hypopharyngeal site and beyond also demonstrated reflux at the nasopharynx. Therefore the inference that acid detected above the oesophagus reaches the nasopharynx cannot be assumed.

Ambulatory 24-hour oesophageal pH monitoring is becoming increasingly important as the standard investigation in the diagnosis of gastro-oesophageal reflux disease.¹³⁶ It is quoted to have a sensitivity of 77% - 100% with a specificity of 85% - 100%.¹³⁷ Its role, however, in the identification of patients with supra-oesophageal reflux is less distinct.¹³⁷ In the past, attempts in monitoring pH above the oesophagus has been hampered by technical difficulties.¹²⁸ A constant electrical contact between the pH sensor and the reference skin electrode is required for a stable recording. The intermittent drying of an electrode in the pharynx often resulted in a wandering baseline as well as the phenomenon known as "pseudoreflux".¹²⁸ In a recent study of 20 healthy volunteers using a 3 channel catheter, 10 of the subjects exhibited pseudoreflux at the hypopharyngeal probe.¹³⁸ Such normative data is of concern when one interprets the current literature and raises the possibility that the abnormally high rate of pharyngeal reflux observed by Ulualp et al may have been erroneously produced, at least in part, by pseudoreflux. In contrast, we found that the

circumferential “band sensor” used in the current study was able to maintain mucosal contact and produce a stable baseline without any documented episodes of pseudoreflux.

DelGaudio⁷³ reported his investigation into nasopharyngeal reflux amongst a group of patients with refractory chronic sinusitis in a study sponsored by AstraZeneca. The patient group consisted of patients requiring revision endoscopic sinus surgery whereas the control group consisted of both patients who had successful endoscopic sinus surgery as well as patients without chronic sinusitis. He studied these patients with a 3 channel catheter with sensors positioned at the upper oesophageal sphincter, the distal oesophagus and at the nasopharynx. He was able to demonstrate a statistically higher rate of nasopharyngeal acid reflux in the patient group with refractory sinusitis compared with the control group. Fifteen out of the 38 patients with refractory sinusitis showed nasopharyngeal reflux, whereas 3 of the 30 subjects in the control group showed nasopharyngeal acid reflux. DelGaudio concluded that direct nasopharyngeal acid reflux is a contributing factor in refractory chronic sinusitis, which is in stark contrast to the results presented in the present study.

There are several possible reasons why DelGaudio returned such different results in comparison with the findings of our current study. There is a clear difference in the design of the pH probes used in the respective studies. DelGaudio utilised a single catheter with 3 sensors which is placed under endoscopic control to ensure placement of the upper-oesophageal sphincter sensor. The other two

sensors are at a fixed distance away from this sensor. Although this catheter is ideal for the otolaryngologist to measure laryngopharyngeal reflux, it unfortunately cannot guarantee the placement of the other two channels in the nasopharynx or the oesophagus. Thus it is conceivable that in a patient with higher pharyngeal height, the nasopharyngeal sensor may well be situated in the oropharynx. This is a problem which we overcame with the bifurcated design of our catheter, which allows individual adjustment of the oesophageal as well as the nasopharyngeal sensors. As described earlier, the problem with pseudoreflux would interfere with pH monitoring results obtained using conventional sensors above the oesophagus. It seems that there is at least some artefact affecting DelGaudio's results, as one of his controls without sinusitis registered 46 episodes of nasopharyngeal acid reflux in a 2 hour period. DelGaudio excludes this "outlier" in some of his statistical analyses.

If direct acid exposure was responsible for mucosal inflammation perpetuating chronic sinusitis, then one might expect that the most posteriorly placed sinus, namely the sphenoid sinus, to be involved more frequently than the other sinuses. Recent studies have shown that isolated sphenoid disease is uncommon, representing only 1% of all cases.¹³⁹ The results of experiment 1 conclusively demonstrate that reflux of gastric acid up to the nasopharynx is a rare event and rejects the hypothesis that direct acid exposure is responsible for the inflammation leading to chronic sinusitis. The fact that there was no statistical difference in the distribution of reflux episodes between the patients with chronic

sinusitis and the healthy volunteers of experiment 2 provides further support that an alternative mechanism exists.

Experiment 2

In experiment 2, we set out to attempt to investigate a reflexive link between the oesophagus and the nasal cavity. To our knowledge, this had not been endeavoured by any other research group in the past, and as such there are no studies in the literature for comparison of our results. The protocol that we used in our effort to research such an oesophago-nasal reflex is based on the Bernstein challenge test which simulates reflux by instilling acid into the oesophagus. This is similar to the method utilised by respiratory researchers to elicit a reflex between the bronchial airway and the oesophagus.

We chose healthy volunteers without sinusitis or gastro-oesophageal reflux symptoms for this experiment as these subjects will be least likely to have any pre-existing reactivity in either their nasal cavity or their oesophagus. Thus any change that was observed in any of the outcome measures utilised in this experiment can be unequivocally attributed to a simulated reflex, rather than any concurrent disease states. We were meticulous in our screening of the volunteers for any evidence of sinonasal disease, and it can be seen in table 1 that this group of subjects had extremely low sinonasal symptom scores.

There was a small rise in mean symptom score from baseline after the infusion of saline and at 15 mins following acid infusion, with a fall back towards baseline level at 45 mins following acid infusion. A similar pattern can be seen in both of the other two outcome measures utilised in this experiment. With nasal inspiratory peak flow, once again, a trend can be seen with a fall in nasal patency from baseline after the infusion of normal saline and after acid infusion. The patency then returned to baseline levels 45 mins following the infusion of acid. The same trend is also seen in the nasal lavage fucose levels. There was a rise in the nasal mucous production from baseline levels after the infusion of normal saline, which then appeared to wane 15 mins following the infusion of 0.1N HCl. As in the other parameters, there was a fall back to baseline levels at 45 mins after the infusion of acid. Although a clear trend can be seen in all 3 of the parameters, as presented in graphical form, these changes did not quite reach statistical significance due to the small number in our series. However, because the same pattern can be seen in all three parameters, we can be relatively confident that the changes observed are due a *real* effect rather than produced by chance alone, even though it does not meet this criteria by statistical standards.

The results of experiment 2 were somewhat surprising to us, as there appeared to be trend towards demonstration of a parasympathetic nasal response when the oesophagus was stimulated with saline. The design of the protocol was aimed at showing the effect of acid infusion, with the infusion of normal saline beforehand intended as a control. This was based on previous research carried out to demonstrate a reflexic response of the bronchial airway when acid is

infused in the oesophagus, which can be seen in both animal and human experiments. In the majority of these studies, no effect was detected after the infusion of normal saline, but a response was obtained in the presence of acid in the oesophagus. Some of our subjects appeared to have responded to normal saline infusion which was unexpected and certainly not predictable from the results of previous studies from the lower airways. This is obviously worthy of further research. There is however, discrepancy in the literature even amongst the studies performed investigating the bronchial airways, as outlined below.

Schan et al¹¹⁹ was able to demonstrate a reduction in peak expiratory flow rate with the Bernstein challenge. Similar changes in airway hyper-responsiveness was documented by Wu et al¹²². These and other confirmatory studies followed initial work by Mansfield in both humans and dogs, who was able to demonstrate reduced airway conductance when the oesophagus was infused with HCl.¹¹⁴ During the canine experiment, Mansfield was also able to document an identical reflex with distension of the oesophagus alone. Hence it would appear that the reflex induced by the oesophagus on the airway is indiscriminate of the type of sensory afferent which is triggered by the initiating event. In contrast to these studies however, other authors, such as Perpina et al¹¹⁸ and Field et al¹¹⁶ failed to demonstrate any change in respiratory parameters when their subjects were infused with either normal saline or HCl.

Wright et al¹²¹ studied 136 subjects utilising a similar protocol using a Bernstein challenge test, which is perhaps the largest study of this type in the literature. The

authors were searching for both a pulmonary as well as a cardiac reflexive response with acid challenge of the oesophagus. The authors of this study were able to elicit both bradycardia and bronchoconstriction in response to the presence of acid in the oesophagus. However, what is interesting about this study in comparison to our data is that Wright et al were also able to demonstrate the same reflex in response to saline infusion. Thus the results we obtained in experiment 2 are not the first to show a respiratory response to saline infusion in the oesophagus in human subjects. Wright et al offered no explanation in their discussion as to why their subjects responded to normal saline in their paper.

There has been an enormous amount of effort in the literature delineating the sensory afferents of the oesophagus. The impetus for this volume of research stems not only from the quest to understand the pain caused by oesophageal disease, but also for the fact that these sensations are often similar to that induced by myocardial ischaemia. Indeed, it is a frequent clinical dilemma for both emergency physicians and cardiologists when a patient presents with epigastric or retrosternal complaints. There are a number of different sensory afferents which have been identified to arise from the oesophagus.¹⁴⁰ These may be stimulated by electrical, mechanical, chemical as well as thermal inputs. Recent research has mapped the location of the sensory nerve endings responsible for the perception of these afferent inputs in relation to their position in the oesophageal wall. It is of interest to note that the thermal receptors are preferentially located on the luminal surface whereas the chemical receptors are close by within the mucosa.¹⁴¹ Responses from the chemical receptors have also been reputed to be

notoriously difficult to reproduce. Some authors in fact are of the opinion that chemical responses from the oesophagus can only be detected if there had been some preceding erosion or deficiency in the epithelium of the mucosa, thereby allowing the nerve endings to come into contact with the chemicals.¹¹⁴ These factors may account for the sometimes conflicting results obtained by respiratory researchers in their attempt to demonstrate a bronchospasmodic reflex when oesophagus is challenged with acid.

The response that our subjects demonstrated with saline infusion could conceivably be due to the stimulation of thermal receptors. Although none of our subjects reported any discomfort with either of the infusions (i.e. had a positive Bernstein test), most of our subjects were able to detect a “cold” sensation when the infusions commenced. This sensation would disappear as the oesophagus is cooled to room temperature by the infusion and the subjects become accustomed to the sensation. It had already been demonstrated by Mansfield, as stated previously, that a respiratory response can be reflexively triggered by the oesophagus irrespective of the type of sensory input that initiates it. Mansfield was also of the opinion, as stated previously, that a response to acid would only be present in the presence of oesophagitis, and in fact induced oesophagitis in his dogs prior to his canine studies. This would be in keeping with the original theory of Bernstein and the basis of the test named after him, that a positive response to acid would only be present in patients with erosive oesophagitis and not in patients with intact oesophageal mucosa. Therefore, for the purpose of the current study, the unexpected response to normal saline does not jeopardise the

theories postulated herein. Clearly what is important is that a reflexive response can be demonstrated linking the oesophagus and the nasal cavity, which supports our hypothesis for an oesophago-nasal reflex. We would reasonably expect that a similar, if not a stronger reflexive response to acid would be present in patients who have oesophagitis.

An alternative explanation for the results obtained in our experiment could perhaps be stimulation of mechanical or pressure receptors in the oesophagus. The likelihood of this occurring would be small as the infusion of the solutions were not at a sufficiently high rate as to distend the oesophagus. There was some discrepancy in the literature with respect to the rate of solution infusion amongst the studies which involved a Bernstein challenge in asthmatic patients. These ranged from 2 mls/min¹²² up to 12 mls/min¹¹⁹. The infusion rate utilised in the current study was specifically chosen in the middle of that range at 6.67 mls/min (100mls of solution over 15 mins), and have not been reported to cause significant oesophageal distension in previous studies.

With regards to the results obtained specifically for nasal inspiratory peak flow, it is unclear as to the reason behind the significant increase in nasal patency at 30 mins following the infusion of acid, but a statistically insignificant drop from baseline following saline infusion. One possibility is that a certain amount of variability would be expected on account of the physiological nasal cycle.⁸³ Other possibilities may be attributed to the measurement of nasal inspiratory peak flow itself. There is much debate in the literature regarding the accuracy of

measuring nasal inspiratory peak flow using the Youlten meter. Whilst some studies show that it is a reliable measurement of nasal patency^{142 143}, others have found the converse result^{144 145}, with its sensitivity questioned by still others¹⁴⁶. It is also unclear how having a manometry catheter in one nostril would affect the results. Potentially, a person with a larger nasal cavity may still permit some airflow through the side with the catheter in-situ, where as in a person with a smaller nostril, the same size catheter might totally occlude that side from the test. An alternative to measuring nasal inspiratory peak flow may have been using acoustic rhinometry, which has been shown to be a more sensitive test of nasal patency.¹⁴⁴ It is however, a much more cumbersome test, requiring more sophisticated equipment than the Youlten meter. It may also have been difficult to interpret the results when a tube is held across the soft palate, as in our study. The position and motion of the palate has been documented to alter acoustic rhinometry results.¹⁴⁷

Fucose has been shown to be an accurate and sensitive marker of nasal mucous production in response to parasympathetic stimuli.¹⁴⁸ Out of the three outcome measures utilised in this experiment, it is probably the most objective and sensitive. Recent studies by Greiff et al however has demonstrated that the stores of nasal mucin may be depletable in the short term, and that successive challenges by methocholine does not produce any further response.¹⁴⁹ This may provide an alternative explanation for why a rise in fucose level was not seen after the acid challenge following the response to normal saline. The differences that we observed in fucose levels came close to but did not quite reach statistical

significance. It is clear that the small number in our study was a factor for this. However, it is also a possibility that the oesophago-nasal reflex may not be inducible in every individual, as can be interpreted from figure 31. It was of interest to note from figure 31 that subject two who showed the greatest response, was also the only subject amongst this group that returned an abnormal 24 hour pH monitoring result.

Some proponents of the direct reflux model have suggested that the injury seen in chronic sinusitis may be due to pepsin or even helicobacter. As discussed in the review of the literature, Dinis et al⁷⁷ was able to demonstrate *H. Pylori* in controls as well as patients with chronic sinusitis. In the same study, the authors never found that the nasal pepsin levels rose above that of serum. The role of pepsin in tissue injury in oesophageal disease has been studied recently. Increasingly, gastroenterologists are suspecting that the digestive enzymes be of importance in the erosion of oesophageal epithelium.^{150 151} The activity of these enzymes are pH dependent and pepsin will digest protein very effectively up to pH 4.0. However, more recent data have shown that pepsin will bind to its substrate at a pH of 5.5, even though its activity will be much reduced.¹⁵² From our data, as presented in Figure 26, it can be seen that the nasopharyngeal pH never dropped below pH of 6, thus any pepsin that may find its way that far cephalad would certainly be inactive, further dispelling the theories that it plays a role in pathogenesis of chronic sinusitis.

Conclusion

Mankind had been battling chronic sinusitis since prehistoric times. This war, which had been waging for centuries, has exploded into enormous scales. Through our discussion we have seen that it is a disease of increasing prevalence, now affecting some 13% of the adult population. And since ancient times, we have tried various weapons in our armamentarium in this fight, from needles and trocars, to the current golden era of endoscopic sinus surgery, which has revolutionised the treatment of this disease. But still, this tool is not perfect, and as illustrated previously, there is still so much we do not understand about this disease, even in this modern era. There is no doubt that chronic sinusitis is a complex condition, and various aetiological factors have been identified which contribute to its pathogenesis. The purpose of this thesis was to examine the role which gastro-oesophageal reflux plays in this increasingly complicated picture.

There appears to be good evidence in the literature for the association between gastro-oesophageal reflux disease and chronic sinusitis, and our data are supportive of this relationship as about half of our subjects with chronic sinusitis returned abnormal 24 hour pH studies. However it is assumed in the current literature that the chronic sinusitis seen in patients with gastro-oesophageal disease is due to refluxed acid in the nasopharynx, leading to mucosal damage in the paranasal sinuses. The evidence for this is poor, and in our critique, we have outlined the shortcomings of the few studies frequently quoted in support of this theory. We proposed an alternative mechanism, and our hypothesis is that the inflammation of the sinuses seen in the patients with gastro-oesophageal reflux disease is neurogenic, as a result of a reflexive response mediated by the vagal

oesophageal afferents. We have discussed how we extrapolated this theory from the work of the respiratory physicians in demonstrating an oesophageal-pulmonary reflex in asthmatic patients with gastro-oesophageal reflux.

To test our hypothesis, we needed to demonstrate initially that refluxed acid is not capable of reaching the nasopharynx in order to injure the nasal mucosa. We were able to show this convincingly in our data as out of the 809 episodes of reflux recorded in our patients with chronic sinusitis, only 2 were recorded in the nasopharynx. Having confirmed with this first experiment that direct acid exposure is not responsible for the sinusitis seen in these patients, we set out to demonstrate a reflexive nasal response from oesophageal stimulation. When we challenged the oesophageal mucosa of the subjects as described in our second experiment, we observed a trend in nasal response in this group of healthy volunteers. This supports our hypothesis for a neural link between the oesophagus and the nasal cavity. The fact that we observed a response to normal saline was unpredicted and we have proposed the rationalisation of these results which we obtained. These findings are interesting and worthy of further investigation. The relationship between gastro-oesophageal reflux and chronic sinusitis is complex, but the work entailed in this thesis has provided some insight into its pathophysiological mechanisms.

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