



Airway reflux as a cause of respiratory disease

Summary

Reflux is the cause of much respiratory disease. More commonly still, it is the unrecognised agent provoking the symptoms of respiratory disease. That the reflux entering the airways from the gastrointestinal tract is central to the diagnosis, therapy and understanding of respiratory pathology has been missed because the paradigm of peptic disease has been applied. Airway reflux is however unlike gastro-oesophageal reflux disease (GORD). GORD is liquid acid reflux causing heartburn and indigestion. Airway reflux consists of a mainly gaseous non-acid mist which, when deposited in the upper and lower airways leads to inflammation, fibrosis, bronchoconstriction and cough. Here, the hypothesis that airway reflux is responsible for chronic “idiopathic” cough, late onset asthma, exacerbations of COPD, ‘idiopathic’ pulmonary fibrosis and even the lung disease of cystic fibrosis is outlined. The exclusive focus of clinicians on the extrinsic origins of these conditions and the rejection of an obvious intrinsic aetiology causes millions of patients to be denied an explanation for their symptoms and simple, effective, treatments. In many cases idiopathic should be no longer considered idiopathic.

Statement of Interest

None declared.

Reflux is the cause of all respiratory disease. An exaggeration of course, but I hope to convince you in this article that there is more than a germ of truth in this outrageous statement. There have been two barriers to the revelation that reflux is a major contributor

to respiratory pathology. First, we have been labouring under the diagnostic criteria of reflux as gastroesophageal reflux disease (GORD). There is no doubt that GORD exists and the gastroenterologists have defined and characterised the disease which causes heartburn,



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B.1, B.7, B.15.1

dyspepsia and oesophagitis; however, they have been very reluctant to accept that this is merely the tip of the reflux iceberg, with extra-oesophageal reflux being out of their home territory. Respiratory professionals, being largely ignorant of reflux, its aetiology and manifestations, have accepted the wisdom of the gastroenterologists, since this is “their” area. So blinkered has this attitude become that, with one or two exceptions, one should not talk to a gastroenterologist about what has been termed airway reflux. You might as well talk to a tree!

Secondly, within the respiratory community there has been marked reluctance to accept reflux as even the potential cause of respiratory disease; although it has not always been so. Indeed, in 1698, Sir John Floyer in his great book, *A Treatise on the Asthma* (fig. 1), vividly describes what he terms as flatulent asthma [1]. In 1881, Congreve described “a dry or nervous asthma”, which is accompanied by flatulence and he observes that dyspepsia is “an accompanying evil and perhaps the exciting cause” [2]. However, with the discovery of the cellular and molecular basis of allergic disease and its emphasis on allergens, the entire focus of research has been towards external factors which are inhaled. This extrinsic hypothesis is the current, exclusive, paradigm used to explain respiratory disease. The balance needs redressing. Forty years ago, asthma was

termed either extrinsic or intrinsic. This is the true pathophysiology of respiratory disease. Extrinsic factors are important but we have lost sight of intrinsic factors in the form of reflux. Thinking in this way opens the door to understanding many of the otherwise inexplicable phenomena described by our patients. It also suggests alternative avenues of therapy to end the intractable suffering of “difficult” patients who steadfastly refuse to respond to conventional respiratory treatments.

Airway reflux is not GORD

Human beings are prone to reflux and aspiration because of their evolutionary origins. We are the only genuinely bipedal mammal. As a consequence of our upright posture, the oesophagus hangs vertically and the lower oesophageal sphincter (LOS) is located directly above the stomach. In quadrupeds, there is a right angle between the oesophagus and stomach, aiding LOS closure. A second evolutionary adaptation which makes human beings prone to aspiration is in the laryngeal apparatus. In all other mammals, the soft palate, arytenoid cartilage and epiglottis form a highly efficient valve preventing aspiration of matter into the respiratory tract. In babies, the same mechanism applies. However, as we begin to talk the laryngeal apparatus descends while the soft palate remains in the pharynx allowing the space below to be used for vocalisation [3]. This however causes the valve to become inherently incompetent. Thus, human beings are prone by their bipedalism to reflux and because of speech to aspiration through an inadequate laryngeal sphincter.

GORD is a real disease. Acid liquid reflux from the stomach into the oesophagus causes oesophagitis and the associated symptoms of heartburn and dyspepsia. Highly accurate diagnostic criteria such as the DeMeester score have been developed to quantify the acid exposure required to produce this disease. However, this is NOT the disease which is causing respiratory symptoms. The reflux which causes respiratory consequences is a gaseous mist which is partially or even wholly non-acid. This mist can travel up the oesophagus without a peristaltic wave since the oesophagus, as is usually seen on thoracic computed tomography, is patent; a so-called common cavity. This retrograde transit of gas is a normal

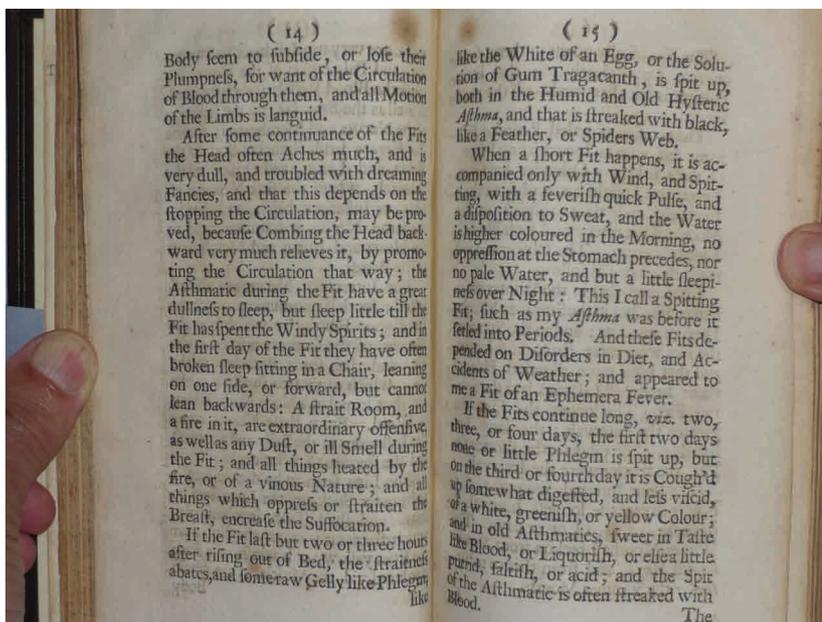


Figure 1
Floyer's 1698 treatise on asthma. He describes attacks precipitated by food and uses the term “flatulent asthma” caused by “Windy Spirits”.

phenomenon. We all eat air as we eat our food and the LOS opens to allow this gas to escape [4]. In patients who have undergone fundoplication, this mechanism is inhibited, and gas bloat and excessive flatulence are very common side effects. When this gaseous mist is excessive or when the airway is sensitised it can lead to inflammation of the whole of the respiratory tract, including the nose, ears, sinuses and, when inhaled, the lower airways. We all occasionally taste our food after meals and this is nothing more than an everyday expression of airway reflux.

There are currently no simple objective measures of airway reflux, although tests such as salivary pepsin in the form of the Peptest can be useful markers [5]. The diagnosis of airway reflux is reliant on the clinical history. Questionnaires such as the Hull Airways Reflux Questionnaire (HARQ; available at www.issc.info) are used to score the characteristic clinical features of such reflux, such as postprandial coughing, a funny taste in the mouth or symptoms on phonation (fig. 2). In the validation of this questionnaire, heartburn was found to be the least-associated symptom, reinforcing the importance of the non-acid nature of this phenomenon [6].

The respiratory conditions associated with reflux

Chronic cough

It is through the clinical observation of patients with chronic cough that the nature and associations of airway reflux as a causal mechanism of respiratory disease have been elucidated. The great puzzle and therefore the clue in chronic cough is that it has always eluded easy categorisation. Patients rarely fit into the common established and familiar patterns of respiratory disease. There was clearly something missing in our understanding of its aetiology. The other great lead in this mystery is that chronic cough, unlike symptoms such as dyspnoea, has a physical and objectively measureable signal. The poor patient who complains of dyspnoea which is unexplained through conventional investigation is clearly mad and given the label of dysfunctional breathing, whereas a patient coughing hundreds of times an hour is more readily recognised as having a physiological disorder. The question is, what is it?

HULL AIRWAY REFLUX QUESTIONNAIRE

Name: _____

D.O.B: _____ UN: _____

DATE OF TEST: _____

Please circle the most appropriate response for each question

Within the last MONTH, how did the following problems affect you?						
0 = no problem and 5 = severe/frequent problem						
Hoarseness or a problem with your voice	0	1	2	3	4	5
Clearing your throat	0	1	2	3	4	5
The feeling of something dripping down the back of your nose or throat	0	1	2	3	4	5
Retching or vomiting when you cough	0	1	2	3	4	5
Cough on first lying down or bending over	0	1	2	3	4	5
Chest tightness or wheeze when coughing	0	1	2	3	4	5
Heartburn, indigestion, stomach acid coming up (or do you take medications for this, if yes score 5)	0	1	2	3	4	5
A tickle in your throat, or a lump in your throat	0	1	2	3	4	5
Cough with eating (during or soon after meals)	0	1	2	3	4	5
Cough with certain foods	0	1	2	3	4	5
Cough when you get out of bed in the morning	0	1	2	3	4	5
Cough brought on by singing or speaking (for example, on the telephone)	0	1	2	3	4	5
Coughing more when awake rather than asleep	0	1	2	3	4	5
A strange taste in your mouth	0	1	2	3	4	5

TOTAL SCORE _____/70

Figure 2

The Hull Airway Reflux Questionnaire. This self-administered questionnaire is used to diagnose the characteristic feature of airway reflux. A score of greater than 14/70 is indicative of reflux disease. © AH Morice; version 6, September 2010.

Initial attempts to explain the suffering of patients with a chronic cough ascribed the syndrome to three established existing diagnoses: a form of asthma; postnasal drip or rhinitis; and more latterly reflux disease [7]. However, many of the typical middle-aged female patients with chronic isolated cough, in the absence of any other obvious lung pathology, do not fit the conventional paradigms for these conditions. Asthmatic cough was described in patients without bronchoconstriction but who had hyper-reactivity to challenge with bronchoconstricting agents such as methacholine [8]. The definition was then stretched to include patients who had

isolated cough but with sputum eosinophilia. Some went further, calling this a separate condition of eosinophilic bronchitis [9]. However, all of these asthmatic cough syndromes are characterised by sputum eosinophilia but are unlike classic asthma with its childhood onset and atopy. Patients with asthmatic cough were usually middle aged and without obvious allergic disease despite the sputum eosinophilia. Similarly, chronic cough patients with nasal symptoms were ascribed to having postnasal drip (or more latterly, upper airways cough syndrome) on the basis of no objective measures but a response to first-generation antihistamines, particularly of the alkylamine family [10]. Finally, it was realised that many patients with cough suffer from symptoms of reflux, but the paradigm of GORD was applied and, as a consequence, the incidence of reflux disease was grossly underestimated in early surveys [11]. Despite being able to place some patients in these elongated diagnostic categories many stubbornly refused to fit into their straightjackets and so a fourth group of patients, that of chronic idiopathic cough, was created [12]. However, if one looks at the patients attending a specialist cough clinic they provide a very uniform clinical picture. The history of the association of cough with certain activities of daily living, such as rising in the morning, talking and laughing, and eating or drinking are frequent and all can be associated with opening of the LOS [4]. Other features, such as loss of voice and throat clearing are very frequent, symptoms which are easily explicable by gaseous reflux affecting the upper airway [13]. The full symptom complex has been validated in the HARQ questionnaire. In 178 consecutive patients attending a cough clinic, all but a handful scored greater than the upper limit of normal on this questionnaire specifically designed to detect airway reflux [6]. It is indeed a red letter day in the cough clinic when a patient does not give a high score, and this usually indicates that the cough has cleared up! There are of course other causes of cough, just as there will be other causes of the respiratory diseases discussed below. However, the overwhelming majority of patients with chronic cough have airway reflux, which is mostly due to gaseous oesophago-pharyngeal reflux associated with oesophageal dysmotility. High-resolution manometry has recently provided graphic evidence of this phenomenon (fig. 3) [14] and explains the

otherwise mysterious association of chronic cough with hiatus hernia, irritable bowel syndrome, obesity [15] and neurological illness, the latter through vagal neuropathy [16, 17].

Recently, studies in cough have clearly demonstrated that blocking acid is not effective in the treatment of this condition [18, 19], reinforcing the hypothesis that non-acid, usually gaseous, reflux is the main aetiological agent leading to the afferent neuronal hypersensitivity which underlies cough hypersensitivity syndrome. This paradigm of gaseous reflux and sensory hypersensitivity explains almost all of the otherwise mystifying phenomena reported by patients with chronic cough.

What then of the early subdivision of chronic cough patients into those with asthma, reflux and rhinitis? In patients with postnasal drip, clearly the reflux is irritating the nasal passages and sinuses. Those with an asthmatic (although not classic asthmatic) cough have an eosinophilic inflammation precipitated by the airway reflux. Of the majority who have chronic neutrophilic inflammation, some may have symptoms of acid reflux, but since acid is not the aetiological agent, heartburn and indigestion should be viewed as a comorbidities.

Other respiratory disease: the problem of definitions

Even the most hardened opponent of the reflux hypothesis will acknowledge that a proportion of patients with chronic cough suffer from reflux disease. Indeed, it would be hard to argue that a patient with a full house of reflux symptoms, both peptic and non-acid related, who is subsequently shown to have an anatomical abnormality of the oesophago-gastric junction such as a hiatus hernia and is then cured by fundoplication, does not clearly demonstrate the validity of the concept. It is thus simply a question of how much one believes that reflux is atypical rather than peptic in origin. The additional problem with other respiratory disease is that, unlike cough, there are established diagnostic criteria built up over many years, often soundly based on clinical and biomarker studies. A large body of the respiratory scientific community depends for their living on these diseases having specific criteria exclusive to their specialism and expertise. If reflux is accepted as being a major cause of these

illnesses, where does it leave their grant funding and all of the workers in their laboratories? In the following paragraphs I outline the case for a significant proportion of morbidity in these conditions being due to reflux.

It is clear that not all respiratory patients suffer from reflux disease. Thus, no one would deny the well-established condition of childhood atopic asthma associated with allergy to cats, dogs and house dust mites, and due to a familial hyper-responsiveness to aero allergens. However, this paradigm of asthma has now been extended into what was called intrinsic asthma (which ironically is literally intrinsic) where no allergen can be found. Similarly pulmonary fibrosis undoubtedly can be caused by exposure to external factors, such as asbestos. Idiopathic pulmonary fibrosis however has resisted all attempts to find the external stimulus and, until recently, clinicians have steadfastly refused to accept it as part of an intrinsic process.

Asthma

There is no need to invoke reflux as a major factor in classic atopic asthma in young people. The many volumes devoted to the aetiology, pathogenesis and treatment of this condition are not wrong. The problem comes when our understanding of this disease is extended to cover all types of wheeze. Indeed, national and international guidelines clearly state that it is impossible to define what is now termed asthma because it is too broad a definition [20]. However, regulators require defined entry criteria for studies and simply resort to bronchodilation with inhaled β -agonists. Yet anyone who has suffered from a viral respiratory tract infection knows that not all that wheezes is asthmatic.

This confusion over terminology has origins in the distant past. Sir John Floyer in 1694 in his *Treatise on the Asthma* gives what is still one of the best clinical descriptions of an attack of asthma (fig. 1). He describes the attack as being precipitated by eating, particularly after a meal of meat and also vividly describes the gastric disturbance associated with its onset. He attempts to explain the pathogenesis using the then current paradigm of Galenic humours, much as today the modern allergist would ascribe this to food intolerance. However, in an extremely acute

observation he describes the condition as “flatulent asthma”.

In the modern era, epidemiological surveys have repeatedly demonstrated that late-onset or treatment-resistant asthma is associated with GORD [21, 22]. Indeed it has been claimed that “most asthmatics have (acid) gastroesophageal reflux” [23]. Many asthmatics have also been shown to suffer from reflux unrelated to peptic symptoms [24]. Despite this wealth of data, the failure of large-scale trials of anti-reflux medication (in reality, merely anti-acid therapy) [25] have been taken as proof that reflux is not a factor in asthmatic airway disease. The striking epidemiological association is consequently dismissed as two common diseases coexisting. In reality, it is the obsession with acid reflux and failure to appreciate that it is the non-acid component of gaseous reflux that is pathogenic, which is responsible for this confusion. Trials of promotility agents such as azithromycin, and of fundoplication are awaited with interest.

Cystic fibrosis and non-cystic fibrosis bronchiectasis

Cystic fibrosis (CF) is clearly a genetic disease. However, the consequence of mutation in the *CFTR* gene is still not fully understood at a molecular level. The gene codes for a transporter of chloride ions yet the main physiological consequence is an inability to move sodium with the end result of abnormally thickened secretions. CF is a multi-system disease and, since the majority of patients present with respiratory complications, it was naturally assumed that the abnormalities in the mucus within the respiratory tract caused this component of the disease. However, a number of lines of evidence point to this being incorrect. Lung inflammation in neonates predates any infection [26]. So what causes this inflammation? Even in babies, CF-related reflux can be detected [27] and I suggest that aspiration is the provoking agent causing this inflammation. It is undoubtedly true that the abnormal mucus produced by the CFTR is responsible for an abnormal response within the airways; but nonetheless, reflux and aspiration are the major precipitants. For reasons which are unclear, older children and adults have uniformly high levels of both acid and non-acid reflux as shown by conventional pH

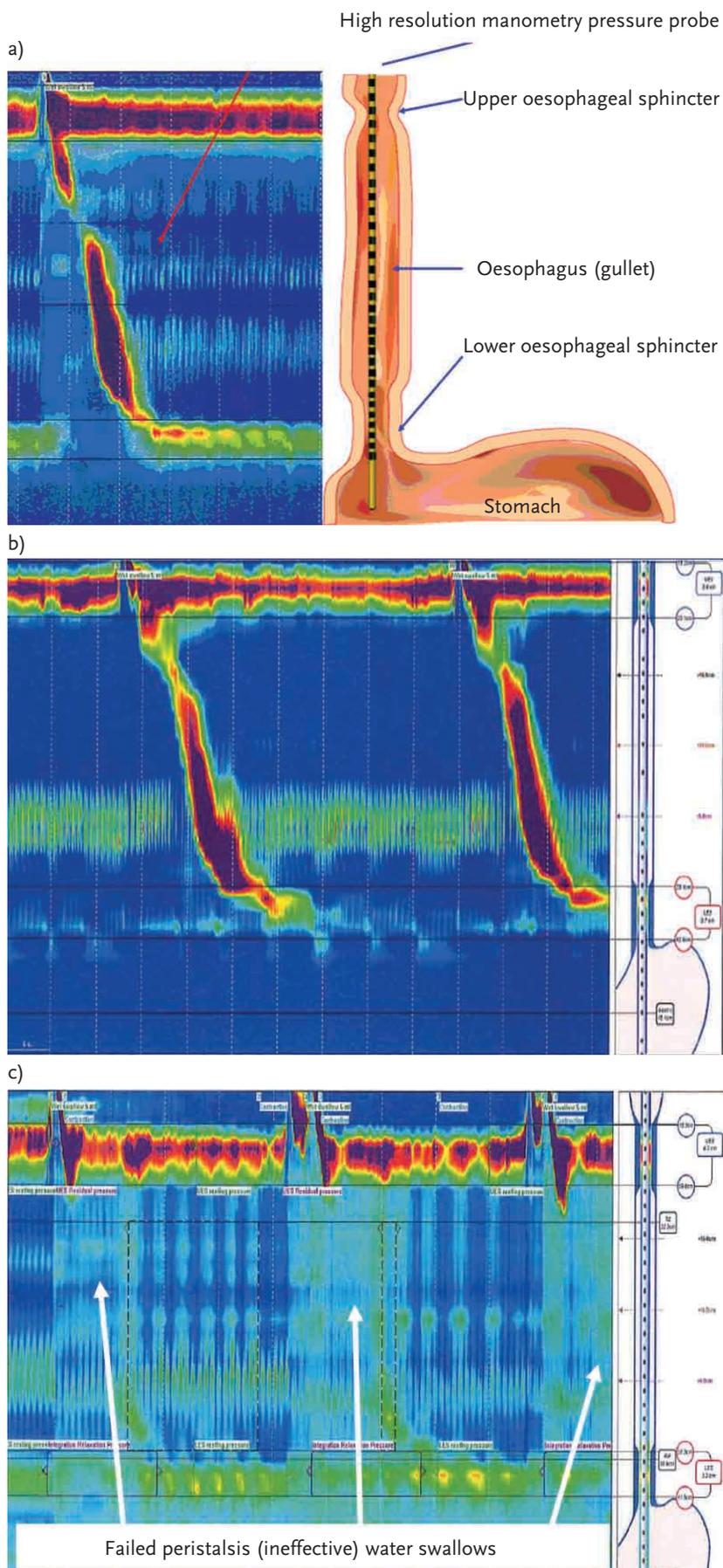


Figure 3
High resolution oesophageal manometry. a) The trace shows a normal pattern of oesophageal contraction descending with preceding opening of the lower oesophageal sphincter. b) Lack of lower oesophageal sphincter tone in a patient with chronic cough. c) Failed peristalsis with accumulation of food and secretions causing increase in pressure.

monitoring [28, 29]. In consequence, many CF centres have been administering proton pump inhibitors (PPIs) to patients in the mistaken belief that these drugs prevent reflux. In fact, they solely remove the acid so the patient no longer complains of heartburn. The reflux, however, continues unabated. Such therapy may actually make the situation worse since any pathogens which are ingested (*e.g. Burkholderia cepacia*, a natural pathogen of the onion) are now no longer killed by the stomach acid and are then refluxed up and aspirated into the airways. Here the associated food debris makes a nice culture medium for the bacteria to take root. This helps to explain why such unusual organisms are also found in the sputum in bronchiectasis.

If one considers the gut as the major organ affected in CF then the fact that animal models have failed to reproduce human respiratory diseases is explicable by our unique predisposition to aspiration. CF mice have the gut disease, but they do not aspirate and have lung problems. In the pancreas, these CFTR-induced abnormal secretions lead to blockage and atrophy of the pancreas with consequent diabetes. In the gut disease, distal ileal obstruction syndrome (DIOS), abnormal enteric secretions block the distal ileum and ileo-caecal junction. DIOS occurs when there is absolute obstruction, but in the majority of patients with CF, sub-acute obstruction and slowing of gut transit is a major feature. This then causes retrograde flow and as a consequence, reflux; and, as has been discussed, a major symptom will be cough. However, if one views CF as mainly a respiratory disease, cough arises from the chest, and reflux will not be considered as a cause. Non-acid reflux has been objectively demonstrated as an important component in CF, even using the less than perfect impedance technology [28]. The clinical history of a sudden onset of breathlessness and coughing associated with voice change and abnormal taste in the mouth is, however, diagnostic but almost universally mistaken as evidence of a CF exacerbation. That is correct, but the origin is by aspiration. The bacteria that live in the damaged lung then feast on the aspirate but the exacerbation is not driven or caused by the bacteria, they are merely the not-so-innocent bystanders in the process.

Diagnosis is simple. Many CF patients complain of two types of cough: one dry and irritating, which is the gaseous non-acid

reflux; and a cough when they have an exacerbation, usually described as an infection, but in reality, due to an aspiration event. Because of the profound nature of the problem, only limited relief is obtained with promotility agents, such as metoclopramide. Azithromycin is popular in the treatment of CF [30] because, as an agonist of motilin, it improves poor gut motility preventing reflux and aspiration [31]. In our centre, we routinely perform fundoplication on all CF patients presenting with significant reflux-associated cough and have demonstrated that it halves the exacerbation rate [32].

In non-CF bronchiectasis, again the clinical history gives the clue to the reflux origin of the disease in the majority of cases. There are clearly exceptions. Bronchiectasis distal to a proximal obstruction in the airways is not reflux related but the vast majority of diffuse bronchiectasis score very highly on the HARQ. Anatomical upper gastro-intestinal disorders, such as hiatus hernia, are extremely common in patients with bronchiectasis [33]. The harrowing treatment dealt out to patients with tracheo-oesophageal fistula because of a failure to recognise consequent reflux has been vividly described in LOVE and MORICE [34]. Respiratory complaints were both explicable and treatable once the correct diagnosis had been appreciated but ignorance led to years of unnecessary suffering. Recently, anti-reflux treatment in the form of azithromycin has also been demonstrated to be highly effective in the management of non-CF bronchiectasis [35].

Pulmonary fibrosis

Of all of the respiratory subspecialties those dealing with pulmonary fibrosis have been quickest to appreciate the role of reflux in this “idiopathic” disease. Studies again have shown a high incidence of upper GI abnormalities, such as hiatus hernia [36]. Progress however has been hampered by the failure to appreciate that it is non-acid reflux of a gaseous nature, settling in the basal terminal airways, which provokes a fibrotic reaction. The advocates of reflux as a cause of IPF have advocated high-dose PPIs as the major form of therapy [37]. While we do not have the evidence from randomised controlled trials, unlike the position in asthma and chronic cough, to say that this is definitely ineffective, the risk of increasing aspiration by removal of an irritant has potential for harm. Such a

strategy may make the patient feel better but may make the disease worse. Given the recent failures of almost all of the other medications previously used for the treatment of IPF there is an urgent need for trials of anti-reflux medication in this disease and particularly trials of fundoplication. However, since this is a disease of the elderly characterised by a late presentation and compromised lung function we may have to wait for less invasive techniques to be developed.

COPD

COPD is not really a disease. It is a collection of syndromes put together under a banner headline and characterised by airflow obstruction. I had the pleasure of working for Tony Dornhorst who invented the terms “pink puffer” and “blue bloater” to describe two of the common phenotypes of COPD, which I still call emphysema and chronic bronchitis. In emphysema, there is dilation and destruction of the terminal airways and airflow obstruction is consequent on the collapse of the surrounding parenchyma. The expansion of the lung volume leads to flattening of the diaphragm and distortion of the lower oesophageal sphincter predisposing to reflux. The reflux and aspiration then causes a bronchitis which is the main precipitant of the cough, phlegm and wheezing, which characterises the patient with COPD. These factors are highly significantly associated with the decline and ultimate demise from COPD and occur in the absence of the initiating event, smoking. Thus, the aetiology of COPD in the reflux view of the world is that smoking initiates the lung destruction which leads to alteration of the anatomy and mechanics which control reflux. The patient thus has episodes of reflux induced bronchoconstriction on top of chronic airflow obstruction secondary to the lung destruction. The patient stops smoking but the airway reflux continues. Hence the inexorable decline and the strong association with symptoms of airway reflux: cough, wheeze and sputum production. This association has become clear in epidemiological surveys of COPD, such as ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints), where classic peptic related gastro-oesophageal reflux is the feature most associated with

decline [38]. Understanding this aetiology explains the increasing number of patients recognised as having COPD but who have no significant smoking history. Diagnosis is straightforward if the clinical history is taken. I write this having just completed a ward round in the Admission Unit that included four patients with a diagnosis of acute exacerbations of COPD. All had a very clear history of an acute onset of symptoms precipitated by posture and associated with voice change and a funny taste in the mouth. Formal assessment using the HARQ of unselected acute admissions of COPD revealed an association with non-acid reflux in two-thirds of patients. The most effective agent for reducing exacerbations, azithromycin, reduces the number of events by one-third which is a better outcome than with any inhaled therapy [39]. We suggested that the mode of action may be by reducing non-acid reflux [40]. The authors replied by saying that PPI therapy did not work. Of course it didn't!

Conclusions

Reflux may not be the cause of all chest disease but it is “the exciting cause” of many. Even in disease where reflux is not the aetiological agent it may be the cause of significant symptoms. Thus, in lung cancer, where even I have yet to find a strong association with reflux, patients who complain of cough frequently have a clinical history of reflux disease. Cancer-associated direct or indirect vagal neuropathy diminishes control of the LOS. Alternatively reflux may be precipitated by the anxiety associated with the diagnosis.

The diagnosis of airway reflux is easy. The patient provides the clues through the history. The problem is that the clinician usually does not ask the right questions. A story of rapid-onset dyspnoea or a cough should elicit further probing as to the associated features. The HARQ questionnaire is self-administered and can lead the questioning without significant extra effort. I use it myself to remind me of the variety and apparently unconnected nature of the symptom complex of airway reflux. By recognising and treating this syndrome one can restore the health and wellbeing of an untreatable, unresponsive patient.

Key points

- Reflux which enters the airways is frequently a gaseous mist that is non-acid in nature.
- The body's reaction to airway reflux depends on the individual patient and ranges from fibrosis of the terminal airways, to both neutrophilic and eosinophilic bronchitis and upper airway pathology.
- Treating the acid component of airway reflux is ineffective in preventing disease.
- Reflux should always be considered if there is a failure of conventional treatment in "other" respiratory disease.

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Educational questions

1. Proton pump inhibitors
 - a. Are effective treatments of reflux
 - b. Should be used at high dose in troublesome cough
 - c. May cause worsen of airway disease
 - d. Are useful add-on therapy in severe asthma
 - e. Improve oesophageal motility
2. Characteristic features of the symptoms of airway reflux do not include
 - a. Attacks of rapid onset
 - b. A worsening at night
 - c. Upper airway involvement such as voice change
 - d. An association with food
 - e. Throat clearing
3. Which of these factors do not increase the probability of reflux?
 - a. Hyperexpanded lungs
 - b. Male sex
 - c. Hiatus hernia
 - d. Neuropathy
 - e. Obesity
4. Which of the following are consequences of airway reflux
 - a. Pulmonary fibrosis
 - b. Squamous carcinoma of the bronchus
 - c. Episodic wheeze
 - d. Eosinophilic bronchitis
 - e. Haemoptysis

Suggested answers

1. c.
2. b.
3. b.
4. a, c, d.

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