is evidence that tissue neutrophilia is more frequent in severe asthma.[22]

Despite these unavoidable limitations, the report by Qiu *et al* is important because it promotes a better understanding of the events contributing to the development of severe exacerbations. Indeed, this study provides the framework for the cellular changes occurring in the airway tissue and the molecular mechanisms responsible for inflammatory cell recruitment. As a consequence, these observations will encourage new research into therapeutic strategies to prevent exacerbations, one of the most important aims of asthma management.

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Dietary supplements and asthma

Dietary supplements and asthma: another one bites the dust

Johanna Feary, John Britton

No effect of selenium supplementation on symptoms of asthma

Throughout history, clinical observation and clinical trials have identified links between nutritional deficiency and disease. For example, scurvy was described by Hippocrates over 2000 years ago, and native cultures have known its cause and cure for centuries. The first intervention study to demonstrate the successful treatment of scurvy with citrus fruits was published in 1753 by Captain James Lind in ''*A Treatise of the Scurvy*''. Moving forward to the 20th century, one of the resounding achievements in this field has been identification of the importance of folic acid supplements in the prevention of spina bifida, leading to an overall reduction in incidence in the Western world. The possibility that nutritional factors may play a similarly important role in the aetiology of chronic respiratory disease is therefore intriguing and has recently attracted a great deal of interest.

The aetiology of asthma remains unclear, but it is widely accepted that environmental factors play a major role and, of these, diet is a potentially important contender. Evidence for this arises from the observations that the prevalence of asthma increases as societies move from a rural subsistence towards a more Western lifestyle; this is associated, among other factors, with a change in dietary pattern including adoption of a more processed and ''convenience-orientated'' diet. The result of this dietary change is an overall increase in the intake of refined sugars, fats and additives, and a relative reduction in the intake of complex carbohydrates and micronutrients. This change is a relatively modern phenomenon, occurring in the UK since the end of wartime rationing and also resulting from increased industrialisation of the food supply chain.

There is now an extensive literature on the relationship between diet and respiratory disease.[1–3] In asthma, observational studies have shown encouraging evidence of a protective effect of several nutrients on disease prevalence and symptoms, including vitamin C,[4 5] vitamin E,[6] selenium[7] and magnesium.[8] However, and disappointingly in view of early promise with vitamin C,[9] these findings have not generally translated into consistently positive outcomes in intervention studies. For example, in a recent randomised placebo-controlled trial of vitamin C, magnesium or placebo in 300 patients, we found no effect of either supplement on clinical asthma control.[10] Similarly, an intervention study of vitamin E in adults with asthma also showed no evidence of a benefit.[11] While fish oil supplements have been

shown to reduce exercise-induced bronchoconstriction in asthma,[12] other studies have not shown convincing evidence of an effect on asthma symptoms or medication usage.[13] The Heart Protection Study which randomised over 20 000 adults at high risk of heart disease to receive antioxidant vitamin supplementation or placebo looked at respiratory disease as a secondary outcome. No difference was found in spirometry or in admission to hospital for chronic obstructive pulmonary disease (COPD), asthma or any non-neoplastic respiratory disease between the two groups.[14] The Cochrane collaboration reviews of a range of dietary interventions in asthma (including vitamin C supplements, sodium restriction and fish oil supplementation) all report negative or, at best, inconclusive findings.[15–17]

Of the many potentially relevant nutrients identified to date, selenium is of interest because case-control studies in both New Zealand[18–20] and the UK[7] have found a relation between low dietary selenium and an increased risk of asthma. However, the only intervention study of selenium supplementation in asthma published to date included only 24 patients with asthma and found no effect on objective markers of disease.[21] In this issue of *Thorax*, Shaheen *et al*[22] report the results of a definitive randomised controlled trial of selenium supplementation in asthma performed in 197 people living in London (***see p 483***). No effect of selenium supplementation was found either on quality of life or objective measures of asthma symptoms and control.

So why have observational epidemiological study findings of dietary benefit failed to translate into a positive clinical trial result? Confounding is always a potentially major problem in observational studies, and although the effects of smoking, socioeconomic status and other factors have been allowed for in many of the observational study analyses, it is always possible that these or other effects have still influenced the results. There is also the difficulty of isolating the effects of specific nutrients, given the close correlation that exists between nutrients in individual diets. For example, diets low in fruit and vegetables provide low intakes of both vitamins C and E, making it difficult to determine which, if either, single nutrient is important, and may lead to erroneous identification of nutrient effects in the observational studies. Further, the tendency for diet to track throughout life means that exposure to (or lack of) certain important nutrients identified in observational studies might also reflect effects of exposures occurring over a very long period of time, including childhood and even the prenatal period.[23] In contrast, intervention studies have mostly been performed in adults and typically last for a few weeks or, at most, months. The intervention studies may therefore be delivering too little too late in the natural history of disease to have an effect.

Another consideration is that many intervention studies have focused on single nutrient supplements, when it is plausible that a combination of factors is more likely to be effective. This argument is supported by the results of trials showing protection against ozone-induced bronchoconstriction by a combination of vitamins C and E relative to placebo in adults with asthma,[24] and by a combination of vitamins C, E and β-carotene in subjects without asthma.[25] These studies did not, however, include single nutrient supplement groups, so it is not clear whether the effect is indeed due to the combination or whether the results are specific to the ozone challenge exposure and have relatively less relevance to the clinical control of typical asthma.

Another possibility is that other as yet uninvestigated micronutrients or co-factors are more important. Taking a step further, it could be that entire foods rather than nutrients are important, the most obvious candidates being fruits, vegetables or oily fish; for example, in one case-control study the intake of apples was negatively associated with the prevalence of asthma.[7] To date, however, there is no evidence that individual food or food group supplements are effective in improving or preventing the disease. Furthermore, it may be that dietary supplementation only works in nutritionally deplete populations and that no additional beneficial effect will occur in well-fed and consequently over-supplemented individuals. This does not account for the findings in the study by Shaheen *et al*,[22] however, as restriction of analyses to subjects with low plasma selenium levels did not change any of the study outcomes and also did not explain the negative findings in our study of vitamin C and magnesium.[10]

These and other potential problems may account for the failure to find a clinically useful dietary intervention for asthma, but what are the implications for future work in this area? The optimists among us may continue to pursue the increasingly elusive missing link, exploring the roles of other possible candidate single or multi- micronutrients or even try whole food supplements. They may also hope that future improvements in understanding the scientific basis of nutrition and potential roles in airways diseases may lead to the development of new hypotheses that can be tested in interventional studies. However, the pragmatists may take the view that, since single nutrient supplements appear to be ineffective and a balanced diet which includes a range of fresh fruit and vegetables is beneficial in so many other aspects of health, the best approach, at least for the time being, is simply to recommend people with asthma to eat a healthy balanced diet.

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Gastro-oesophageal reflux and tachykinins

Gastro-oesophageal reflux and tachykinins in asthma and chronic cough

Alyn H Morice

A possible new therapeutic option

There is no doubt that gastro-oesophageal reflux can cause a chronic cough. However, how frequently reflux is the underlying cause in patients presenting to the readers of *Thorax* is a matter of much debate. This confusion can be laid squarely at the door of the gastroenterologists who have taken one symptom of acidic reflux—heartburn—and made it the sine qua non for gastro-oesophageal reflux disease. This characterisation of gastro-oesophageal reflux disease as heartburn has led to the denial of the non-acid extra-oesophageal symptoms of reflux. In reality, however, reflux is almost universal in humans because our upright posture has disrupted the anatomy of the lower oesophageal sphincter. Measurement of electrical impedance within the gullet in fact shows that only a small number of reflux episodes are acidic (below pH 4)[1] and, while it takes a lot of acid to burn the hardy oesophagus, anyone who has performed a bronchoscopy will know that the delicate larynx and airways respond to the most gentle of stimulation. The difference between reflux causing respiratory symptoms and gastro-oesophageal reflux disease is neatly demonstrated by cough after meals. Patients with postprandial reflux cough do so approximately 10 min after food.[2] This is the time of peak transient opening of the lower oesophageal sphincter and combats aerophagy. However, heartburn does not occur until later because stomach acid has been neutralised by the meal.

What evidence is there that reflux is an important cause of chronic cough? In a recent survey of normal subjects, Ford *et al*[3] found that 7% reported a chronic cough sufficient to interfere with activities of daily living. After correction for factors such as cigarette smoking, gastrointestinal symptoms including regurgitation and irritable bowel (but not heartburn) were highly correlated with cough. However, as with cigarette smoking and lung cancer, epidemiology can never prove a causal link—merely suggest associations. Can we be sure if there is no specific diagnostic test? The answer is not yet but, for the clinician, the precipitation of cough by factors known to cause transient opening of the lower oesophageal sphincter such as rising, phonation and postprandially gives the game away. Other extra-oesophageal symptoms such as dysphonia, rhinitis and a funny taste in the mouth are also present in subjects with cough with proven reflux disease.[2]

The approach taken in this latter study, to explore the symptoms of reflux cough by assessing patients with proven acid reflux, has been adopted in a study by Patterson and colleagues published in this issue of *Thorax* (***see p 491***).[4] They investigated the profile of tachykinins present in induced sputum from patients with asthma (as defined by bronchial lability) and patients with cough without reversibility or methacholine hyperresponsiveness. They performed 24 h pH monitoring to define those in each group who had acid reflux and found that patients with acid reflux had higher tachykinin levels. Of the several possible explanations for this phenomenon, they favour the reflex neurogenic release of the peptides. What is very interesting about this study is that, for the first time, a difference has been detected in the profile of patients with different phenotypes of cough. When patients with chronic cough have previously been studied by histological examination,[5] induced sputum inflammatory markers[6 7] or neurotrophin profiles,[8] no difference has been detected, suggesting to some that chronic cough is a single syndrome. While this is still possible, and acid reflux may be merely stimulating an epiphenomenon of tachykinin release, this is the first study to define a unique phenotype which may have important consequences for treatment. Current treatment for reflux of respiratory importance is less than satisfactory. Because this sort of reflux is less acid-dependent, even twice daily proton pump inhibitors only produce a response in at most half of patients. Unsurprisingly, drugs that act on the motility of the gullet such as metaclopramide and domperidone can produce pleasing responses. Baclofen, which mimicks vagal inhibition of lower oesophageal sphincter opening, is our last specific treatment for reflux cough. The finding of higher levels of tachykinins in sputum from patients with acid reflux-related asthma and cough suggests an urgent need for neurokinin antagonists to be studied in these patients.

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