conditions such as TB, interstitial lung disease, lung cancer, or heart failure. If these tests do not confirm a specific diagnosis which can be treated, based on the history I would start empirical treatment for postnasal drip, gastro-oesophageal reflux,¹⁴ or asthma, and review the patient after four to six weeks to find out if symptoms have improved.¹⁵ If the patient has not improved and the diagnosis is still not clear I would refer to the pulmonologist for further investigations such as spirometry or bronchoscopy.

The primary care context

Primary Care Centres offer free consultation and medicines, though demand is high. Patients with health insurance also use these services increasing the expenditure of resources. There is a need to standardise the use of clinical guidelines in primary care; although there are national guidelines for the management of TB and HIV-TB co-infection,^{10,16} the guidelines for asthma and COPD are not standardised, thus leading to considerable variation in practice. Healthcare professionals are often distracted from their clinical role by having to engage in addressing the deprivation, economic and psychosocial situation of the patients.¹³ Access to health services is acceptable, but often the people who most need care are the least demanding and the health team may need to go in search of them.¹⁷

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PERSPECTIVE

Following referral: a secondary care perspective from the UK

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Chronic cough is not a trivial problem and by the time a patient has been referred to a specialist cough clinic they (and their family) are likely to be thoroughly fed up! We know that persistent cough adversely impacts quality of life,¹ and a significant proportion of patients referred to specialist clinics have measurable levels of

psychomorbidity.² Although females account for more than two-thirds of patients referred for specialist advice, the clinical scenario outlined in this case is not at all unusual. Asking directly about urinary incontinence during bouts of coughing is important as this is not always volunteered by the patient.

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A systematic approach

The recommended approach to managing chronic cough is to assess each case systematically, beginning with history and physical examination and review of baseline investigations. CXR and spirometry should be performed as a minimum and in many countries can be easily undertaken in primary care [see Kaplan's perspective above] followed by additional diagnostic tests (not always available in primary care) and therapeutic trials based on the clinical features of the case.³⁻⁵

Although a commonly held position is that the clinical history offers little diagnostic information, my experience over the years has been that a carefully taken history is invaluable. Simply asking the patient to describe their cough is helpful; establishing whether the patient is actually coughing rather than 'throat clearing', for example, is important. In the case described above with the past history of smoking, chronic bronchitis and lung cancer are likely to have been carefully considered in primary care. Nonetheless, the threshold for bronchoscopy in a smoker with a normal chest radiograph and persistent cough is low. Other fairly obvious features in the history such as daily cough productive of large volume of mucus would suggest bronchiectasis and prompt a high resolution CT scan of the chest.

Patients often report worsening of their cough with respiratory tract infections (as in this case) but what is usually more disruptive for them is the daily aggravation of cough by relatively innocuous stimuli such as aerosols, scents and odours, a change in air temperature or even when simply talking or laughing. The term 'cough hypersensitivity syndrome' has been used to describe this clinical scenario,⁶ although doubt has been raised as to the validity of this as a distinct, but poorly understood clinical entity.⁷ Other important components in the history may be cough in association with the work place raising the possibility of occupational asthma, a seasonal pattern suggesting atopic cough, or co-existent symptoms of snoring and excessive daytime sleepiness suggesting obstructive sleep apnoea which is a well-recognised association.

However, the main value in taking a history is to identify typical and atypical symptoms that may help direct additional investigations and trials of therapy. The physical examination is frequently normal.

Further investigations and management strategies

Cough variant asthma and eosinophilic bronchitis are characterised by eosinophilic airway inflammation and both usually respond well to corticosteroids.^{8,9} The routine use of induced sputum for the assessment of airway inflammation in cough clinics has not been widely adopted. However, fractional exhaled nitric oxide (FeNO) is measured in all patients attending my specialist clinic. FeNO measurement is relatively simple, non-invasive and levels correlate well with eosinophilic airway inflammation.¹⁰ As FeNO levels are increased in asthmatic coughers and patients with eosinophilic bronchitis, the measurement of FeNO represents an attractive means of selecting patients for steroid treatment. However, there is no consensus on the optimal method of assessing airway inflammation, the dose and duration of oral corticosteroid trials, and the required

length of treatment with inhaled corticosteroids.

The presence of reflux symptoms or prominent upper airway symptoms should prompt empirical treatment first, with further investigations withheld until the patient has had an adequate trial of therapy. Most patients referred to my specialist clinic have had numerous trials of therapy, but careful questioning establishes that many have had suboptimal doses of therapy often of inadequate duration and many admit to non-compliance. Until fairly recently, the treatment of gastro-oesophageal reflux disease (GORD) has focused mainly on the treatment of acid reflux and, based on fairly limited evidence, recommendations for high dose acid suppression for an extended duration (three months or longer) have been made. However, the notion that cough despite high dose acid suppression is not due to reflux is wrong. Recent findings suggest that non-acidic reflux episodes are strongly associated with episodes of cough.¹¹ Multichannel intraluminal impedance (MII-pH) monitoring,¹² which has the advantage of identifying and characterising both acidic and non-acidic reflux episodes is likely to supersede 24-hour ambulatory pH monitoring which offers little in the assessment of patients with cough.¹³ The value of prokinetic agents or treatments such as baclofen (which act directly on lower oesophageal tone) or surgical techniques such as laparoscopic fundoplication in managing cough associated with volume reflux remain to be confirmed.

The association of cough with post nasal drip has been questioned,¹⁴ and unless the patient reports marked upper airway symptoms which have persisted despite an adequate trial of nasal therapy I would rarely refer for ear, nose and throat assessment. The recent adoption of the term upper airway cough syndrome (UACS) moves away from a symptom profile (postnasal drip) and towards likely causative factors (rhinitis or rhinosinusitis). Recommendations from North America for the treatment of UACS suggest sedating first-generation anti-histamines which although not universally available on prescription are preferred over newer agents.¹⁵ Intranasal corticosteroids are recommended but there is a lack of necessary detail as to the dose and duration of therapy.⁴

Unfortunately, up to 15% of patients with chronic cough remain unresolved despite numerous investigations and exhaustive trials of therapy.¹⁶ Patients with unexplained or idiopathic cough are known to benefit from cognitive behavioural therapy.¹⁷ The reality is that patients referred to specialist cough clinics rarely experience complete, long term resolution. I believe the best we can achieve with current treatments is to control the cough and I make this clear to all patients from the outset. New, more effective treatments for cough remain an unmet clinical need.

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PERSPECTIVE

Chronic cough: don't forget drug-induced causes

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Drugs have the potential to cause a myriad of respiratory syndromes: here we consider specifically drug-induced cough. It is important to recognise that cough may be the initial manifestation of more serious drug-induced pulmonary syndromes such as interstitial lung disease, acute lung injury, pleural disease and pulmonary vascular disease caused by a number of well-recognised drugs (amiodarone, nitrofurantoin, methotrexate to name a few) which are not considered here. For more extensive reviews and an online drug database of pneumotoxicities which can be a useful reference of described toxicities if in doubt, see www.pneumotox.com.^{1,2} This short paper will consider the commonly used drugs that may be implicated in chronic cough.

ACE inhibitors

Angiotensin converting enzyme (ACE) inhibitors cause dry nocturnal cough in about 5-35% of people. Release of bradykinin, which is normally metabolised by ACE in the lungs, results in a typical tickling, scratchy or itchy sensation in the throat.³ There is a poor dose-response relationship and it normally occurs within the first week of treatment – but onset can sometimes be delayed for up to six months. In addition, although most cases subside after four weeks, a significant proportion of cases can take up to three months to resolve after stopping the drug.⁴ Although theophylline and cromoglycate

have been advocated in the past to treat this cough, the only effective treatment is stopping the drug. It is more common in women (perhaps due to the heightened cough reflex in women) and also, interestingly, in Chinese people.⁵ Airflow obstruction is not usually a feature, and the presence of asthma does not change the likelihood of its occurrence.⁶ It is a class effect, and generally recurs if any other ACE inhibitor is reintroduced.

A2R blockers

Angiotensin 2 receptor (A2R) blockers are commonly used as a first substitute when ACE inhibitor cough appears, though they have a similar side effect profile to ACE inhibitors. However, cough can still occur with A2R blockers but is typically three to four times less common.^{7,8} Cough recurrence rates are also lower with A2R blockers but they should not be overlooked as a cause of chronic cough.

β-blockers

Cough may be the initial manifestation of drug-related airway hyper-responsiveness or bronchoconstriction that is described with β-blockers; associated wheeze and dyspnoea may occur. β-blockers (including eye drops) cause bronchoconstriction via bronchial β₂ receptor blockade. A meta-analysis has confirmed no evidence of long-term decline in lung function in reversible obstructive lung

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