A decade ago several research studies highlighted the underdiagnosis of asthma, particularly in children, but also in the elderly, and most general practitioners felt an increased pressure on them to diagnose this common chronic respiratory disorder. It was implied that asthma should be considered whenever a patient presented with a persistent cough and that far more people “deserved” to be on effective treatment with inhaled steroids. Undoubtedly, as a consequence of this message, many with asthma gained treatment which otherwise would not have been provided and, presumably, improved their morbidity and quality of life.

However, there has emerged a down side to this campaign in that some subjects with other respiratory conditions and some with no lung disease at all have been labelled as having asthma, leading not only to years of receiving unnecessary medication but also to the development of psychological dependence on the asthma label and its associated quest for improvements in symptom control. Most of such subjects have chronic obstructive pulmonary disease (COPD), but in my clinical practice I have also found cases of hyperventilation, recrudescent tuberculosis, and severe sleep apnoea syndrome. The records of the asthma diagnosis in one subject (now correctly labelled as having COPD) read merely: “Cough. Wheeze. Ventolin. Bectotide”. It is now clear that, as a consequence of this message, many with asthma gained treatment which otherwise would not have been provided and, presumably, improved their morbidity and quality of life.

Within the last decade in the UK, and similarly elsewhere, there have been consensus publications on the management of asthma and COPD. Much is written in these documents about the management of these conditions but less on diagnosis. The 1995 review and position statement on asthma management said only that “If the variable nature of airway narrowing which is characteristic of asthma cannot be demonstrated by any other means, then in adults and older children a trial of high dose oral steroids with peak flow monitoring for a minimum of two weeks is essential”. The COPD guidelines are more specific, grading the condition into mild, moderate, and severe categories on the basis of forced expiratory volume in one second (FEV₁) as a percentage of predicted as well as symptoms and signs.

General practitioners in the UK have been able to prescribe peak flow meters on the National Health Service since 1990 and are thus most likely to use these devices for both the diagnosis and management of asthma and COPD in the community. The benefits of peak flow monitoring in the management of established asthma have become clear since Beasley et al first published their initial study of self-management. However, it is much less clear that measurements of peak flow alone can be considered sufficient in the diagnosis of asthma and COPD. A primary and secondary care respiratory specialists working group, with representation from the UK and the Netherlands, clearly stated that formal spirometric testing was necessary.

In this issue of Thorax Thiadens et al. another group from the Netherlands, have carefully compared the usefulness of peak flow recordings and their changes in response to bronchodilators with the presumed gold standard of changes in FEV₁. They gathered data from 240 adults not previously labelled as having either COPD or asthma who presented with cough persisting for at least two weeks to one primary health care centre over a 15 month period. Low peak flow (found in 86 subjects) had a positive predictive value (PPV) of only 47% for low FEV₁ (found in 48 subjects) but a negative predictive value (NPV) of 95%. Several different definitions of increase in peak flow with a bronchodilator challenge were compared with a 9% or more change in FEV₁. The PPVs for both absolute and percentage changes were all less than 66%, though the NPVs were 88–93%.

With the recent focus on COPD as well as asthma and the resultant increased clarity in how these conditions should be managed, it is clearly imperative that patients with obstructive pulmonary diseases are correctly diagnosed from the outset. Thiadens et al did not examine reversibility testing with courses of oral prednisolone nor the usefulness of diurnal variation in peak flow, but doubt has correctly been expressed about the importance of the finding of a low peak flow rate in patients who present with cough. The message appears to be that the finding of normal peak flow at presentation makes COPD unlikely (though not excluding asthma), but that low peak flow should be taken as a trigger for spirometric testing. This presents a considerable challenge for primary care practitioners.

Spirometric measurements can be conducted “in house” in general practices or in the lung function laboratories of local hospitals, either by consultant referral or by open access arrangements. The former route has the advantage of convenience for patients but a major disadvantage in relation to quality control, with difficulties in equipment selection, staff training, and interpretation of results. The local hospital service, though less convenient, obviates these disadvantages but there is a considerable risk of it being overwhelmed if anything like all the potential patients are referred to it. There may well be scope for locally based services, set up by primary care groups, whereby one primary care team provides spirometric services for others in its vicinity with quality control achieved by links to hospital staff. If these issues are not tackled in a coordinated fashion, there is a risk that future patients will continue to be diagnosed with the wrong condition in primary care and not receive the best treatment for their symptoms.

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The CF gene: 10 years on

D M Geddes, E W F W Alton

These days everyone is looking for genes. Grant money, media interviews, self-esteem, Nobel prizes, and lots of interesting biology lure researchers into molecular genetics, and diseases as diverse as asthma, chronic obstructive pulmonary disease and lung cancer will soon be mastered by brave new understanding. All true, but will it make any difference? Cystic fibrosis got there first, and 10 years after the discovery of the CF gene it is a good time to take stock. Compared with polygenic diseases, cystic fibrosis is easy and therefore paints the rosier picture of what can be achieved by genetic research. If the CF gene has helped patients, then the discovery of genes associated with other diseases may do the same. The steps involved in the genetic revolution were well illustrated in a recent review article as shown in fig 1.

Pathogenesis

By sequencing the CF gene, the protein was deduced and found to resemble a family of ATP binding membrane proteins with both ion channel and macromolecule transporter properties. Cystic fibrosis transmembrane conductance regulator protein (CFTR) is a chloride channel which opens in response to phosphorylation by ATP and is found in sweat and pancreatic ducts, gut, seminiferous tubules, and conducting airways—all sites of cystic fibrosis disease. Interestingly, CFTR is also expressed in the heart, choroid plexus, and renal tubules, organs with normal function in cystic fibrosis. Other properties of cystic fibrosis have been proposed such as the regulation of apical membrane sodium transport in the airways and acidification of intra-cellular organelles. No transporter function of CFTR has yet been found.

Over 800 disease associated mutations of the CF gene have been described; these differ with ethnic origin but only a handful are common. These mutations have been classified according to their molecular pathology into five groups: (1) no protein, (2) defective intracellular trafficking (typically the commonest mutation AF508), (3) and (4) altered channel function, and (5) reduced levels of functional protein, and this mechanistic information may point the way to new pharmacological treatments. The link between the various mutations and disease is still being worked out; abnormal channel function goes with altered electrolyte and water content of secretions, thus explaining high sweat electrolytes and dehydrated viscid pancreatic secretions. The pathogenesis of lung disease is, however, more controversial and there are three schools of thought, all of which concern a defect in sodium absorption and UTP to enhance chloride secretion, (3) and (4) based on airway surface liquid changes. A high salt school proposes that increased sodium and chloride levels limit the activity of antibacterial defences such as lysozyme and defensins, while a low volume school proposes that increased sodium and consequently water absorption from the airways leaves a depleted sol layer which impairs mucociliary clearance. All three mechanisms may co-exist and each is open to pharmacological correction. Finally, one of the surprises of cystic fibrosis research is how poorly genotype predicts phenotype and, although the typical presentation of cystic fibrosis with pancreatic insufficiency goes with AF508, the high variability in clinical expression of lung disease is not yet explained.

From pathogenesis to treatment

This increased understanding has led to the investigation of a range of possible new treatments. Firstly, knowledge of the molecular pathology has suggested various agents to increase gene expression (phenylbutyrate, gentamicin), enhance trafficking (glycerol), or enhance ion channel activity (milrinone, CPX). Naturally, such approaches will only work with the appropriate genotype. Phenylbutyrate and glycerol have shown promise in initial clinical trials but greater potency and precision of action are still needed. Secondly, an understanding of organ pathophysiology has suggested ion transport modifying drugs, although admittedly this line of investigation was being pursued before the discovery of the gene. Agents include amiloride or benzamil to reduce sodium absorption and UTP to enhance chloride secretion, all of which are at different stages of testing in human trials. These approaches are logical to either high salt or low volume theorists. In addition, those in favour of the high salt theory would favour some method of adding water to airway surface liquid (ASL) or developing salt resistant defences while proponents of the low volume theory favour addition
of salt and water to ASL, perhaps by nebulising hypertonic saline or some other less well absorbed osmolyte. Finally, the sheer number of possible drug mechanisms which might be involved has persuaded others to screen the whole pharmacopoeia in a mindless (but intelligent) medium throughput screening system to see if any agent already in use might work in cystic fibrosis.

**Diagnosis and screening**

Before the discovery of the gene some were predicting a single mutation which would greatly simplify both diagnosis of cystic fibrosis and carrier detection, as well as opening the door to population screening and eventual eradication of the disease. Instead, the discovery has, if anything, made things more difficult. The large number of mutations together with the finding of new gene associated disorders has made diagnosis more complex. The typical patient with cystic fibrosis usually has one of the four commonest mutations so genotype analysis confirms the diagnosis in those for whom no confirmation is really needed. For patients with borderline clinical disease, genotyping may reveal one or none of the common mutations and, since routine laboratories cannot take on the task of screening for all 800+ mutations, the situation usually remains unclear.

The presence of two disease associated mutations is diagnostic, the finding of one may be suggestive but is certainly not diagnostic since the carrier frequency in the population is high (1:25 in the UK), and the failure to find a mutation in no way excludes the disease. Furthermore, studies have now found convincing linkage between some mutations of the CF gene and idiopathic pancreatitis or male infertility in people with no other evidence of cystic fibrosis, so extending the clinical expression of the disease. Preliminary reports have also suggested linkage to allergic bronchopulmonary aspergillosis, while mutations of the CF gene in association with asthma have been reported as more than expected, less than expected, and just about right. So, while genotyping sometimes makes the diagnosis of cystic fibrosis more certain, the exclusion of cystic fibrosis and knowing precisely what a diagnosis of cystic fibrosis means has become more difficult.

In contrast, genotyping has greatly assisted the identification of carriers of the CF gene and provides clear cut evidence when no mutation is found or allows better informed reproductive decisions when the test is positive. Naturally, a negative test does not rule out the possibility that the individual is a carrier, but it makes it extremely unlikely. In the antenatal setting, screening of mothers to identify carriers followed, when positive, by screening of fathers allows identification of at-risk pregnancies. In the well designed Edinburgh study the parents of such pregnancies chose to proceed to fetal genotyping and, when a fetus was diagnosed as having cystic fibrosis, most couples opted for termination of the pregnancy. Wide spread adoption of such screening programmes could have a very major effect on the frequency of cystic fibrosis in the future, whilst carrier screening in affected families already provides a high level of reassurance and occasionally assists family planning decisions.

**Gene therapy**

In theory, cystic fibrosis should be ideal for gene therapy. The main technical problem is in the airways and the likely target is the surface epithelium. Furthermore, methods of topical delivery to the airway surface are already well developed. Progress was rapid at first: the gene, although large, could easily be inserted into a virus or produced as a plasmid; cellular studies showed that CFTR gene transfer could produce clinical improvements which worked and subsequently showed that cystic fibrosis cell lines could be corrected. The next steps were the demonstration of relatively efficient gene transfer to the airway epithelium using reporter genes in rodents, followed by partial correction of the disorder in the airway epithelium of CF mice. Clinical trials soon followed and, to date, over 150 volunteers with cystic fibrosis have taken part. The results have been both encouraging and frustrating. There is good evidence of low levels of gene transfer and patchy evidence of small changes in ion transport but progress has been hampered by inefficient gene transfer, immunity to viral vectors, and a systemic inflammatory reaction provoked by plasmid DNA. The efficiency of gene transfer is improving as techniques to overcome the biological barriers and cell defence mechanisms are better understood and the gene delivery agents improve. The immune and inflammatory reactions may prove more intractable but eventually will be overcome. However, at this stage no gene therapy methodology has yet approached the desired levels of safety and efficacy needed for large scale clinical trials. Too many enthusiasts promised too much in the early stages and, when they failed to deliver, scepticism set in.

Gene therapy is an entirely new technology and it will take another 5–10 years before such a treatment is available. This is neither slower nor faster than the development of any other new drug.

**Conclusions**

What then has been achieved? Firstly, a mass of new knowledge and understanding; secondly, some tangible benefits in terms of screening and diagnosis; thirdly, some new directions of therapeutic research with reasonable promise of improved treatments to come; fourthly, considerable progress towards gene therapy with likely success within a decade; and finally, the path from gene discovery to clinical application has been cleared and this will speed progress for other genes and other diseases in the future. However, it is worth re-stating that the path is much easier for a single gene defect like cystic fibrosis than it will be for polygenic disorders with major environmental components such as asthma, chronic obstructive pulmonary disease, and lung cancer. When gene linkages are found in these and other diseases, as they certainly will be, do not expect a quick fix.

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Gas cooking and respiratory disease

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More than half of British homes use gas as their cooking fuel and even a small risk associated with either acute or chronic inhalation of the by-products of gas combustion—such as other nitrogen containing species, formaldehyde, sulphur dioxide and particulates—would have a substantial influence on public health. Surveys have been performed to assess these risks, variably defining exposure by the presence of a gas cooker in the home or by direct measures of related pollutants. Results from these surveys are remarkable by their lack of consistency. While some large and powerful cross sectional studies have found no association of the presence of a gas cooker with respiratory disease in children, others report an increased risk of lower respiratory illness. Those who use the cooker the most—arguably adult women—may be the group at greatest risk. The European Community Respiratory Health Survey (ECRHS) which analysed data collected from young adults aged 20–44 years living in 23 centres in 11 countries showed no association of gas cooking with wheeze in men but an overall positive association in women. However, there was marked heterogeneity in the association in women across the centres despite the common methodology used to define exposure and outcome, with the strongest positive association being observed in women in East Anglia.

There are few data on the association of gas cooking with symptoms and lung function in the elderly, although a study in Krakow, where gas is almost universally used as the cooking fuel showed that women over the age of 65 years who reported heavy usage of their cooker had more symptoms and worse lung function than those using it less frequently. In this issue of Thorax Dow et al publish findings from a cross sectional postal survey of elderly adults living in Bristol. They found no overall increase in the prevalence of respiratory symptoms in those owning a gas oven, gas hob or gas fire, but their results showed that the risk of respiratory symptoms was consistently higher in women with a gas hob than in those without. The association was less apparent in men. They conclude that gas cooking is unlikely to be an important source of morbidity in the elderly population. The atopic status of those who took part in the study is unknown. Although the prevalence of atopy is lower in older populations than younger populations, this omission may be of importance because there is some research to suggest that the effect of exposure to gas may be different in those who are atopic and non-atopic. In the analysis of data collected in East Anglia as part of the ECRHS, atopic women had more symptoms and worse lung function if they cooked with gas rather than electricity. This observation is consistent with small clinical trials suggesting that inhalation of high levels of nitrogen dioxide, as might be experienced around a gas cooker at the time of use, enhance bronchial responsiveness to inhaled allergen and enhance the allergen induced late phase asthmatic reaction.

Another recent study collected information on reported exposure to gas cooking in childhood and currently in 35 year old subjects from the 1958 national birth cohort and assessed atopy (by skin tests) and lung function. Overall there was no association between the incidence or severity of asthma and use of gas for cooking, although in women current gas cooking was associated with a significantly increased risk of persistence of asthma from childhood to adulthood. Men and those with established asthma had lower forced expiratory volume in one second and forced vital capacity if they cooked with gas than with electricity. None of the analyses performed showed effect modification by atopy.

Although these recent studies offer some reassurance to the general public, some doubt remains as to whether there are subgroups of individuals—such as those with atopy, asthma, or poor lung function—who are more susceptible than others. Until this is resolved everyone should be advised to take sensible precautions to reduce their exposure to gas flames. These precautions include regular servicing of gas appliances to ensure they are working safely and efficiently and adequate ventilation of the kitchen when the cooker is on or by opening a door or window to the outside or by use of an appropriate extractor fan. The gas rings should never be used to heat the kitchen. Meanwhile the potential interaction between pollutants from gas cookers and allergen, both acutely and long term, warrants further investigation. Large longitudinal studies that assess changes in symptoms and decline in lung function in populations of known atopic status and which also measure exposure to gas cooking and allergen are required. This will help to determine whether the resources currently invested in reduction of exposure to house dust mite should be supplemented or replaced by a change from gas to electric cooking in some homes.

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