GRESHAM COLLEGE

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ASTHMA AND CHRONIC AIRWAYS DISEASE

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Chronic diseases are those which once they start continue for a prolonged time, and potentially lifelong. They may come and go, or remain steady, or get worse, but they are not over in a single short episode like diseases such as pneumonia.

This talk will consider three major chronic lung diseases; asthma which is the commonest chronic lung disease in the UK, chronic obstructive pulmonary disease (COPD) a major cause of illness and mortality, and cystic fibrosis. Chronic diseases are determined by a combination of genes, environment and chance. These three lung diseases illustrate this interaction in different ways. The genetic make up of a population usually changes slowly, but the environment can change very rapidly. The environment in London for example is completely different now compared to when Gresham College started. Environment can include exposure to infectious diseases, our living space, internal and external pollution, and things we are exposed to as part of our occupation.

Asthma

Everybody will know people who have asthma, some in the audience will have it. Around 5.4 million people living in the UK currently receive asthma treatment: 1.1 million children (1 in 11) and 4.3 million adults (1 in 12). In the UK the NHS spends around £1 billion a year treating and caring for people with asthma. Globally there are over 235 million cases according to the WHO, causing 250,000 deaths annually. Whilst asthma can be severe and is occasionally fatal, in most people it is mild or moderate, interfering to some degree with their lives but not restricting them, even in professions where extreme breath control is essential. Asthma for example is not a bar to being a great athlete with famous examples of stars with asthma from almost every major sport, nor has it prevented internationally acclaimed musicians and public speakers. Receiving a diagnosis of asthma yourself, your family or your friends should therefore in no way be seen as restricting life or ambitions. It should however be taken seriously.

Asthma causes its problems by narrowing the airways in the lung and therefore restricting people's ability to breathe. It does this through three mechanisms; narrowing the overall diameter by tightening the muscles around airways, causing inflammation of the airway wall, increasing sputum production. Many people have almost no problems from asthma except during specific attacks whilst others may have permanently slightly restricted breathing, at least until they have treatment.

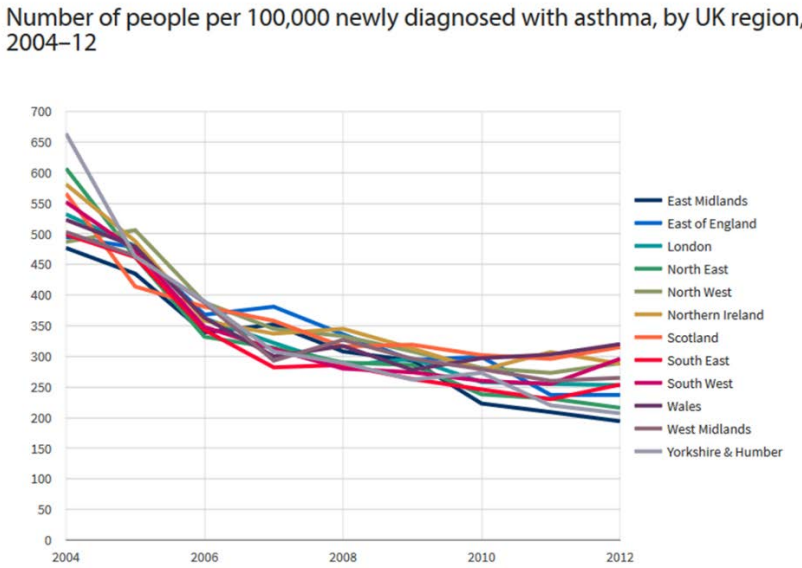
Asthma, which clusters in families, is caused by a combination of genetic inheritance and environmental factors. It is more likely for a child to have asthma if a parent has it, and more likely if both parents have asthma. For someone with an identical twin with asthma there is a 20-30% chance of having the disease. This is however not caused by a single gene. Over a hundred genes have been associated with asthma many of which are linked to other atopic (allergy-associated) diseases.

Asthma attacks are often triggered by particular environmental factors. These triggers vary between different people. Chest infections are a common cause, but pollen, chemical fumes, pets, bugs, pollution, cigarette smoke,

dust, cold, exercise and strong emotions are capable of triggering attacks in some people. Avoiding all of these is impossible.

There appeared to be a steady increase in asthma from the mid-1970s in the UK through the 80s, peaking in the 1990s. Since this time new cases of asthma have peaked and begun to go down. The extent to which this is due to changes in diagnosis and to what extent it is a real phenomenon are debated. There does however appear to be a fall in new diagnoses of asthma throughout the UK in the last 10 years, although this is levelling out.

Figure 1. New asthma diagnoses over time, UK, by region.



Whilst the slow temporal increase or decrease of asthma in the community is occurring around the world at different rates there is a lot of seasonal variation in asthma attacks. There is a clear winter peak in asthma GP diagnoses, for example, linked mainly to infection (and sometimes cold). There are peaks at other times of year for particular people which vary by geography. Examples include different trees and other plants producing pollen at particular times of year, which through hayfever, trigger asthma in some people, or children going to school and being exposed to the current infections. Seasonal asthma admissions to hospital, which tend to be mainly in the winter, are particularly pronounced in the very young (0 to 4 years) and at the other end of the age spectrum in those over 75 years old.

Diagnosing asthma is not always straightforward. The first attack of wheeze in a child often is not asthma. Whether symptoms improve on current treatment is part of the diagnosis. Asthma treatment goes back to ancient times but safe and effective treatment only started in a widespread way from the 1950s. Much traditional or historic treatment such as the blood of owls or wild horses, centipede in honey, cigarettes and psychoanalysis are unlikely to have had useful effects. Current asthma drugs are however highly effective in the great majority of people. They can be broadly divided into those which are for relief of asthma symptoms, and those designed to prevent asthma.

It has been known from at least 1910 that injecting adrenaline (which at that stage had only recently been identified) could have an effect on reducing the symptoms of asthma. Adrenaline has a very wide range of effects in the body meaning it has many side effects so the current mainstay is a much more selective drug which stimulates adrenaline receptors in the lung, salbutamol, developed in 1966 in the UK. This is an example of a drug class called β2-adrenergic agonists. These drugs when used during an asthma attack can rapidly lead to relaxation of smooth muscle which is constricting airways and have some degree of anti-inflammatory activity. Almost everybody with asthma will carry a salbutamol or similar inhaler to take when the symptoms get bad. Concentrated forms of salbutamol are used for treatment of severe asthma attacks in hospital. Long-acting drugs which affect the same receptors are also used in some people.

The second major class of drugs in asthma is to prevent disease and this is steroids. Much of the effect of asthma is through inflammation and steroids are anti-inflammatory. From the 1950s we have known that

injections of steroids could have prolonged effects on reducing asthma. In the 1970s this moved onto oral steroids and then from the mid-1970s inhaled steroids. Steroids are very effective if used regularly at reducing the risk of asthma attacks. Oral steroids are only used in severe attacks because of their side effects but inhaled steroids have very limited effects elsewhere on the body but do substantially reduce asthma. To work inhaled steroids have to be used regularly rather than just during attacks.

The third common drug class was originally from herbal medicine. Smoking stramonium, dried Thorn-apple / devils snare, was used for asthma from the 1900s. The active ingredient, alkaloids of Belladonna (also found in deadly nightshade), an anticholinergic similar to atropine. A stable form, ipratropium bromide, was developed for inhalation. Other drugs are available, such as the leukotriene receptor antagonists, for people with more difficult asthma.

There is a ladder of intervention using these inhaler classes starting with people who only need occasional rescue treatment, through the majority who require inhaled steroids to more powerful combinations depending on the severity of disease.

For severe disease there are new advances likely to occur over the next few years in the form of biologic agents. Monoclonal antibodies are revolutionising the treatment of many severe inflammatory diseases. These target particular bits of the immune system. Early trials of several agents are promising in severe asthma although none are yet ready for widespread deployment.

For practical purposes we treat mild-moderate asthma as if it is a single disease but it is not. It is likely to turn out to be a range of diseases which have very similar effects but the different basis of asthma will in the future almost certainly give rise to different treatments for people with severe disease.

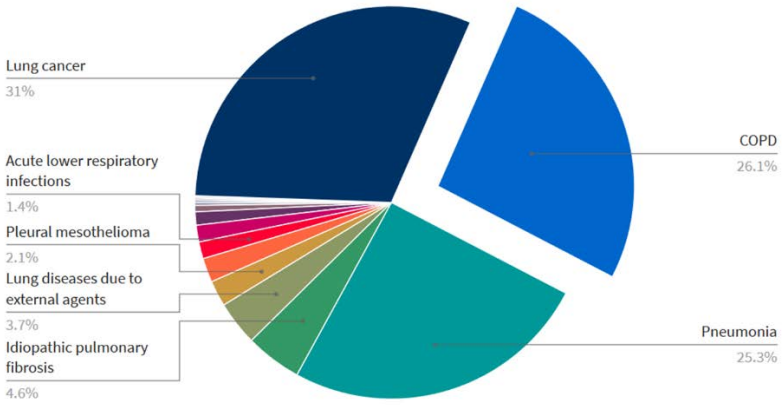
Only a minority of people with asthma ever need hospitalisation, but asthma is very common so this minority is still significant numbers. Severe asthma, which tends to occur in the same people in some cases, is life-threatening. People who have suffered, or watched, a severe asthma attack will realise it is extremely frightening, and can be fatal if left untreated. The treatment is generally with much higher doses of the same drugs used in asthma control (salbutamol and steroids) along with oxygen but some people may also need respiratory support for ventilation. In the most recent year which we have data around 1400 people in the UK die from asthma. These deaths tend to be concentrated in older people (over 75) and in winter months but some deaths tragically occur in every age group.

Chronic Obstructive Pulmonary Disease (COPD)

Asthma and the second major chronic lung disease, chronic obstructive pulmonary disease (COPD) overlap. Most people who suffer have only one or the other but some have both. Uncontrolled asthma can occasionally lead to COPD. COPD is a broad term for a group of lung conditions where there is damage to the lung, but the major ones are emphysema (damage to lung sacs) and chronic bronchitis (inflammation of airways). Except in rare genetic conditions, in contrast to asthma it comes on in middle or old age. The main symptoms are shortness of breath and chronic cough. The natural history is gradually to get worse over time but with particular flareups (exacerbations). In severe cases there is substantial destruction to the lung and people with COPD can be highly restricted in what they can do due to severe breathlessness.

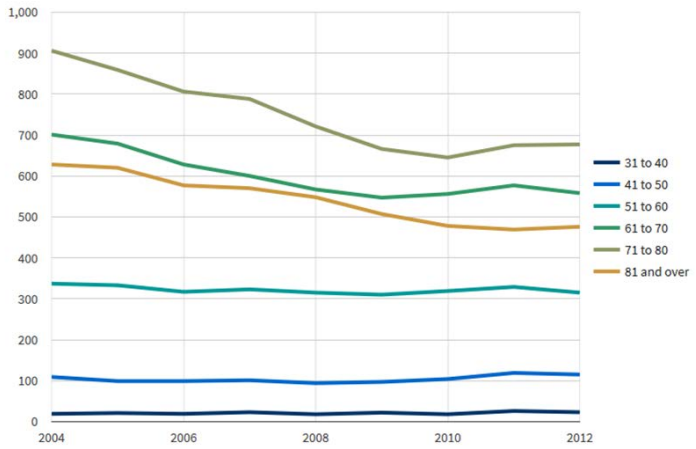
Although less well-known than asthma, COPD is a much more major cause of mortality. In the UK there are around 29,000 deaths a year due to the disease, just behind lung cancer as a cause of respiratory deaths and it is responsible for 5% of all deaths in the country. WHO predict it will be the third leading cause of mortality worldwide by 2030.

Fig 2. Respiratory causes of mortality, UK. British Lung Foundation.



Although there is a genetic element, this is largely an environmental disease. There are several potential environmental causes. Historically all countries, and still in many less wealthy countries indoor air pollution due to cooking or heating with wood, coal or charcoal is a major cause. Outdoor air pollution is a risk factor along with many occupations, particularly those with dusts including mining, brickmaking, welding, stonemasonry, flour and grain workers, agriculture textile and foundry workers. Historically these would have been the main causes of COPD in the UK. In high-income countries now and depressingly increasingly in developing countries, smoking causes the great majority of cases. In the UK smoking is probably responsible for 9 out of every 10 cases of COPD, an entirely preventable environmental hazard, and the epidemiology of COPD is essentially the epidemiology of smoking. Smoking has been gradually declining in the UK in every age group. This is both the number of people who smoke, and the amount those who use cigarettes smoke. As a result the number of people with a new diagnosis of COPD (incidence) has been declining and is likely to continue to decline.

Figure 3. New diagnoses of COPD over time, by age. British Lung Foundation.



Because, in part, of improvements in medicine discussed in previous lectures, including in cardiovascular disease which otherwise kills many people who smoke, people are living longer so the number of people living with COPD (prevalence) is increasing. The amount smoked in the UK vary by region with the highest smoking rates in the north-east and the lowest in the south-east; unsurprisingly rates of COPD are highest in the north-east of the country.

Treatment of COPD has three elements. The most important by some distance is for people to stop smoking. COPD is made worse in both the short and long-term by continuing to smoke. The second is to try to reduce other triggers for exacerbations, so for example people with COPD should all have influenza vaccination. The third is drugs which do reduce the symptoms. The drugs used are similar classes to those used for asthma but unlike with asthma are unlikely to return people back to essentially normal lung health.

Because smoking is the cause of COPD and it cuts short the lives of very many people, ruining their last few years by severely restricting their activities due to extreme breathlessness they often feel they are to blame for smoking (or that others blame them). Doctors are well aware a very large and extremely well financed industry (the cigarette industry) has put considerable resources into getting them addicted to nicotine and keeping them there. Smoking is a health problem to be solved, not a source of blame to the individual smoker.

Although the great majority of COPD is due to avoidable environmental factors, there is also some genetic components in particular the genetic condition alpha-1 antitrypsin deficiency (A1AT). Around 25,000 people in the UK probably have this, most of whom have no symptoms. It does however make COPD much more likely and at a much earlier age, especially in smokers. Having it reduces some of the protective layer of the lung, so inflammation which would have caused limited damage, causes much more severe damage. Significant alpha-1-antitrypsin deficiency is autosomal recessive and requires inheritance from both mother and father.

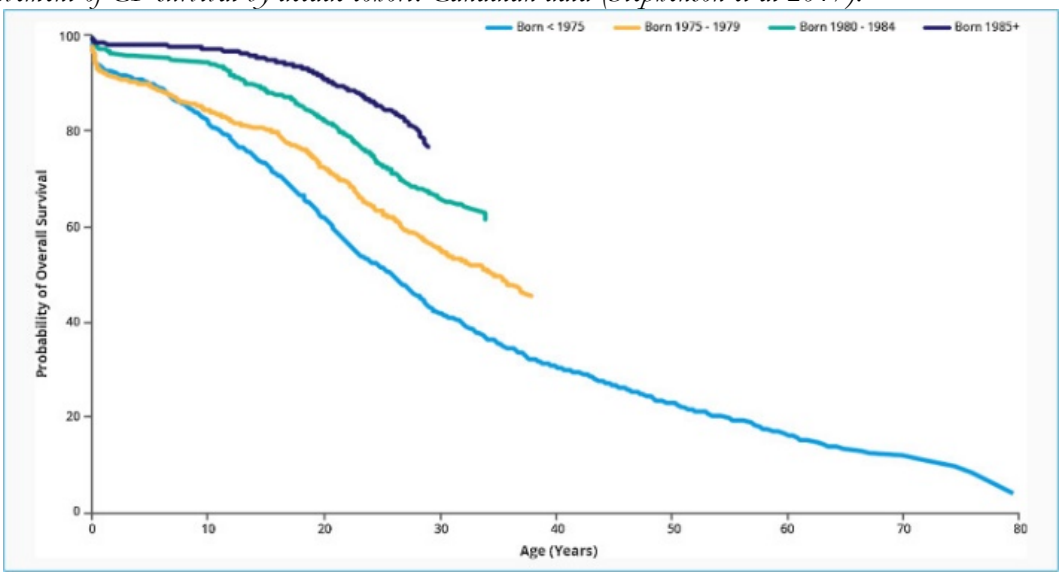
Cystic Fibrosis (CF)

Different genetic prevalences of A1AT deficiency are found across Europe and the world. This is even more marked for the third major disease to be considered here, cystic fibrosis (CF). People of UK origin have a particularly high rate of carrying the genes. CF is the commonest autosomal recessive condition in Caucasians. Around 1 in 25 people in the UK carry one faulty gene of which there are over 2000 possible mutations known. Around 10,500 people (1:2500 babies) have 2 faulty genes, one from each parent, and will develop cystic fibrosis. The biological basis of cystic fibrosis is that cells in various organs of the body, but most importantly the lung, handle chloride and water abnormally. This leads to buildup of thick mucus. People with CF will have repeated atypical infections of the lung as well as other effects on the body and most will go on to die of lung complications.

The outlook for cystic fibrosis is steadily improving every decade. In the 1960s the majority of children with cystic fibrosis did not reach their 10th birthday. Now it is common for many of those with CF to reach their 40s or beyond. This improvement has been built up of on a series of incremental advances in CF management, some of which is prophylactic treatment and some change of environment including, preventing people with CF from meeting one another and therefore potentially infecting one another.

There are now however increasing advances targeting the protein which is the cause of CF directly. Currently a number of drugs are used which can improve the function of the protein if taken lifelong. If current rates of progress continue improvements in CF survival will be substantial. Mortality rates have dropped annually by 2% over the last decade and half of CF babies born today and those aged 30 and above now can expect to survive until at least their fifth decade.

Figure 4. Improvement of CF survival by decade cohort. Canadian data (Stephenson et al 2017).



Although there are environmental factors involved in mortality and morbidity from CF, it is an almost purely genetic disease. In principle it is possible to correct faulty genes in people living with CF; this is still experimental but has been achieved in other genetic diseases such as sickle cell. Two possible approaches are to insert a normal gene in addition to existing ones or to edit the faulty gene by cutting out and replacing abnormal section in people who have CF. In theory it would be possible to edit the gene of the early embryo so people do not have CF at all but the ethical issues in manipulating embryonic genes are not trivial and currently this would not be legally possible in the UK.

Asthma, COPD and CF are three important chronic lung diseases. CF is an example of an almost purely genetic disease but where environmental factors can lead to significant differences in outcome. COPD is a disease where environment can play a part but is almost entirely environmental in origin, and in the context of higher income countries the relevant environment is largely smoking which is modifiable. Asthma combines some genetic and some environmental factors. For different reasons the outlook for all three diseases has improved and will continue to improve over the next decades.

We cannot alter our genes as easily as we can alter our environment, although altering the environment we live and work in can also be challenging. Smoking is an example of environmental risk which can be largely avoided by individuals. In contrast air pollution, another major environmental risk factor for respiratory disease is much more difficult for individuals to avoid and has to be seen as an issue for society as a whole. This will be the subject of the next lecture in this series.