The lung and the world about it

The Tudor Edwards Lecture 1996

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Much of the work of a thoracic surgeon of Tudor Edwards' day involved the surgery of tuberculosis and its late complications. It is perhaps difficult for younger doctors in Britain to realise the importance that this disease assumed in all areas of clinical practice at the time. However, the year before Tudor Edwards died, Waksman in the USA had described the antimycobacterial properties of streptomycin. With the almost simultaneous discoveries of *p*-aminosalicylic acid (PAS) and isoniazid, antituberculous chemotherapy offered a potential cure for that disease and the elimination of the need for surgical intervention was under way.

The lung and the soil

Waksman was a soil biologist, and it is in the soil that this story begins. I have taken as the title of my lecture 'The lung and the world about it', as a means of drawing attention to the fact that human beings are but one part of a much wider biological picture, and that nothing that happens to the lung is solely a matter of chance or ill-fortune. Tuberculosis became the greatest of all killers of men, Bunyan's 'Captain of all these men of death', because of the organism's evolved ability to live and reproduce within a phagocytic cell—an adaptation to survival in the soil where one micro-organism is food for another, but one micro-organism's meat may become another one's poison. Waksman knew this and, building on the work of René Dubos, searched for an organism that could control the tubercle bacillus and ensure that the balance of nature in the soil was maintained [1]. He found it in *Actinomyces griseus*. The pharmaceutical industry has not forgotten this lesson, and spends considerable sums of money looking for new antibiotics in soil samples.

The microscopic appearance of the two important structural components of the lung's defences, the macrophage and the respiratory tract cilia, shows how close we are to the soil whence we came. The macrophage is an amoeba, adapted to life in the animal body but still behaving as though it were in the soil. The ultrastructure of cilia is exactly the same whether they are moving protozoa around or removing particles from a human airway. Any organism that can successfully paralyse cilia or stop protozoa phagocytosing will have a survival advantage in the soil. If it becomes airborne and inhalable, it will have the potential to harm the lung of the inhaling organism. For example, *Aspergillus fumigatus* (Fig 1) lives in the soil and requires only a compost heap or a dead leaf for survival [2]. It gains no obvious biological advantage from causing lung disease in birds, cattle or people, and rarely sporulates in these environments—yet it is the cause of a wide range of human and animal respiratory tract diseases, and indeed in temperate climates is the only fungus commonly to cause such problems [3]. *A. fumigatus* lives comfortably in lung cavities; it becomes a particular problem in immunosuppressed patients, in whom today's transplant surgeons sometimes encounter it. Why should this micro-organism, rather than the multitude of other airborne fungal spores, cause these problems?

If a suspension of *A. fumigatus* spores in saline is filtered and the filtrate added to a culture of macrophages, the cells curl up; chemotaxis, spreading and phagocytosis are all inhibited [4–6] (Fig 2). The same apparent consequence follows addition of the filtrate to an amoeba or to a culture of the common

Fig 1. *Sporing head of Aspergillus fumigatus*

This article is based on the Tudor Edwards Lecture given at the Royal College of Physicians in January 1996 by **Anthony Seaton**, Head of the Department of Environmental and Occupational Medicine, University Medical School, Aberdeen

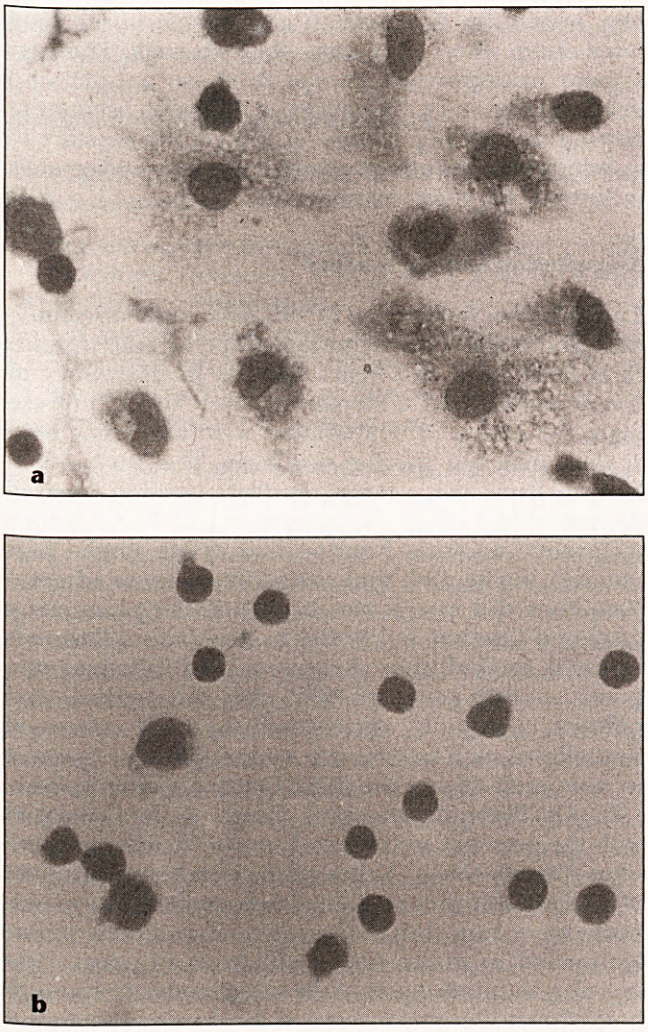


Fig 2. *(a) Control macrophages in culture showing normal spreading; (b) macrophages in culture after treatment with diffusate from Aspergillus fumigatus, showing contraction of cytoplasm*

soil organism, *Cercomonas* sp, which becomes immobilised within a few minutes [7]. In the soil, *A. fumigatus* presumably paralyses its intending predator and then may use it as a substrate; this clearly happens when it is added to a culture of lung macrophages (Fig 3). Particularly interesting observations are:

- *A. fumigatus* is more efficiently phagocytosed by lung macrophages in the *absence* of complement, and
- the presence of serum in *in vitro* cultures seems to assist it to resist phagocytosis [8].

This implies that, in the soil, some primitive opsonising mechanism may be used by protozoa in their feeding. I speculate that this may represent the evolutionary start of the complement system. It also explains why the inflammatory exudate characteristic of the airways of asthma and cystic fibrosis is so congenial to the survival of *A. fumigatus*.

The precise chemical constituent of the substance diffusing from the surface of these spores is not yet known, but work currently under way by Donaldson and colleagues at Napier University, Edinburgh, has shown it to act not only on motility but also on the genetic control of cytokine release. They have confirmed our earlier observation that it is a small molecular weight substance, and suggest that it may be a glycopeptide whose effect is on energy-dependent mechanisms of the cytoskeleton and cytokine synthesis.

Air pollution and the lung

The as yet unfinished story of *A. fumigatus* illustrates nicely the interrelationships between the lung and the world around it, and the interdependence of all the organisms living on this planet. Human beings have become vastly more complex in an organisational sense than the single-cell creatures from which they evolved, but still retain these reminders of their origins. Our reactions to attack by competitors for survival on the planet also invoke these more primitive responses, and this is where air pollution comes in. The defences of the lung are designed to cope with micro-organisms, and presumably treat all invaders of their territory in the same way, phagocytosing particles whatever their make-up. The lung's defences are well able to deal with the small amounts of wind-blown minerals that we all inhale, but have greater difficulty clearing the larger amounts accumulated in industrial situations such as coal mining, resulting in the diseases known as the pneumoconioses. Some dust particles are particularly toxic, either because of their surface chemistry or their shape, and initiate the more severe and progressive forms of pneumoconiosis, silicosis and asbestosis. In these conditions, an inflammatory reaction at bronchiolo-alveolar level, far from protecting it from the invader, may lead to lung damage, resulting in fibrosis and sometimes emphysema, for example, in coal miners [9].

Particle size

In all good inhalation toxicological studies of the lung, an inert control dust is used. This has usually been titanium dioxide (TiO_2), a dust so harmless that it was used experimentally to produce bronchograms without subjecting the patient to discomfort. However, in investigating the relevance of the size of particles to their interstitialisation in the alveoli, Oberdörster has studied the effects on rats of inhalation of extremely finely divided TiO_2, generated freshly as a fume and has shown that this substance, far from being inert, produces intense alveolar inflammation [10]. Similar results were obtained using equally fine (< 50 nm diameter) Teflon fume particles in very low concentrations [11]. These results will ring a bell in those who have seen patients with metal and polymer fume fever,

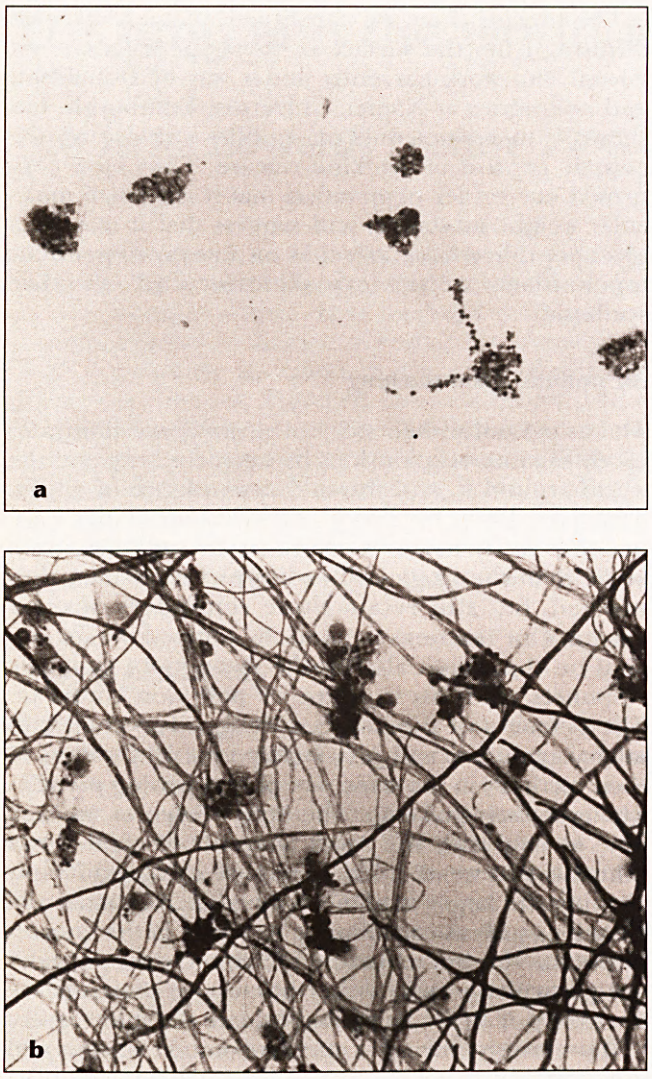


Fig 3. *(a) Culture of macrophages with cell-associated spores of Aspergillus fumigatus; (b) same culture six hours later showing growth of hyphae*

conditions in which workers exposed to fume (which, by definition, contains extremely finely divided, freshly generated aerosol) develop fever, cough, rigors and often dyspnoea—in fact, all the characteristics of an acute pulmonary inflammatory reaction.

It seems likely that it is not just the *chemistry* of particles which is important in determining toxic effects on the lung, but also their *size* and, by implication, their collective surface area and the activity of their surfaces, possibly modified by adsorbed toxic substances. These microfine particles are smaller than bacteria and are inherently unstable, condensing into larger particles. They have a huge collective surface area, with the potential to carry toxic molecules deep into the lung. It is perhaps not surprising that the amoeba-like macrophages in the lungs have not evolved effective mechanisms to deal with these particles, which are thus able to gain access to the lung interstitium where they cause their damage. This may appear unimportant except to those people who develop temporary discomfort or illness on account of cutting or welding metal—at least until we start to wonder about the effects of urban (as opposed to most industrial) air pollution on health.

Air pollution and the weather

The effects of weather on health were studied scientifically in the mid-19th century, and the increased death rates from lung and heart diseases in the winter in London were well documented even then. Interestingly, the effects of temperature were also recognised at that time, but parallel studies in New York, which had the same mean temperature as London, showed distinctly less effect on mortality [12]. An obvious difference was that London had dense smoke fogs (smogs) in the 19th and early 20th century whereas New York did not. It was not until the pioneering studies of Lawther and Waller in the Medical Research Council Air Pollution Research Unit following the great London smog of 1952, that the medical and political community appreciated the huge effects on mortality of such smogs, with some 4,000 excess deaths in one week during the 1952 London winter episode [13,14]. These deaths were shown to be associated with the presence in the air of smoke particles and sulphur dioxide (SO_2). Although the precise mechanisms of and the interrelationships between the two pollutants were not clarified, appropriate government action led to progressive reductions in urban coal burning with subsequent falls in the concentrations of both. Smogs became a thing of the past and we forgot about air pollution.

More recently, however, the increase in vehicles on our roads has caused a resurgence of the problem; many people who do not remember the smogs of the 1950s and 1960s are now aware that the air they breathe in our cities is becoming less pleasant. Worse than this, studies, first in the USA and more recently in a dozen other countries, have shown consistently that as pollution concentrations rise so also do the numbers of people who suffer what may well be ill-effects. Death rates go up, and more people consult their doctors or are admitted to hospital with respiratory illnesses. None of these indices of morbidity associated with air pollution is more curious than the repeatedly observed increase in deaths from stroke and cardiovascular disease [15]. Over a two-year period in Birmingham, during which the average concentration of particles (measured as particles less than 10μm aerodynamic diameter, PM10) was 25 μg/m^3 and the peak 24-hour concentration never exceeded 131 μg/m^3, studies by Wordley and colleagues [16] have demonstrated a relationship between admission to hospital for cardiovascular disease and particle concentration. Is it really plausible that inhalation of, at

most, a few milligrams of dust over a day or two could cause people to die from stroke?

Air pollution, stroke and heart attack

This apparent implausibility becomes less when two facts are considered:

- the excess deaths from chronic lung and cardiovascular diseases, conditions that are the end-result of multifactorial causes operating over a prolonged period, occur among older people, and
- the epidemiological studies all use single local measurements of air pollution to represent the actual exposures of populations.

Thus, when a concentration of, say, 50 μg/m³ is quoted as associated with an excess incidence of stroke, this in fact represents a wide but unknown range of *actual* exposures of individuals. The link becomes more easily understood if some people who, by reason of compromised cerebral (or coronary) circulation, are particularly vulnerable to the effects of pollution may also be among those exposed to the upper extreme of the distribution of individual exposures. For example, a study in a group of traffic wardens, working close to traffic but some metres from an area monitor [17], showed that over a shift they had personal exposures of over 100 μg/m³ when the local monitor recorded a 24-hour average of 10–20 μg/m³. It is possible to envisage elderly people with atheromatous cerebral circulation living in houses next to a busy city street being at risk of relatively high exposures, sufficient perhaps to cause low-grade alveolar inflammation if the aerosol to which they are exposed contains large numbers of ultrafine particles.

In the 1960s, studies by Lawther and colleagues showed that urban pollution contained huge numbers of particles below 1 μm in diameter [18]; more recent studies by Collins and Harrison in Birmingham have confirmed that this remains the case today [19] (Fig 4). These very small particles are of two sorts, those coming directly from the combustion chamber as carbon with a wide range of organic and inorganic chemicals adsorbed on their surfaces, and those formed over a period of minutes to hours by condensation of exhaust gases. Both are inherently unstable and quickly aggregate into larger particles of 0.5–1 μm diameter. However, someone close to the source will be exposed to very large numbers of tiny particles with the potential to cause inflammation by the mechanism discussed above [10,11]. This remains a hypothesis; if it is true, there is still the problem of explaining why pulmonary inflammation should cause stroke and heart attack.

Here we need to move to the work of the cardiac epidemiologists and consider the role of fibrinogen, an important predictor of risk for these common diseases. Heart attack and stroke show a marked seasonal variation in incidence, rising in winter. This is

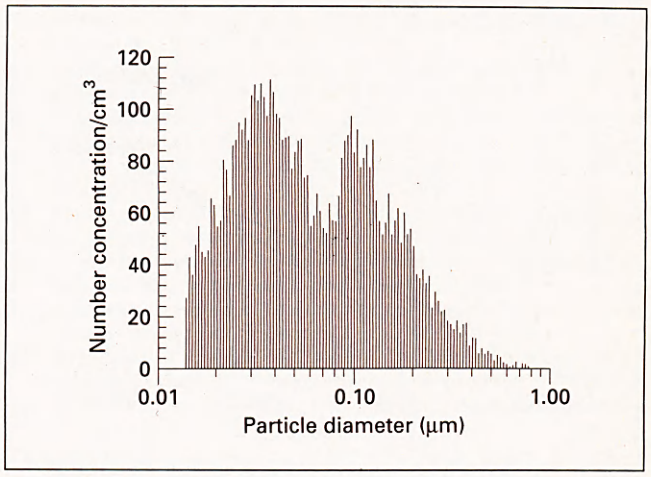


Fig 4. *Distribution of particle sizes in Birmingham air* (from Ref 19, with permission)

mirrored by changes in blood fibrinogen concentrations [20], possibly as a consequence of winter lung infections [21]. Pulmonary inflammation can lead to the production of interleukin (IL)-6 by macrophages, and this mediator may induce hepatocytes to release fibrinogen. Evidence in support comes from studies of the effects of inhalation of welding fume; this causes an influx of inflammatory cells into the alveolar space and is associated with release of IL-6 over a 24-hour period [22]. It is at least plausible that exposure to traffic fume could have the same effects, causing subtle changes in blood coagulability and leading in the vulnerable to stroke and heart attack [23].

Diet and the increase in asthma

Khaw and Woodhouse have recently shown that these seasonal changes in blood coagulability accompany variations in vitamin C intake. They have suggested that reduction in intake of this vitamin in winter makes the lung more vulnerable to viral infections, thus amplifying the pollution effect on coagulability [24]. Vitamin C, with reduced glutathione, is a major contributor to the lung's defences against the free radicals of oxygen released when the lung resists invasion by micro-organisms.

In Aberdeen, as elsewhere, the prevalence of asthma and other atopic diseases has doubled over the last 30 years (Fig 5) [25–27]. Several hypotheses have been proposed to explain this remarkable and, in public health terms, extremely serious change. Some of them are too far-fetched to be taken seriously because of the substantial rise in the toxic factor that would be required to produce such changes in prevalence [28]. For example, the increase in hay fever can hardly be explained by an increase in house-dust mites, and is demonstrably not a consequence of the unchanging concentrations of grass pollen [27] (Fig 6). Similarly,

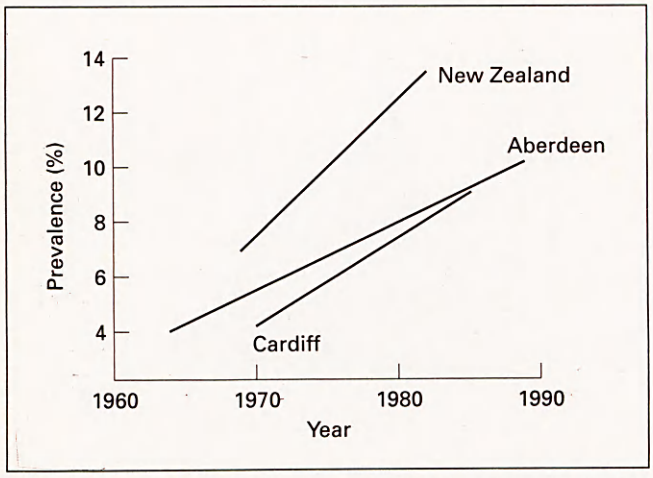


Fig 5. *Change in prevalence of asthma in schoolchildren in Aberdeen, Cardiff and New Zealand over the past three decades*

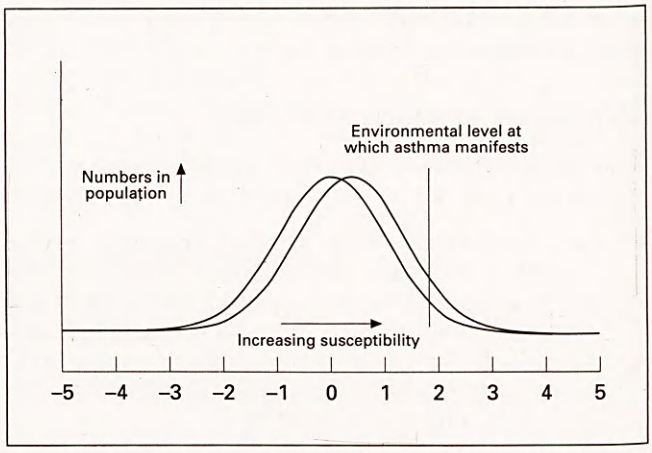


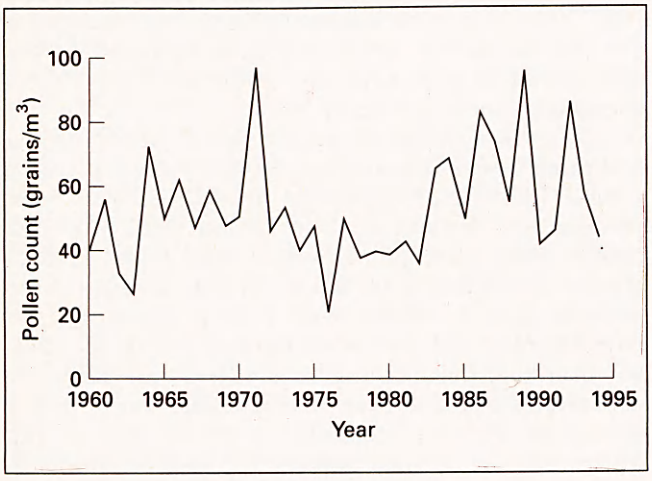
Fig 7. *Illustration showing how a small change in susceptibility of the whole population may produce a large change in disease prevalence*

the increase in asthma cannot plausibly be attributed to the observed decrease in particulate air pollution in cities or to the unchanged or slightly reduced prevalence of smoking in pregnant women [29,30]. More plausibly, the rise in prevalence is likely to be a consequence of a population increase in susceptibility to inhaled allergen and irritants, a mechanism whereby a relatively small change over the population can cause a doubling of prevalence of disease (Fig 7). Less exposure of young children to acute infections may be part of the explanation, by altering early immune responses from immunoglobulin (Ig) G- to IgE-mediated [31].

The one dramatic change for the worse which has coincided with the period over which the change in atopic disease has occurred is in the diet of the population, in particular, the reduction in intake of fresh fruit and vegetables which has almost halved over this period [32]. There is evidence that changes in vitamin C intake influence lung function and bronchial reactivity, and that a greater intake can give some protection against the harmful effects of inhalation of SO_2 and ozone.

Could it be that a generation of children has been born with diminished antioxidant defences at the very time they first meet the main antigen, the house-dust mite? Has the population's susceptibility to asthma increased? If so, the instinctive wish to blame an increasingly toxic environment may be wrong and could lead to an expensive and ineffective preventive strategy. The urgent need is to discover why such an increase in atopic disease is evident at an early stage in life. If, as seems likely, this is due at least in part to changes in diet, a simple remedy based on public education would be to hand. Unattractive though this would perhaps be to those who wish to wage chemical warfare against the mite (incidentally, such biological tactics have a history of causing more problems than they solve), it has the attractions of being both practicable and likely to have other benefits at low cost.

Fig 6. *Grass pollen concentrations in summer in Cardiff. Hay fever prevalence increased by 59% in 12 year old children between 1973 and 1988* (not reflecting changes in pollen counts over the preceding decades) (from Ref 27, with permission)



Conclusions

As human beings, we have evolved in balance with our fellow organisms and our environment. This balance is easily disturbed. As doctors and medical scientists, we have been more inclined to look inwards for the proximate causes of disease than to look for the environmental changes that have disturbed the balance between health and disease, so well discussed by René Dubos in his seminal book, *Mirage of health* [33]. Ancient physicians spoke of the causes of illness in terms of imbalance of the humours and attack by demons. Medical research has of late concentrated on humoral imbalance, driven by an urge to discover

drugs which will correct it. It is, however, important to remember that the origins of what is likely to prove only a temporarily successful battle in the war against infection lay in a study of soil organisms. It is my belief that it is now time for researchers to concentrate their efforts to a much greater extent on understanding the demons in our environment and how they interact with the human organism. This may not be so glamorous, and rarely attracts the big research grants, but it holds much greater hope of improving the health of the whole human race, for the majority of whom expensive drugs will never be available.

References

1 Ryan F. *The greatest story never told.* Bromsgrove: Swift Publishers, 1992.
2 Mullins J, Harvey R, Seaton A. Sources and incidence of airborne *Aspergillus fumigatus* (Fres). *Clin Allergy* 1976;**6**:209–17.
3 Seaton A, Seaton D, Leitch AG. *Crofton and Douglas's respiratory diseases,* 4th edn. Oxford: Blackwell, 1989: Ch. 17.
4 Robertson MD, Seaton A, Raeburn JA, Milne LJR. Inhibition of phagocyte migration and spreading by spore diffusates of *Aspergillus fumigatus. J Med Vet Mycol* 1987;**25**:389–96.
5 Robertson MD, Seaton A, Raeburn JA, Milne LJR. Resistance of spores of *Aspergillus fumigatus* to ingestion by phagocytic cells. *Thorax* 1987;**42**:466–72.
6 Seaton A, Robertson MD. Aspergillus, asthma and amoebae. *Lancet* 1989;**i**:893–4.
7 Darbyshire JF, Elston DA, Simpson AEF, Robertson MD, Seaton A. Motility of a common soil flagellate *Cercomonas* sp. in the presence of aqueous infusions of fungal spores. *Soil Biol Biochem* 1992;**24**:827–31.
8 Robertson MD, Kerr KM, Seaton A. Killing of *Aspergillus fumigatus* spores by human lung macrophages: a paradoxical effect of heat-labile serum components. *J Med Vet Mycol* 1989;**27**:295–302.
9 Seaton A. Coalmining, emphysema and compensation. *Br J Indust Med* 1990;**47**:433-5.
10 Oberdörster G, Ferin J, Gelein R, Soderholm SC, Finkelstein J. Role of the alveolar macrophage in lung injury: studies with ultrafine particles. *Environ Health Perspect* 1992;**97**:193–9.
11 Oberdörster G, Gelein R, Ferin J, Weiss B. Association of particulate air pollution and acute mortality: involvement of ultrafine particles? *Inhal Toxicol* 1995;**7**:111–24.
12 Buchan A. The influence of weather on mortality from different diseases and at different ages. *J Scot Met Soc* 1886;**4**:187–265.
13 Ministry of Health. *Mortality and morbidity during the London fog of December 1952.* London: HMSO, 1954.
14 Schwartz J, Marcus A. Mortality and air pollution in London: a time-series analysis. *Am J Epidemiol* 1990;**131**:185–94.
15 Schwartz J. What are people dying of on high pollution days? *Environ Res* 1994;**64**:26–35.
16 Wordley J, Walters S, Ayres JG. Short-term health effects of particulate air pollution. *Thorax* 1996;**50**(Suppl 2):A34.
17 Watt M, Godden D, Cherrie J, Seaton A. Individual exposure to particulate air pollution and its relevance to thresholds for health effects: a study of traffic wardens. *Occup Environ Med* 1995;**52**:790–2.
18 Lawther PJ, Ellison JMcK, Waller RE. Some medical aspects of air pollution research. *Proc Roy Soc* A 1968;**307**:223–34.
19 Committee on the Medical Effects of Air Pollutants. *Non-biological particles and health.* London: HMSO, 1995.
20 Stout RW, Crawford V. Seasonal variations in fibrinogen concentrations among elderly people. *Lancet* 1991;**343**:9–13.
21 Woodhouse PR, Khaw K-T, Meade TW, Stirling Y, Plummer M. Seasonal variations of plasma fibrinogen and factor VII activity in the elderly: winter infections and death from cardiovascular disease. *Lancet* 1994;**343**:435–9.
22 Gordon T, Chi Chen L, Fine JM, Schlesinger RB, *et al.* Pulmonary effects of inhaled zinc oxide in human subjects, guinea-pigs, rats, and rabbits. *Int Indust Hyg Assoc J* 1994;**53**:503–9.
23 Seaton A, MacNee W, Donaldson K, Godden D. Particulate air pollution and acute health effects. *Lancet* 1995;**345**:176–8.
24 Khaw K-T, Woodhouse P. Interrelation of vitamin C, infection, haemostatic factors, and cardiovascular disease. *Br Med J* 1995;**310**:1559–63.
25 Ninan TK, Russell G. Respiratory symptoms and atopy in Aberdeen schoolchildren: evidence from two surveys 25 years apart. *Br Med J* 1992;**304**:873–5.
26 Omran M, Russell G. Continuing increase in respiratory symptoms and atopy in Aberdeen schoolchildren. *Br Med J* 1996;**312**:34.
27 Seaton A, Soutar A, Mullins J. The increase in hay fever: susceptibility or environment? *Quart J Med* 1996;**89**(in press).
28 Strachan DP. Time trends in asthma and allergy: ten questions, fewer answers. *Clin Exp Allergy* 1995;**25**:791–4.
29 Committee on the Medical Effects of Air Pollutants. *Asthma and air pollution.* London: HMSO, 1995.
30 Wald N, Kiryluk S, Darby S, Doll R, *et al. UK smoking statistics.* Oxford: Oxford University Press, 1988:34–5.
31 Strachan DP. Epidemiology of hay fever: towards a community diagnosis. *Clin Exp Allergy* 1995;**25**:296–303.
32 Seaton A, Godden DJ, Brown K. Increase in asthma: a more toxic environment or a more susceptible population? *Thorax* 1994;**49**:171–4.
33 Dubos R. *Mirage of health: utopias, progress and biological change.* London: Allen and Unwin, 1960.

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