Occupational Medicine

Occupational lung diseases other than asthma*

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Introduction

To cover this topic completely would need a book too heavy to handle and too expensive to buy. Moreover, others have discussed some aspects so well that I could not better their work. Instead, I shall try to describe the classic occupational lung diseases in a wider context to help those approaching the A.F.O.M. or M.R.C.P. diplomas understand and remember them, and give a background for assessing new ideas. I shall be dogmatic, citing research references and review articles for wider discussions of the issues, and ignoring many fascinating minor or rare disorders. I can supply a fuller list of references for anyone who wants to check the provenance of the assertions I shall make. I recommend two and a half textbooks: Morgan and Seaton¹ for general reading. It is, however, somewhat uneven and may not cover particular topics sufficiently. Parkes' tome² is like the Bible; comprehensive but impossible to read from cover to cover without fervent enthusiasm. It is encyclopaedic, but tends to summarize every published paper without fully reviewing them; it is ideal for a one-stop overview of the literature, but leaves you to digest some of it for yourself. For the occasional query about long forgotten hazards in long dead industries, try Hunter's classic text (not the edition written since his death).³

Beginning with some background anatomy and physiology should help explain the diseases, and make the usual lists easier to learn.

The response of the lung to injurious substances: the effect of anatomy

The site of an insult to the lungs is one important determinant of the effect. I shall discuss applied

anatomy briefly in order from the nose downwards. The nose and pharynx warm and humidify the incoming air. Particles are caught by nasal hairs, or impact on the walls of the pharynx and are swallowed.⁴ The nose is so efficient that the difference between breathing through it or the mouth can determine whether exposure leads to disease. Airways down to terminal bronchioles (that is, not involved in gas exchange and without gas exchanging areas opening directly off them) are lined by ciliated epithelium. This is covered by a layer of mucus from secreting lining cells (and mucous glands in the walls of the bronchi), which is swept up to the pharynx and swallowed.⁵ The largest airways (bronchi) have cartilage in their walls, so they cannot be closed by muscular action alone, unlike the smaller bronchioles without cartilage or mucous glands. Muscular action, excess secretions and inflammatory changes can narrow them. Pathology at this level is the principal cause of airflow limitation. Smaller airways still (respiratory bronchioles) have flimsy walls with little muscle. They lie within the lung and are kept open by the elastic pull of the surrounding tissue.⁶ If this pull is reduced, as by the lung destruction of emphysema, they narrow. They are not lined by mucus; their defence is phagocytes,⁷ and immunoglobulins.⁸ Large airways therefore have defence mechanisms (mucus, cilia) ideal for large particles; the more distal regions have mechanisms (phagocytosis, immunoglobulins) better for smaller particles.

The fate of an inhaled particle⁹

This depends on its aerodynamic properties, which are in turn determined by its shape, size and density. A long, thin, light particle behaves differently from a short, fat, heavy one, will end up in a different place in the lung, and meet different defence mechanisms. If particles carry an electrical charge, or change size by adsorbing water from intra-pulmonary air, their fate is also affected.

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Human factors such as smoking, the rate of airflow, the depth of breathing and the size of the lungs are important; those with larger lungs retain more particles, and familial factors affect clearance. Nevertheless, some idea of where particles are likely to land and go can be given. Large particles in an airstream will tend to impact by inertia on the walls where the airstream bends or turns. The nose and pharynx trap most particles over $10\text{ }\mu\text{m}$ in this way. Most between $10\text{ }\mu\text{m}$ and $5\text{ }\mu\text{m}$ veer out of the airstream by inertia and impact on to the walls of the large airways. Smaller particles will continue forwards where airways divide, and impinge on to the walls and the mucociliary escalator. Still smaller ones sediment on to airway walls below the escalator where airflow is far slower, and are phagocytosed by alveolar macrophages migrating up to it. Particles between $3\text{ }\mu\text{m}$ and $5\text{ }\mu\text{m}$ reach the alveoli, cross to the alveolar wall and are phagocytosed by lining macrophages which penetrate the alveolar wall and go to the lung lymphatics. Particles under $3\text{ }\mu\text{m}$ leave the lung in the expired air with few deposited in the lung at all. Those smaller than $0.5\text{ }\mu\text{m}$ diffuse to the alveolar wall by Brownian movement, so proportionally more are deposited.

Assessing the pathogenicity of a substance

The following therefore determine the effect of a substance on the lung:

1. Its chemistry and toxicology; particularly whether it is irritant, a carcinogen or capable of stimulating allergy or fibrosis.
2. Its physical state; heat or cold can damage the lung and determine whether the substance is a solid, fluid, or gas; and its solubility and charge.
3. Its size and shape if it is particulate, and so where it goes in the lungs.
4. Whether it is pure or contaminated; mixtures can produce different pictures from a simple sum of the effects of each component.

The response of the lung to insults: pathological pictures

No pathological change

A harmless metal of high molecular weight may simply produce an abnormal chest radiograph without damaging the lung. The only such 'benign pneumoconiosis' likely to occur in clinical practice is in welders inhaling iron fume; one survey found 7% of arc welders in a factory were affected.¹⁰ A similar picture used to occur in steel workers, and polishers of steel or silver who used iron oxide. Occasionally foundry workers, boiler scalers, and

iron miners developed it. The basic radiographic abnormality is pin-point round opacities, though they may coalesce into lesions up to 2 mm across. Septa and the hilar glands can be outlined, but are normal. Tin produces a similar picture, but the lesions are more radio-dense, and outlining commoner; there may be a few UK cases left in old people's homes. Antimony, barium (baritosis), zirconium, hafnium, rare earth elements, chromite and titanium produce similar changes. Sometimes the dose of a harmful substance is too low to produce disease; asbestos fibres occur in the lungs of town dwellers, and even more are found if the town has an asbestos mine, but disease need not necessarily result.¹¹

Asthma

This was considered elsewhere in this series.¹² Remember that occupational asthma can become chronic despite ending exposure, and can lead to chronic airflow limitation and present as such.

Chronic bronchitis

Substances which irritate the larger airways and their mucus glands can produce chronic bronchitis, defined as persistent cough and sputum production. Such chronic bronchitis itself does not cause airflow limitation with death from respiratory failure. However, they often occur together as the commonest cause of chronic bronchitis, smoking, produces both effects;¹³ possibly from different fractions of the fume. Chronic bronchitis increases the likelihood of chest infections; important in an occupational setting if they produce absence from work! Chronic bronchitis has been seen as a harmless concomitant of exposure to smoking, air pollution, or occupational atmospheric pollution. However, first, it acts as a marker of toxic exposure; as anyone exposed to one toxin is probably more likely to meet others, it is likely to be associated with increased morbidity and mortality. Secondly, an irritant gas may worsen the effects of a concurrent occupational exposure or of asthma. Thirdly, just as tobacco smoke can cause airflow limitation as well as producing chronic bronchitis, so may occupational exposures. The symptoms of chronic bronchitis should, therefore, not be ignored.

Acute lung damage

This was described well on the Western Front in the First World War. Basically two pictures result: *pulmonary irritants* (for example, chlorine and phosgene) produce pulmonary oedema with rapidly developing dyspnoea; if basic lung structure is undamaged, and gas transfer is not too severely impaired, subjects can recover though many die

and there may be permanent sequelae. Probably the most important such occupational exposure is to oxides of nitrogen produced in farm silos. These are not particularly irritant to the upper respiratory tract, though very damaging to the lungs; workers may not be aware that they are receiving lethal exposures. *Vesicants*, such as nitrogen mustard, damaged epithelial surfaces with effects appearing after 2–4 hours. Death occurred between 2 and 14 days from sloughing of the lung lining, or from delayed bronchopneumonia. Finally, some metal fumes, notably cadmium, may produce *metal fume fever*, a 'flu-like illness, worse with the first exposure of the working week, occurring some hours after it, but neither serious nor fatal.

An oddity—byssinosis

Somewhere between asthma and bronchitis comes the curious disorder *byssinosis* produced by cotton dust. Workers complain of chest tightness and breathlessness, initially worse on returning to work after the weekend break, then extending gradually through the working week, and finally becoming permanent.¹⁴ They may show airflow limitation with these symptoms, and are more likely to do so as they worsen. Finally, as the symptoms become constant so do airflow limitation and dyspnoea. The disease was said to have caused deaths in the past. The radiographic changes, lung function tests and histopathology are indistinguishable from chronic bronchitis and emphysema, though the disease existed before cigarette smoking was common. Diagnosis is therefore by history; unique amongst disorders for which the government pays compensation, and making research difficult. There is no evidence of allergy; all kinds of toxins can be extracted from cotton, but none completely reproduces the disorder. Moreover, a number of different disorders follow work with cotton, and must be distinguished from each other, and from byssinosis.¹⁵ Reduction of cotton dust levels, and decline of the industry, mean that it is now difficult to find cases in countries where the disease could be fully investigated.

Emphysema

Particles which are not destroyed after phagocytosis may damage cells scavenging them so that they leak enzymes. Emphysema, local fibrosis, or generalized lung fibrosis may result. If lung tissue is destroyed, alveoli are lost, the elastic properties of the lung decrease and *emphysema* occurs. Natural α -1 antitrypsin counteracts the most potent of these enzymes. Subjects congenitally lacking it, who smoke, develop basal emphysema. Cadmium blocks its action, and seems to concentrate in emphysematous smokers' lungs. Cadmium expo-

sure has been associated with emphysema in man, and cadmium chloride aerosol exposure gives rats centrilobular emphysema. This elegant occupational pathogenesis, often reproduced in textbooks, unfortunately has no adequate epidemiology to support it. More interesting are the lung function changes in workers heavily exposed to the proteolytic enzyme alcalase; they could represent early emphysema.¹⁶

Fibrosis

(a) *Silica* Continuing inflammation produces fibrosis. The commonest substance involved is silica, though it produces various clinical pictures. Heavy, acute, relatively pure quartz exposure leads to a severe illness like alveolar proteinosis with an alveolitis; mortality is high.¹⁷ Silicosis is now excessively rare in workers doing occupations known to involve exposure, because they are strictly controlled. Occasionally, procedures are not recognized as risky, high exposures occur, and an acute form of silicosis with fever and dyspnoea follows which may be fatal; sandblasting without adequate protection (outlawed in the UK), compulsive inhalation of 'Ajax' scouring powder and repairing the tracery of cathedral windows¹⁸ are recently reported causes. The classic lesions of 'silicosis' produced by low-level long-term exposure to quartz or flint are nodules of hyaline collagenous fibrosis, predominantly in the upper lung fields, appearing as well-defined rounded opacities of 1–3 mm on the chest radiograph and without symptoms, though lung function tests may be mildly abnormal. Since the tests correlate better with the amount of dust inhaled than with the radiographic change, they may be due to chronic silica obstructive bronchitis (which certainly occurs) rather than fibrosis. With increasing exposure opacities multiply and extend down the radiograph. Septa, the pleura and hilar glands may be outlined and calcify. The upper lobe lesions may conglomerate into masses called progressive massive fibrosis (PMF), causing enough shrinkage to produce dyspnoea but rarely cavitating unless there is tuberculosis. The incidence of tuberculosis is increased; ingested silica damages alveolar macrophages so they cannot kill the tubercle bacillus. A diffuse fibrosis of the alveolar walls and spaces without nodules 'fibrosing alveolitis' follows inhaling calcined diatomaceous earth – 'diatomite pneumoconiosis'. It predominantly affects the upper lobes and there is obvious dust in lung sections.

(b) *Mixtures of silica and other dusts, including coal* The picture changes with mixed dusts. Foundry workers and iron miners more commonly show 'mixed-dust disease' from inhaling silica and iron than classical silicosis; defined nodules are replaced

by irregular stellate opacities, and upper lobe PMF (defined as opacities over 3 cm in size) is common. Silica and aluminium, in plants producing abrasives from bauxite, cause Shaver's disease,¹⁹ with upper lobe fibrosis and emphysema, leading to honeycombing, pleural emphysematous blebs and pneumothorax. Another major disorder from silica mixtures is the pneumoconiosis of coal workers, perhaps the most complex of all occupational lung diseases to describe. Coal is basically rotten vegetation, sandwiched between layers of sandstone. The time and temperature of the rotting may vary in different locations affecting the composition of the coal, as do variations in the sandstone. A rough classification is by the 'rank' of coal which does relate to the disease produced. The role of a worker will determine the balance of coal and sandstone (silica) exposure; those making or maintaining the tunnels of a deep mine will meet more silica than coal as opposed to miners (though some of these changed jobs in their careers). The picture is further complicated because miners smoked, kept pigeons, heated their homes with free coal from their employers so polluting them with fumes, met nitrous fumes from diesel engines and explosives in the mines, and got tuberculosis; all contributing to their undoubted respiratory ill health. Many epidemiologists spent useful careers failing to elucidate the respiratory problems of miners; with the current decline in the industry it may well be that breathless miners will disappear from the UK before their problems are understood. In brief (and I shall not try to give references for a vast literature full of controversies), miners suffer from chronic bronchitis, emphysema, and pneumoconiosis. The pneumoconiosis is similar to silicosis, but the nodules range up to 5 mm, and are less well-defined. PMF develops, and the lesions may cavitate, the contents are then expectorated, and the lesions refill, without tuberculosis (the incidence of which is increased) necessarily being present. Simple pneumoconiosis (that is, without PMF) is not associated with significant reduction of pulmonary function or loss of life expectancy; the presence of PMF is. Since the risk of PMF increases with the profusion of simple pneumoconiosis, regular chest radiography has been used to identify all miners developing simple disease so they can be removed from further exposure. This policy meant most working miners had normal radiographs. Although PMF is rare amongst them, it does occur and the group is so large that it now includes most new PMF cases, though affected miners have had higher dust exposures. Mine dust produces chronic bronchitis, which may be associated with impairment of pulmonary function, and there is good pathological evidence that coal miners develop emphysema. There is a relationship between dust exposure, loss

of lung function, and irregular radiographic opacities, but there is furious controversy over whether dust alone, without smoking, can produce sufficient impairment in the absence of silicosis to produce disabling dyspnoea.²⁰ If it does, no-one knows how to quantify the contributions of the different possible causes in an individual claiming benefit.²¹

No M.R.C.P. student can forget Caplan's syndrome. Classically,²² this was the occurrence of multiple well-defined round opacities 0.5–5 cm in diameter distributed throughout the lung fields but particularly at the periphery, in miners with slight or absent simple pneumoconiosis and rheumatoid arthritis. The lesions came in crops, often with exacerbations of the arthritis, and could cavitate so mimicking PMF. As redefined,²³ the syndrome was of an increased incidence of rheumatoid arthritis, both clinical and detectable only by serological tests, in coal miners with radiographic shadowing either like simple pneumoconiosis and/or nodules. It rarely occurs with other minerals, such as asbestos.

(c) *Asbestos* This contains silicates, but produces various disorders quite different from those already described. Most of the asbestos used was blue asbestos (crocidolite), or white asbestos (chrysotile); some brown (amosite) was also used, and chrysotile from some Canadian mines is contaminated with a further variant, tremolite, which also occurs in talc. A little anthophyllite has been used commercially. A given asbestos firm might knowingly mix the different types, or use the same but from different mines and so with different compositions; many mixed loads indiscriminately. Asbestos users, such as ladders and sprayers, were often not sure exactly what type they had worked with. Even if they were, processing changes the fibre geometry modifying the biological effects; flake-like tremolite produces no disease, fine-fibred produces mesothelioma, and coarse-fibred pleural plaques.²⁴ Toxic or carcinogenic oils may be adsorbed during milling and grinding. Nevertheless, studies of miners and users of one fibre type allow some classification of the disorders produced.

1. Asbestos corns, lesions resulting from fibres penetrating the skin and resolving after their removal, were simply a sign of heavy exposure.
2. Pleural plaques which may calcify, characteristically appearing at least 20 years after exposure, are found with other mineral exposures including silicosis. They have not been shown to cause significant functional impairment and dyspnoea, but they are a marker of exposure. In one series for example, 4.5% developed clinical asbestosis within 10 years.²⁵
3. Asbestos pleural effusions, which can be fol-

lowed by pleural fibrosis and disability, may occur during exposure or after it has ceased. The fibre type and mechanism are unknown, but the relative rarity of new cases, and the regular mention of pleural fibrosis in reports of post mortems on cases of asbestosis 60 years ago, suggest it may reflect intermittent high exposure, an idea supported by more recent studies.²⁶ Pericardial effusions occasionally occur.

4. Asbestosis is a fibrosing alveolitis. In the 1920s, it was an acute condition leading to death within a few years. More recent cases follow lower exposures after some latency, and are chronic; indeed, only 20% of cases diagnosed in Medical Boarding Centres (Respiratory Diseases) die of it now, though 68% die of an asbestos-induced disorder.²⁷ Current exposures should never produce it.
5. There is clear evidence of an excess of lung cancer in asbestos workers, but the relationship to smoking and asbestosis is unclear (see below). There is some evidence for an increased incidence of other tumours in men²⁸ but not in every series studied, and of the ovary.²⁹
6. Crocidolite, amosite and tremolite, but rarely chrysotile, produce a serosal tumour (mesothelioma) 20 years or more after exposure. Usually this is pleural, but it can occur in the peritoneum or pericardium; factors determining the site are unknown.

Granulomatosis

A type IV allergic reaction producing granulomata can follow an occupational exposure. The commonest is *berylliosis*. Allergy may be detected by skin tests analogous to the Mantoux (the beryllium patch test), or by *in vitro* lymphocyte testing. The disease pictures are as follows.

1. Granulomata in beryllium-contaminated wounds preventing them healing until all the metal is removed. Casualty officers should remember that beryllium is not radio-opaque.
2. Conjunctivitis, corneal ulceration, allergic blepharitis, contact dermatitis, an acute tracheo-bronchitis and pneumonitis from irritant beryllium vapour. The last may be fatal, resolve or go on to chronic granulomatous disease.
3. A chronic granulomatous disorder clinically rather like sarcoidosis after a latency of up to 20 years in up to 5% of those exposed to lower levels of fume, contamination from workers' overalls, or from neighbouring factories.

Rarely, the presenting problem may be renal colic following hypercalcaemia, and all berylliotics should be screened for hypercalciuria and renal tract disease.

More usually a type IV reaction is also associ-

ated with circulating precipitins, so producing type III Arthus type reactions (as well as the possibility of type II), and mast cell involvement. The result is *extrinsic allergic alveolitis*; a misnomer for 'an acute granulomatous interstitial pneumonitis' with alveolitis and bronchiolitis. There is a long list of such disorders (Table I); they are commoner in non-smokers. The multiple immune mechanisms involved are reflected in the variety of clinical courses. There may be multiple acute episodes with 'flu-like symptoms and minimal dry cough. The chest radiograph will show a fine ground-glass opacification, which may be difficult to detect, sometimes with larger patchy shadows. As exposure continues, a chronic stage with multiple small irregular opacities like fibrosing alveolitis may develop. Like all such opacities, these seem more dense at the bases because the rays for a PA film pass through more lung there than at the apices. As the disease progresses, this shadowing lessens but bands of apical fibrosis appear, the lungs shrink, and persistent dyspnoea develops. Sometimes this chronic stage appears to develop insidiously, without acute episodes. Conversely, some pigeon fanciers seem to lose symptoms and live happily with their pigeons and their precipitins. The significance of precipitins depends on the condition and the method used to detect them; in general, budgerigar precipitins are always associated with lung disease³⁰ but perhaps only a third of those with pigeon ones show disease.³¹ By far the commonest extrinsic allergic alveolitis is 'farmer's lung', due to inhaling mouldy hay. The problems of precipitin testing are well seen in this disorder. A survey of 91³² Devon farmers found 23% had precipitins against mouldy hay. Eighteen per cent of the men (23) reported breathlessness; the proportion with precipitins was similar to that in those not reporting breathlessness. Precipitins seemed best correlated with a picture of attacks of breathlessness, fever and shivering; of ten such cases, five already had been diagnosed as having the disease, but five without precipitins had not. In Somerset, only 43% of clinically diagnosed patients had precipitins.³³ A Canadian study in which precipitin tests were repeated after 4 years showed farmers losing and gaining precipitins, and that symptoms were not related to them.³⁴ The absence of precipitins may be because the particular organism has not been tested for, or because the wrong antigen of it has been used. Sometimes, the alternative pathway of complement activation not involving precipitins may be involved in a particular case.

Carcinogenesis

Any lung fibrosis can give rise to tumours, be it local scars, or cryptogenic fibrosing alveolitis

Table I Types of extrinsic allergic alveolitis

Name	Agent
Farmer's lung	Fungi in mouldy hay
Bird fancier's lung	Avian protein
Bagassosis	Mouldy sugar cane
Mushroom workers' lung	Fungi in compost dust
Malt worker's lung	Fungi on mouldy barley
Suberosis	Fungi on mouldy cork dust
Maple bark strippers' lung	Fungi on mouldy bark
Wood pulp workers' disease	Fungi on mouldy bark
Humidifier disease	Organisms growing in the water
Sewage sludge disease	Bacteria in the sludge
Sauna-takers' disease	Contaminated steam
Sequoiosis	Mouldy giant redwood sawdust
Cheese washers' lung	Fungal dust
Dry rot lung	Mould dust
Wheat weevil lung	Mite antigen
Animal handlers' lung	Serum and urine protein
Fish meal workers' lung	Fish protein
Diisocyanate 'alveolitis'	TDI and HDI
Pyrethrum 'alveolitis'	Insecticide aerosol
Pituitary snuff taker's lung	Pig or ox protein
Tobacco worker's lung	Tobacco dust

where the risk interacts with that of smoking and the cell types produced are indistinguishable. A substance producing lung fibrosis is therefore likely to increase the incidence of cancer even if it is not a carcinogen. Deciding whether a substance (such as asbestos) can cause cancer without fibrosis is therefore difficult. An attempt was made on the basis that tumours occur at asbestos exposure levels below those associated with fibrosis, though this has been disputed; cases are few and measurements of low-level fibre exposure particularly difficult. Sorting out the carcinogenic effects of asbestos and smoking is equally difficult. Attempts to show whether the cell type of tumours associated with asbestos differ from those associated with smoking show the proportion of adenocarcinomas may be higher, but it is not certain that this is a real difference as proper groups for comparison are difficult to find.³⁵ The simplest extrapolation of observed facts to try and link cause and effect is hazardous; smoking can affect the clearance of asbestos from the lung by increasing the retention of short fibres; the pathological effects of smoking vary between subjects for unknown reasons; studies are difficult because workers with more disease may stop smoking or leave the industry; asbestos may adsorb carcinogens from tobacco smoke and carry them into cells; chrysotile in textile mills seems to produce more tumours than chrysotile mining or milling. Finally, most surveys rely upon the workers to identify themselves as smokers and non-smokers since there is no test for

life-long non-smoking, and their statements may well be inaccurate. An increased incidence of lung cancer can be demonstrated where the carcinogen is not fibrogenic, but these are all rare. The commonest involve miners working on rocks contaminated with radioactive elements.

Conclusions

Much of my survey will seem rather historical, and only the imminence of exams is likely to make a young physician try to remember baritosis – but this was true of tuberculosis before AIDS. Apart from such unforeseen developments, I suggest knowing something about the classic occupational lung diseases is worthwhile because of the following.

1. They show the patterns of disease the lung can produce, and these can occur with other exposures, such as to drugs.
2. It will be increasingly rare for workers to enter an industry on leaving school at 15 and work until 65 in the same fumes. We will probably never understand any occupational diseases as well as the classic occupational lung diseases, and most of our knowledge of the relationships between occupational exposure and disease comes from them. In the future, we will often only be able to extrapolate from that knowledge to new disorders where the data will be even less, and all the pressure will be to close down a

process suspected of being unsafe before adequate epidemiology can be done. The classical diseases will be the only guide to the new ones we shall certainly be seeing. Most branches of medicine include some occupational disorders, but few have so many as well investigated as those affecting lungs; even an orthopaedic surgeon wanting to investigate work-related bone and joint disorders could best learn how to do so from studying occupational lung diseases and their epidemiology!

3. Workers with occupational lung diseases do appear in the clinics of physicians and general

practitioners, and deserve to be diagnosed competently. Some will have symptoms of disease and will expect them to be explained. Others may have findings irrelevant to their complaints; unnecessarily doing computerized tomography or biopsying the lungs of a man with welder's siderosis is wasteful and bad practice; a good chest radiograph, a good history, and a doctor with a good memory is what is needed. An occupational diagnosis will always impress the patient, particularly if compensation can be obtained!

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