REVIEW ARTICLE

Recent advances in respiratory medicine

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Introduction

In the past tuberculosis so dominated both public and professional views of respiratory medicine that it seemed obvious that the speciality must atrophy, at least in developed countries, when effective therapy for tuberculosis became available. The reality has been rather different. New discoveries in understanding of pathogenesis, in diagnostic methods, and above all in treatment, continue to keep respiratory medicine to the fore amongst the major sub-specialities of medicine, a position that the burden of such disease on society clearly merits. The topics chosen for this review are necessarily personal, but aim to indicate some areas where these discoveries are being applied in clinical practice today.

Adult respiratory disease syndrome (ARDS)

The adult respiratory distress syndrome (ARDS) first described by Ashbaugh *et al.* (1967) is now recognized to be the end result of lung damage which starts by involving the pulmonary endothelial cells, which thus allow a protein-rich oedema fluid to leak at first into the lung interstitial space, and then subsequently into the alveoli. An alternative term for the condition is thus non-cardiogenic pulmonary oedema. Recognized causes of the syndrome include pneumonia (either bacterial, viral or fungal), non-thoracic trauma (the original shock lung), fat embolism, pancreatitis, drug reactions, aspiration pneumonia, oxygen toxicity and intravascular coagulation. ARDS is characterized by the onset of acute respiratory distress within 24-72 hr in a patient with previously normal lungs, coupled with arterial hypoxaemia which persists despite an increase in inspired oxygen concentration; diffuse bilateral infiltrates on the chest X-ray; stiff lungs; and a pulmonary capillary wedge pressure below 12 mmHg, so serving to exclude cardiogenic pulmonary oedema. The mortality from established ARDS is 50-80%. Pathogenesis remains obscure, and at least in animal

models bradykinin, which may be generated by respiratory acidosis, can increase pulmonary vascular permeability (O'Brodovich *et al.*, 1981). There is now a wealth of evidence that complement components can also damage the lungs, possibly as the latter components of the complement system (C₃, onwards) are potent neutrophil chemotactic factors, which thus attract neutrophils to the already damaged lungs (Shaw *et al.*, 1980).

Hypoxaemia in ARDS

The hypoxaemia of ARDS poses a difficult clinical problem. The patient may clearly be dying of hypoxia, yet increasing the inspired oxygen concentration causes little rise in arterial PO₂, due to the severe shunt of de-oxygenated blood through unventilated alveoli; nonetheless this high oxygen level potentiates the pulmonary damage. The mechanism of this effect is now becoming clearer. Pulmonary oxygen toxicity results from transient activated forms of oxygen (superoxide, activated hydroxyl radicals, singlet oxygen, and hydrogen peroxide) (Symposium, 1981), which damage biological membranes by peroxidation. Active oxygen constituents are probably released from the lysozymes of pulmonary neutrophils, in the process of bacterial killing by their myeloperoxidase halide system. Oxygen recruits neutrophils to the damaged lungs (Fox *et al.*, 1981) and the interaction of neutrophils, oxygen radicals, and oxygen toxicity can clearly potentiate ARDS (McGuire *et al.*, 1982). In practice the physician faces the agonising problem of oxygenating his patient, and so preserving his life, without at the same time producing further lung damage. This dilemma originally led to the development of extracorporeal membrane oxygenation (ECMO) (Peirce, 1981). However, a controlled trial of ECMO in desperately ill patients showed those treated conventionally by artificial ventilation with positive end expiratory

pressure (PEEP) and high inspired oxygen concentrations fared as well (or as badly) as those receiving ECMO, with at least a 90% death rate in both groups. The rationale of ECMO is to allow the lungs to recover while the ventilatory function is taken over by the extracorporeal circulation. However, Gattinoni *et al.* (1980) have shown that life can be saved in some patients by using a partial extracorporeal membrane circulation to remove CO₂, whilst providing oxygen through low frequency mechanical ventilation to the lungs, at only two breaths per minute. An alternative approach may be to consider high frequency ventilation (see below). However, until we have reliable markers to indicate in which patients the lungs can recover, as distinct from those in whom the lungs are so severely damaged that recovery is impossible, decisions to use these very expensive and technically demanding regimens will remain very difficult.

High frequency positive pressure ventilation

In 1969 Sjostrand showed that ventilation through a jet, at 60–100 breaths per min, with very small tidal volumes approximating to the size of the calculated dead space, could nonetheless produce effective gas exchange in man. The exact details are still to be worked out, largely because the technology of making accurate measurements at these high frequencies is yet uncertain. However, it appears that gas mixing in the major airways can result from local turbulence, with a greater role for diffusional mixing down to alveolar level than when breathing at conventional respiratory rates. This work is still experimental, but has already been extended to man. The technique seems to be potentially valuable in patients with bronchopleural fistula, with damaged airways following surgery, and it holds promise for both patients with chronic obstructive lung disease, and in treating ARDS. The technique seems to provide gas exchange without the large swings in pleural pressure or high positive pressure in the airways which occur with PEEP. These high pressures in turn reduce the cardiac output and can thus impair transport of oxygen to the tissues (Sjostrand and Eriksson, 1980). A recent exciting development has been the demonstration of effective CO₂ elimination by high frequency ventilation in normal subjects, who were not intubated (Goldstein *et al.*, 1981). High frequency ventilation may also improve oxygenation by reducing the shunt fraction in patients with obstructive lung disease (Butler *et al.*, 1980).

We thus seem to be at the threshold of clinically important new developments for the treatment of patients with ARDS, or even in preventing the development of the syndrome, from this improved understanding of cellular and immune mechanisms

of lung injury, and by provision of oxygenation without excessive respiratory pressures using high frequency ventilation.

Chronic bronchitis and emphysema

Resources devoted to the enormous socio-economic burden resulting from chronic bronchitis and emphysema in Britain contrast markedly with the advanced technology described above (Royal College of Physicians, 1981).

The proteolytic theory of the pathogenesis of emphysema

The proteolytic theory of the pathogenesis of emphysema is now clearly established (Snider, 1981). This theory stems from the original observation that rare patients with alpha-1 anti-trypsin deficiency could develop devastating emphysema in early life if they smoked cigarettes. Today the theory proposes an interlinked series of biochemical and cellular events, mostly established by animal studies, but supported by observations in man. In cigarette smokers, pulmonary alveolar macrophages are known to cluster around the terminal airways, even in otherwise healthy lungs. Cigarette smoke damages these cells, which then release neutrophil chemotactic factors, which in turn attract circulating polymorphonuclear leucocytes to this site. The polymorphs may then be further damaged by cigarette smoke, and thus release some of their endogenous proteolytic enzymes, particularly neutrophil elastase, which can lyse the structural proteins of the lungs: elastin, collagen, proteoglycans, and basement membranes. In health this proteolytic activity is mainly opposed by the alpha-1 anti-trypsin (alpha-1 Pi) present in lung lining fluids, but it is now known that cigarette smoke contains oxidants, which attack alpha-1 Pi by oxidizing the terminal methionine residues, and so inactivate its capacity to neutralize neutrophil elastase. Thus the balance within the lungs of the cigarette smoker is swung towards proteolysis; this process, possibly continuing over many years, eventually produces the centri-lobular emphysematous spaces which is such a common pathological finding in the lungs of cigarette smokers. The steps of this theory have now been shown in animal models, and are largely confirmed by *in vivo* studies of alveolar macrophages obtained from patients by broncho-alveolar lavage. Prevention of centri-lobular emphysema would thus be easy—if people would only never smoke cigarettes!

Sleep disordered breathing

The recent recognition of severe transient hypoxaemia during sleep in 'blue and bloated' bronchitis

(Douglas *et al.*, 1979) has now been confirmed on both sides of the Atlantic. This hypoxaemia, which can involve arterial PO_2 levels falling to 20–30 mmHg, occurs most commonly during rapid eye movement (REM) sleep, and can be associated with a further rise in mean pulmonary arterial pressure, and possibly some increase in cardiac output (Catterall *et al.*, 1982a). These observations have supported the earlier proposal (Flenley, 1978) that such recurrent transient hypoxaemia in REM sleep in these patients may contribute to the sustained pulmonary hypertension and eventually cor pulmonale which is so common in these 'blue and bloated' bronchitics, which in turn is known to carry a very grave prognosis. Very recent studies in animals also tend to confirm this notion, by showing that intermittent transient hypoxaemia, even for as little as four hours in the 24-hr day, can provoke both secondary polycythaemia and right ventricular hypertrophy—at least in rats! (Moore-Gillon and Cameron, 1982).

Long-term domiciliary oxygen therapy

This treatment has now been the subject of two controlled trials (Nocturnal Oxygen Therapy Trial, 1980; MRC Working Party, 1981) which have shown that life of useful quality can be prolonged in patients with severe hypoxaemia from chronic bronchitis and emphysema. Most benefit from this treatment is obtained when the oxygen is given for 24 hr in the 24-hr day. The practical problems of long-term oxygen therapy are being gradually solved. In Britain it is still true that the only method of providing oxygen for patients in their own homes, by the NHS Drug Tariff, is through the very costly and inconvenient method of providing oxygen cylinders. This treatment, which to provide 2 litre/min of oxygen for 20–24 hr per day requires up to 20 of such F-size cylinders being delivered to the patient's home each week, and costs around £5,000 per patient per year. Alternative sources are now being studied. It seems clear that the oxygen concentrator, a device which uses a molecular sieve to remove oxygen from air, and only requires an electricity supply, is by far the cheapest and most convenient way of providing long-term oxygen treatment in the patient's home. This proposition, now widely accepted by workers in this field, may yet influence NHS prescribing, but it seems that much bureaucratic red tape remains to be cut. In contrast, in France much money is already being saved by the provision of over 800 concentrators through a centrally organized association. An alternative method, using a source of liquid oxygen delivered to the patient's home in a container on a twice weekly basis, is still cheaper than oxygen in cylinders, provides for the patient to have a portable oxygen supply for use when away from his home, but

is more expensive than the oxygen concentrator. A delivery arrangement for the liquid oxygen supply is so far only available in Edinburgh in the United Kingdom.

Whatever source of oxygen is provided, however, it is important to emphasize that this treatment has only been shown to be of proven value in patients with definite hypoxaemia, when awake, due to chronic bronchitis and emphysema. These patients will thus fit into the 'blue and bloated' pattern of this disease, with secondary polycythaemia, central cyanosis, CO_2 retention, pulmonary hypertension and cor pulmonale, in addition of course to their fixed airways obstruction.

Pneumococcal vaccine

A polyvalent polysaccharide vaccine against *Streptococcus pneumoniae* infection is now available, which provides immunity against 14 of the most common serological types of this organism. The United States Center for Disease Control has recommended that the vaccine may be useful for patients with splenic dysfunction (when pneumococcal infections can be devastating), and also to control pneumococcal outbreaks in closed institutions. However, there is no evidence that penicillin-resistant pneumococci are becoming any more frequent, and in most centres the penicillin-resistant rate is below 2% of clinically significant isolates. Although clearly chronic bronchitics and patients with other pre-existing chronic pulmonary disease may benefit from such a vaccine, there are no controlled studies of the efficacy of this regime in such patients on which to base recommendations for routine administration. The vaccine appears to be safe, the only side effects being erythaema and mild pain at the site of injection in about half of those vaccinated. The vaccine should be given once only to adults, but can be combined with influenza vaccination at the same time, provided that this is given in a different site (Center for Disease Control, 1982; Schwartz, 1982).

New and old antimicrobial drugs

The penicillins, ampicillin, and cotrimoxazole are all well tried drugs for treatment of the common bacterial infections of the respiratory tract. Nonetheless the recent introduction of Augmentin, a combined preparation of clavulanic acid and amoxycillin, active against beta-lactamase-producing bacteria, of trimethoprim, and the ever increasing number of cephalosporin antibiotics, are already beginning to change prescribing habits in this field. Should they?

Trimethoprim

The well known antimicrobial cotrimoxazole is a

combination of the folic acid antagonist trimethoprim and sulphamethoxazole. This is very active against *Haemophilus influenzae* and *S. pneumoniae* and is thus an effective treatment for purulent exacerbations of chronic bronchitis and emphysema. Recently trimethoprim alone has been compared with cotrimoxazole in the treatment of 216 adults with respiratory tract infection (mostly bronchitis, chronic bronchitis or pneumonia) (Lacey *et al.*, 1980). The most common pathogens isolated from the sputum were *H. influenzae* and *S. pneumoniae*, and none of the strains were resistant to either cotrimoxazole or trimethoprim. The clinical effects were uniformly good, there being no difference between the agents, and only three patients in this whole series died. However, side effects were about twice as common with cotrimoxazole. Furthermore, trimethoprim is cheaper than the combined preparation, but as these costs are very small in contrast to the high costs of cephalosporins (see below) the price factor seems to be unlikely to be a major determinant in selection of the appropriate drug.

Beta-lactamase

Penicillins and cephalosporins share some chemical similarities as both molecules include a beta-lactam ring leading to their designation as beta-lactam antibiotics. Even in 1940 it was recognized that penicillin could be inactivated by an extract of *Escherichia coli*, this property being attributed to a penicillinase. However, with discovery of the cephalosporins other inhibiting enzymes were recognized, and the general term beta-lactamase was coined to describe enzymes which can open the beta-lactam ring of cephalosporins or penicillins, so inactivating their antibacterial properties (Wise, 1982). Resistance to this attack has depended either upon modification of the molecule, as in cloxacillin and other anti-staphylococcal penicillins, or in ampicillin, or by discovery of inhibitors of beta-lactamase enzymes. This latter route led to the development of Augmentin, in which amoxycillin is combined with clavulanic acid, which inhibits beta-lactamases, including those produced by many Gram-negative organisms. The beta-lactamase field is very complex, some of those produced by Gram-negative organisms being chromosomally mediated, and some by plasmids, and so transmissible to other bacteria. This latter group already includes at least four classes of beta-lactamase enzymes from Gram-negative organisms (Augmentin: First Symposium, 1980).

Augmentin

Augmentin (amoxycillin 250 mg plus clavulanic acid 125 mg per tablet), given in a dose of 2 tablets three times daily for 5–20 days resulted in 'satisfac-

tory response' in 97% of patients with pneumonia, bronchiectasis and bronchitis (Graham *et al.*, 1982). Transtracheal aspiration yielded *H. influenzae* or *S. pneumoniae* in about a quarter of these cases. However, the only beta-lactamase-producing organism isolated in this study was a *Neisseria catarrhalis* which was not considered to be a primary pathogen, and comparison with amoxycillin alone was not attempted (Graham *et al.*, 1982). Minor gastrointestinal disturbance or skin rashes occurred in 30% of these patients, but this was somewhat higher than that found in Japanese patients treated with Augmentin (Augmentin; Second Symposium, 1982).

Cephalosporins

In 1945 Brotzu isolated the intriguingly named fungus *Cephalosporium acremonium* from a Sardinian sewage outfall. Cephalosporin C, the last of the original seven antibiotics derived from this fungus, was resistant to staphylococcal beta-lactamase and also active against a wide range of organisms. Today, over a dozen cephalosporins (or the related cephamycins) are already in use or under investigation. Many are bactericidal for the common pathogens causing respiratory infections. Of the ten cephalosporins listed in the 1982 British National Formulary only cephalexin, cephadrine and cefaclor are active when given by mouth, whereas the others (cefotaxime, cefoxitin, cefuroxime, cephaloridine, cephalothin, cephamandole, and cephalazolin) must be given parenterally. All are more expensive than the penicillins, including ampicillin and amoxycillin.

What is the role for this plethora of cephalosporin antibiotics in today's practice of respiratory medicine? It is difficult to answer this definitively from the available clinical studies of new antibiotic regimens in this area. Few studies are confined to patients with proven bacterial infection; previous antibiotic treatment is rarely described adequately; the outcome of treatment is usually described as 'excellent' to 'poor', with little objective description of the basis of these judgements; and double blind randomized comparisons of new agents with established antibiotic regimens are rare. These strictures are important when trying to decide if the high costs of treatment with these new drugs is justifiable, as compared to well tried and cheaper (if older) regimens, particularly in the common problems of pneumonia or acute exacerbations of chronic bronchitis and emphysema.

The new cephalosporins clearly have few side effects. Pain following intramuscular injection is rare, but can be controlled by adding lignocaine to the injection. Most of the cephalosporins are excreted unchanged, by both glomerular filtration and tubular secretion, so that renal failure can lead to toxic levels, and probenecid prolongs their half life. Dosage may

therefore need to be modified in patients with severe renal failure. Hypersensitivity rashes possibly arise in 2–5% of all recipients, but drug fever or anaphylactic shock is rare. Patients with penicillin allergy can also have cross-reactivity to cephalosporins, and about 5–16% of such patients develop a reaction to these drugs. A combination of a cephalosporin with an aminoglycoside may carry a risk of nephrotoxicity (Murray and Moellering, 1981; British National Formulary 3, 1982).

Major bacterial infection of the lower respiratory tract presents clinically in a number of ways: pneumonia acquired outside hospital; an acute exacerbation of chronic bronchitis and emphysema; pneumonia in a previously compromised host; chronic infection as in cystic fibrosis, and bronchiectasis, and localized infections such as lung abscess or empyema. The role of cephalosporins in treating these conditions will be briefly discussed.

Pneumonia

Pneumonia acquired outside hospital by a previously healthy patient is still most commonly due to infection with *S. pneumoniae* (the pneumococcus). Penicillin, either as benzylpenicillin or phenoxymethylpenicillin, is at least as active against *S. pneumoniae* as any currently available cephalosporin (Garrod, Lambert and O'Grady, 1981). This laboratory experience is borne out clinically, so that there is no justification for using cephalosporins in preference to a penicillin in treatment of pneumococcal pneumonia (Neu, 1980) except in the rare instance where the strain of *S. pneumoniae* is known to be resistant to penicillin. Such strains are occasionally encountered, and in Canada have been described in up to 2–3% of all isolates—they do not produce beta-lactamase. Pneumococci which are also resistant to other common antibiotics are very rare, but have also been encountered in South Africa (Cameron and Phillips, 1980).

Chronic bronchitis and emphysema

Pathogens found in sputum in an acute exacerbation of chronic bronchitis usually include either *S. pneumoniae*, or *H. influenzae* (or both) (McHardy *et al.*, 1980). Earlier cephalosporin antibiotics were relatively inactive against *H. influenzae*, but of the oral agents only cefaclor is active against both. However, a ten day course of cefaclor in a dose of 250 mg three times a day is about three times more expensive than an equivalent course of ampicillin (Monthly Index of Medical Specialities, 1982). In a comparative trial of these two drugs in lower respiratory tract infection, carried out in 50 patients aged 65–85 years, there was no difference in clinical outcome with the two drugs, although the bacterial

pathogens in sputum were not determined (Lee, Kakati and Mahmoud, 1980). Cefaclor produced 'clinical cure' in 93% of patients with pneumonia or an acute exacerbation of chronic bronchitis in a dose of 250 mg three times a day for 5–15 days, and this rose to 97% when 500 mg was given three times a day (Mattson *et al.*, 1979). However, 250 mg ampicillin three times a day for seven days was as effective in 199 patients as 500 mg of ampicillin four times a day, or amoxycillin both 250 and 500 mg four times a day in a double blind comparison (MacKay, 1980). Thus in the treatment of purulent exacerbations of chronic bronchitis and emphysema there seems to be little justification for using oral cefaclor in preference to oral ampicillin, and clearly cephalixin or cephadrine are not indicated. The only exception to this would be for strains of *H. influenzae* which are ampicillin resistant, as recently found in 6% of 1841 *H. influenzae* strains isolated throughout Britain (Philpott-Howard and Williams, 1982), most of the resistance being due to production of a beta-lactamase. Cefaclor has considerable resistance to beta-lactamase of *H. influenzae*. Nonetheless, this 6% incidence of ampicillin resistant strains of *H. influenzae* still seems too low to justify oral cefaclor (or Augmentin) as a first-line treatment of an acute exacerbation of chronic bronchitis and emphysema, in preference to ampicillin, amoxycillin, cotrimoxazole, or trimethoprim.

The position with the newer parenteral cephalosporins may yet prove to be different. Cephamandole is as active as cefaclor against non-beta-lactamase producing *H. influenzae*, but failed to eliminate an ampicillin resistant strain of *H. influenzae* type B (Hib) which caused pneumonia and empyema in a woman with rheumatoid arthritis (Markham *et al.*, 1981). Cefuroxime is active against *H. influenzae*, though not (at least in the laboratory) to such an extent as cefotaxime and ceftazidime (see below), and it is also resistant to beta-lactamase. Bacteriocidal concentrations of cefuroxime have been shown to be achieved rapidly in sputum, and these are also prolonged after 750 mg intramuscularly (i.m.) in patients with chronic bronchitis and emphysema (Havard *et al.*, 1980). However, a recent randomized comparison of cefuroxime (750 mg i.m., three times daily) with i.m. cotrimoxazole, in 40 patients with either clinical pneumonia or an acute exacerbation of chronic bronchitis showed no difference in outcome, but positive sputum cultures (often showing *H. influenzae*), were only obtained in about half of the cases (Mehtar, Papr and Morgan, 1982). In a comparison of cefuroxime with ampicillin, both antibiotics being given parenterally in exacerbations of chronic bronchitis and emphysema, with or without pneumonic consolidation, cefuroxime was claimed to give a better 'clinical response', with more

rapid clearances of purulent sputum. However, *H. influenzae* and *S. pneumoniae* were isolated from few of these patients, whereas *E. coli* was relatively common, possibly as half the patients had received antibiotics previously (Pines *et al.*, 1981).

The two new agents cefotaxime and ceftazidime are both highly active against *H. influenzae*, as well as against *S. pneumoniae*, and both are still active against beta-lactamase-producing strains of *H. influenzae* (Cefotaxime Symposium, 1980; Ceftazidime Symposium, 1981). Two grams of cefotaxime given i.m. twice daily yielded bacteriocidal concentrations against *H. influenzae* in sputum, with excellent clinical results in acute exacerbations of chronic bronchitis and emphysema (Maesen *et al.*, 1980). Early clinical experience with ceftazidime in respiratory infection (Ceftazidime Symposium, 1981) suggests it will live up to the promise indicated by its *in vitro* activity, but again there are as yet no controlled comparisons with ampicillin in patients with acute exacerbations of chronic bronchitis and emphysema. When an infective episode precipitates an exacerbation of pre-existing type II respiratory failure, as shown by arterial hypoxaemia with CO₂ retention, the case fatality rate lies between from 9–24% (Warren *et al.*, 1980, 1982). The value of rapid elimination of *S. pneumoniae* and *H. influenzae* in such severely ill patients, which would seem to be a potential gain from use of these new parenteral cephalosporins (cefuroxime, cefotaxime, and ceftazidime) thus seems to be worth exploring in the future.

Klebsiella pneumoniae

In addition to the organisms discussed above, bacterial pneumonia in the compromised host can also be due to infection with *Klebsiella* species, or *Pseudomonas aeruginosa*, in addition of course to anaerobic organisms. *Klebsiella pneumoniae* carries a mortality of over 40%. In Britain, where chloramphenicol is rarely used for treating other conditions, previous experience has suggested that chloramphenicol (2 g daily), combined with streptomycin (2 g daily) is often effective, coupled possibly with ampicillin or tetracycline if the organism is shown to be sensitive to these agents. However, cefotaxime is very active against *Klebsiella* species *in vitro*, and cephamandole also appears to be useful, and most of the parenteral cephalosporins have some activity (Garrod *et al.*, 1981). Cefotaxime (Cefotaxime Symposium, 1980) and ceftazidime (Ceftazidime Symposium, 1981) show the greatest *in vitro* activity against *Klebsiella* species. This activity of cefotaxime appears to have been confirmed clinically, as *klebsiella* was eliminated in 91% of 189 adult cases (Cefotaxime Symposium, 1980). However, it is not clear from this study how many of these patients suffered from

klebsiella pneumoniae, so that a definitive assessment as to the role of cefotaxime in clinical *klebsiella pneumoniae* is not yet possible. There is thus as yet no extensive clinical experience to support the *in vitro* potential of ceftazidime in the treatment of *klebsiella pneumoniae* in man. Nonetheless, as cefotaxime (and presumably ceftazidime) may be the only drugs active against gentamicin resistant strains of *klebsiella* (Casewell and Talsania, 1981), it may be wise to consider restricting the use of these drugs entirely to treatment of such life-threatening infections alone.

Pseudomonas infections

Pseudomonas aeruginosa is rarely a cause of primary pneumonia, but occurs more commonly as a potential pathogen in patients with bronchiectasis, and is particularly dangerous as a mucoid strain in adult patients with cystic fibrosis, where such infection implies a grave prognosis. Although carbenicillin and gentamicin given by aerosol over many months can arrest the progression of cystic fibrosis in adults with mucoid *pseudomonas* strains (Hodson, Penketh and Batten, 1981), ceftazidime appears very promising, being more active than any other cephalosporin against *P. aeruginosa*, at least in laboratory testing. The present small clinical experience with this agent would suggest that it is indeed also active in clinical practice, and controlled trials of parenteral ceftazidime, as compared to gentamicin and carbenicillin by aerosol in adult patients with mucoid strains of *pseudomonas* in cystic fibrosis must be considered, but will be very difficult to carry out. It may be important that ceftazidime still appears to be active against *pseudomonas* strains which are resistant to carbenicillin, again at least in the laboratory (Ceftazidime Symposium, 1981).

Anaerobic infections

In localized respiratory infections (lung abscess or empyema) and in aspiration pneumonia, anaerobic organisms may be important. Penicillin, clindamycin and metronidazole are recognized to be of value in this context, but of the new cephalosporins cefotaxime is particularly active against *Bacillus fragilis*, at least in the laboratory. As with so much of this story this remains to be shown to be of value in clinical practice.

Costs of cephalosporins

Both new and old cephalosporins are expensive, giving rise to the highest costs of any group of antibiotics in hospitals. In a University hospital in Pittsburg a voluntary restriction to cephalosporins as the principal parenteral cephalosporin yielded savings of nearly 50% in the cost of cephalosporin prescribing.

Surprisingly enough the approved programme included cephalosporins for pneumococcal pneumonia, but cefuroxime, cefotaxime, and ceftazidime, which might be more appropriate for treatment of patients with respiratory problems, were not included (Britton, Schwinghammer and Romano, 1981). Nonetheless, this experience indicates that substantial cost savings can be achieved by rational choice of cephalosporin antibiotics, without appearing to impair patient care. British experience with a hospital pharmacopoeia would suggest that this approach could yield similar benefits in the National Health Service. Thus two grams of cefotaxime per day for seven days would cost £90–£130, compared to about £1.00 for 250 mg ampicillin three times daily for seven days (British National Formulary 3, 1982). If all new episodes of exacerbations of chronic bronchitis in the U.K. were treated with cefotaxime (which is certainly *not* recommended), it can be estimated that the U.K. drug bill could be around £100–£200 million per year as compared to £1–£2 million per year if ampicillin were used (Royal College of Physicians, 1981).

Bronchial asthma

Leukotrienes

The biological activity of slow reacting substance of anaphylaxis (SRS-A), long known as a potent bronchoconstrictor, is now recognized to arise from leukotrienes. These are hydroxy-fatty acids generated *in vivo* by lipoxygenase enzymes from arachidonic acid, which is derived from the lipoproteins of the mast cell membrane. The mast cell degranulation which results from the interaction of antigen with specific cell bound IgE, as in the type I reaction which can initiate an attack of allergic asthma, is one of several mechanisms leading to generation of leukotrienes, but more absolute proof of their role in the pathogenesis of asthma must await the development of specific antagonists. Leukotrienes are very potent bronchoconstrictors, some 1,000 times more active than histamine, but also have complex effects on vascular smooth muscle. Some leukotriene components are chemotactic, attracting inflammatory cells to the site of release of the leukotrienes. The full impact of these recent discoveries for both the understanding and treatment of bronchial asthma is yet awaited, but it is already possible that calcium channel blocking drugs such as nifedipine which have a bronchodilator effect in some patients with exercise induced asthma (Cerrina *et al.*, 1981) may be related to the inhibition of leukotrienes. Cromoglycate and corticosteroids may similarly prevent or inhibit asthmatic attacks by interfering with the generation of leukotrienes and prostaglandins. However, specific leukotriene antagonists, currently being

developed by the pharmaceutical industry, have yet to undergo clinical trials in human asthma. The results of these studies are awaited with great interest (O'Driscoll and Kay, 1982).

Bronchial hyperreactivity

Asthma can best be defined as recurrent episodes of acute limitation of airflow, remitting either spontaneously or in response to treatment. The notion that the asthmatic has 'twitchy airways', which constrict excessively in response to a variety of potential trigger stimuli is now moving out of the laboratory into clinical practice. Allergens, cold air, sulphur dioxide, histamine, and methacholine have all been used to demonstrate this property of the asthmatic airways, the responses to such challenge depending upon both the characteristics of the patient and the methods used. Tidal breathing for 2 min of solutions nebulized by a Wright nebulizer, with assessment of the response by forced expiratory volume in one sec (FEV₁) measured 30 and 90 sec after the end of the inhalation, allows the response to be assessed by PC₂₀, the dose of the agent required to produce a 20% fall from the base line FEV₁. Responses are compared to control inhalations, the methacholine or histamine concentrations being progressively doubled over the range 0.03–8 mg/ml (Hargreave *et al.*, 1981).

This method yields reproducible responses, and allows them to be related to the spontaneous peak flow rates in asthmatics. Indeed, during the pollen season in asthmatics with clear cut pollen induced asthma, bronchial hyperreactivity and spontaneous airflow limitation may both be marked, but during winter months when the pollen allergens are less prevalent, bronchial hyperreactivity may also wane in such patients. It is also claimed that such measurements give guidance on the potential response of an asthmatic patient to treatment.

Nonetheless, most clinicians feel that asthma can nearly always be diagnosed by a careful history, if necessary supplemented by measurement of FEV₁ or peak expiratory flow rate, particularly if this is made several times each day so as to reveal the characteristic variability in airflow limitation. However, these challenge methods have been of great value in understanding the pathophysiology of airway constriction, and of the mechanisms of action of bronchodilator drugs. It is interesting that these methods show a continuous distribution of bronchial responsiveness in the general population, with no clear-cut separation of the asthmatic, possibly leading to a similar debate to that on the definition of hypertension some 20 years ago. The fundamental question in asthma remains to be answered—why do some asthmatics develop an acute attack on one day, whereas an apparently similar environment the

previous day does not produce an attack? The laboratory has not yet answered all the clinician's problems in understanding asthma.

House mites and asthma

Reagin mediated allergy to the house mite (*Dermaphagoides pteronyssinus*) is now widely recognized to be common in atopic asthma, both in Europe, rural Africa, and urban Shanghai and no doubt worldwide. The mechanism by which this reaction causes the allergic bronchospasm is now clearer, following the identification of the very high concentrations of allergen (antigen Pi) in the faecal pellets of the house mite. These pellets, encased in a membrane which can be easily defined on electron microscopy, are some 20 μm in diameter, so that most must be impacted in the nose, and very few penetrate to the lower airways where they could encounter mast cells bearing specific cell-bound IgE lying free in the airway lumen. Natural exposure to the allergen must be at a much slower rate than that encountered in an experimental bronchial challenge study with commercial house mite preparations being inhaled. However, the natural allergen is at a much higher concentration. Mite faecal particles only become airborne for a short period during domestic activity, and rapidly fall to the ground due to their relatively large size. Nonetheless, inhalation of even a few particles into the lower airways presumably causes an intense local inflammatory reaction, as a result of the very high concentrations of antigen which such particles contain. The well known prevalence of house mites, and thus faecal particles, in bedroom dust and particular in mattresses, may account for the nocturnal asthma now being recognized as so characteristic a feature of the asthmatic (Tovey *et al.*, 1981).

Occupational asthma

In March 1982 occupational asthma became a prescribed industrial disease in the United Kingdom, for which disablement benefit can be paid under the Industrial Injuries Scheme. For these purposes the claimant must have been exposed to one of the following at work within 10 years before the claim: isocyanates; platinum salts; fumes or dust of hardening agents (epoxy resin, curing agents, etc); rosin as a soldering flux; proteolytic enzymes; animals or insects in research or education; and dusts of barley, oats, rye, wheat or maize. The diagnosis of occupational asthma depends upon an accurate occupational and clinical history revealing a sensitizing agent at work, a symptom-free period of exposure before the asthma develops, and symptoms which improve when away from work but recur on exposure to a very small dose of the agent. Diagnosis may depend upon skin prick tests (platinum salts, proteo-

lytic enzymes and laboratory animal exposures) and only rarely on bronchial provocation tests. The most valuable clue is often yielded by the history, confirmed by serial measurements of peak expiratory flow, several times a day, over at least two weeks including a weekend away from work. Preventive measures are important. These include substitution of less hazardous chemicals, total enclosure of the process, exhaust ventilation at the point of emission of the dust, and personal respiratory protection (such as an Air-Stream helmet) or protective clothing (Department of Health and Social Security, 1982; Newman-Taylor and Davies, 1981).

Theophylline

Theophylline is an old drug, but its value as a bronchodilator has received considerable attention in the last 10 years, particularly in North America, possibly as modern beta₂ sympathomimetics, such as salbutamol, only became available there in 1981. The notion that theophylline acts by inhibiting phosphodiesterase, and thus raising 3'5'c AMP levels (Butcher and Sutherland, 1962) is less readily accepted today, as this action seems to require a drug concentration which is much higher than can be achieved *in vitro* (Kolbeck *et al.*, 1979). Nonetheless the improvement in FEV₁ in the asthmatic following theophylline is proportional to the logarithm of serum concentration between 5–20 $\mu\text{g}/\text{ml}$ (Mitenko and Ogilvie, 1975). Side effects, varying from centrally mediated nausea, vomiting and diarrhoea to irritability, tachycardia, and eventually convulsions and cardio-respiratory arrest, all become more prominent as serum levels rise above 20 $\mu\text{g}/\text{ml}$. Life threatening arrhythmias or convulsions are a very real risk at levels of over 40 $\mu\text{g}/\text{ml}$, but may not always be heralded by less serious side effects (Zwillich *et al.*, 1975). This narrow toxic/therapeutic ratio indicates the value of monitoring serum concentrations if the theophyllines are to be used to maximum effect in clinical practice. Decreased elimination of theophylline occurs in the obese, the very young and the very old, following a high carbohydrate diet, and in patients receiving cimetidine and possibly erythromycin (Jackson *et al.*, 1981). Hepatic cirrhosis, congestive heart failure, pulmonary oedema, chronic obstructive lung disease, acute febrile episodes and anti-viral vaccines can also prolong elimination, whereas cigarette smoking and possibly phenobarbitone increase the rate of elimination of theophylline. In patients who have not previously been receiving theophyllines, an intravenous loading aminophylline dose of 6 mg/kg body weight is recommended, followed by 0.7 mg/kg body weight/hour for the next 12 hr, followed by 0.5 mg/kg body weight/hr for the next 12 hr in otherwise healthy non-smoking adults. In older patients, or in

those with cor pulmonale, this infusion rate should be lower (but with the same loading dose), at 0.6 mg/kg body weight/hr initially, followed by 0.3 mg/kg body weight/hr. Even lower infusion doses should be used in those with congestive heart failure or liver disease. In smokers the maintenance infusion should be at a level of 1.0 mg/kg body weight/hr in the young adult, falling to 0.8 mg/kg body weight/hr after 12 hr (Jenne, 1981). In patients who currently receive theophylline it is clearly safer to measure the serum level before starting treatment. This is also true for acutely ill patients who are receiving continuous intravenous therapy, when serum levels measured at 12 and 24 hr after starting the infusion are the best guide (Ogilvie, 1981).

Serum theophylline measurement

Serum theophylline concentrations can be measured by high pressure liquid chromatography (HPLC), or the newer enzyme multiplied immunoassay technique (EMIT, SYVA). In the best hands they appear to be of similar accuracy, with marginally higher precision with HPLC, but this requires more technical skill and initial outlay than EMIT, whereas running costs are some eight times less with HPLC than with EMIT (Koup and Brodsky, 1978). However, the clinicians' reliance on laboratory measurements to guide treatment is a little shattered by finding that in inter-laboratory comparisons between 28 hospital, private and commercial laboratories in Iowa, U.S.A., 28% of the results gave a measurement of serum theophylline on a standard specimen which fell outside 2 standard deviations, including one sample where the concentration was read as 6.1 µg/ml when it was in fact 15.7 µg/ml. Handling or performance errors appear to account for these alarming results, and the authors noted that the 'reliability of the laboratory was not correlated with the amount charged!' (Bonham *et al.*, 1980). Theophylline is partly protein bound in plasma, so that the concentration of free drug, the active agent, will be higher if plasma protein levels are low.

Oral theophyllines in asthma

The long-term use of slow release preparations of oral theophylline or aminophylline as a prophylactic against attacks of asthma is increasing in Britain. The idea behind this use is supported by computer simulations (Weinberger, Hendeles and Bighley, 1978), and from a placebo-controlled randomized trial in children with asthma (Nassif *et al.*, 1981). It seems possible that once proper dose regimens have been established these may remain stable over long periods at least in children (Ginchansky and Weinberger, 1977). Again, measurement of serum concentrations are invaluable in ensuring correct dosage,

but these measurements should be taken at the same time each day, and also at the same time after taking the tablet, which should preferably be 4 hr after a slow release preparation by mouth (Lesko *et al.*, 1980). Spontaneous attacks of asthma may frequently disturb sleep in the latter half of the night (Catterall *et al.*, 1982b) but it seems possible that sustained release theophylline preparations given on retiral may prevent them (Barnes *et al.*, 1982). Further studies will need to find out if theophyllines, whose side effects include tachycardia and restlessness, do in fact interfere with normal nocturnal sleep. Ketotifen, an oral anti-asthmatic agent which has both antihistamine and possibly anti-allergic properties, can improve the quality of sleep in adult stable asthmatics, without provoking more nocturnal bronchospasm with transient hypoxaemia during REM sleep (Catterall *et al.*, 1982c).

It is still not certain if there is a useful interaction, or synergism, between an oral theophylline and an inhaled or oral beta₂ agonist, such as salbutamol or terbutaline, in either the treatment or prevention of acute attacks of asthma. Some authors, using different doses of the two agents, different routes of administration, and in different types of subjects both children and adults, do find valuable interaction (Wolfe *et al.*, 1978; Campbell *et al.*, 1977; Lonnerholm, Foucard and Lindstrom, 1981; Leitch *et al.*, 1981), whereas others, again using different patients, and different combinations of the two agents, do not (Eggleston, Beasley and Kindley, 1981; Handslip, Dart and Davis, 1981). As with many studies in asthmatics, the variability of airflow limitation, the very hallmark of asthma, renders statistically valid comparisons difficult, and often means that only patients with relatively stable airflow limitation are studied. However, such patients form a relatively small percentage of all asthmatics encountered in clinical practice. Clearly further double blind studies, using theophylline serum levels to assess the adequacy of theophylline dosage, along with repeated measurements of peak expiratory flow and diary cards, to record both symptoms and use of beta agonist by inhaler medication (Nassif *et al.*, 1981), will be needed over many days in large numbers of patients to establish finally the value of such interaction on a proper scientific basis. However, the recent suggestion that there may be addition of toxicity between theophylline as a sustained-release oral preparation, and inhaled beta-agonists, which might be dangerous to asthmatics (Wilson, Sutherland and Thomas, 1981) has been seriously challenged (Grant, 1981; Koeter *et al.*, 1981; Henry *et al.*, 1981; Beaglehole, Harris and Rea, 1981).

Finally, a new physiological mechanism for the potential important role of aminophylline in acute asthma has been proposed. In normal healthy sub-

jects aminophylline, at a therapeutically effective serum level, increased the contractility of the diaphragm, and rendered it less susceptible to fatigue (Aubier *et al.*, 1981). If this result can be confirmed, particularly in asthmatic patients, it seems possible that this could explain some of the clinical benefits of aminophylline in addition to that which can be attributed to improvement in airway obstruction. In the asthmatic attack, with hyperventilation as shown by the characteristically low arterial PCO_2 , the work of the diaphragm must be greatly increased, for it is acting against an increased airways resistance, as well as at a mechanical disadvantage from the marked hyperinflation of the asthmatic chest.

Ipratropium bromide

The anticholinergic drug ipratropium bromide has been shown to dilate the airways in normal man when given by metered dose aerosol, presumably by inhibition of the normal vagally mediated bronchomotor tone. The drug has also a useful interaction with β_2 agonists in producing bronchodilatation, also given by metered dose aerosol, in patients with severe chronic bronchitis and emphysema (Douglas, Sudlow and Flenley, 1977). Although earlier studies suggested that ipratropium was less effective in asthmatics (Petrie and Palmer, 1975) it has recently been shown that 500 μ g of ipratropium by wet nebulization enhanced bronchodilatation produced by 10 mg of salbutamol, (again given by wet nebulization) of 22 adult patients admitted to hospital with an acute attack of asthma (Ward *et al.*, 1981). However, as with most such studies the patients were also given large parenteral doses of hydrocortisone, as indeed most physicians would regard as entirely appropriate in treatment of severe asthma, but nonetheless this makes it difficult to be scientifically certain on the exact role of the ipratropium and salbutamol in improving their severe airway obstruction (Ward *et al.*, 1981).

This study emphasizes the tendency to use higher doses of ipratropium than those originally recommended, such as the 40 μ g contained in one puff from the metered dose aerosol. As very little of the drug is found in the plasma after such delivery to the airway alone, it seems that these larger doses are safe. Earlier work showing that 40 μ g did not impair mucociliary clearance in patients, although this theoretical possibility from an atropine-like drug (Pavia *et al.*, 1979) will need to be repeated at these higher doses. Even after 120 μ g by metered dose aerosol there were no significant side effects, but FEV₁ in men with partially reversible airways obstruction rose more than that seen after the conventional dose, and, possibly even more importantly, the bronchodilatation was preserved for up to 6 hr (Allen and

Campbell, 1980). The conventional dose (2 puffs of 40 μ g from the metered dose aerosol), gave a positive interaction with an oral theophylline in producing bronchodilatation, when the serum theophylline concentration was within the therapeutic range (Krisman *et al.*, 1981).

Pneumonia in the immune compromised host

Infective agents

Pneumonia is the commonest infection in the immune compromised patient, whether the immunosuppression arises spontaneously as in granulocytopenia, Hodgkin's disease, hypogammaglobulinaemia or multiple myeloma, or is therapeutically induced in the treatment of leukaemia, solid tumours, or to prevent rejection of a transplanted organ. Experience is now beginning to relate the probability of different types of infection to the specific immune defect (Rubin, 1980). Thus in granulocytopenia pulmonary infections are likely to be due to coliforms, aspergillus, or pseudomonas; whereas in hypogammaglobulinaemia and multiple myeloma, *S. pneumoniae* and *H. influenzae* infections are common. In disturbances of cell mediated immunity, fungal infections, virus infection (cytomegalovirus, herpes, etc) and mycobacterial infections are common, in addition to the widely known risk of *Pneumocystis carinii* infection.

The usual clinical presentation in such a patient is a pulmonary infiltrate on the chest radiograph, associated with fever, breathlessness and cough. The differential diagnosis will include radiation pneumonitis, drug-induced lung disease, spread of neoplasm to the lung, pulmonary oedema and pulmonary haemorrhage from thrombocytopaenia. A previous tuberculous infection may be reactivated in such a patient, as a positive tuberculin test emphasizes. Acute consolidation on the chest radiograph developing within a 24-hr period suggests bacterial pneumonia, pulmonary haemorrhage, or thromboembolism. An interstitial infiltrate appearing over this time scale would suggest pulmonary oedema, or a leucoagglutinin reaction, in which the patient's plasma reacts with leucocytes of a recent blood transfusion, causing fever, chills, cough and respiratory distress, along with widespread interstitial infiltrates on the chest film (Thompson *et al.*, 1971).

Consolidation developing over several days to weeks suggests a fungal infection, tuberculous infection, or spread of the primary tumour. An interstitial infiltrate occurring over this time suggests viral infection. *Pneumocystis carinii*, radiation pneumonitis, or a drug reaction (bleomycin, cyclophosphamide, chlorambucil or methotrexate). Sub-acute or chronic nodular infiltrate on the chest film suggests

spread of primary tumour, or possibly fungal or tuberculous infection.

Diagnostic methods

Diagnosis can be difficult, for these sick patients rarely raise sputum, and potential pathogens in the upper respiratory tract can confuse the picture even in those who do. A new sampling catheter for use through a fiberoptic bronchoscope, consisting of a double catheter of which the outer sheath encloses an inner catheter which in turn carries a nylon brush, can be used to obtain uncontaminated samples from the lower respiratory tract. The nylon brush is protruded into the sampled bronchus by ejecting an occluding biodegradable plug, the nylon brush, after obtaining the sample, then being withdrawn into the sheathing catheter, and the whole device withdrawn from the bronchial tree (Wimberley, Faling and Bartlett, 1979). An alternative approach if sputum is not obtained is to use trans-tracheal aspiration, whereby a cannula is inserted through a needle in the cricothyroid membrane, and specimens withdrawn, after a few ml of saline are instilled (Kalinske *et al.*, 1967). The technique is safe, provided that the patient's platelet count can be maintained over 50×10^9 /litre for more than 12 hr afterwards, but an uncontrollable bleeding tendency, an unco-operative patient, and local anatomical abnormalities make trans-tracheal aspiration unduly hazardous. Specimens from either of these techniques should be examined for pneumocystis infection, legionella and acid-fast bacilli, and cultured both anaerobically and aerobically (Ramsay *et al.*, 1980).

When neither trans-bronchial aspiration nor trans-tracheal aspiration is helpful yet the patient is clearly deteriorating, open lung biopsy may be essential to achieve the diagnosis. However, this carries a grave risk in the severely neutropaenic patient, bacteraemia and post-bronchoscopy pneumonia being well described, but antibiotic cover with ticarcillin and tobramycin may avoid these dangers (Beyt, King and Glew, 1977). This heroic diagnostic procedure can therefore only be justified if tissue is obtained which may yield a correct diagnosis of a treatable condition. The role of the newer cephalosporin antibiotics in treating common bacterial infections in such patients is discussed earlier. *S. pneumoniae* still remains a common and treatable bacterial pathogen in these cases, so that penicillin may still be an appropriate antibiotic to include in a treatment regimen. High doses of cotrimoxazole (Winston *et al.*, 1980), for a period of at least 3 days, and possibly a week, should produce clinical improvement if pneumocystis is the major pathogen. Systemic fungal infections may be amenable to therapy with amphotericin B (Medoff

and Kobayashi, 1980). The new antifungal agent ketoconazole, although effective in systemic candidosis, histoplasmosis and rarer fungal infections (Symoens, 1981) does not seem to have a major role in treatment of systemic aspergillus infection. Legionnaires' disease can respond to erythromycin, probably best combined with rifampicin (Randolph and Beekman, 1979), in these desperately ill patients.

Lung cancer

Smoking

Bronchogenic carcinoma remains the commonest cause of malignant death in men in the U.K., and is second only to cancer of the breast in women, although the rate of increase of the disease may now be slowing. The highest incidence is in older age groups. All accept smoking as a major aetiological factor in at least three of the common cell types (squamous, small cell and large cell) although this may be less clearcut in the case of adenocarcinoma, which appears to be increasing in incidence in the U.S.A. (Cox and Yesner, 1979) but not in Europe. Smokers are known to be inaccurate in their own account of their smoking habits (Sillet *et al.*, 1978). Cigarette smoke yields 8–20 mg carbon monoxide (CO) for each cigarette, with filter cigarettes often yielding more CO than plain tipped brands (Fairweather *et al.*, 1981). It has recently been shown that blood carboxyhaemoglobin (COHb), resulting from inhalation of this CO in cigarette smoke, is well correlated with blood nicotine levels in smokers, when measured immediately before smoking. Thus a COHb level over 3% strongly suggest that the patient is a chronic cigarette smoker (Ashton, Stepney and Thomson, 1981).

Screening for early lung cancer

Two important studies of the value of screening for detection of lung cancer at an early stage in chronic smokers have recently been reported. The first, The New York Lung Cancer Detection Programme (Melamed *et al.*, 1981) screened just over 10,000 smokers aged over 45 years, using an annual chest radiograph and four-monthly sputum cytology. This study yielded an incidence of 3 lung cancers per 1,000 man years, and the results suggested that up to 40% of these patients were in an early stage, with a good chance of survival following resection. However, in contrast, the impeccably planned Mayo Lung Project (Taylor *et al.*, 1981), again carried out in smokers aged over 45 years, but only in men, yielded less sanguine results. In this project the initial screening programme only included those in whom careful studies including sputum cytology had failed to reveal bronchogenic carcinoma at the outset of the

study. The screened group had chest radiographs, sputum cytology, and a health questionnaire every four months. One hundred and four cancers were subsequently discovered in this group, compared to 72 in the control group patients, who only had annual chest radiographs, coupled with advice to stop smoking. However, so far this study has shown that intensive screening can detect squamous cell carcinoma and adenocarcinoma at an early stage, and thus make a difference in their survival, but not in that for small cell or large cell cancer. It may be uncharitable but nonetheless realistic to ask if similar money and effort devoted to strong repetition of anti-smoking measures could save more lives at the end of the day; but this may be more a moral and political question than a medical one (Peto, 1978).

Staging of lung cancer

Whole-body computed axial tomography (CAT) may not only help to localize a pulmonary tumour, but possibly also detect metastases (Schaner *et al.*, 1978). CAT scans may also give important clues as to the possible pathology of lung nodules, so allowing distinction between benign and malignant coin lesions on the basis of the CT number. Higher CT numbers indicate a greater probability of calcium in the lesion, whereas a lower number implies that the lesion is less likely to be calcified (Siegelman *et al.*, 1980). However this may only be true in a geographical location where calcified pulmonary nodules due to histoplasmosis are particularly common, as in some areas of the U.S.A. (Holle *et al.*, 1982).

Rapid (2 sec) CAT scans have been shown to be a sensitive non-invasive and accurate method of assessing mediastinal node involvement in lung cancer, but to be less effective in detecting hilar gland involvement (Faling *et al.*, 1981). Remarkably enough this was not compared with the much cheaper method of using indentation of the barium swallow to indicate mediastinal gland involvement. Gallium 67, a radio-pharmaceutical which accumulates in both malignant tissue and in inflammatory or granulomatous lesions, has also recently been shown to be of value in both staging and diagnosis of lung cancer. Thus, a coin lesion with a positive gallium uptake suggests malignancy, whereas a negative gallium scan in a coin lesion implies that it is probably benign. A gallium 67 scan can also help to detect tumour spread to hilar glands, whereas a negative gallium scan of the mediastinum implies that mediastinoscopy is not necessary before thoracotomy, as these glands are probably not involved by tumour (Pannier *et al.*, 1982).

Treatment

The conventional view that small cell lung cancer

is disseminated at the time of diagnosis, and is therefore not amenable to surgical cure, has recently been challenged by Shore and Paneth (1980) who have described 10 patients with small cell cancer who survived for 5 or more years following resection. Prophylactic cranial irradiation in patients with small cell lung cancer has shown that although this can delay the appearance of cerebral metastases, it does not improve survival. Chemotherapy for small cell lung cancer is now well established, using pulses of cytotoxic drugs in combination, such regimens often including cyclophosphamide (up to 1.5 g/m²), with or without vincristine, doxorubicin (45–60 mg/m²) and methotrexate. In patients who show an initial response a minimum of six pulses each at 3-week intervals appears most effective. Side effects include febrile episodes in 30% of treated patients (associated with the granulocytopenia), infections which are documented in about 5%, and fatal infections in 2% (International Association for Study of Lung Cancer 1982). Fungal infections are not common in such patients, in contrast to their relatively higher prevalence in cytotoxic treatment of leukaemia. There are no major new advances in therapy, but trials continue (Livingston, 1980; Weiss *et al.*, 1980) and preliminary reports suggest that etoposide (VP-16-23), in combination with cisplatin may prolong survival time in such patients (Sierocki *et al.*, 1979).

Treatment of non-small cell lung cancer still largely depends on surgery, provided that the patient's respiratory function will be adequate after resection (Ali *et al.*, 1980), or radiotherapy, if surgery is technically impossible. The role of immunotherapy using BCG in squamous carcinoma remains controversial (Jansen, The and Orie, 1980). As in earlier years, the message for lung cancer seems to be well summarized by the words King Edward VII used about tuberculosis—"if preventable, why not prevent?"

Interstitial lung disease

Although the aetiology remains unclear, cryptogenic fibrosing alveolitis (known in the U.S.A. as idiopathic pulmonary fibrosis) and sarcoidosis, two of the more frequently encountered varieties of diffuse interstitial lung disease, are now beginning to yield important clues for both their diagnosis in clinical practice, and also for better understanding of their pathogenesis. This has come about by the use of three recently introduced diagnostic techniques.

Fibreoptic bronchoscopy

Fibreoptic bronchoscopy is now in wide use (Mitchell and Collins, 1980) and the combination of this with trans-bronchial biopsy has yielded strong evidence that the characteristic lesions of sarcoidosis,

the epithelial tubercles, can occur within the lungs of patients even with stage I sarcoidosis, with only bilateral hilar adenopathy and no radiological involvement of lung parenchyma (Israel, 1980). Nonetheless, doubt has been cast recently on the specificity of such diagnosis by trans-bronchial biopsy for the wider spectrum of interstitial lung disease. Thus diagnostic tissue was only obtained by fiberoptic trans-bronchial biopsy in 38% of 53 patients with clinical evidence of diffuse pulmonary disease, whereas open biopsy yielded specific diagnoses (which were often different from that suggested by the trans-bronchial biopsy), in 92% of the remaining 33 patients (Wall *et al.*, 1981).

Broncho-alveolar lavage

The second new approach is to use broncho-alveolar lavage through the fiberoptic bronchoscope, whereby five 20 ml aliquots of normal saline are instilled into a peripheral bronchus, at up to three separate sites. This is then followed by suction aspiration, aspiration, the procedure yielding both cells and protein of the alveolar fluid from deep within the lung (Hunninghake *et al.*, 1979). The technique is safe, provided that the patient's FEV₁ is more than 1 litre, arterial Po₂ more than 75 mmHg and the arterial PCO₂ not raised. Transient fever, rapidly responding to antibiotics, occurs in less than 3% of cases (Greening, 1982). In the normal non-smoker 90% or more of the cells obtained are alveolar macrophages, 10% lymphocytes, and only 1% or less polymorphonuclear leucocytes. In the cigarette smoker more cells are obtained, and there is a greater proportion of neutrophils, which may be up to 5% of the total. In active sarcoidosis 60% of the cells from broncho-alveolar lavage will be macrophages, and 40% lymphocytes with a predominance of T cells, leading to the notion that T cells are sequestered within the lungs in sarcoidosis (Crystal *et al.*, 1981). This idea has led to the hypothesis that the epithelioid tubercle of sarcoidosis is formed as a result of a complex interaction between monocytes, macrophages and lymphocytes, modulated by the release of lymphokines from activated T lymphocytes. This hypothesis implies that the primary pulmonary abnormality in sarcoidosis is an inflammation of the alveolus (an alveolitis), which precedes the development of the granuloma.

In contrast, in cryptogenic fibrosing alveolitis, broncho-alveolar lavage reveals a great increase in alveolar macrophages and neutrophils, which constitute up to 5–50% of the cells recovered (Reynolds *et al.*, 1977; Turner-Warwick, Burrows and Johnson, 1980).

Gallium scanning

The last new approach has been the use of gallium 67, a radiopharmaceutical which localizes in inflammatory cells, as well as in neoplastic cells. A few days after an intravenous injection of the radioisotope, the lungs are scanned with either a gamma camera with appropriate collimator, or with a rectilinear scanner. The radiation dose involved for the whole-body is equal to that in a barium enema. The normal lungs do not take up gallium, whereas in active interstitial lung disease such as active sarcoidosis or fibrosing alveolitis there is a significant uptake within the lungs (Line *et al.*, 1978, 1981).

Serum angiotensin-converting enzyme

Finally, the source for the well known rise in serum angiotensin-converting enzyme (SACE) in active sarcoidosis may now possibly have been found. This enzyme can be located by immunofluorescence to lie in the epithelioid cells at the perimeter of sarcoid granulomata (Pertschuk, Silverstein and Freidland, 1981). In clinical practice it remains true that SACE is raised in only 50–80% of patients with sarcoidosis, and high values can also be found in at least up to 15% of patients with other types of lung disease. The measurement by itself is thus non-specific. However, a combination of a positive lung gallium scan, with a raised SACE level, strongly suggests that active sarcoidosis is involving the lungs.

Controversy remains as to when to treat patients with sarcoidosis, using corticosteroids in a relatively high dose for a period up to 6 months or more, but attempts are now being made to resolve this dilemma by means of a long-term prospective trial, under the auspices of the British Thoracic Association—now reborn as part of the new British Thoracic Society. It is tempting to conclude that a patient with a positive gallium scan, lymphocyte excess in his alveolar lavage fluids, and also elevated SACE levels does have active alveolitis due to sarcoidosis, and should be treated. However, this notion, although challenging, yet remains to be proven.

Acknowledgments

I would like to thank Dr P. M. Warren, Dr A. Morgan, Dr J. A. Gray and Dr M. F. Sudlow for help with references to recent literature in compiling this review.

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(Received 9 August 1982)