Reviews in Medicine

Respiratory diseases

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Introduction

We have chosen to review prominent papers of 1989 which influenced chest physicians' thinking and practical management. We have drawn attention to some manuscripts which will carry even a 1990 reference and provide stop press information. We review, in this order, techniques, metabolic functions, Wegener's granulomatosis, adult respiratory distress syndrome, asthma, interstitial pulmonary disease, lung cancer, transplantation, occupational lung disease, infections and therapeutics.

The garden is full of the most enchanting flowers. We have plucked and offer for you, dear readers, our very personal choice. We have made up a bunch of other men's flowers; we have only provided the string that ties them together. Now go forth, sew your own seeds or gather a fresh crop in the inviting field of respiratory medicine and surgery.

Techniques

The study of respiratory disease has become more scientific and sophisticated with new techniques or revitalized old ones. We are nearer the heart of the matter because of fiberoptic bronchoscopy, bronchoalveolar lavage (BAL), computed tomographic (CT) scanning, fine needle biopsy and physiological tests of lung function.

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This article is the first in a series of critical reviews of major developments within the previous year which will be a regular feature of the *Journal*. The remaining topics covered in 1990 will be Oncology (February), Clinical Pharmacology (March), Cardiology (April), General Surgery (May), Nephrology (June), Gastroenterology (July), Psychiatry (August), Haematology (September), Dermatology (October), Endocrinology (November) and Infectious Diseases (December).

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Bronchoscopy

Bronchoscopy is usually combined with BAL and bronchial biopsy to obtain the maximum information in the differential diagnosis of interstitial lung disease for the clinician, histopathologist and immunologist. BAL is already well recognized to be helpful in providing some additional information in differentiating sarcoidosis from extrinsic allergic alveolitis (hypersensitivity pneumonitis) and fibrosing alveolitis. Attention is being increasingly focused on this technique worldwide in the detection of subclinical infection of human immunodeficiency virus (HIV). Higher percentages of neutrophils and lymphocytes have been noted in BAL fluid of patients with acquired immunodeficiency syndrome (AIDS) and pulmonary infection¹ contrasting with the decrease in the number of lymphocytes in blood, suggesting early or subclinical infection in the pulmonary parenchyma. This is often due to *Pneumocystis carinii* but not always so, as revealed by a recent study² in which eight symptom-free HIV-positive patients underwent bronchoscopy, BAL and bronchial biopsy. *P. carinii* was absent from lavage fluid, biopsy or brush material.

BAL has also shed light on primary biliary cirrhosis (PBC) in which an intense lymphocytic alveolitis identical to that observed in sarcoidosis may be found. This brings closer together two entirely different granulomatous disorders, formerly separated by the diaphragm, but now reflecting a close lung-liver interface³. Let us hope that this will lead towards a better understanding of the aetiology of these two idiopathic granulomatoses.

Fine needle biopsy

When bronchoscopy and sputum examination are negative, percutaneous core needle biopsy using the Hausser needle is commonly done in the University of Saarland, Federal German Republic.⁴ About two-thirds of the lesions in this study

were peripheral and 40% were 2 to 4 cm in diameter. The biopsy needle was inserted under biplanar fluoroscopic control; breath holding was limited to the time the needle was crossing the pleura and thereafter shallow breathing was allowed. The specimen, about 10 to 20 cm in length was removed, trapped between the blades. There was a high diagnostic yield of about 90% and a comparatively low rate of complications of 15%. Interestingly, the diagnostic yield was high in undifferentiated large cell carcinoma, squamous and adenocarcinoma, but was low in carcinoid, alveolar cell and metastatic carcinoma, cylindroma and small cell anaplastic cancer. Benign lesions included tuberculosis, aspergillus, histoplasma, haematoma, organizing pneumonia and non-specific granulomas. Complications were minor and should be weighed against an alternative exploratory thoracotomy; they included pneumothorax, haemoptysis, haemothorax and intrapulmonary haematoma.

Drainage

In 1938, Monaldi⁵ of Naples introduced the technique of intracavitary intubation and drainage for the treatment of tuberculosis. This technique has been modified for the treatment of severe bullous emphysema.⁶ Twenty two operations were carried out on 20 patients with bullous lung disease, all of whom had severe debilitating dyspnoea. There were 12 males and 8 females; the median age was 56 (range 43–71) years. All patients had respiratory function tests, arterial blood gas measurement and posteroanterior and lateral chest radiography. A few patients had computed tomography in order to obtain three-dimensional measurement of the bullae, both before and after surgery. Open intubation drainage via a limited thoracotomy (10 cm) was performed. Dyspnoea improved in 16 patients. It was accompanied by objective improvement in lung function with a 22% median improvement in forced expiratory volume in one second (FEV₁) and a 26% median reduction in residual volume. One patient remained unchanged. Three patients died after surgery: two due to progressive respiratory failure and the third because of staphylococcal septicaemia. The surgical treatment of bullous lung disease carries a high mortality. The Brompton Hospital technique requires a limited surgical approach and avoids resection of the functioning lung tissue, which is important for patients with limited lung reserve. The results are encouraging and provide a ray of hope to some respiratory cripples.

Drainage procedures may also be helpful in patients with carcinomatous pleural effusions. Thirty eight patients underwent thoracentesis with a finebore silastic catheter introduced under ultrasound guidance.⁷ Pleurodesis using *Corynebacter-*

ium parvum, tetracycline, thiotepea or bleomycin was achieved in 27 patients. The other 11 patients had their effusions drained for the relief of symptoms but did not have pleurodesis because of the terminal nature of their illness. All patients tolerated the procedure well. The mean interval from pleurodesis to death in 17 patients was 225 days (range 80 days–28 months); none had a recurrence of effusion before death. This is a simple technique, comfortable for the patient and preferable to the commonly used wide bore chest tube.

Lung function

The long term effects on lung function of treatment of idiopathic spontaneous pneumothorax by talc poudrage or simple chest tube drainage was assessed in 114 consecutive patients treated at the chest clinics at Oresundshospitalet and Bispebjerg Hospital, Copenhagen.⁸ Ninety nine patients were men. At the time of the first pneumothorax 99 (87%) of the subjects were under 41 years of age. Eighty patients were treated with talc pleurodesis and 34 with simple pleural drainage. Seventeen of the 114 patients died from causes unrelated to the initial complaint, so finally 75 subjects participated in the study. A mild restrictive impairment of lung function was noted in those who were treated with talc insufflation compared with those who received simple drainage via an intercostal tube. One patient treated with talc poudrage had extensive pleural calcification and mild pulmonary fibrosis. None of the patients developed a mesothelioma despite a long observation extending up to 35 years. It can be concluded that the long term prognosis with regard to lung function in idiopathic spontaneous pneumothorax is quite good regardless of the therapeutic technique employed.

Lung function and exercise performance have also been assessed in hyperthyroidism before and after treatment since many hyperthyroid patients are breathless. In order to investigate the mechanism of dyspnoea a Bristol team has performed extensive lung function tests including spirometry, lung volumes, transfer factor (diffusing capacity) for carbon monoxide, methacholine challenge, arterial blood gases and exercise in 16 patients with untreated hyperthyroidism.⁹ Methacholine challenge tests showed mild increased hyperactivity in only three of 14 patients. Functional residual capacity and maximal inspiratory and expiratory pressures were reduced in some patients. Diffusing membrane capacity for carbon monoxide was reduced in two patients. Exercise ventilation, respiratory rate, and respiratory exchange ratio were abnormally high; 14 of 16 patients discontinued exercise tests because of dyspnoea. The maximum oxygen uptake achieved by the group was 53% of predicted maximum oxygen consump-

tion.

Nine patients were studied after being rendered euthyroid by treatment; they showed improved exercise performance. Respiratory muscle function is weak in hyperthyroid patients and this improved following treatment. It has been suggested that there is a link between thyroid disease and asthma but it was not evident in this series. The occurrence of increased airways hyperreactivity was no greater than could be expected in healthy controls.

Respiratory muscle fatigue has also been correlated with lung function in systemic lupus erythematosus (SLE). Extensive lung function tests and electromyography were performed in 23 consecutive patients with SLE and 17 healthy controls in Dusseldorf.¹⁰ Lung function included total lung capacity (TLC), vital capacity (VC), residual volume (RV), airway resistance (body plethysmography), the single breath transfer factor, and lung compliance. Maximum inspiratory and expiratory mouth pressures, P_Imax and P_Emax, were measured at forced residual capacity (FRC). Fatigue of respiratory muscles (diaphragm, external intercostal muscles), and of leg muscles was assessed by electromyography. VC and TLC were significantly lower in SLE patients than in the controls. However, no significant difference between SLE patients and controls was found for RV, FEV₁, FEV/VC and airway resistance. Lung compliance was slightly reduced in SLE patients. The patients with SLE showed significantly ($P < 0.05$) lower values of P_Imax and P_Emax than the controls. Fatigue of all muscles occurred in a significantly ($P < 0.01$) higher percentage at lower external loads in SLE patients. The reduction in VC and TLC was most pronounced in SLE patients with signs of respiratory muscle fatigue while the patients without signs of fatigue showed normal or slightly reduced ($< 10\%$) lung volumes. This study noted a significant correlation between duration of symptoms and respiratory muscle dysfunction but this muscle fatigue did not correlate with activity of SLE. The degree of dyspnoea often correlates with inspiratory muscle dysfunction.

Diaphragmatic fatigue may sometimes contribute but this is controversial. Laroche *et al.*¹¹ have reported an elegant study of diaphragm strength in the shrinking lung syndrome of SLE from the Brompton and Hammersmith Hospitals and another authoritative review of respiratory muscle weakness and fatigue from the Brompton and King's College Hospitals.¹² They conclude that the shrinking lung syndrome of SLE is not explained by a primary abnormality of the diaphragm. There is unlikely to be one single index of fatigue, but rather a whole sequence of closely inter-related changes that occur in response to loading. Their elegant techniques will undoubtedly lead to an improved understanding of the role of respiratory

muscle dysfunction in ventilatory failure. Those particularly interested in the clinical and pathological features of lung involvement in SLE should read a recent review¹³ and are also reminded that it is the silver anniversary of a pioneer article on unexplained dyspnoea and shrinking lungs in SLE by the editor of the *Postgraduate Medical Journal* (Hoffbrand and Beck, 1965).¹⁴

Positron emission tomography (PET)

PET is a powerful, quantitative, nuclear medicine imaging technique, useful for studying many problems in lung physiology and biochemistry.¹⁵ It allows measurements of lung density, extravascular lung water, blood volume, pulmonary blood flow, ventilation-perfusion relationships, vascular permeability, glucose metabolism, amine clearance, hypoxic tissue markers and tumour imaging. Compounds are labelled with positron-emitting isotopes which include labelled oxygen, carbon, gallium, nitrogen, fluorine and neon, and may be administered intravenously or by inhalation. The tissue activity concentration of the isotope is determined with an imaging device similar in appearance to an X-ray CT scanner. Its applications for the investigation of pulmonary problems in health and disease are numerous, but PET research has its drawbacks. It represents a major collaborative effort in which the lung physiologist must work with radiation chemists, physicists, computer programmers and mathematicians. The costs in personnel and equipment are high, but Schuster¹⁵ outlines attractive lines of study for lung physiologists of the future.

Metabolic functions

The lung has important metabolic functions, and much of our pulmonary pharmacology is directed at blocking the effects of lung mediators on bronchi, parenchymal cells or lung vasculature. The modern chest physician must be able to do more than interpret a chest radiograph correctly and be conversant with endoscopy and lung function tests. Nowadays he must also understand the role of surfactant, serotonin, eicosanoids, platelet-activating factor, oxygen free radicals and the application of molecular biology to pulmonary disease. This information is all brought together in a special issue of *Clinics in Chest Medicine*.⁴ This is published quarterly and useful back numbers have included Respiratory Muscles (June 1988), Pulmonary Effects of AIDS (September 1988) and Inflammatory Disorders of the Airways (December 1988). The present issue consists of eleven authoritative chapters on metabolic functions of the lung. It is impossible to find such a scholarly

and stimulating update on the physiology and biochemistry of the lung elsewhere so it is well recommended.

Serotonin, also known as 5-hydroxytryptamine (5-HT) is one of the many substances processed by the pulmonary vascular endothelium, which removes it from the circulation and metabolizes it intracellularly. When lung injury causes endothelial cell damage, ability to remove 5-HT is impaired resulting in increased concentrations of circulating 5-HT. This increase affects airways and vascular muscle tone, and also leucocyte and platelet function. Because 5-HT is a potent platelet-aggregatory agent and activator, increased 5-HT concentrations cause platelets to adhere to damaged vascular endothelium. Likewise, leucocytes adhere to vascular endothelium by the same mechanism. Refined techniques for the measurement of 5-HT will in the future provide early evidence of lung injury in such emergencies as the adult respiratory distress syndrome and in latent pulmonary embolism, and hopefully provide a signal for early treatment.¹⁷

Surfactant acts by lowering surface forces at the air-liquid tissue interface. It is well-recognized that premature newborns are unable to produce adequate amounts of functional surfactant so surface forces collapse the lung at resting transpulmonary pressures, resulting in atelectasis and impaired gas exchange. The metabolism of alveolar surfactant protein and surfactant lipid turnover are discussed,¹⁸ particularly since surfactant replacement therapy is being introduced in a variety of clinical conditions.

Eicosanoids are metabolites of the essential fatty acid, arachidonic acid which is an integral part of all cell membranes. Fast and sensitive enzyme immunoassay techniques aided by high performance liquid chromatography separation of extracts and of mass spectrometry have facilitated the identification and quantification of prostaglandins, leukotrienes and platelet-activating factor in bronchoalveolar lavage and lung tissue. The authors of this scholarly review¹⁹ then proceed to discuss the treatment of human lung disease based on manipulations of the eicosanoid system. They consider two diametrically opposed treatment strategies, namely by inhibiting eicosanoid synthesis or by the use of eicosanoids.

The reader will also be interested in other quarterly issues which include Pulmonary Function Testing (June 1989), Mycobacterial Diseases (September 1989) and Pulmonary Manifestations of Systemic Disease (December 1989).

Wegener's granulomatosis (WG)

Friedrich Wegener lives in happy retirement in Lubeck, Germany.²⁰ Now aged 82 years, he has lived to witness two important advances in knowledge of a disorder he first described in the German literature in 1937, and reprinted in English to mark the 50th anniversary of a classic paper.²¹ The two important advances concern diagnosis and treatment. Serum autoantibodies against cytoplasmic components of neutrophils (ANCA for antineutrophil cytoplasmic antibodies or ACPA for anticytoplasmic antibodies) show a high specificity for WG and microscopic polyarteritis and as a monitor of activity of the disease. A Dutch-Danish team made a decisive step forward with the demonstration of fine granular centrally accentuated immunofluorescence staining pattern, due to IgG autoantibodies, in the cytoplasm of neutrophils.²² Fluorescence is additionally seen in monocytes but not in lymphocytes. There has been a recent splendid review by another German pioneer,²³ and an Edinburgh group has laid down strict criteria for patterns of immunofluorescence, which distinguish the bright coarsely granular pattern which is specific for WG from other non-specific patterns. The technique is simple, inexpensive, rapid and reproducible.²⁴ Associated with this article is an admirable balanced editorial.²⁵ A new ELISA-test, based on purified antigen derived from normal human neutrophils, has yielded results equivalent to those obtained by indirect immunofluorescence in a joint study by Kiel University and the Mayo Clinic.²⁶ This multicentre study is based on 277 patients with WG and 1657 control patients. Both tests are highly specific and are helpful in diagnosis and as markers of disease activity.

The second advance which Wegener has lived to enjoy is treatment, which has significantly changed the morbidity and mortality. His twelve patients died and the mortality in that era was 100%; but with corticosteroid therapy and cyclophosphamide it has fallen to about 5%. If WG progresses despite this oral combination of drugs, then cyclophosphamide should be given as monthly intravenous bolus treatment in a dose of 0.5 to 1 g/sq metre together with high dose steroid therapy.²⁷ Cyclosporin has also been shown to cause dramatic improvement in fulminant disease resistant to cyclophosphamide and in a patient with renal failure.²⁸

Adult respiratory distress syndrome (ARDS)

This is a state of shock lung which has also been termed adult hyaline membrane disease or the stiff lung syndrome. Pulmonary oedema is associated with normal rather than raised pulmonary vascular

pressure. There are numerous precipitating causes – septic shock, burns, pancreatitis, drug abuse amongst them – to be followed within 24 hours by dyspnoea, tachypnoea, a low arterial oxygen tension ($\text{PaO}_2 < 50 \text{ mmHg}$) despite high inspired oxygen concentrations, and diffuse fluffy patchy infiltrates in the chest radiograph. It has been described as refractory hypoxaemic respiratory failure with radiographic evidence of pulmonary oedema occurring in the setting of an appropriate risk factor.²⁹ The oedema fluid is protein-rich because of increased pulmonary vascular permeability to plasma proteins. This protein leak has been assessed by a double-isotope method for the detection of transferrin accumulation in the lungs of patients with widespread pulmonary infiltrates.¹ In 22 patients with ARDS the mean transferrin accumulation rate was threefold greater than a control group. However, there was some overlap between ARDS and controls so it cannot be regarded as a diagnostic test. However, it is a relatively simple method for serial bedside determination of pulmonary microvascular permeability to transferrin.

Prematurity

Premature low birth-weight children with immature lungs suffer severe bronchopulmonary dysplasia; it is a major medical problem in neonatal intensive care nurseries. It has been the subject of a recent important editorial based on two articles in the same issue of the *New England Journal of Medicine*. The editorial³⁰ describes the dedication of neonatal physicians and nurses and the grief of parents who watch helplessly as their infants struggle to survive with assisted ventilation, oxygen, correction of poor nutrition, antibiotics and surfactant.

Dexamethasone therapy for 42 days improves pulmonary and neurodevelopmental outcome in these circumstances,³¹ but this is on the principle of buying time for the very existence of the infant and the cost in longterm complications may be infection, hypertension or hyperglycaemia. An alternative procedure is prophylactic surgical closure of the open ductus arteriosus for recurrent pulmonary oedema is associated with large left-to-right shunts;³² but this has proved disappointing. Stahlman's editorial³⁰ is an illuminating background of the wretched contributing social problems which still exist; it is compulsive reading.

Asthma

Pregnancy

There have been detailed studies of asthma during pregnancy in Helsinki and in Bristol. The Finnish

authors³³ monitored 198 pregnancies lasting 24 weeks or more in 181 women with asthma. All patients received optimum treatment including inhaled adrenergic drugs, beclomethasone, sodium cromoglycate, oral theophylline, and systemic corticosteroids. Clinical case records and labour histories of the 198 non-asthmatic women, matched for age and parity were reviewed. During pregnancy 18% needed less and 42% more medication. Pre-eclampsia occurred more often in asthmatic than in control subjects, particularly in those with severe asthma. Hypoglycaemia occurred more often in infants of mothers with severe asthma. Theophylline did not influence either labour or delivery. Twenty eight per cent of babies among the asthma subjects were delivered by Caesarean section compared with 17% in the control group. There was no difference between asthma patients and control subjects with regard to length of gestation, birth weight, incidence of perinatal deaths, low Apgar scores, neonatal respiratory difficulties, hyperbilirubinaemia or congenital malformations. The authors concluded that severe asthma or systemic corticosteroid therapy or both during pregnancy seems to increase the incidence of mild pre-eclampsia in the mother and hypoglycaemia in the infant. The outcome of pregnancy is not significantly altered by asthma. Although breast feeding was encouraged, antiasthma drugs did not affect the infant.

The Bristol team³⁴ followed 31 asthmatic women during pregnancy and for 6 weeks of the puerperium. Subjectively 22 (69%) women considered their asthma to have improved, two were worse and in seven (22%) there was no change. The results suggest that in patients with mild or moderate asthma an improvement is likely to occur during pregnancy, particularly in the last trimester, but that in over one-third there may be a post-natal deterioration.

Nocturnal asthma

It is well-known that gastro-oesophageal (GO) reflux can cause aspiration and a constellation of respiratory disorders including recurrent pneumonia, asthma, atelectasis and fibrosis. A high incidence of GO-reflux has been observed in asthma patients. It has been suggested that nocturnal asthma is triggered by GO-reflux.

Thirty seven adults with nocturnal asthma for more than 100 days a year and a history of GO-reflux have been under close medical supervision in Sweden.³⁵ Determination of 24-hour pH monitoring of the oesophagus and hourly measurement of peak expiratory flow (PEF) rate were made during waking hours. Half of the patients had severe nocturnal GO-reflux, the other half had no such symptoms. Respiratory symptoms and the use

of β -2-agonists during the night were recorded and PEF was measured in the morning. There was a significant relationship between the presence of GO-reflux at night and the degree of bronchospasm in the early morning, but there was no correlation between the night time reflux and nocturnal respiratory symptoms. It appears that GO-reflux in most of the asthmatics does not immediately precipitate asthma and produce clinical symptoms although it does seem to influence vagal bronchomotor tone as was demonstrated by a low morning PEF value.

Patients with asthma and gastro-oesophageal reflux should be given a trial of conservative treatment including elevation of the head of the bed and smaller and solid meals in the evening. One or two doses of antacids after meals and at bedtime may produce marked relief, or alternatively an H₂ receptor antagonist may be given. A careful review of medications is important because anticholinergic drugs, calcium-blocking agents, and theophylline may exacerbate gastro-oesophageal reflux.

There has also been an excellent review of the many other factors which contribute to nocturnal asthma, including body temperature and cold, snoring, autonomic nerve activity, and circadian rhythm.³⁶ The severity of nocturnal asthma correlates with the degree of bronchial reactivity; the more exaggerated the hyper-responsiveness to various stimuli, the more marked is the nocturnal bronchoconstriction. Long-acting inhaled bronchodilators should simplify the management of nocturnal asthma.³⁶

Mechanics

A Vancouver group has studied the histology of the airways in post-mortem specimens of lung obtained from 18 asthma fatalities.³⁷ The results were compared to similar airways from 23 patients without asthma. Seventeen of 18 patients had severe steroid dependent asthma; one patient had mild disease. Each airway was projected onto a digitizing board of a microcomputer to trace the internal and external perimeter of the airway and to calculate the submucosal and mucosal thicknesses. The relaxed length of the airway smooth muscle and the shortening required to occlude the airway lumen were calculated. The wall area in the membranous and cartilaginous airways of asthmatic patients was greater ($P < 0.001$) than non-asthmatic airways. This increase in wall area was due to increased areas of epithelium, muscle and submucosa. The airways smooth muscle shortening required to occlude the lumen was less in asthmatic than non-asthmatic airways ($P < 0.001$).

Chronic inflammation causes thickening of the walls of the airways, a fact which has been

emphasized in Southampton by elegant techniques which display subepithelial fibrosis in the bronchi of asthmatics.³⁸ This study highlights the extensive deposition of collagen beneath the bronchial epithelium of young patients with mild atopic asthma. Endobronchial biopsy specimens were examined by immunochemistry and electron microscopy. They suggest a pathogenic role for two of the classic cellular protagonists of asthma – the mast cell and the eosinophil leucocyte – as stimulants of fibrogenesis. They recommend further studies to determine the cellular basis of this excessive deposition of collagen and its role in the natural history of bronchial asthma, particularly with respect to the pathogenesis of chronic irreversible airways obstruction.³⁸

Interstitial pulmonary disease

There was a recent internal medicine conference at Southwestern Medical Center, Dallas, based on idiopathic pulmonary fibrosis. By way of an introduction, Weissler's Table 1 (which runs into 2 pages) presents the differential diagnosis of interstitial pulmonary diseases.³⁹ It has 10 main headings, each of which is followed by about 5 subheadings and each subheading by between 6 and 16 topics representing about 150 different interstitial pulmonary diseases. This encyclopaedic table would form an admirable list of contents for an exhaustive textbook. Weissler's 130 references also make it a comprehensive review of the topic. The pages between Table 1 and the references encompass collagen homeostasis, the cytology of bronchoalveolar lavage fluid, injury by lymphocytes, fibroblast participation in idiopathic pulmonary fibrosis (IPF), the role of growth factors and cytokines. It ends with a summary of newer therapies for IPF, including colchicine, gamma-interferon and lung transplantation. It is hoped that readers will derive as much information and learning as Dr Weissler must have done in composing and compiling this splendid review.

Langerhans' cell granulomatosis (LCG)

The alternative name is histiocytosis X. It encompasses a group of disorders of unknown aetiology characterized by granulomatous infiltration of lungs, bones, skin, lymph nodes and brain. It is sometimes mistakenly diagnosed as sarcoidosis. Consider it in young adult heavy-smoking males with interstitial lung disease, presenting with recurrent pneumothoraces or diabetes insipidus. The group with the most experience of this disorder have recently published an exhaustive review of their experience in Paris.⁴⁰ Lung biopsy reveals a mixed cellular exudate, foam cells, eosinophils and

characteristic X bodies in macrophages. X or Langerhans' bodies are an ultrastructural feature in 90% of patients. They are identical to the granules in Langerhans' epidermal cells, and consist of intracytoplasmic rod-, plate-, or cup-like pentalaminar structures, which are diagnostic of this disorder.

Paul Langerhans (1847-1888) was born and studied medicine in Berlin and became professor of pathology in Freiburg. His special interest in skin pathology led to his description in 1873 of the granular cells in the exterior portion of the Malpighian layer of the epidermis, the stratum granulosum or Langerhans' layer. He is also remembered by the islets of Langerhans, and now has been provided with yet another eponymous disorder, one hundred years after his death from tuberculosis in Madeira.

Talcosis

Another interstitial lung disease has recently been brought into focus in Montreal by longterm follow-up of six drug abusers who injected intravenously talc-containing drugs intended for oral use.⁴¹ Although these patients had discontinued the addiction, in the course of 10 years or more they developed severe granulomatous inflammation and fibrosis surrounding the talc particles. Talc (hydrated magnesium silicate), starch and cellulose are insoluble fillers commonly used in the preparation of oral medicines; they keep the medicinal components together and act as lubricants preventing the tablets from sticking to punches and dyes during manufacture. When talc-containing drugs are injected intravenously the talc is trapped in pulmonary arterioles and capillaries causing inflammation, thrombosis, granuloma formation and fibrosis. At necropsy, the lungs show severe panacinar emphysema with focal bulla formation and dense perihilar tissue. Chest X-rays reveal diffuse micronodular interstitial infiltrates progressing into conglomerate shadows in the upper lung fields. Lung function studies reveal both restrictive and obstructive patterns early in the course but eventually become markedly obstructive. Death is due to severe respiratory failure which occurs tragically many years after drug abusers have overcome and discontinued this particular addiction.

Chronic eosinophilic pneumonia

There has been a comprehensive review of 119 cases of chronic eosinophilic pneumonia (CEP).⁴² The authors personally evaluated 19 patients with CEP over an 11-year period and reviewed an additional 100 cases from the literature. The majority of patients with chronic eosinophilic pneumonia are

middle-aged women. Pre-existing atopic disease is present in half of the cases. Despite the atopic history, most patients are well before the onset of CEP. Peripheral blood eosinophilia of greater than 6% is present in 98% and the erythrocyte sedimentation rate is more than 20 mm/h in 94% of the patients. Pulmonary infiltrates are peripherally distributed; pathological findings include an intra-alveolar and interstitial infiltrate comprising eosinophils, histiocytes and other inflammatory cells. Bronchiolitis obliterans occurs in about one quarter of patients, and rarely there are eosinophilic micro-abscesses.

This is an elegant review⁴² based on sound clinical judgement. The authors emphasize that the clinical diagnosis of CEP in most cases can be made with reasonable certainty without lung biopsy. These patients are exquisitely sensitive to corticosteroids and an initial therapeutic trial without tissue diagnosis is worthwhile in most instances.

Mediastinal fibrosis

Most infections with *Histoplasma capsulatum* are asymptomatic or produce minimal symptoms. Mediastinal granuloma and fibrosis are infrequent, but serious, complications with a mortality rate of 30%. A Tennessee survey⁴³ describes the clinical and radiographic features of 71 patients with mediastinal fibrosis. This group of 71 patients included 65 selected from the medical literature and 6 previously unreported cases. All patients had clinical evidence of occlusion of major central airways (trachea or mainstem bronchus) or major vessels (pulmonary arteries or veins) and the absence of any other disease which might cause such obstruction. The majority of patients were between ages 20 and 40 at the time of diagnosis. Dyspnoea, cough and haemoptysis were common symptoms. A loud pulmonary second sound was the most frequent clinical sign followed by wheezes, rales and rhonchi. A systolic murmur was heard in 26% of patients. Radiographic abnormalities included mass lesions and infiltrates or loss of volume. In many patients chest X-ray films were normal, even in the presence of a major central airway or vascular occlusion. In some cases computed tomography revealed large subcarinal masses with pulmonary vascular invasion when the chest X-ray was normal; CT scans are helpful in delineating the location and extent of mediastinal abnormalities. Surgery was of limited therapeutic value and there is no evidence that antifungal therapy modifies the course of the disease since granuloma and fibrosis are late consequences of mediastinal adenitis.

Cystic fibrosis (CF)

The Cystic Fibrosis Research Unit has just celebrated its twenty-fifth anniversary by launching a £5 million fund-raising campaign. When the Trust was set up in 1964 about 90% of those born with the disease died in early childhood, but now there is a 75% chance of survival into adulthood. CF arises from a single gene defect on the long arm of chromosome 7. The defect probably involves a regular protein responsible for control of ion and water movement across epithelial cell membranes. This causes high levels of sodium and chloride in sweat and is the basis of the helpful diagnostic sweat test. Chorionic villus sampling of fetal DNA permits prenatal diagnosis in one day. The combination of genetic screening, the development of heart-lung transplantation, new antibiotics, improved nutrition, and the development of special centres have all contributed to a new healthy air of optimism for the future of CF sufferers.⁴⁴ The establishment of a network of regional units is also recommended.⁴⁵

Lung cancer

CT scanning

Is CT scanning essential in the pre-operative assessment of lung cancer? This is the increasingly common question Pearson poses and answers authoritatively.⁴⁶ CT scanners are expensive, both to buy and run, and alternative imaging methods should be employed whenever possible. Abdominal ultrasound is valuable in demonstrating hepatic and para-aortic metastatic disease. The most valuable role of CT is its ability to demonstrate mediastinal lymph nodes. Whilst 95% of nodes greater than 2 cm in size are infiltrated with malignant cells only half of those between 1 and 1.5 cm are neoplastic; a node greater than 1 cm in size is pathologically enlarged. If the patient is already in the scanning room, the brain can be examined in approximately 10 minutes. This may uncover latent distant metastases which render thoracotomy inappropriate.⁴⁶

Lymphangitic carcinomatosis

Transbronchial lung biopsy is the diagnostic procedure of choice for histology of pulmonary carcinomatosis. If this is refused or considered hazardous, then a worthwhile alternative is pulmonary microvascular cytology. Blood is drawn through a wedged pulmonary artery catheter. Malignant cells were found in seven of eight patients with lymphangitic spread of carcinoma from prostate, breast, oesophagus and lung.⁴⁷ Cytology was normal in 16

of 17 patients with cancer but without pulmonary metastases and in 22 of 23 patients with non-malignant pulmonary disorders. In a patient with cancer with tumour embolism to the lungs, the findings were positive because of extensive intravascular tumour in large hepatic veins. One false positive occurred in a patient with extensive pulmonary infarction. Megakaryocytes, present in large numbers in the pulmonary capillary bed, are the hallmark of a satisfactory pulmonary vascular blood sample for pulmonary microvascular cytological study.

Malignant mainstem bronchial obstruction

If a patient with known or suspected lung cancer has a significant reduction in forced vital capacity and a normal slope to the expiratory limb of flow volume, then consider mainstem bronchial obstruction. The flow volume (FV) loops of 11 patients with unilateral, mainstem bronchial obstruction before and after Nd-YAG laser or surgical treatment were studied.⁴⁸ There were 6 males and 5 females ranging from 21 to 78 years in age (59 ± 18). Each patient had photoendoscopic evidence of malignant tumour causing either complete occlusion or severe unilateral mainstem bronchial narrowing. Maximal expiratory flow volume (MEFV) curves in the three patients with underlying emphysema showed a diffuse intrathoracic obstructive pattern before and after treatment; in the other patients, MEFV curves were consistent with a restrictive abnormality. After treatment, all patients showed an increase of forced vital capacity with a roughly parallel shift of the MEFV curve and little change in the slope of the descending limb of the MEFV curve. These results indicate that in the absence of underlying emphysema, severe unilateral bronchial obstruction produces a restrictive ventilatory pattern. In the presence of emphysema, however, the mainstem bronchial obstruction may remain physiologically masked. In selected patients, laser therapy offers palliative relief.

Solitary pulmonary nodule

Geddes and Elliott⁴⁹ have reviewed succinctly the continuing problem of management of the symptom-free patient found to have a solitary pulmonary nodule; is it benign or malignant? Should the chest physician do nothing, recommend thoracotomy or undertake invasive investigations?

A diagnosis may be made by transbronchial lung biopsy in a quarter of cases in which the nodules are smaller than 2 cm and in about two-thirds of cases in which they are larger. Percutaneous needle biopsy is simpler but may be contraindicated. The authors reproduce a pretty diagram relating nodule

diameter to age and to various management strategies. There is, however, little to choose between the various strategies and since there is little in it, perhaps the patient's choice should also be respected.

Radiation pneumonitis

Radiation pneumonitis occurs within 3 months after thoracic irradiation, and it is generally regarded to be direct radiation-induced lung injury. Investigators in Sydney regard this as an unlikely explanation and show that it is more likely to be a hypersensitivity pneumonitis by an immunologically-mediated mechanism.⁵⁰ Four patients who developed pneumonitis after unilateral thoracic irradiation for carcinoma of the breast were studied with bronchoalveolar lavage, gallium scan of the lung, and respiratory function tests. On the irradiated side of the chest, all four patients showed an increase in total cells recovered and a marked lymphocytosis in both relative and absolute terms. However, surprisingly, a similar prominent lymphocytosis was noted in the lavage fluid obtained from the non-irradiated lung. Likewise, gallium scans showed increased uptake in both irradiated and non-irradiated lungs, providing further evidence that the changes extended well outside the irradiated area. Could these changes be due to hypersensitivity pneumonitis, resembling chronic beryllium disease, sarcoidosis or extrinsic allergic alveolitis. Further studies will undoubtedly be performed to characterize the T cell subsets, macrophages and cytokines involved in this process.

Transplantation

Six patients, four females and two males with chronic obstructive pulmonary disease underwent a double lung transplant procedure in Toronto.⁵¹ The obstructive lung disease was emphysema secondary to alpha 1-antitrypsin deficiency in 3 patients, familial emphysema in one, post-viral bronchiolitis obliterans in one and eosinophilic granuloma in another. All patients had progressive, disabling disease with a life expectancy of 12 to 18 months and right ventricular ejection fractions greater than 20%. They were all well 5 to 15 months after surgery. It appears that double lung transplants are effective for patients with advanced chronic obstructive lung disease. It is an instant technological triumph: ethical, social and political viewpoints will follow in Toronto and elsewhere.

Bone marrow transplants may be followed by pulmonary complications. Approximately two-thirds of the deaths following allogeneic bone marrow transplantation (BMT) are due to graft-versus-host disease (GVHD) and non-bacterial,

non-fungal pneumonitis known as interstitial pneumonitis (IP). IP is defined as a clinical syndrome characterized by hypoxaemia, a diffuse pulmonary infiltrate in the absence of heart failure and without any fungal or bacterial cause of the pneumonitis. During a 9-year period 166 (43%) of 386 patients with BMT developed interstitial pneumonitis at the Johns Hopkins Hospital.⁵² Tissue examination was helpful in defining 113 episodes of IP. Forty percent were caused by cytomegalovirus (CMV) alone or by CMV plus another pathogen; *Pneumocystis carinii* or a virus was responsible for 10% risk but 50% had no recognizable cause. Risk factors for IP overall were acute graft-versus-host disease, leukaemia, and GVHD prophylaxis with drugs other than cyclosporin. Risk factors for CMV IP were pre-transplant CMV seropositivity, CMV excretion, age more than 10 years, GVHD prophylaxis with drugs other than cyclosporin and a remote transplant date.

The chest physician should also be aware of the pulmonary complications of liver transplantation which are clearly set out in a review of the liver lung interface.⁵³ The lungs and liver may be involved simultaneously or in tandem in many pathological processes. Chronic liver failure (cirrhosis) is marked by pulmonary circulatory changes related to pulmonary vasodilatation, arterio-venous shunting and ventilation-perfusion inequality. Pulmonary oedema may complicate fulminant liver failure. Pleural effusion in cirrhotic patients is largely due to defects in the diaphragm. Sclerotherapy for oesophageal varices has been associated with chest pain, pleural effusion and aspiration pneumonitis. The liver transplant patient develops lung problems due to the surgical procedure, intensive antibiotic therapy, poor cellular immunity and immunosuppressive drug therapy.

Papworth Hospital, Cambridge

This hospital deserves a heading of its own because of the exciting transplant programme undertaken by its superb team. They have already recounted their early experience of lung transplantation in the *Journal*,⁵⁴ but their continuing experience with heart-lung transplantation is even more impressive. The patients receiving heart-lung transplants suffered from cystic fibrosis, bronchiectasis, sarcoidosis, histiocytosis X, fibrosing alveolitis, emphysema, Eisenmenger's syndrome and primary pulmonary hypertension (PPH). One patient with both PPH and primary biliary cirrhosis underwent a triple organ transplant of heart, lungs and liver. Three main complications occur in longterm survivors: opportunistic infections, acute pulmonary rejection and chronic rejection causing disabling obliterative bronchiolitis.⁵⁵ Transbronchial biopsy

(TBB) has eliminated the need for endomyocardial biopsy (EMB) in heart–lung recipients.⁵⁶ Although EMB is a safe procedure it is invasive and causes unnecessary discomfort. A switch from EMB to TBB has also resulted in significant economic savings. TBB provides an early warning of rejection so that intensive specific treatment may be given early in the clinical course and decrease the incidence of obliterative bronchiolitis.⁵⁷ At least four biopsies are recommended using a larger alligator forceps to obtain bigger samples of tissue. Following heart–lung transplantation, cytomegalovirus infection is the cause of considerable mortality and morbidity. It is recommended that CMV antibody-negative recipients should receive organs only from antibody-negative donors. If a donor-recipient mismatch occurs, hyperimmune globulin and ganciclovir may improve survival.⁵⁸

Occupational lung disease

Asbestos-related diseases

Asbestos is a family of crystalline hydrated silicates with a fibrous geometry (defined as a ratio of length to diameter, or aspect ratio, of more than 3:1). Disorders associated with it are the subject of a recent exhaustive and authoritative review of mesothelioma, lung cancer, cancer of the larynx and gastrointestinal tract, interstitial pulmonary fibrosis, pleural fibrosis and plaques.⁵⁹ The average latency period between the first exposure to asbestos and the clinical diagnosis of malignant mesothelioma is 35 to 40 years, with most deaths occurring in patients over 60 years of age. Advances in histochemistry, immunocytochemistry and electron microscopy contribute to earlier and more accurate diagnosis if sufficient biopsy material is available. This means open thoracotomy rather than cytological smears or needle-biopsy specimens. Bronchoalveolar lavage may confirm asbestos exposure. Asbestos appears to be a complete carcinogen, initiating interaction with cellular DNA to produce heritable changes in the genetic material and also promoting the proliferation and expansion of the initiated cells in a manner that encourages the development of malignancy.⁵⁹ Ear lobe oximetry discloses significant oxygen desaturation on exercise in asbestos patients.⁶⁰

Cobalt

For 40 years cases of interstitial pneumonia and bronchial asthma have been described in hard metal workers, that is alloys of tungsten carbide and cobalt. A Belgian team has now recognized and defined fibrosing alveolitis or hypersensitivity pneumonia due to cobalt in diamond cutters.⁶¹

Exposure is due to diamond cobalt discs used for polishing diamonds. About 1% of those exposed present with bronchopulmonary lesions including bronchial asthma and/or alveolitis. The diagnosis is established by lung biopsy or bronchoalveolar lavage, which reveals characteristic multinucleated giant cells. There are significant changes by specific inhalation provocation tests to cobalt or by lung function measurements at the place of work. Tungsten carbide does not produce pulmonary lesions but its association with cobalt intensifies the effects of the latter.

Farmers' lung

A *Lancet* editorial⁶² reviews respiratory symptoms in farmers in its broadest sense, including grain dust, animal danders, unventilated pig house air and bacterial endotoxin. Atopy is a risk factor in novice seasonal workers. In terms of prevention, the main thrust is towards reducing dust exposure by ventilation and respirators.

Beryllium

Laser microprobe mass spectrometry (LAMMS) detects elements in low concentration and has proved invaluable in identifying, amongst others, beryllium in organic tissue, and its recognition in granulomas. There are few, if any rival techniques. Conventional histology sections, 5 µm thick, are obtained with simple aniline dyes, preferably toluidine blue, and viewed through a standard optical microscope which enables the laser beam to be directed to specific features. Fifty or more areas are examined in each section, yielding qualitative but not quantitative results. In an extensive and elegant study,⁶³ beryllium was detected in the granulomas of patients with chronic beryllium disease (CBD) but not in those with sarcoidosis or other granulomatous disorders. This exhaustive study also delineated the central birefringent crystals of Schaumann bodies and proved that these crystals are calcite and confirmed the presence of calcium and iron in the conchoidal bodies. Schaumann bodies persist in scarred lungs and their presence indicates previous granulomatous disease.

CBD is a hypersensitivity disease in which beryllium is the specific class II-restricted antigen, stimulating local proliferation and accumulation in the lung of beryllium-specific CD4 positive helper-inducer T cells. This study⁶⁴ was made on T cells obtained from peripheral blood and by bronchoalveolar lavage in 8 patients with CBD and 5 healthy controls. The wider implications of this study embrace comparison of the pathogenesis of several granulomatous diseases including sarcoidosis and tuberculoid leprosy, in which antigen-

specific T cells at the site of disease have the CD4 + phenotype and are selectively granulomagenic. In the case of CBD, the CD4 + lung T cells are primed to recognize beryllium specifically and to proliferate through the interleukin-2-interleukin-2 receptor pathway onwards to granuloma formation and to granulomatous interstitial fibrosis. Since CBD only develops in a fraction of workers exposed to beryllium, the terrain or soil of the CBD sufferer is surely all important in the development of this hypersensitivity disease.

Infections

Nosocomial infections

It is important to draw attention to a special article from the Centers for Disease Control (CDC), who have developed a new set of definitions for surveillance of nosocomial infections. Since it appears in the *American Journal of Infections Control*⁶⁵ it might be missed and we might also have overlooked it but for this special annual research for the *Journal*. The definitions are based on several important principles; the clinical findings and results of laboratory tests, supported by X-ray studies, ultrasound examination, CT scan, endoscopy, biopsy, needle aspiration and magnetic resonance. To be defined as nosocomial, the infection is acquired in hospital even if it becomes evident after hospital discharge. It also includes newborn infection as a result of passage through the birth canal. This report sets out authoritatively the 23 criteria for nosocomial pneumonia, including symptoms and signs, chest X-ray abnormality, microbiology, histology and immunology. There are also criteria for lower respiratory tract infection, excluding pneumonia, and the chest physician would also like to know the CDC criteria for cardiovascular system and throat infection. This will become a widely quoted document on standards and criteria.⁶⁵

Human retroviruses

Semenzato and Agostini of Padua⁶⁶ have clarified our understanding of human retroviruses and lung involvement. Bronchoalveolar lavage (BAL) has opened a fresh window on the respiratory tract providing information on host–lung defences following invasion by members of the Retroviridae family of viruses. Retroviruses are schematically composed of a characteristic dense icosahedral viral core containing two single strands of RNA, which, in turn, is surrounded by an envelope derived from the membrane of previous host cells. The viruses infect susceptible cells by means of a specific interaction between viral envelope proteins

and normal cellular protein. Once inside the cell, viral particles containing RNA chains are used as a template for conversion to a double-stranded DNA by a reverse transcriptase. This backwards system makes retroviruses different from all other viruses; and hence the term Retroviridae. The DNA intermediate enters the nucleus and covalently integrates into a chromosome of the host cell. This integrated DNA sequence is termed provirus; it may remain in this form throughout the life of the cell or it may pass on to daughter cells.

Alternatively, transcription of the integrated provirus may result in synthesis of new RNA particles in cytoplasm and thereafter exit from host cells. This is the basic life cycle of this family of human T leukaemic viruses (HTLV), which are now prominently associated with various pulmonary disorders (Table I). The lungs are preferential targets for HIV infection. There is a selective depletion of pulmonary CD4 subsets expressing T4 epitopes with high affinity for HIV. This permits *Pneumocystis carinii* pneumonia, which is the commonest cause of death in patients with AIDS. BAL is now a good window for recognizing lymphocytic alveolitis in patients and carriers of HTLV-1, which also seems to have a special tropism for the lung. Semenzato's⁶⁶ review is academic, thoughtful, balanced and a powerful stimulus for chest physicians to collaborate closely with virologists, molecular biologists and other basic research workers to solve many of our present pulmonary problems.

Pulmonary infection in AIDS is also comprehensively covered in a report from Denver.⁶⁷ It is anticipated that by 1991 the total number of cases of AIDS will increase to 270,000 with 179,000 deaths, mainly as a result of pulmonary complications. Cytomegalovirus is a major cause of morbidity almost always associated with reactivation rather than primary infection since the major population at risk of AIDS – homosexuals and drug abusers – are nearly all virus carriers.⁶⁸ Examination of induced sputum is an easy, inexpensive and non-invasive technique for the diagnosis of *Pneumocystis carinii* pneumonia in patients with AIDS.⁶⁹ In 40 consecutive patients with known or suspected HIV infection sputum was produced by deep coughing induced by 3% saline via a jet nebulizer. The specimen was liquefied with dithiothreitol and cells were sedimented and stained. A total of 28 patients were found to have *P. carinii*, which was detected in concentrated sputum in 21 of 38 patients, and by bronchoscopy in 25 of 37 patients. Sensitivity of concentrated sputum compared with bronchoscopy was 78% with a negative predictive value of 71%. Values for unconcentrated sputum were 43% and 48% respectively. Liquefaction of adequately induced sputum facilitates processing and interpretation and increases yield for *P. carinii*, eliminating the

Table I Human retroviruses and lung involvement

<i>Retrovirus</i>	<i>Alternative name</i>	<i>Disorder</i>
HTLV- I	ATTLL (adult T leukaemia/ lymphoma)	Cutaneous T cell leukaemia Tropical spastic paraparesis Lung leukaemia Progressive pulmonary fibrosis ? Multiple sclerosis ? Red cell aplasia ? Malignant hypereosinophilic syndrome
HTLV- II		? Leukaemia
HTLV- III	HIV 1 LAV	AIDS Lymphoid interstitial pneumonitis
HTLV- IV		Mycosis
HTLV- V		Fungoides
HIV-2		Immunodeficiency ? AIDS

need for invasive procedures in most patients. This study shows that sputum adequate for the diagnosis of *P. carinii* can be obtained in most HIV-infected patients by using this simple technique. The process may in the future replace bronchoscopy and bronchoalveolar lavage as further studies validate the test.⁷⁰

Hydatid cyst

Hydatid cyst due to *Echinococcus granulosus* is particularly common in rural Turkey with an incidence of 20 per million. This has provided considerable experience and an authoritative report from Ankara of the surgical management of 1055 cases of pulmonary hydatidosis.⁷¹ The preferred technique was aspiration of the cystic material, opening of the cyst with cautery (cystotomy), suction, removal of the germinative membrane, irrigation of the residual cavity, and then obliteration of the space with pursestring sutures (capitonage). This conservative technique, preferred to more radical measures was followed by a complication rate of 3.8%, and an overall mortality of 1%. Chemotherapy with mebendazole was disappointing, and is now only given to patients who are inoperable. If there are liver cysts, the thoracic transpleural approach is used to remove both lung and liver cysts. The Casoni skin test and blood eosinophil count have been abandoned because of their low diagnostic yield and false negative results. Abdominal ultrasonography is routinely performed to disclose liver cysts.

Therapeutics

Alpha-1-antitrypsin deficiency

The hepatocyte synthesizes plasma proteins, including alpha-1-antitrypsin (α 1 AT) which are discharged into the plasma. Falls in concentration usually reflect decreased hepatic synthesis, and a defect of α 1 AT causes a well-recognized pattern of emphysema and hepatic cirrhosis. It is an inhibitor of trypsin and other proteases so its deficiency causes a tissue imbalance of protease-antiprotease and severe pulmonary disease.

Its genetic control is by a single autosomal dominant gene responsible for 30 different alleles labelled alphabetically, B to Z. The clinical picture of emphysema clearly seen with the homozygous deficiency ZZ is that of increasing dyspnoea and basal emphysema in young smokers under 40 years of age. Death and severe ill-health is now being brought under control by weekly intravenous infusions of human α 1 AT prepared from pooled plasma. The pioneering hard work done at the National Institutes of Health, Bethesda, is now to be matched by well designed trials conducted under the auspices of European and North American Thoracic Societies.⁷² The present cost of weekly treatment is about 20,000 US dollars annually (R. Crystal, personal communication).

Protriptyline

Protriptyline is a tricyclic antidepressant which may benefit patients with chronic obstructive lung

disease by influencing sleep architecture, reducing the sleep-induced falls in arterial oxygen saturation and improving diurnal arterial oxygen tension. Controlled trials are necessary to confirm these Quebec observations.⁷³ Care should be exercised in its use in men because it causes dysuria and may precipitate urinary obstruction; and it causes dry mouth in both sexes.

Protriptyline is also helpful in the management of sleep apnoea, which has been well reviewed.⁷⁴ Sleep apnoea is a serious medical problem which is being diagnosed more frequently. The authors give a clear and concise definition of sleep apnoea followed by a description of obstructive sleep apnoea and a classification of the population at risk. Investigations, including a full assessment by an otolaryngologist, measurement of overnight arterial oxygen desaturation and polysomnography, are discussed. While evaluating the available medical and surgical management, the authors emphasize that little attention had been paid to the psychological and psychiatric disturbances resulting from the condition. Consider it in the overweight heavy-drinking smoker because these factors demand immediate correction. Protriptyline is given in doses varying from 5 to 30 mg daily. Much attention is now being given to this problem as a cause of traffic accidents in sleeping drivers, particularly weary long distance lorry drivers. Adrian Williams (personal communication) says that there is only one animal model for this disorder, namely the English bulldog, a syndrome well-recognized by veterinarians.

Muscarinic receptor subtypes

Barnes⁷⁵ has contributed an elegant editorial on the implications of muscarinic receptor subtypes for lung disease and a masterly classification and helpful line drawings. Nobel Laureate Henry Dale showed that acetylcholine produced two types of response, which were mimicked by nicotine and by muscarine, and that the muscarinic action was blocked by atropine. Barnes has now brought us up-to-date with his classification of muscarinic receptors. M1 receptors may be found in parasympathetic ganglia, M2 receptors on cholinergic nerves (autoreceptors) and M3 receptors on airway smooth muscle and mucus-secreting glands. A defect in M2 receptor function may help to explain

why asthma may be induced by beta blocking drugs. If you have read this far then, read in full the original editorial.

Conclusion

Bronchoalveolar lavage (BAL) is an exciting technique which provides a new window on respiratory disease. Through this window we have observed fresh phenomena which will influence our current and future management of disease. Let us heed Dr Semenzato of Padua (page 11) who urges the chest physician to hold hands with the virologist, molecular biologist and other basic research workers in a joint endeavour using such techniques to solve many of our present pulmonary problems. It may help solve problems in transplantation as Dr Higinbottom (Papworth) (page 12) indicates and as the Center for Disease Control (Atlanta) finds (page 11) in reassessing nosocomial infections. BAL has proved helpful in the management of AIDS, hypersensitivity pneumonitis, asbestosis and sarcoidosis.

Wegener (page 4) has lived to see two major advances since he first described this malignant granulomatosis 53 years ago. A highly sensitive, specific and easily performed autoantibody test is diagnostic, and will allow the disorder to be recognized at a much earlier stage. Secondly, treatment with steroids and cyclophosphamide have reduced the mortality from 100% to 5%.

There has been a similar fundamental revolution in the prognosis of cystic fibrosis (page 8). When the Cystic Fibrosis Research Unit was launched 25 years ago, about 90% of those born with the disease died in early childhood, but now there is a 75% chance of survival into adulthood. This improved outlook is due to improved nutrition, new antibiotics, the development of special management centres and transplantation. There is future optimism based on genetic screening, chorionic villus sampling of fetal DNA permitting prenatal diagnosis in one day, and the establishment of a network of special regional units.

Dr Schuster (page 3) argues persuasively that positron emission tomography promises to be an attractive research technique for lung physiologists of the future - and that is surely the way we should be looking.

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