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What does "chronic bronchitis" mean?

CM FLETCHER, NB PRIDE Whereas the word "emphysema" has, since the Ciba Symposium in 1959, been used with clarity to denote a pathological abnormality, confusion is still caused by the unqualified use of the words "chronic bronchitis" to describe anything from simple expectoration to fatal respiratory failure caused by airflow obstruction. This was recognised by a report to the Medical Research Council in 1965. Since then numerous epidemiological, physiological, and pathological studies have indicated that mucous hypersecretion is probably not causally related to airflow obstruction emphasising the need for reconsidering present terminology. We suggest that "chronic bronchitis" (or, preferably, "chronic bronchial catarrh") should be used solely to denote bronchial hypersecretion, qualified by adjectives such as mucous (or simple), mucopurulent, purulent, or eosinophilic. The unqualified term should not be used to indicate accompanying obstruction to airflow, while "chronic obstructive bronchitis" is unsuitable because it suggests the same pathological process is responsible for obstruction and hypersecretion. A new term is needed to indicate the common, destructive, and obstructive disorder of peripheral airways, caused almost invariably by smoking, which causes limitation of expiratory airflow. The term "chronic obstructive bronchiolitis" would be more precise than "small airways disease". Alternatively terms such as "chronic bronchitis with airflow obstruction", which do not imply any particular site or pathology, could be used.

Saprophytic invasion of infarcted pulmonary tissue by Aspergillus species

DR BUCHANAN, D LAMB Involvement of pulmonary tissue by Aspergillus species is usually considered to include three main patterns: development of a fungal ball of mycetoma in a pre-formed cavity, allergic bronchopulmonary aspergillosis, and true invasive aspergillosis as an opportunistic infection in patients with lowered tissue defences. We present five cases of a form of pulmonary involvement by Aspergillus species which has previously only received passing reference in the literature. All five are examples of saprophytic invasion of infarcted pulmonary tissue. The characteristic features are widespread invasion of the dead tissue by fungal hyphae, with in three cases liquefaction of the dead tissue resulting in cavitated lesions. Two cases were found incidentally at necropsy, two cases presented as isolated peripheral pulmonary opacities and were resected as possible tumours, and one case presented as a complication of a pneumonic episode. Only this latter case had mycological confirmation of the presence of Aspergillus fumigatus. It may be that examples of such saprophytic invasion of extensive pulmonary infarcts are the basis for some reported cases of primary Aspergillus pneumonia.

Familial sarcoidosis in an Irish population

NJ BRENNAN, PA CREAN, D LONG, MX FITZGERALD Studies in the Republic of Ireland have demonstrated that sarcoidosis is common, with a prevalence on mass radiographs of 33·3 cases per 100 000 individuals screened. Observations in our Sarcoid Clinic suggested a high prevalence of familial cases. We therefore surveyed all patients to quantify this phenomenon. The study group comprised 85 index patients with biopsy-proven sarcoidosis with a sibling pool of 416 individuals. Eleven siblings derived from nine families were identified as having sarcoidosis. In seven there was biopsy proof while in the remaining four there was highly suggestive clinical and radiological evidence of the disease. There was no significant difference in the mode of presentation between sibling pairs or between familial or non-familial cases. In only two instances was the temporal profile of onset of the disease suggestive of intrafamilial spread of a transmissible agent. The high prevalence of familial sarcoidosis reported here (10·5%) dictates that siblings of affected patients should be screened for this disease.

Dihydrocodeine improves breathlessness in airways obstruction

AA WOODCOCK, ER GROSS, A GELLERT, M JOHNSON, S SHAH, DM GEDDES We have compared the acute effects of dihydrocodeine (1 mg/kg) with placebo on breathlessness, exercise tolerance, ventilation, and oxygen consumption in 12 patients with fixed airways obstruction, moderate or severe breathlessness on exertion, and normal or low arterial carbon dioxide tensions. Breathlessness was measured by visual analogue scales while walking on a treadmill immediately before, and 45 and 180 minutes after ingestion. Ventilation and oxygen consumption were measured at rest and 50% maximum exercise on a bicycle ergometer, 75 minutes after ingestion. Dihydrocodeine reduced breathlessness (20% at 45 minutes; 18% at 180 minutes, $p < 0.05$) and increased exercise tolerance (18% at 45 minutes; 9% at 180 minutes, $p < 0.05$) without changing spirometry. Dihydrocodeine reduced ventilation (rest 6·0%, exercise 5·5%, $p < 0.05$) and oxygen consumption (rest 9·5%, exercise 9·0%, $p < 0.05$)

compared with placebo. Oxygen also reduced breathlessness and the benefits of oxygen and dihydrocodeine (180 minutes) were additive. (Improvement in breathlessness: DHC 18% oxygen 22% DHC + oxygen 32%.) Opiates may be a valuable treatment for breathlessness in selected patients, but further evaluation of long-term benefits and safety must clearly precede haphazard prescribing. The results of an outpatient study will be discussed.

Relationships of exposure to coal mine dust with lung function in British miners and ex-miners

CA SOUTAR, JF HURLEY A follow-up study has been completed in British coalminers in order to compare the effects of exposure to dust in men who continue to work in the industry and in those who leave. A cohort of men working in the coal industry in the 1950s has been traced and examined 22 years later. Men still working in the industry were also examined at five-year intervals in the intervening period. Levels of lung function at follow-up and changes in lung function over an 11 year period, have been compared in 1592 miners and 2540 ex-miners who had completed a further 10 years in the industry after the first survey, and the relationship with cumulative dust exposure examined. Ex-miners had lower lung function and more rapid loss of lung function than the miners, and had experienced greater cumulative exposure to dust. Dust exposure was found to be related to level of lung function and also to loss of lung function over a period. Interesting patterns of change of lung function variables in response to dust exposure and smoking were observed. There was no evidence that the relationships with dust exposure were different in ex-miners and miners.

Occupational asthma in steel coating plant: population study leading to identification of a cause

MB DALLY, PS BURGE, G DAVIS, CF TAYLOR, AJ NEWMAN TAYLOR In 1979, asthma was diagnosed in two workers engaged in roller coating paint on to steel, and history suggested an occupational cause. A prevalence survey of all 241 employees was undertaken, to identify the cause and estimate the size of the problem. Lower respiratory symptoms, better away from work, were present in 76 out of 229 responders (33%), including 33 out of 67 (49%) line workers and 16 out of 40 (40%) maintenance workers. Symptoms were not associated either with smoking or with skin test atopy, and no differences were found in lung function. Occupational asthma was identified in 20 workers, of whom 19 first had symptoms after 1971: from that year, and unknown to the factory, a paint which released free toluene diisocyanate (TDI) had been in use. Two of the 20 "cases" had bronchial provocation testing with TDI, and gave asthmatic reactions at concentrations up to 0·02 ppm. The TDI paint was excluded, and 195 manufacturing employees were seen again. Work-related symptoms had decreased from 49% to 31% and from 40% to 30% in line and maintenance workers respectively. In 13 "cases", work-related symptoms had improved or resolved. The two surveys identified the major cause of the problem and avoided further investigation in most "cases".

Occupational asthma in a hairdressing salon

AD BLAINEY, S OLLIER, RJ DAVIES Occupational asthma among hairdressers was first investigated in depth by Pepys *et al* (*Clin Allergy* 1976;**6**:399) who described two subjects who developed asthma after exposure to bleaches used in tinting hair. We have recently investigated all the employees of a hairdressing salon amongst whom a high incidence of respiratory complaints had been reported.

Of the 23 employees in the salon, five complained of asthma; four of these believed that their symptoms were caused or exacerbated by exposure to powder bleaches. Six subjects had rhinitis, which was considered to be work-related in four.

Bronchial provocation testing with histamine supported a diagnosis of asthma only in the five subjects with symptoms of this disease, but peak flow recordings over a three week period suggested an occupational relationship in one subject only. Bronchial provocation testing with bleach powder in 14 subjects demonstrated late asthmatic reactions in all four subjects with symptoms of work-related asthma, but in none of the others.

Skin prick testing was performed with four common inhalant allergens and persulphate solutions, which are the main constituents of the bleaches used by these subjects. Twelve subjects were atopic, including four of the five patients with asthma, but skin prick testing with persulphate solution was positive in one patient only. This patient also had a positive reaction to bronchial challenge with bleach powder.

The pathogenesis of these respiratory reactions will be discussed.

Breathlessness, pneumoconiosis, and compensation

P HOWARD, J WATERHOUSE, QA SAYED, VE SHERBURN Breathlessness measured by Visual Analogue Scales was compared with measurements of FEV_1, FVC, and distance achieved during standard walking tests in patients with chronic obstructive airways disease and patients submitting themselves for compensation to a pneumoconiosis panel on account of presumed respiratory fibrosis. Patients with chronic bronchitis and advanced airways obstruction (FEV_1 around 0·5 litres) rated their breathlessness from mild to extremely severe. Applicants to the pneumoconiosis panel almost invariably rated their breathlessness as severe despite spirometric values at least double those of the bronchitics. There was no relation between breathlessness in panel patients, spirometric values, and compensation awarded. The findings suggest that compensation tribunals might attract patients who have a heightened awareness of sensory perception which bears little relation to the natural history of the causative disorder.

Early pulmonary reactions after bronchography using oily propyliodone (Dionosil)

AG WARDMAN, RF WILLEY, NJ COOKE, GK CROMPTON, IWB GRANT Serious pulmonary reactions to oily propyliodone are rare. We report three such reactions occurring within five days of bronchography. The main symptom in each case was breathlessness. This was associated with hypoxaemia and diffuse patchy shadowing on the chest

radiographs. The cases responded rapidly both symptomatically and radiologically to prednisolone. In the absence of histological proof, the nature of these reactions is speculative. In one of the patients the pulmonary reaction was associated with a widespread urticarial rash, suggesting an allergic phenomenon. Another explanation is that of direct chemical damage causing a "chemical pneumonitis". There was no clinical evidence of an infective aetiology. Despite the rarity of this reaction, it is obviously important to recognise it as a complication of bronchography and to treat it promptly with prednisolone.

Melanoma of the oesophagus

AG NORMAN, JR GOEPEL Melanoma of the oesophagus is a very rare tumour. Two cases are reported. The tumour presents with a very slow onset of dysphagia, unlike carcinoma of the oesophagus, and is usually a large size when first diagnosed. Doubt has been cast on melanoma of the oesophagus being a primary tumour but it is now agreed this tumour could originate in the oesophagus. Resection is the treatment of choice. One of the reported patients is alive four years after excision of the tumour.

Site of airflow obstruction in immediate and late reactions to bronchial challenge with Dermatophagoides pteronyssinus

D MACINTYRE, G BOYD The density dependence of maximum flow in 10 atopic asthmatics was assessed by response to breathing a helium-oxygen mixture. Eight were responders with a change in density dependence and two were non-responders. They were then subjected to bronchial challenge by *Dermatophagoides pteronyssinus* and density dependence reassessed during early and late bronchial reactions. There was considerable individual variation in the change in density dependence during induced bronchospasm. Four patients showed an increase in density dependence, five a decrease, and one no change. However, for any given individual the results were similar during early and late reactions. The major site of airflow obstruction may vary from one asthmatic to another. There is uncertainty about the value of density dependence in indicating precise site of airway obstruction in a given individual. However, these results suggest that when antigen challenge is followed by a dual early and late reaction the site of obstruction is similar at each stage, despite the difference in duration and intensity between the two reactions.

Effects of sublingual nifedepine on inhaled histamine and methacholine-induced bronchoconstriction in atopic subjects

S MALIK, J O'REILLY, MF SUDLOW Drugs which inhibit transmembrane calcium ion flux such as nifedepine and verapamil, have been shown to decrease exercise-induced bronchoconstriction. We have studied airway responses to histamine and methacholine challenge with placebo or nifedepine in a double-blind trial in 10 atopic subjects. We measured FEV_1, maximal flow volume curves, and partial flow volume curves. Six of the subjects had both histamine and methacholine challenge during separate weeks. For each study subjects were given 20 mg nifedepine or placebo sublingually half an hour before challenge. They were then asked to inhale a fixed amount of histamine or methacholine solution from a nebuliser for two minutes during tidal breathing. The subjects were then seated in a whole body plethysmograph and sequential measurements made. Nifedepine did not affect baseline FEV_1 or $\dot{V}max_{40}$ in any subject. The mean maximum percentage drop in FEV_1 on histamine was as follows: for placebo $31{\cdot}5 \pm 15{\cdot}12$ and after nifedepine $22{\cdot}42 \pm 12{\cdot}2$ ($p < 0{\cdot}01$). The percentage falls for $\dot{V}max_{40}$ were $54{\cdot}57 \pm 15{\cdot}8$ on placebo and $40{\cdot}6 \pm 19$ on nifedepine ($p < 0{\cdot}001$). The percentage falls induced by methacholine challenge were as follows: placebo FEV_1 $36{\cdot}06 \pm 19{\cdot}4$, after nifedepine FEV_1 $21{\cdot}0 \pm 13{\cdot}5$ ($p < 0{\cdot}001$); placebo $59{\cdot}3 \pm 20{\cdot}6$, after nifedepine $41{\cdot}4 \pm 12{\cdot}5$ ($p < 0{\cdot}001$). These results show that nifedepine may modify bronchial reactivity by virtue of inhibiting smooth muscle contraction in response to a bronchoconstrictor stimulus. No significant difference was noted between the effect of nifedepine on methacholine or histamine challenge.

Factors involved in control of airways responsiveness to histamine

EH WALTERS, BH DAVIES, AP SMITH The responsiveness of the airways to bronchoconstrictor agents can be divided into the threshold dose causing bronchoconstriction (sensitivity) and the slope of the subsequent dose-response curve (reactivity). Inhalation histamine challenges were performed on groups of normal and asthmatic subjects. On each occasion a regression line for the descending part of the log cumulative dose-response curve was computed. The dose of histamine causing a 20% fall in sGaw was taken as an index of sensitivity. Baseline sGaw was lower in the asthmatics ($p < 0{\cdot}05$). Sensitivity to histamine was significantly greater in the asthmatics ($p < 0{\cdot}00001$) but reactivity was less, though not significantly so. All subjects took the prostaglandin synthesis inhibitor indomethacin (50 mg qid) or identical placebo capsules in a random, double-blind manner. On the third day of each treatment histamine challenge was performed. Indomethacin was associated with a small but significant increase in baseline sGaw in the normal but not in the asthmatic subjects. Sensitivity was markedly decreased after indomethacin in the asthmatic ($p < 0{\cdot}005$) but unchanged in the normal subjects. In both groups there was a highly significant increase in reactivity (steepening of slope) after indomethacin. The relationship between baseline sGaw, sensitivity, and reactivity to histamine, and the possible contribution of prostaglandins to their control will be discussed.

Mechanism of antigen-induced late asthmatic reactions

TH LEE, L NAGY, RA THOMPSON, AB KAY After bronchial challenge with specific allergen many asthmatics have a second, usually more severe, rise in airway resistance which is maximal six to eight hours after exposure. The pathogenesis of the late asthmatic reaction is unclear although it has been suggested that there may be bronchial infiltration of inflammatory cells, either as a result of

release of mast cell-derived chemotactic factors or deposition of immune complexes in the airways with subsequent activation of complement. For this reason we have measured the mast cell-associated high molecular weight neutrophil chemotactic factor (NCF) as well as the concentrations of C3 and C4 in the circulation of seven asthmatics, who gave both an early and late fall in FEV_1 after antigen bronchial challenge. NCF was detected during both asthmatic responses with a time course of appearance which paralleled the falls in FEV_1. In contrast, there was no appreciable change in the concentrations of C3 and C4. Four asthmatics who gave an immediate reaction only had a single early rise and fall in NCF activity with no further increases up to 24 hr. NCF released in both the early and late reactions eluted as macromolecules after Sephadex G-200 gel filtration. Since high molecular NCF is believed to be a mast cell-associated mediator, these observations suggest that mediators are involved in the early and late asthmatic responses.

Comparison of partial and maximal expiratory flow-volume curves for measurement of response to histamine in small airways

J WHITE, N EISER, P CHOWIENCZIJK We have compared the effects of inhaled histamine on large and small airways responses in seven normal subjects. Large airways calibre was monitored with specific airways conductance (sGaw) measurements. Since full inspiration may modify induced bronchoconstriction, small airways response was compared on separate days with measurements from maximal and partial expiratory flow-volume curves (MEFV; PEFV), and repeated to assess reproducibility. On each occasion eight baseline measurements of sGaw followed immediately by either MEFV or PEFV manoeuvres were made in a body plethysmograph. Histamine was inhaled from a dosimeter-triggered Hudson nebuliser in concentrations from 0·2-6·4%. Three further measurements were made after each dose, and eight after the final concentration. Histamine induced constriction in large and small airways. The reproducibility of residual volume, flow at 25% of total lung capacity, and mean transit time measurements was similar whether calculated from MEFV or PEFV curves at baseline or after the final dose of histamine. The response of large and small airways to histamine was reproducible whether MEFV or PEFV curves had been performed. The most sensitive indicator of induced bronchoconstriction was sGaw, which fell significantly before any other measurements changed. However, the response to histamine in large and small airways was smaller after MEFV than PEFV manoeuvres. Thus, during bronchial challenge, changes in small airways function are better monitored with measurements from PEFV curves.

Timing of surgery for infective endocarditis

PH KAY, P OLDERSHAW, SC LENNOX, M PANETH Acute endocarditis remains a formidable challenge to the clinician. After the introduction of antibiotic therapy cardiac failure has replaced sepsis as the major cause of death. Thus, the timing of operation in patients with severe valvar lesions is crucial. During the last decade 60 patients with active endocarditis of the native valve have been treated by valve replacement at the Brompton Hospital. Forty-five patients with severe pulmonary oedema underwent operation, with 14 deaths. Premature closure of the mitral valve (PCMV) on M-mode echocardiography was observed to be a sign of impending pulmonary oedema in patients with acute aortic regurgitation. Fifteen patients developing this sign alone underwent valve replacement, with a single death. We now regard PCMV as an indication for immediate operation. This policy of early valve replacement does not appear to have been detrimental in that there have been no subsequent cases of prosthetic valve endocarditis. Conversely, six of the 16 patients who had received antibiotics for six weeks still had active organisms on the excised valve. Furthermore, two of these patients subsequently developed opportunistic infection of their prosthetic valves. Thus, prolonged antibiotic therapy may allow haemodynamic deterioration to occur, does not guarantee bacteriological sterilisation, and may predispose to opportunistic infection.

Surgical aspects of bacterial endocarditis

T RAYCHAUDHURY, A FAICHNEY, EWJ CAMERON, PR WALBAUM Over a period of eight years, between 1971 and 1978, 31 valve replacements were performed on 29 patients for acute and subacute bacterial endocarditis. Twenty-four operations were performed for native valve endocarditis (NVE) and seven for prosthetic valve endocarditis (PVE). Twenty-seven native valves were excised of which 22 were aortic and five were mitral. The aetiology, clinical course, findings at operation, and mortality (25%) for NVE will be discussed and compared with that in published reports. Surgery for prosthetic endocarditis is well known for its high mortality (40-80%) (Wilson WR *et al, Ann Intern Med* 1975;**82**:751-6; Richardson JV *et al, Circulation* 1978;**58**:589-97). In all but one patient in our series the prostheses were partially detached from the annulus causing severe haemodynamic failure. All these patients underwent operation within 48 hours of their clinical deterioration and all survived. The risk factors and current therapeutic guidelines for the PVE group will be discussed. We have also confirmed, like many others, that delay in surgery for more than seven days in patients with poor haemodynamic state is related to a higher mortality, and cardiac arrest before operation appeared to be an important prognostic factor with a sinister significance.

Late results of the triple valve replacement with Björk-Shiley prostheses

B FABRI, TK KAUL, SA PHOTIOU, JB MEADE Ten patients underwent triple valve replacement with Björk-Shiley prostheses between May 1974 and April 1978. All the patients were women with a mean age of 44·4 years (range 33-59 years), and all had organic tricuspid stenosis. Mitral stenosis was the dominant lesion in eight patients, and mitral regurgitation in two; aortic stenosis was the dominant lesion in eight patients, and aortic regurgitation in two. Before operation five patients were in New York Heart Association's (NYHA) class 4, four were in class 3, and one was in class 2b. The total bypass time varied

between 59-159 minutes (mean 105 minutes). There was one early death. The two late deaths which occurred between two and three years were unrelated to prosthetic valve replacement. The survivors have been followed for three to seven years (mean six years), four of them have improved by two, and three by one functional class of the NYHA classification. All survivors have remained free of thromboembolic episodes. Traces of haemosiderin have been detected in two survivors but no other biochemical or haematological evidence of haemolysis was found in these patients. None of these patients required permanent pacing postoperatively. We would now recommend the use of a bioprosthesis in the tricuspid position despite the satisfactory performance of the Björk-Shiley valve in this position in these patients.

Effect of vagal stimulation on the normal and abnormal oesophagus

JAC THORPE, HR MATTHEWS, G LITTLE Many factors have been implicated in the development of hiatal hernia, but the actual cause remains unknown. It has been suggested that hiatal hernia may be caused by excessive longitudinal shortening as a result of abnormal vagal activity. Reflex shortening of the oesophagus has been demonstrated in experimental animals, but it is not known whether a similar response occurs in man. In order to investigate this, we decided to observe the effects of direct electrical vagal stimulation during operation in patients undergoing thoracotomy for both oesophageal and thoracic disorders. Vagal stimulation was performed using a facial nerve stimulator in 34 patients. Group A comprised 12 patients without oesophageal disease who were regarded as controls. Group B comprised nine patients who underwent hiatal hernia repair. Group C comprised 10 patients with disordered motility—seven with achalasia, two with diffuse oesophageal spasm (DOS), and one with hiatal hernia (HH), associated with a hypertensive lower oesophageal sphincter (LOS). *Group A:* in all control patients stimulation produced brisk longitudinal muscle contraction. *Group B:* seven patients with sliding hiatal hernia showed diminished contractility. Two other patients, one with a para-oesophageal hernia and another with significant reflux but no HH exhibited a normal response to stimulation. *Group C:* seven patients with achalasia showed no response. Two patients with DOS showed moderate contractility. A further patient with HH and hypertensive LOS also showed minimal contraction on stimulation. These findings will be discussed in relation to current pathophysiology and the surgical management of patients with hiatal hernia and disordered motility.

Factors determining susceptibility to chronic airway narrowing in smokers

SJ CONNELLAN, H JOYCE, F HOLLAND, R CARSON, NB PRIDE We have examined factors determining rate of decline in FEV_1 (ΔFEV_1, expressed as ml yr^{-1} m^{-3} to allow for differences in height) in 153 working men born between 1916 and 1931 who formed part of the group studied by Fletcher *et al* and have had regular measurements since 1961. The largest mean ΔFEV_1 ($14{\cdot}2 \pm 7{\cdot}0$) occurred in eight men with a diagnosis of asthma. Seven smokers treated with β-blocking drugs had greater mean ΔFEV_1 ($9{\cdot}9 \pm 2{\cdot}6$) than 60 continuing smokers ($7{\cdot}8 \pm 3{\cdot}2$) or 22 lifelong non-smokers ($6{\cdot}0 \pm 2{\cdot}7$). The 60 smokers without a diagnosis of asthma and not treated with β-blockers were divided into 34 men with a positive family or personal history of allergy or serum IgE $\geqslant$ 120 units ml^{-1} or positive skin tests (POS) and 26 men without any of these features (NEG). Mean ΔFEV_1 was greater in the POS than the NEG group ($8{\cdot}8 \pm 3{\cdot}3$ vs $6{\cdot}4 \pm 2{\cdot}5$, $p < 0{\cdot}01$). Eleven of the 60 smokers showed bronchial reactivity to inhaled histamine at a concentration $\leqslant$ 8 mg ml^{-1}; in these men ΔFEV_1 was $10{\cdot}1 \pm 3{\cdot}7$ compared with $6{\cdot}9 \pm 2{\cdot}5$ in non-reacting smokers. These findings confirm an earlier pilot study and support the hypothesis that an atopic predisposition, insufficient to lead to the clinical diagnosis of asthma, may predispose a minority of male smokers to develop chronic airway narrowing.

How often do we miss steroid reversible airflow obstruction?

TC STOKES, JM SHAYLOR, JR O'REILLY, BDW HARRISON In the outpatient management of patients with chronic airflow obstruction, the physician may wish to determine if oral corticosteroids will bring about improvement in addition to that achieved by bronchodilators. Even if there is a response, the decision to continue corticosteroids can be difficult. We have evaluated the response to oral prenisolone, 30 mg daily, in 31 outpatients with chronic airflow obstruction. All had stopped smoking and were on maximal bronchodilator therapy for at least six months before these studies. Placebo tablets were given for the first two weeks, followed by prednisolone for two weeks. FEV_1, FVC, and PEF were measured at each outpatient visit. Patients also monitored their PEF three times daily at home. When the placebo and prednisolone responses are compared, five patients showed an improvement of 20% or greater in FEV_1, FVC, or PEF but when compared with the best values recorded during the previous six months on bronchodilators, only three patients showed a response, mainly improved PEF. No placebo effect was demonstrated. Home measurement of PEF did not provide any further information to that gained from measurements made in the clinic. No patient was given long-term steroid therapy as a result of the trial. A review of similar studies shows that less than one in 10 patients shows a response to oral steroids but even fewer receive them long term. The modest improvements are maintained only if large doses of steroids are used.

Response to inhaled salbutamol in chronic "irreversible" airflow obstruction

PA CORRIS, E NEVILLE, S NARIMAN, GJ GIBSON Responses to bronchodilators have been well studied in asthma but there is little information on use of different doses in patients with chronic, largely irreversible airflow obstruction. It has been suggested that spirometry may not be the most appropriate technique for detecting improvement in such patients. We selected a group of eight patients without asthmatic features (no sputum or blood eosinophilia, negative skin tests, and a previously negative trial of oral corticosteroids). All had been heavy cigarette smokers and were significantly disabled by airflow obstruction (mean FEV_1 0·7 l). Beta stimulants were withdrawn 10

days before the study and on successive mornings each subject inhaled in double-blind randomised order, 0, 200, 400, 800, or 1600 μg salbutamol powder. Before and up to six hours after the inhalation FEV_1, vital capacity, maximum expiratory and inspiratory flow volume curves, and a 12-minute walk were performed. Analysis of variance of the results showed significant relationships to increasing dose of drug for each of the measurements. Larger doses also had a longer duration of action. We conclude that there is a dose-response relationship to inhaled salbutamol in patients with chronic "irreversible" airflow obstruction and, in our experience, simple spirometric measurements are as useful in providing objective evidence of benefit as more time-consuming tests.

Right ventricular function in chronic obstructive pulmonary disease

W MACNEE, QF XUE, WJ HANNAN, DC FLENLEY, AL MUIR Cardiac function in chronic hypoxic cor pulmonale is poorly understood as the dynamics of the right ventricle (RV) are difficult to assess. We have used gated equilibrium cardiac blood pool nuclear angiography (Xue *et al*, *Clin Sci* 1982; in press) to measure right and left ventricular ejection fraction (RVEF, LVEF) in 45 patients with chronic bronchitis and emphysema (CB and E) [29 M, 16 F; Pao_2 6·9 SD 1·3 kPa; $Paco_2$ 6·9 SD 1·2 kPa; FEV_1 0·7 SD 0·3 l] and in 33 patients (25 M, 8 F) with angina pectoris, (A) but normal lungs. RVEF was significantly lower ($p < 0·001$) in patients with CB and E (0·46 SD 0·11) than in those with angina (0·59 SD 0·07) whereas LVEF was similar in both (CB and E 0·58 SD 0·13; A 0·57 SD 0·14). In comparison of CB and E patients with clinical cor pulmonale (CP), at the time of study, with CB and E patients without cor pulmonale: LVEF was significantly lower (CP 0·43 SD 0·14 no CP 0·62 SD 0·08, $p < 0·001$) as was RVEF (CP 0·38 SD 0·07, no CP 0·52 SD 0·12 $p < 0·001$) Pao_2 (CP 6·2 SD 0·9, no CP 8·1 SD 1·3 $p < 0·001$ kPa) whereas $Paco_2$ was higher (CP 7·3 SD 1·0, no CP 6·2 SD 0·8 kPa $p < 0·001$). In 12 patients with CB and E, who were treated for 15 hours/24 hours day with long-term oxygen therapy over one to five years, RVEF when breathing air was higher ($p < 0·001$) than in CB and E patients with similar hypoxaemia (Pao_2 5·9 SD 0·6, Pao_2 6·1 SD 0·8) but who had not received long-term oxygen. Right ventricular ejection fraction is low in chronic hypoxic patients with CB and E particularly in those with cor pulmonale, but can be improved by long-term oxygen.

Cystic fibrosis: survival into adult life

ME HODSON, FR DUNCAN, JC BATTEN Two hundred and twenty-five patients with cystic fibrosis who had reached 16 years of age attended the Brompton Hospital between 1965 and 1980. There were 127 males and 98 females. One hundred and forty patients were still alive on 31 December 1980. This group of patients was selected as they had to survive to 16 years of age to attend the adult cystic fibrosis clinic at the Brompton Hospital. Survival data on this group of patients show an actuarial probability of survival of 0·85 to 20 years, 0·63 to 25 years, and 0·46 to 30 years. The oldest patient is now 48 years of age. Details of clinical status of these older patients with such important social factors as marriage, children, and occupations will be presented. Factors which may have contributed to the survival of a patient into adult life will be discussed. A positive approach by paediatricians and adult physicians caring for patients with cystic fibrosis should be encouraged.

Management of pneumothorax in adults with cystic fibrosis

ARL PENKETH, ME HODSON, RK KNIGHT, JC BATTEN The majority of patients with cystic fibrosis (CF) now survive into adult life, and many are coming under the care of thoracic physicians. Pneumothorax is common, and often recurrent, in those patients with severe airflow obstruction and chronic *Pseudomonas aeruginosa* infection. It is an important cause of both morbidity and mortality in CF. Two hundred and forty-three cases of adults with CF were reviewed; 46 experienced one or more pneumothoraces (18·9%), and seven patients died of this complication of the disease. There was a high incidence of recurrence on the same side after conservative management (50%), or intercostal drainage (55·2%). Persistent air leaks were common, and prolonged intercostal drainage for longer than seven days was associated with a mortality of 50%. Twenty thoracotomies were performed with three deaths, and a low incidence of recurrence (15%). Severe airflow obstruction was not a contraindication to surgery. We recommend that a first asymptomatic pneumothorax should be managed conservatively. A symptomatic first episode should be treated by intercostal drainage, but a persistent airleak at seven days is an indication for surgery. In a second or subsequent episode the risk of a further recurrence may justify immediate surgical management.

Radiological features of pulmonary emphysema in alpha$_1$antitrypsin deficiency

P GISHEN, AJS SAUNDERS, M TOBIN, DCS HUTCHISON In a multicentre survey of alpha$_1$antitrypsin deficiency, established by the British Thoracic Association, chest radiographs were obtained in 165 subjects homozygous for Pi type Z. There were 127 "index" cases who had presented to a chest physician and 38 "non-index" cases, identified through family studies. Radiological evidence of emphysema (vascular attenuation or bullae) was observed in 91% of the index cases and in 66% of the non-index cases. The lower zones were affected in all but three of the 140 subjects with radiological emphysema. Chest radiographs were obtained in 23 subjects heterozygous for Pi type SZ (14 index cases and nine non-index cases). Emphysema was observed in eight of the 14 index cases; all those affected were males who were current or ex-smokers. None of the non-index SZ subjects had radiological emphysema. Homozygotes of Pi type Z have a high risk of developing emphysema; the risk in heterozygotes of type SZ appears to be very much lower.

Respiratory tract disease and obstructive azoospermia

E NEVILLE, WK YEATES, RAL BREWIS, A BURRIDGE, PM HACKING Male infertility may be linked to respiratory

tract disease in conditions such as cystic fibrosis and Kartagener's syndrome. Young's syndrome constitutes another such link in which bronchiectasis is found in association with obstructive azoospermia and normal testicular function. We have studied 32 infertile men with azoospermia in order to assess the frequency and nature of respiratory disease including the upper respiratory tract. Ten patients had bronchiectasis, of whom three had had a lobectomy. All 10 of these patients had abnormal sinus radiographs but only four gave a history of sinusitis. Chest X-ray was abnormal in all 10 of these patients and in two others who had recently developed pulmonary sarcoidosis. Eleven (34%) had chronic bronchitis, of whom two were non-smokers. One patient had asthma with severe airways obstruction and 13 others had minimal airways obstruction. Overall, twenty-five (78%) patients had abnormal sinus radiographs of whom 18 (56%) gave a history of sinusitis and six had had nasal sinus operations. Ten (31%) patients had histories of repeated otitis media, of whom two had had mastoid operations. We conclude that Young's syndrome may be recognised in young men with obstructive azoospermia and associated sino-respiratory disease but that nothing in their history, examination, or investigations explains why some have respiratory tract disease while others do not.

Cytological sampling at fibreoptic bronchoscopy: comparison of catheter aspirates and brush biopsies

MF MUERS, MM BODDINGTON, M COLE, D MURPHY, AI SPRIGGS A prospective study was undertaken to compare bronchial brushings with dry catheter aspiration for the cytological diagnosis of lung cancer at fibreoptic bronchoscopy. Duplicate samples taken by aspirate and brush were obtained at 103 consecutive routine bronchoscopies. Aspirate and brush samples were reported separately by two cytologists. At the end of the study a 30% sample including the 19 cases with differing reports was subjected to a blind cross-over review, and then an open re-review. Forceps biopsies for histological assessment were taken in 94 cases (92%). Ninety-eight out of 103 (95%) aspirates and 99 out of 103 (96%) brush specimens were technically satisfactory, and malignancy was diagnosed at bronchoscopy on cytological or histological evidence or both in 57 cases. Fifty-five of these (96%) were recognised by either aspirate or brush, 52 (91%) by brush, and 50 (88%) by aspirate. Thirty-four cases (60%) were diagnosable from histological specimens. The order of cytological sampling did not affect yield systematically. We concluded that fine catheter aspirates, permitting smears to be prepared in the laboratory, are a satisfactory alternative to brush smears for the cytological diagnosis of lung cancer at bronchoscopy. The indications for taking cytological samples additional to the standard brush biopsy, will be discussed.

Marrow toxicity of VP-16-213 when combined with other cytotoxics in lung cancer and prevention of this effect

G ANDERSON, ET PEEL, B CHEONG In a preliminary study, 82 patients with advanced lung cancer received VP-16-213 (Epipodophyllotoxin) 200 mg orally daily for five days at monthly intervals. Objective remissions occurred in 24 of 59 evaluable patients with activity in all cell types studied. Unacceptably frequent marrow depression occurred when VP-16-213 in the same dosage schedule was combined with vincristine and two dose levels of methotrexate, with adriamycin, and with cyclophosphamide. An explanation based on cell kinetics was given for this interaction. The drug doses given were rescheduled and the same total VP-16-213 and cyclophosphamide doses which previously caused pancytopenia were shown to be made safe.

Production of a growth stimulating factor by lung tumours

J MINTON, D MALONEY, D LAMB In surgically resected lung tumours we have observed a sub-perichondral proliferation of new cartilage in the bronchial rings. This proliferation is not associated with tumour invasion of cartilage, the presence of adjacent tumours, or the presence or absence of clubbing or pulmonary osteoarthropathy. The cartilage change is related to cell type being found in association with 45% of squamous carcinomas, 15% of adenocarcinomas, and only 5% of small cell undifferentiated carcinomas. Short-term culture of tumour fragments in vitro from such cases releases into the culture medium a factor which stimulates uptake of radioactive sulphate into chick embryo cartilage. The chick embryo cartilage bioassay is the standard bioassay for somatomedins. It seems likely that those pulmonary tumours associated with abnormalities of the bronchial ring cartilage are producing a somatomedin or somatomedin-like substance.

Paramalignant manifestations of lung cancer

ET PEEL, G ANDERSON, S DAS In a prospective study we documented the paramalignant disorders present at the time of diagnosis in all histologically proven lung cancer patients presenting between 1968 and 1981. Seven hundred and sixty patients were reported. The distribution of cell types was 397 (52%) squamous, 98 (13%) small cell, 71 (9%) adenocarcinoma, and 194 (26%) unspecified. Fifty-four patients (7·1%) had hypercalcaemia and in all the cell type was squamous. Twenty patients (2·6%) had hyponatraemia, and of these 11 had small cell carcinoma and nine unspecified malignant cells. Other less common metabolic manifestations included 10 (1·3%) new diabetes, five (0·7%) gynaecomastia, four (0·5%) hyperthyroidism, and only three with inappropriate ACTH secretion. The most common occurrence was weight loss of more than one stone (6·4 kg) present in just over half of all patients. In contrast to this, weight gain was seen in only 11 patients. Anaemia was present in 45 (5·9%) patients, and hypertrophic pulmonary osteoarthropathy in 13 (1·7%). Nonmetastatic disorders are common in lung cancer, and their prevalence reflects the enthusiasm with which they are sought.

Effect of bromhexine on sputum sol phase proteins in chronic obstructive bronchitis: importance of daily variability

J WIGGINS, RA STOCKLEY The mucolytic agent bromhexine is often prescribed for patients with chronic cough

and sputum production. Previous studies (Gotz and Fischer, *Clin Chim Acta* 1970;**30**:53) have suggested that this drug causes an increase in sputum sol phase IgA and serum-derived proteins, especially albumin. However, these findings were semi-quantitative, based on data from one control and one treatment day only and have been questioned. In contrast Brogan *et al* (*Br J Dis Chest* 1974; **68**:28) found no effect during an acute chest infection which in itself may have prejudiced the results. Therefore we have studied the sputum sol phase proteins of 12 patients with chronic obstructive bronchitis in the stable state on five consecutive days before and during bromhexine 32 mg daily. During the placebo period, considerable day-to-day variability of all the individual sputum-to-serum protein concentration ratios were observed. For example, sputum-to-serum albumin concentration ratios varied from $0{\cdot}332 \times 10^{-2}$ to $2{\cdot}177 \times 10^{-2}$ in one patient (average $1{\cdot}522 \times 10^{-2}$ SD $\pm$ 0·751). When this inherent variability was taken into consideration, no consistent change occurred during bromhexine treatment, even though individual patients demonstrated apparent rises and falls with treatment. Standardisation of other proteins, including alpha$_1$ antitrypsin (α_1AT), alpha$_1$ antichymotrypsin (α_1ACh), and IgA, for albumin greatly reduced the variability. For example, α_1AT standardised for albumin in the patient shown above varied only from $1{\cdot}002 \times 10^{-2}$ to $1{\cdot}251 \times 10^{-2}$ (mean $1{\cdot}115 \times 10^{-2}$ SD $\pm$ 0·091). However, even when such standardisation was used, bromhexine had no demonstrable effect on α_1AT, α_1ACh, and IgA. The results show the wide day-to-day variability of sputum protein concentration, confirm the usefulness of standardisation for albumin, and suggest that previous results may have reflected methodological errors.

Direct labelling of the active component of a metered dose inhaler and its deposition pattern

SG SPIRO, M PARTRIDGE, CA SINGH, S GALVIN, PJD HEAF, MD SHORT The deposition of aerosol medication from a metered dose inhaler (MDI) has usually been measured by substituting inert γ-radiolabelled particles and has assumed that similar deposition patterns would occur with the corresponding active commercial product. We have devised a method for directly labelling ipratropium bromide (IB) with the γ-emitter bromine^{77} in an MDI to assess the actual deposition pattern of a bronchodilator after conventional inhalation. Bromine^{77}, adjusted to appropriate chemical form is mixed in solution with IB. The mixture is frozen, dried, and remicronised to the particle specifications of the commercial product. The MDI cannister is constituted by adding the radiolabelled drug to surfactant and fluorocarbon propellants in the correct proportions at -60°C. The can is capped and allowed to warm to room temperature. Seven normal men (aged 23-38 years) each inhaled 10 puffs of IB which released a total mean dose of 203 μg ($\pm$ 16·9; 1 SD). Only 23 μg (11·2%) of IB entered the lungs, of which 28% ($\pm$ 2·3%) reached the peripheral two-thirds of the lungs, 34% ($\pm$ 2·7%) the central zone, and 38% ($\pm$ 4·5%) remained in the middle area between the medial borders of the lungs—that is, trachea, oesophagus. This study provides further direct evidence for the small quantity of medication reaching the lung from an MDI when inhaled from residual volume.

Radioaerosol and ^{81m} krypton assessment of regional ventilation in asymptomatic asthma

JE AGNEW, JRM BATEMAN, D PAVIA, SW CLARKE The possibility of ventilatory abnormalities in asymptomatic asthmatics has been studied in 20 patients (mean age 32 years, range 19-59 yr; mean FEV_1 102% predicted, range 75-142) who were compared with 16 non-smoking normal control subjects (mean age 33 years, range 18-72 yr; mean FEV_1 117% predicted, range 79-150). Large field-of-view Gamma camera images obtained with 5 μm diameter ^{99m}Tc-labelled polystyrene aerosol particles and with ^{81m}Kr gas were assessed by blind marking and by quantitative, computer-derived, indices. Blind marking scores were significantly lower in asymptomatic asthma than in normal controls, both with aerosol ($p < 0{\cdot}001$, Wilcoxon rank-sum test) and with ^{81m}Kr ($p < 0{\cdot}02$). Central aerosol deposition was also significantly greater ($p < 0{\cdot}01$). Penetration into the lungs of radioaerosol relative to ^{81m}Kr was measured by "penetration index", the ratio of peripheral to inner zone radioactivity, and was significantly lower in asymptomatic asthma than in the control subjects ($p < 0{\cdot}05$). Inhomogeneity of radionuclide distribution within radioaerosol images relative to the ^{81m}Kr images was assessed by histogram analysis giving a "distribution index" significantly higher in asymptomatic asthma than in control subjects ($p < 0{\cdot}001$). The dependence of these indices on "large" and "small" airways effects in asymptomatic asthma was tested by partial regression analysis using FEV_1 (% predicted) as an index of "large airways function" and the mean of MMFR (% predicted) and $\dot{V}max_{25}$ (% predicted) as an index of "mean small airways function". Neither penetration index nor distribution index related significantly to FEV_1 but both related significantly to "mean small airways function" ($p < 0{\cdot}05$ and $p < 0{\cdot}01$ respectively).

Bacteria, viruses, and sputum cytology in acute asthma

VAL GRAHAM, AF MILTON, RJ DAVIES Infection is thought to be an important precipitant of acute episodes of asthma. We have recently carried out a study evaluating the use of antibiotics in the management of adult patients admitted to hospital with acute asthma and were unable to demonstrate any advantage in using an antibiotic, amoxycillin, as compared with a placebo. Eighty-one patients were studied, 50% were able to expectorate specimens of sputum on admission. Routine bacteriological assessment of sputum revealed the presence of potential pathogens in eight specimens only. Tissue culture of nasopharyngeal washings and serological testing of paired acute and convalescent sera provided supportive evidence of recent viral infections in 11·8%. Because of the well-known difficulties in carrying out accurate sputum bacteriology, transtracheal aspiration was performed in 15 selected patients and more detailed studies were carried out. Significant numbers of potential pathogens were cultured from 40% of specimens. Sputum cytology was performed on all admission sputum specimens and the findings were correlated with the patients'

histories, atopic status, smoking habits, and also with the bacterial and viral results.

Clinical review of pulmonary infection caused by Myobacterium xenopi

MJ SMITH, KM CITRON *Mycobacterium xenopi* is an uncommon non-tuberculous mycobacterium. In Britain there is a remarkable preponderance of isolations from the South-East of England. In the Brompton Hospital Bacteriology Laboratory, London this organism comprised 56% of all non-tuberculous mycobacteria isolates found during a six-year period. The clinical and bacteriological features and response to treatment of the 23 patients from whose sputum *M xenopi* was cultured are reviewed. Pulmonary disease caused by this organism was considered to be present in 15 and their radiographs showed pulmonary cavitation in 11, apical shadowing in three, and left upper lobe fibrosis in one. Most of the patients had longstanding respiratory symptoms and evidence of the X-ray appearances developing over many years, but in a few the disease appeared to be of recent onset. Another four patients had lung disease of known cause and *M xenopi* was thought to be saprophytic. The remaining four patients had single isolates of *M xenopi* and no lung disease which could be attributed to this organism. Sixty-five per cent of the organisms showed in vitro resistance to one or more of the first line anti-tuberculous drugs. Chemotherapy given to 12 patients resulted in sputum conversion and clinical cure in eight. Criteria for relating *M xenopi* to pulmonary disease and the indications for chemotherapy are suggested.

Role of blood culture in acute respiratory infection

CR PAYNE, DM JONES The taking of blood for bacterial culture in acute respiratory infection is standard clinical practice but the value of this procedure is doubtful. We have analysed the results of blood culture in 100 patients with lobar pneumonia, bronchopneumonia, or non-specific acute respiratory infection. No patient had received previous antibiotics. Blood was inoculated into a two-bottle Casteneda system for aerobic and anaerobic culture. Fifty-six patients had lobar pneumonia, 20 had bronchopneumonia, and 24 had non-specific acute respiratory infection. Significant positive bacterial cultures were obtained in only five patients, all of whom had lobar pneumonia. The organism was *Pneumococcus* in each case. Cultures of contaminating skin organisms were obtained from 24 patients and organisms of doubtful significance were isolated from a further three. In only one patient was the initial choice of antibiotic therapy altered on the basis of the result of blood culture. This study demonstrates the poor value of routine blood culture in acute respiratory infection. It is possible that this procedure should be limited to patients with lobar pneumonia. The high incidence of contaminating organisms suggests that greater attention should be paid to the technique of collecting blood for bacterial culture.

Long-term survivors after surgery for lung cancer

JW JACKSON Sixty patients—51 men and nine women—surviving more than five years after surgery for lung cancer form the basis of this review. The average age at the time of surgery was 56 years. The longest living follow-up is 22 years and the oldest survivor is now 82 years old. Eighteen patients in the series have died, nine from natural causes and nine from recurrence of their disease; in six of these there was no evidence of lymph node involvement and in three the interbronchial lymph nodes in the resected specimen contained tumour. There were 10 patients with interlobar nodes involved and four with hilar node involvement and all these patients are alive and well. Three patients with oat cell carcinoma are still alive. Of the 11 patients with vessel involvement only two have died. The findings are paradoxical.

Stoma drainage of empyema

M MEREDITH BROWN Open drainage of pleural empyema continues to be necessary when medical treatment has failed and when decortication is contraindicated. It must be maintained until healing is complete. Drainage tubes often pose problems. They may become blocked, or cause pain, and often fall out: replacement may require a further anaesthetic. Pleural fenestration avoids the need for any tube. This operation, of somewhat greater magnitude than simple rib resection, creates a stoma or "window" through the chest wall which will not close until the cavity has obliterated. An H-shaped incision allows two skin flaps to be raised. Segments of ribs with intercostal tissues are excised, and the flaps turned in and sutured to the outer lining wall of the empyema to prevent cross-healing. Discharge soon lessens and the patient may resume normal activities, wearing only a simple dry dressing. The cavity closes by centripetal apposition; final ingrowth of epithelium leaves intact skin over an insignificant depression. This procedure is indicated when a long period of drainage is anticipated and when the use of a tube is best avoided—for example, in chronic tuberculous empyema, after pneumonectomy, in old age, or in mental patients.

Cryoanalgesia and post-thoracotomy recovery

O MAIWAND Three hundred patients who underwent thoracotomy for a variety of pathology since late 1980 had their intercostal nerves blocked by cryoanalgesia before closure of the chest. The effect of cryotherapy on their postoperative pain and loss of sensation has been studied. The technique of cryosurgery for thoracic use has been established—the site and the time length of application of the cryo probe has also been evaluated. Local retraction of pleura and insertion of intercostal chest tube within the cryo-treated area are strongly advised. A new probe for thoracic use has been designed and made. Eighty-three per cent of patients in our follow-up series were free of pain with low post-thoracotomy morbidity and loss of cutaneous sensation from three to six months. The effects of cryoanalgesia on physiotherapy and nursing care after thoracotomy were observed. We conclude that the technique of cryotherapy is simple and extremely effective and we think the 10 minutes added to the total operative time is well spent and offers benefits which have not been achieved by any other available technique.

Thoracoscopy: a useful diagnostic tool

CW WRIGHT, KM PAGLIERO Thoracoscopy is not a new

surgical technique. However there is a significant swing towards diagnosis by the physician and as most conditions diagnosable by thoracoscopy are ultimately managed by physicians there is a real possibility that this useful diagnostic tool may become forgotten. Twenty-six patients underwent diagnostic thoracoscopy at the Exeter Thoracic Surgical Unit in a four-year period. In one patient lack of a pleural space prevented the examination. In the other 25 accurate histological diagnosis was achieved in 24, 18 from lung biopsy and six from pleural biopsy. There was one case where biopsy did not prove diagnostic but cytology of the pleural fluid did. The procedure was well tolerated without complications though three patients subsequently died during the same admission from their underlying terminal malignancy. In six of these patients thoracoscopy allowed talc poudrage to control their malignant effusions successfully.

Does beta-adrenoceptor function in the skin parallel beta-adrenoceptor function in the lung of asthmatic subjects?

GS BASRAN, W PAUL, J MORLEY, M TURNER-WARWICK In asthma, it has been proposed that abnormalities in beta-adrenoceptor function are expressed not only in the lung, but may also be evident in other tissues (Szentivanyi, *J Allergy* 1968;**42**:203-32). In the skin of healthy subjects, it is possible to demonstrate inhibition of mediator-induced inflammatory responses by local administration of a beta-adrenoceptor agonist (Basran *et al, Br J Dermatol* 1981; in press). We have compared beta-adrenoceptor reactivity in skin and lung of asthmatic subjects using salbutamol inhibition of the histamine-induced wheal response as an index of the former, and improvement in FEV_1 after salbutamol inhalation as an index of the latter. Twenty atopic asthmatic subjects, with $FEV_1 < 75\%$ predicted, were given intradermal injections of coded solutions containing histamine (0·75 μg) alone or mixed with noradrenaline (0·3 μg) or salbutamol (100 μg) at marked sites on the forearm. Injection volume was kept constant at 50 μl/site and wheal volumes were measured 15 min after injection. Salbutamol and noradrenaline both caused significant inhibition of the histamine-induced wheal response ($p < 0{\cdot}001$). Baseline FEV_1 was estimated before skin testing and the response to inhaled salbutamol (200 μg) was assessed 15 min later. The improvements in FEV_1 with salbutamol correlated significantly ($p < 0{\cdot}01$) with the degree of wheal inhibition by salbutamol but not with wheal inhibition by noradrenaline. These findings indicate that beta-adrenoceptor function in skin may parallel beta-adrenoceptor function in the lung in asthmatic subjects.

Effect of propranolol on mediator release in asthmatics

PW IND, MJ BROWN, PJ BARNES, CT DOLLERY Beta-adrenoceptor antagonists commonly increase bronchoconstriction in asthmatics and this is attributed to unopposed vagal or α-adrenergic constriction of bronchial smooth muscle. Lung mast cells, in vitro, possess β-receptors which modulate mediator release; this release may be estimated in vivo by measurement of plasma histamine. Ten extrinsic asthmatics (seven men, three women) aged 21-36 years with baseline FEV_1 and peak expiratory flow (PEF) greater than 70% predicted were infused with normal saline and then propranolol 0·36 mg/min to a total of 10 mg. Supine heart rate, blood pressure, and erect PEF were measured frequently and venous samples drawn for estimation of plasma histamine by double isotope radioenzymatic assay. In four patients (three men, one woman) initial FEV_1 was 97·0 $\pm$ 3·9 and initial PEF 85·8 $\pm$ 6·2, mean $\pm$ SEM % predicted. In these "non-responders" maximum fall in PEF was 8·2 $\pm$ 2·5 (range 5·0-12·0) % baseline. In the remaining six "responders" initial FEV_1 was 80·6 $\pm$ 1·4, and initial PEF 78·3 $\pm$ 3·2% predicted and maximum fall in PEF was 36·8 $\pm$ 5·6 (range 17·4-53·0) % baseline. There was a poor correlation between maximum fall in PEF and maximum increase in plasma histamine in five patients ($r = -0{\cdot}45$, NS). In three of the subjects with falls of 30·0, 30·1, and 39·4% baseline PEF plasma histamine rose by 74·1, 90·9, and 94·7% from baseline value of 0·27, 0·22, and 0·19 ng/ml. In one of the subjects with a 50% fall in PEF plasma histamine rose 17% from 0·23 ng/ml but in the other subject with a 5·9% fall in PEF plasma histamine rose 104% from 0·23 ng/ml. These preliminary results suggest that enhanced mediator release is not the major cause of β-blocker-induced bronchoconstriction in asthmatics.

Role of smooth muscle beta-receptors in histamine responsiveness in asthma

NC THOMSON, G RYAN, R ROBERTS, EE DANIEL, FE HARGREAVE We examined whether interindividual differences in beta-adrenergic receptor responsiveness of airway smooth muscle is the primary abnormality which determines the variability of bronchial responsiveness to histamine between asthmatics. Dose-response curves to histamine were performed in nine asthmatics after beta blockade with inhaled propranolol (6 mg nebulised during tidal breathing) or after inhaled saline. To exclude vagal influences on airway smooth muscle responsiveness subjects were also pretreated with inhaled atropine (3 mg nebulised during tidal breathing). Responses to histamine were determined by the provocation concentration causing a 20% fall in forced expiratory volume at 1 s (FEV_1) and by the slope of the dose-response curve. After pretreatment with atropine, beta blockade did not significantly alter FEV_1. There was no significant difference in mean PC_{20} histamine after atropine (1·61 $\pm$ 1·11 mg/ml) compared to after atropine plus propranolol (1·60 $\pm$ 1·11 mg/ml). However, after atropine there was a small but significant increase in mean PC_{20} compared to after saline pretreatment (0·83 $\pm$ 1·13 mg/ml) ($p < 0{\cdot}001$). The slope of the dose-response curve to histamine was not altered by atropine or atropine plus propranolol pretreatment. In asthmatics, interindividual variation in responsiveness to histamine was not reduced by cholinergic (muscarinic) receptor or beta receptor blockade. We conclude that variability between asthmatics in responsiveness to histamine is not primarily a result of smooth muscle beta-receptor dysfunction.

Transcutaneous P_{CO_2} in adults

HR GRIBBIN, MD GOLDMAN, RJ MARTIN, L LOH Using a transcutaneous P_{CO_2} (tcP_{CO_2}) electrode (Radiometer Co),

$tcPCO_2$ was compared with simultaneous values of arterial PCO_2 ($PaCO_2$) in eight adults over a wide range of $PaCO_2$ (2·4 to 7·87 kPa). At an electrode temperature of 43°C $tcPCO_2$ was systematically higher but closely correlated with $PaCO_2$; $tcPCO_2 = 1{\cdot}245\ PaCO_2 - 0{\cdot}107$ kPa (0·311, SEE; n = 40; r = 0·98). Heating the skin, which is necessary to increase skin capillary blood flow and reduce the arterial-capillary PCO_2 gradient is largely responsible for the difference between $tcPCO_2$ and $PaCO_2$ since it also raises the temperature of the capillary blood and hence its PCO_2 (anaerobic heating coefficient of blood). The in vivo response time of the electrode was assessed in six normal subjects. The in vivo time constant to a step change in $PaCO_2$ after inhalation of 5% CO_2/95% O_2 was approximately two minutes (mean time to 95% response = 5·3 minutes). This response makes the electrode unsuitable for following rapid changes in $PaCO_2$ but should not be a drawback in clinical practice where more gradual changes in $PaCO_2$ are more likely. Provided skin blood flow is unimpaired, the $tcPCO_2$ electrode can measure change in $PaCO_1$ in adults accurately.

Extravascular lung density in sarcoidosis measured with positron tomography

P WOLLMER, CG RHODES, NB BOWLEY, JMB HUGHES Regional extravascular lung density and blood volume has been measured in patients with sarcoidosis using a technique based on positron emission tomography (Rhodes *et al*, *Clin Sci* 1981;**60**:15p). Lung density was measured (in units of g/ml of thoracic volume) using an external ring source containing positron emitting $^{68}Be/^{68}Ga$. Blood volume was measured after labelling circulating red cells with inhaled ^{11}CO. Extravascular lung density was obtained by subtracting blood volume from lung density. Extravascular lung density was measured in six patients, who also underwent pulmonary function tests and chest radiography. Four patients were studied a second time after treatment with prednisone (20-40 mg/day). Radiographs were scored using a semiquantitative technique. All patients showed increased extravascular lung density (140-180% of normal). Regional blood volume was in most cases slightly reduced. An inverse correlation was found between extravascular lung density and the transfer factor per unit alveolar volume for carbon monoxide (T_{LCO}/V_A). Of the patients treated with prednisone, two showed marked reduction (from 162 and 172 to 118 and 124% respectively) in extravascular lung density. This was accompanied by improvement of the chest radiographs and some improvement in pulmonary function tests.

Why jog?

P BOFFA, R DENT, S GOUGH, D SHAW, T HIGENBOTTAM Many animals change gait from a walk to a trot to a gallop in such a way to minimise their oxygen consumption (Hoyt, Taylor, *Nature* 1981;**292**:239-40), but in man factors limiting speed of walking or running are less well understood (Cavagna, Margaria, *J Appl Physiol* 1966;**21**:271-8). Men were studied on a treadmill, both on walking and running at progressively increasing speeds between 0·9 and 16 kph. Stepping frequency, stride length, and metabolic gas exchange (Davies, Denison, *Respir Physiol* 1979;**36**:261-7) were recorded. In each subject an optimal speed of walking was observed when the amount of oxygen to move a metre was at a minimum. At greater speeds oxygen consumption rose as did stepping frequency but stride length remained at a maximum value related to subject's height. In contrast, running at increasing speed was associated with a progressive rise in stride length, but stepping frequency reached a plateau above optimal speed of walking, when there was a marked reduction in oxygen consumption. In man walking becomes most efficient when stride length reaches a maximum value determined by an individual height. Running was more efficient at higher speeds when associated with a constant stepping frequency. These observations may influence interpretation of exercise tests and aid physical therapy in cardiorespiratory disability.

How well are asthmatics controlled? A simple exercise in medical audit

CK CONNOLLY Five hundred and twenty-eight asthmatics attending five types of clinic in two socially different districts were assessed on their first follow-up visit, in 1980. Atopic status, smoking habits, and therapy were recorded. Eighty-six per cent were assessed as on satisfactory regular maintenance therapy. Of the 74 others, 30 achieved this later, but in 27 treatment was still not satisfactory after a full year. There were two deaths. To allow for "irreversible" airway obstruction, control was assessed by the ratio of actual to maximum recorded peak flow rate for that subject. The response to treatment of most patients with poor pulmonary function had been assessed in hospital. Better control was achieved with personal supervision, and where the patients were of higher social class. As differences in control applied to non-atopic rather than atopic subjects, the explanation might lie in differences in intrinsic asthma between social classes, rather than methods of supervision. Smokers performed worse than non-smokers, while immediate ex-smokers did better than either. The policy and use of drugs was similar in all clinics, though the threshold for starting treatment was probably lower where control was better. Patients on disodium cromoglycate were unique in being better controlled than those not on the drug, suggesting possible underuse.

Breathing, bronchoconstriction, and sleep stage in nocturnal asthma

CM SHAPIRO, I MONTGOMERY, JR CATTERALL Asthmatics often wheeze at night, with an "early morning dip" in FEV_1. We have related EEG sleep stage to ear oxygen saturation (Sao_2) and breathing pattern in 10 stable asthmatics (seven men, three women, aged 22-59 yr) and 10 age-matched control subjects, throughout an undisturbed night's sleep. The lowest Sao_2 during sleep was 91-77% (mean 85%) in the asthmatics, significantly ($p < 0{\cdot}01$) less than the 95-89% (mean 93%) in the control subjects. Hypoxaemia episodes (HE, Sao_1 falls $\geq 4\%$) occurred in nine asthmatics (0-7 HE/night) but in only four controls (0-1 HE/night). Most irregular breathing and most HE (16/28, 57%) in the asthmatics occurred in REM sleep, although this was only 16% of total time

asleep. Expiration (measured for all breaths during sleep) was longer in REM than in non-REM sleep in three of four asthmatics, but in two control subjects. To find if bronchoconstriction in nocturnal asthma is specifically related to REM sleep, we have studied a further eight asthmatics and eight age and sex-matched control subjects, wakening them from different sleep stages to measure FEV_1, FVC, and PEFR. On one night they were awoken twice from non-REM sleep, without intervening REM. On another night they were awoken before their first REM period and again during their second REM period. In the asthmatics, both FEV_1 and PEFR fell significantly ($P < 0.05$) more when they were awoken in REM, but this did not occur in the control subjects, implying that bronchoconstriction may occur particularly in REM sleep in asthma.

Predicting rapid and slow response to treatment in acute severe asthma

GFA BENFIELD, AP SMITH A previous study (Jenkins *et al*, *Thorax* 1981;**36**:835-41) has identified certain clinical features of patients admitted with acute severe asthma which were common to groups of patients who responded rapidly to treatment (maximum PEFR within three days) slowly (maximum PEFR after seven days), and at an intermediate rate (maximum PEFR three to seven days). These features included age, atopy, duration of the present attack, presence of day-long wheeze normally or at least three hospital admissions within the last 12 months, use of maintenance corticosteroids, degree of pulsus paradoxus on admission, rise in PEFR after six hours and Pao_2 after 48 hours. A study was undertaken to apply these features to individual asthmatics on admission and at six and 48 hours after treatment in an attempt to predict the eventual rate of response. Fifty-four patients were studied of whom 53 were initially classified as rapid or slow responders. Forty patients were predicted as rapid responders on admission of whom 14 were correctly reclassified at six hours as slow responders. Thirteen patients were classified correctly as slow responders on admission and in all these patients the combined features of maintenance corticosteroids and the presence of day-long wheeze were present. At six hours 51 of the 53 patients (95%) had been correctly classified as rapid or slow responders ($p < 0.0001$) when compared with the eventual outcome after treatment. The Pao_2 in 34 of the 36 patients in whom it was determined also correctly predicted the eventual response to treatment ($p < 0.0001$). Only two patients were classified incorrectly on admission and at six hours, although the 48 hour Pao_2 reflected the eventual outcome. We conclude that using these clinical and physiological parameters it is possible to predict accurately the response of an individual to the commonly used treatment of acute severe asthma.

Retrospective survey of the management of pulmonary tuberculosis in South and West Wales (1976-78)

JP WHITE, RDH MONIE, AM HUNTER, K ROCCHICCIOLI, IA CAMPBELL, GS KILPATRICK The notes of 753 patients diagnosed as having active pulmonary tuberculosis between 1 January 1976 and 31 December 1978 were reviewed. Diagnosis was based on culturing *M tuberculosis* from sputum in 78% of cases, on histology compatible with tuberculosis in 3%, and on the chest radiograph in 19%. Although 37% of patients received a regimen of EHR/HR or SHR/HR for between nine and 12 months, only 20% of these patients received ethambutol according to the recommendations of the BTA after the short course chemotherapy trial. A further 28% of patients received this regimen for longer than 12 months. Sixteen per cent of patients were given RHE/HE or SHE/HE as many receiving nine months as 18 months. PAS was given to 2·2% of patients as part of their regimen, and 10% of patients received only two drugs. Three patients were given only one drug, and two patients had no chemotherapy. Eleven per cent of patients did not comply with their chemotherapy and there was little evidence in the case notes of any attempt to follow-up these patients. Five per cent of patients died from tuberculosis, in half the diagnosis being made only at necropsy. Fifteen per cent of patients had side-effects from their drugs.

Treatment of pulmonary tuberculosis in England and Wales

SP BYFIELD, KM CITRON, J DARBYSHIRE, W FOX, AJ NUNN The survey of tuberculosis notifications in 1978-79 has provided a unique opportunity to study for the whole of England and Wales the way in which patients are currently being managed at a time when chemotherapy policies are undergoing change. All the adult patients in the survey (over 1400) with previously untreated pulmonary tuberculosis of White or Indian, Pakistani or Bangladeshi ethnic origin were selected for study. The physician in charge completed a special form for each patient giving information (1) on the regimen of chemotherapy and the duration, and (2) whether the patient was admitted to hospital initially, and the reasons for admission. Over 92% of the forms have been returned so far and preliminary analyses on the incomplete population indicate that 25% of the patients did not complete chemotherapy as planned, the most common reasons being death (10%), default or poor co-operation (8%), and toxicity (3%). Although over half of the patients were treated with isoniazid and rifampicin supplemented by ethambutol initially, only about one-third were treated for nine months, the duration recommended by the British Thoracic Association in 1976. In all, 78% of the patients were admitted to hospital and although more than one reason was often given, the most common was for investigation and diagnosis.

Levels of serum calcium and other related parameters in tuberculous patients

PDO DAVIES Rates for tuberculosis in England and Wales are considerably higher in the population of Indian subcontinent ethnic origin than in those of other ethnic origins. Surveys among individuals of this ethnic population have found relative deficiencies in plasma vitamin D ($25\text{-}OHD_3$) and calcium levels. There are conflicting data from experiments pre-dating specific chemotherapy to suggest that calcium levels may be lower in tuberculous patients than in the normal population and as recently as

1951, calcium was being advocated as suitable therapy for tuberculosis. To determine whether there may be an association between tuberculosis and calcium deficiency, serum calcium, 25-OHD_3, parathyroid hormone and other related parameters have been measured in tuberculous patients, and compared with levels in a control population matched for age, sex, and ethnic origin. Tuberculous patients showed a statistically significant deficiency of calcium (uncorrected for albumin) and albumin, but not of 25-OHD_3, parathyroid hormone or corrected calcium. Alkaline phosphatase and gamma-glutamyl transferase were also raised in the patient group.

Pooter's lung

RB DOUGLAS Mosquitoes and their debris are usually removed from cages by sucking them into a pipette by mouth. This technique is known as "pooting" and is used by entomologists in field studies to collect sandflies from crevices in walls. Twelve laboratory workers were divided at random into two groups and then matched as closely as possible for age, height, and sex. One group (the "subjects") was asked to poot mosquitoes freely as necessary throughout the course of a working day. The other group (the "controls") carried out other duties in the same laboratory but refrained from pooting insects. Respiratory function was assessed before and after shift by making five blows into a dry wedge spirometer and also a flow-volume system using an integrating pneumotachograph. The results showed that five out of six subjects showed a reduction in forced expiratory volume (FEV_1) and a somewhat larger fall in forced vital capacity (FVC) over the seven hour shift. Two of the controls had hay-fever and they also showed a drop in FEV_1 and FVC. The other four controls all showed improvement. These results, taken together with a very few complaints of respiratory symptoms (including one man aged 28 years who reported a very severe response to pooting sandflies in France), indicate that the practice may carry a risk of respiratory sensitisation.

Primary seminoma of the thymus

ER TOWNSEND, RA ISWORTH, HM BRADMORE, B GODWIN, IKR MCMILLAN A review of the literature shows 74 cases of seminomas in the mediastinum have been reported but only 14 of these have been proved to originate from the thymus gland. We report a further three cases. These tumours occur in young males with an average age of 26 years. In our cases the mean age was 21 years. One presented with vague chest pain, another with a sternal swelling and the third was found on a routine chest radiograph. In two cases the tumour was totally removed with no recurrence, but in the third the patient was treated with DXT, and an osteolytic secondary developing 11 months later was successfully treated with DXT. To date all patients remain well and apparently free from recurrence. No evidence of a testicular lesion was found in any of these. The histology in all cases was indistinguishable from a primary testicular seminoma, recognisable thymic tumour was present in all cases, but in one case teratoid elements were present. In these very rare tumours surgical excision is usually possible but like their testicular counterparts they appear to respond well to DXT if excision is incomplete.

Correspondence

Hard metal lung disease

Sir,—In a paper which was published in *Thorax* in September 1980 (*Thorax* 1980;**35**:653-9), we described four patients with hard metal lung disease. Among other investigations, the amount of some metals in mediastinal lymph nodes had been measured. Since then, one of the patients (case 2) has died from cardiac infarction. Necropsy confirmed pulmonary fibrosis of moderate degree. Pieces of the lung and mediastinal lymph nodes were investigated as to their metal content, and the results can be seen in the table. Within brackets are the earlier values from the nodes taken at mediastinoscopy.

As can be seen, the values in the lung are much lower than those in the lymph nodes. Thus, there is an efficient clearance from the lung via the lymphatic system, and lung biopsies will therefore only yield low values which would be difficult to evaluate. If exposure needs to be ascertained mediastinal lymph nodes should be excised. Various lymph nodes seem to give slightly different values but this is to be expected since they will take care of other reactions as well and an even distribution would be strange.

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Table *Amount of metals (ug/g dry tissue)*

	Cobalt	*Tungsten*
Lung parenchyma		
Subpleural upper lobe	0·79	2·8
Subpleural lower lobe	0·14	4·9
Central lower lobe	0·17	6·6
Mediastinal lymph node	3·28 (3·1)	135·0(34·0)