

# Proceedings of the Thoracic Society and the British Thoracic Association

The Spring Meeting of the Thoracic Society was held on 31 January 1980 and of the Thoracic Society and the British Thoracic Association on 1 February 1980 at the Royal Free Hospital, London.

## Carcinoma of the bronchus: incremental factors affecting prognosis

M AZARIADIS, R K FIRMIN, A REES, M PANETH, C R LINCOLN, S C LENNOX Between January 1969 and 1973, 661 patients underwent exploratory thoracotomy for carcinoma of the lung at the Brompton Hospital. This group has been studied to determine the factors affecting survival after operation. There were 562 (85.5%) male and 99 (14.5%) female patients. In 568 (86%) patients lung resection was possible, of whom 254 (38%) had a pneumonectomy, 310 (47%) had a lobectomy, and four had a segmental resection. Actuarial survival rate at five years for all patients was 21% and at 10 years was 20.5%. Many sub-sets have been examined to determine the influence of cell type, size of tumour, lymph node involvement, and extent of surgical operation. These have shown a five-year-survival rate varying from 2.3% to 73%. On the data analysed an incremental risk chart has been constructed to determine the likelihood of a patient who has undergone an operation for carcinoma of the lung surviving for five years.

## Preoperative radiotherapy and surgery in the treatment of oat cell carcinoma of the bronchus

V LEVISON Ninety patients with oat cell carcinoma of the bronchus were treated from 1966-76 at the North Middlesex Hospital by preoperative cobalt radiotherapy and radical surgery. The diagnosis was established by bronchoscopy in 85 patients and sputum examination in five. All were regarded as operable initially. The original group of patients was given 1750 rad minimum tumour dose in seven treatments over eight days. The dose was raised in 1970 to 2500 rad in 10 treatments over 11 days. All the patients with oat cell cancer in the latter group died so since 1974 all patients have received the original dose of 1750 rad. Thoracotomy was carried out as soon as possible, the average delay being 2.5 days. Seventy-one patients had a radical pneumonectomy, two a lobectomy, and seven no surgery. The most common complication was a bronchopleural fistula in four patients; all died and recurrence was present in two at necropsy.

Review of the histology when the whole lung was available led to revision of the diagnosis to either squamous or adenocarcinoma in eight patients, and a bronchial carcinoid in one.

Eleven out of the 73 patients (15%) undergoing radical surgery (all histologies and both radiation dose levels) survived four years. Eight of the 45 patients (17.7%) with oat cell carcinoma receiving 1750 rad remained alive and well at four years. These results compare favourably with those of the 1969 Medical Research Council comparative trial of surgery and radiotherapy in this condition.<sup>1</sup> The organisation of multicentre random trial to establish the value of the method of treatment is suggested.

## REFERENCE

- 1 Medical Research Council (1969). Five year follow-up of the Medical Research Council comparative trial of surgery and radiotherapy for the primary treatment of small or oat cell carcinoma of the bronchus. *Lancet* 1969; 2:501-5.

## Carcinoid tumours of the lung: a review of 69 cases

R HURT A review has been made of 69 cases of carcinoid tumour of the lung seen during the period 1951-79. The clinical, radiological, and bronchoscopic presentation is described. The histological similarity on bronchoscopic biopsy between carcinoid tumour and oat cell carcinoma is stressed, especially if the biopsy is small as obtained at fiberoptic bronchoscopy. Treatment was by pneumonectomy, lobectomy or in some patients bronchotomy, in which case the use of a Gebauer skin graft has been most satisfactory in minimising the extent of lung resection. There have been only one known recurrence in the 49 cases followed up for more than five years.

## Dermoid cysts of the mediastinum

J SOUTHGATE, P R SLADE Teratoid tumours in the mediastinum have a varied clinical presentation. Tumours which are mainly cystic tend to be calcified and often symptomless. More solid tumours frequently burrow deeply into surrounding structures. Histological examination shows that "invasive" dermoid often contain glandular structures. It seems likely that the tendency for some dermoids to destroy surrounding tissues may be the result of small capsular ruptures and possible release of digestive enzymes. Clinical cases demonstrate the correlation between the clinical behaviour and histological type of the dermoid cyst. Even in the "invasive" type of teratoid, surgical excision seems to give a satisfactory result.

**Alveolar cell carcinoma: clinical, radiological, and pathological correlations**

A M HUNTER, R M E SEAL, B H DAVIES Alveolar cell carcinoma is an uncommon pulmonary tumour. Twenty-three cases, seen in Cardiff over 20 years, have been reviewed. Radiographic appearances are diverse—eight segmental nodular, five lobar nodular, three lobar diffuse, four bilateral nodular, and three bilateral diffuse. Eight had associated pulmonary fibrosis. Sputum cytology gave positive results in 57% of cases in the past five years. Bronchorrhoea is rare; only two cases had this complication. Pathological distinction from an adenocarcinoma can be difficult.

**Some observations on the surgical treatment of oesophageal cancer**

H V WINGFIELD Active surgical intervention in carcinoma of the oesophagus and cardia is mandatory<sup>1</sup> Most clinicians accept that there is little place for radiotherapy or oncolytics in the treatment of the main symptom—dysphagia—and it is for the relief of this dysphagia that surgery is required.

Oesophageal intubation results in only short-term survival. In over 200 cases in this unit survival is on average only 13 weeks, of which the best part of two are spent in hospital. For these few weeks the patient has to live on a very modified diet, and even so, a considerable number return to hospital on one or more occasion for the clearance of a blocked intra-oesophageal tube.

It has become our practice to carry out resection of the growth or bypass, even in the presence of metastases. To do this in safety the whole technique of major resection has been re-examined. A new exposure is described, together with the use of mechanical suturing instruments and latterly using a gut anastomosing clamp. This, together with improved pre and postoperative care, has resulted in a significant lowering of morbidity and mortality.

The results of surgery in the most recent 115 cases using mechanical surgical aids are discussed. The discussion is illustrated with slides to explain the surgical procedure and the morbidity and mortality figures, with a breakdown of all causes of death in these cases.

REFERENCE

<sup>1</sup> McKeown KC. Carcinoma of the oesophagus. *J R Coll Sur Edinb* 1979; 5:253-74.

**Emergency open-heart surgery: experience with 100 consecutive cases**

F C WELLS, D K C COOPER, B MILSTEIN, T ENGLISH One thousand two hundred and three open-heart operations were performed at Papworth Hospital between January 1973 and December 1978 with an early (30-day) operative mortality of 5.3%. One hundred patients were treated as emergencies. This was defined as operation within 24 hours of referral to the surgeon. The early mortality in this group was 28 (28%) and the total mortality was 38 (38%). These accounted for 60% of all deaths during the period under review.

The main reason for emergency surgery included ischaemic heart disease (37 patients; mortality 20%), critical valve disease (20 patients; 15%), bacterial endocarditis (14 patients; 64%), acute aortic dissection (12 patients; 33%), and problems related to valve substitutes (11 patients; 63.6%).

The incidence of critical valve disease was higher in the earlier years of this study (1973-75; 16 patients) and that of ischaemic heart disease in the latter years (1976-78; 25 patients). Delay in referral for operation from the time of diagnosis was associated with a particularly high mortality in patients with bacterial endocarditis and critical valve disease.

Many factors contribute to the increased risk of emergency open-heart surgery. Of these, dysfunction of other organ systems secondary to acute or chronic low cardiac output is one of the most important. Earlier diagnosis and referral for surgery for correction of severe haemodynamic abnormalities should help to reduce operative mortality in these patients.

**Bronchial artery ligation as the treatment of major haemoptysis**

R FRANKS, S WILLIAMS, O S TUBBS, S C LENNOX Life-threatening haemorrhage from the bronchial tree in the presence of pulmonary disease poses an extremely difficult problem of management. Location of the source of bleeding is very difficult. With already reduced pulmonary reserve, major resection of the lung is undesirable, even if appropriate localisation is possible.

Three patients, one with fibrocystic disease and two with bronchiectasis, presenting with such major haemorrhage came to operation. In each it was possible to localise the haemorrhage to one side, and the bronchial arteries to that side were ligated at thoracotomy. Two patients remain well more than 10 years after operation, the third died a year later of other complications of his fibrocystic disease. In all three, operation was effective in preventing further major haemoptysis, though subsequently minor episodes of blood-stained sputum have occurred.

We have been unable to trace any reports of the long-term effect of bronchial artery ligation on pulmonary function and have investigated two patients by spirometry and regional lung function studies. The background and operation will be described and the results of lung function studies presented.

**Thrombotic obstruction of Björk-Shiley valves**

S A PHOTIOU, D L CHEUNG, M J DRAKELEY, J L MERCER, J B MEADE One thousand and thirty-six Björk-Shiley prosthetic valves were implanted in 915 patients between April 1973 and September 1979. Thrombotic occlusion of a valve occurred in 13 patients, at intervals varying between five and 65 months after insertion, of which four out of 498 (0.8%) were aortic, eight out of 506 (1.6%) were mitral, and one out of 32 (3%) was tricuspid. None of the patients with thrombosed aortic valves were receiving oral anticoagulants, although three were taking dipyri-

damole (Persantin). All the patients with thrombosed mitral prostheses and the one with the tricuspid valve thrombosis were receiving oral anticoagulants. All the patients with occluded aortic and mitral valves presented with symptoms of left heart failure of recent onset, and the patient with the occluded tricuspid valve presented with acute dyspnoea and signs of right heart failure. In all patients the characteristic "click" of the prosthesis was absent. The diagnosis was confirmed by echocardiography in four patients and cardiac catheterisation in one. All patients were treated surgically as soon as the diagnosis was established. Three of the eight patients with thrombosed mitral valves died during operation. Two of the surviving five had xenograft (porcine) valves inserted, one had a new Björk-Shiley valve, and two had removal of thrombus without valve replacement. One of the latter (a patient with chronic lymphatic leukaemia) has subsequently had a further thrombosis. One of the four patients with thrombosed aortic valves had a porcine prosthesis inserted, one had a new Björk-Shiley valve, and two had removal of thrombus without valve replacement. One of the latter has suffered a rethrombosis of the valve after discontinuing warfarin during treatment of bladder papillomas. This has successfully been replaced with a porcine valve. The thrombosed tricuspid valve was replaced with a porcine prosthesis. Early and accurate diagnosis of thrombotic occlusions of a prosthetic valve depends on a high index of suspicion in patients with sudden onset of heart failure. Urgent and aggressive surgical treatment offers the patient the best chance of survival.

#### Scanning electron microscope appearances of glycerol-preserved allogenic dura mater before and after implantation into patients

M A GLASBY, A J GUNNING, M JENKINS, I MUSTAFA, M H YACOB Allogenic antibiotic-sterilised dura mater preserved in glycerol has been used for some years in the fashioning of intracardiac patches, bioprosthetic valves, and vascular conduits. It is a relatively easy tissue to obtain and preserve and has excellent handling properties. Its tensile strength has shown it to compare very favourably with other bioprosthetic materials, and in the short term at least it would appear to be non-thrombogenic.

The present study was designed to compare the surface properties of glycerol-preserved dura before and after exposure to circulating blood. Samples of dura mater retrieved from patients after 48 hours, one month, three months, and nine months were processed and examined by scanning electron microscopy. The changes are compared with dura mater processed but not implanted in a patient.

The electron microscopic appearances are described and the findings suggest that dura mater will serve as a suitable tissue for cardiac bioprostheses irrespective of whether it is a "working" tissue as a valve leaflet or a "passive" tissue as in a patch or conduit. Experimental studies on pigs are being carried out to study the possible changes over long periods.

#### Plasma CEA measurements in the preoperative assessment of lung cancer

T C STOKES, J STEVENS, P LONG, J R BELCHER, A L MILLER Eighty-one patients with clinical and radiographic features suggestive of a resectable lung cancer referred for surgery during one year were studied to determine the value of plasma CEA measurement and its prognostic significance in the preoperative assessment. In addition to routine staging procedures, plasma CEA measurements were made on two occasions before any operative procedure.

Approximately one-fifth of patients had plasma CEA levels greater than 40  $\mu\text{g/l}$ . Such elevations were more common in patients whose tumours had already metastasised and did not bear any relationship to the local extent of the disease. Patients who had a curative resection were followed for two years and serial CEA measurements made. In this group a raised CEA ( $>40 \mu\text{g/l}$ ) was associated with a bad prognosis, and at two years survival was significantly greater in those who had a preoperative CEA in the normal range (less than 20  $\mu\text{g/l}$ ). The value of serial CEA measurements will be discussed.

#### Oesophagectomy in patients with oesophageal speech

D C T WATSON, J HADLEY, J C MARSH, H R MATTHEW Oesophageal resection in patients with oesophageal speech has not been described previously. Two patients who had undergone laryngectomy and later required lower oesophageal resection are discussed. A woman of 58 years had resection for carcinoma of the lower oesophagus five years after laryngectomy for carcinoma, and a man of 58 years had an oesophageal resection for reflux stricture secondary to hiatal hernia nine years after laryngectomy for carcinoma. Both patients had learned oesophageal speech after their laryngectomy and pre and postoperative voice recordings show that their speech was unaffected by oesophageal resection. This emphasises that the mechanism of so-called oesophageal speech is under nasal and pharyngeal control and therefore lower oesophageal resection can be undertaken without affecting the acquired form of speech.

#### Transit time analysis of the forced expiratory spirogram in male smokers

D P OSMANLIEV, E E DAVIES, N B PRIDE Measurement of the mean transit time (MTT) and the dispersion of transit times (DTT) of the forced expiratory spirogram has been proposed by Permutt and Menkes<sup>1</sup> as a simple and sensitive method for detecting slowing and non-uniformity of lung emptying in mild airway disease. We have measured MTT and DTT in 40 male non-smokers and 80 male smokers, aged 25-60 years who are taking part in a study of the natural history of airflow obstruction. Analysis has been terminated six seconds after the start of forced expiration.

Values of MTT and DTT increased with age in both smokers and non-smokers and were significantly greater in older smokers than non-smokers. The rat-

of increase in MTT and DTT in smokers appeared to be most rapid between 25 and 35 years. There were only small changes after bronchodilator treatment. Comparison of MTT and DTT with values taken from maximum expiratory flow-volume curves ( $V_{max_{50}}$  and  $V_{max_{25}}$ ) in the same subjects showed that the two techniques were of similar efficacy in separating smokers from non-smokers.

These results confirm that transit time analysis of the spirogram can provide information usually obtained by more complex tests of lung function, but it remains to be established whether there are circumstances in which MTT and DTT are superior to existing techniques for detecting mild airway disease.

REFERENCE

1 Permutt S, Menkes H. Spirometry: analysis of forced expiration within the time domain. In: Macklem P, Permutt S (ed). *The Lung in the transition between health and disease*. New York: Marcel Dekker, 1979: chapter 6.

**Transit time and derivatives as guides to the reversibility of chronic airflow obstruction**

R BELLO, M J CAMPBELL, G COLLINS, J E COTES, D R TAGARO Mean transit time and derivatives (standard deviation, coefficient of variation, and skewness) are indices of forced expiratory flow with respect to time and have been commended by Neuburger *et al*<sup>1</sup> for describing the ventilatory defect of patients with cystic fibrosis. Others have commented on the relevance for assessing air flow obstruction of peak expiratory flow rate, flow rate at small lung volumes ( $V_{50}$  and  $V_{75}$ ), the changes in flow between breathing air and helium, and the volume of isoflow.<sup>2</sup> We examine the relative usefulness of these and other indices for assessing the response to bronchodilator aerosol of patients with chronic airflow obstruction. The 28 patients were ex-coalminers aged 34–76 years. Their mean initial FEV<sub>1</sub> was 1.781 and the average increase 60 min after inhaling 0.2 mg of salbutamol was 11.3%. The response was assessed on two occasions a month apart from flow-volume curves while breathing air and 80% helium in oxygen obtained using a McDermott dry spirometer with digital incremental output.<sup>3</sup> Similar measurements were made on 25 control subjects in whom the average increase in FEV<sub>1</sub> after salbutamol was 3.6%.

The results were used to assess the reproducibility of the initial measurements breathing air, their inter-relationships, the change between breathing air and breathing helium, and the response to a bronchodilator aerosol. The percentage response to salbutamol was greater in the patients than in the healthy subjects for all indices except mean transit time, standard deviation, and indices which reflected a difference between breathing air and breathing helium. On this account none of the latter indices was suitable for assessing bronchodilatation in patients with chronic airflow obstruction. Of the remaining indices the reproducibility of the response was best for FEV<sub>1</sub> and  $V_{50}$  which remain the indices of choice. But in both cases the residual variability is large so the

result of one assessment must be interpreted with caution.

We are indebted to Mrs P McCarthy for the derivation of mean transit time and Ms C Heywood for help with the analysis.

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 3 McDermott M, McDermott TJ. Digital incremental techniques applied to spirometry. *Proc Roy Soc Med* 1977; **70**:169–71.

**Partial expiratory flow-volume curves and their use in measuring bronchodilator responses in normal subjects**

H R GRIBBIN, P J BARNES, N B PRIDE Airway responses in normal subjects have usually been assessed by changes in airway resistance. This technique assesses the resistance of the whole airway (including the larynx) and many measurements have to be made to overcome the intrinsic variability of the method.

We have examined the value of partial expiratory flow-volume (PEFV) curves as an alternative technique for studying bronchodilator dose-response relationships in normal subjects. The potential advantages are that it is simpler to measure maximum flow ( $V_{max}$ ), that  $V_{max}$  at small lung volumes probably reflects only lung recoil and intrathoracic airway dimensions, and that full inflation manoeuvres (which may alter airway tone) are avoided.<sup>1</sup>

Partial expiratory flow-volume curves were obtained with subjects seated in a variable-volume body plethysmograph. Forced expiration was started from just above functional residual capacity after a period of tidal breathing and  $V_{max}$  was measured when approximately 25% of the forced vital capacity remained to be expired. Adequate resolution was obtained using a large screen storage oscilloscope. Six normal subjects, aged 28–35 years, were studied on three separate days. The coefficient of variation of the baseline  $V_{max}$  varied from 5–15%. Increasing doses of salbutamol were inhaled from specially prepared pressurised canisters to a maximum dose of 410  $\mu$ g, and three or four PEFV curves were obtained 15 minutes after each dose. Satisfactory dose-response curves with a plateau value of  $V_{max}$  30–70% greater than mean baseline  $V_{max}$  were obtained consistently in five of the six subjects.

We have also studied the interaction between inhaled aminophylline and inhaled salbutamol. Preliminary work suggests that an infusion of aminophylline at 1 mg/kg body weight, insufficient to alter significantly baseline  $V_{max}$ , may increase synergistically the response to inhaled salbutamol.

These results suggest that PEFV curves may be a useful method for studying airway responses in normal subjects.

REFERENCE

1 Brown NE, McFadden ER Jr, Ingram RH Jr. Airway responses to inhaled histamine in asymptomatic smokers and non-smokers. *J Appl Physiol* 1977; **42**:508–13.

### Reproducibility of flow rates measured with low density gas mixtures for assessing airways obstruction

I S PETHERAM, C W BIERMAN, J MOXHAM, S G SPIRO  
An increase in expiratory flow rate in the middle of the vital capacity (V50) after breathing a low density gas mixture (helium 80%; oxygen 20%; He/O<sub>2</sub>) compared to V50 breathing air has become an accepted means of identifying the major site of airflow obstruction. Subjects with an increase in V50 with He/O<sub>2</sub> of  $\geq 20\%$  (responders) have predominant large airways obstruction (AWO), and those with  $\leq 20\%$  increase (non-responders) small AWO.<sup>1</sup> Despite its acceptance there has been no systematic examination of the test's reproducibility in experimentally induced AWO. We have measured He/O<sub>2</sub> responses in 12 asthmatic subjects before and during exercise-induced asthma after four identical exercise tests, all on different days, using a standardised exercise protocol.<sup>2</sup>

At rest, before the first exercise run 11 subjects were He/O<sub>2</sub> non-responders. Eight of the 11 remained non-responders before all four runs, and the single responder was also consistent. Of the other three subjects, two showed a response on one occasion and one on two occasions. After exercise, at the nadir of V50 air, the He/O<sub>2</sub> response was much more variable. Of the 11 subjects who became responders after the first run only six remained responders after all four runs—but the percentage increase in V50 with He/O<sub>2</sub> varied widely within each subject. Three subjects remained non-responders after one test only, but had responses of up to 75% after the other three runs. Two subjects remained non-responders after two of their runs. There was no relationship between the He/O<sub>2</sub> response and the severity of AWO measured by spirometry and V50.

Our data show a wide variation in individual changes in V50 with He/O<sub>2</sub> and suggest that the reproducibility of this test is not sufficiently reliable to allow a simple conclusion as to the major site of AWO.

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### Respiratory muscle function and fatigue: studies on the sternomastoid

J MOXHAM, S G SPIRO, C M WILES, R H T EDWARDS  
It is not known whether the function of the respiratory muscles limits ventilatory capacity in normal subjects or patients; or if muscle fatigue is an important factor in respiratory failure. To consider these questions we have devised a method of investigating the contractile properties of the sternomastoid muscle<sup>1</sup> which is important for ventilation in patients with obstructive lung disease and hyperinflation. The results illustrate that the force generating characteristics of the sternomastoid during isometric contractions in response to

electrical stimulation are similar to those that have been established for other skeletal muscles.<sup>2</sup> We have used this technique to demonstrate that inspiratory loading produces respiratory muscle fatigue. Such fatigue could have important implications for the management of patients with respiratory failure. Sternomastoid muscle function and fatigue has been investigated in normal subjects and patients with respiratory disease.

This work is supported by the Wellcome Trust and the Muscular Dystrophy Group of Great Britain.

#### REFERENCES

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- 2 Edwards RHT, Young A, Hosking GP, Jones DA. Human skeletal muscle function: description of tests and normal values. *Clin Sci Molec Med* 1977; 52:283-90.

### Pain relief after thoractomy

J R WEDLEY  
A study was undertaken of postoperative analgesia in 40 patients who had undergone thoractomy. The patients were randomly allocated into four groups. The first group received papaveretum as required. The second group also received papaveretum as required but at the end of the operation were given an intercostal block two segments above and below the drain site and thoractomy wound. The block was performed by the surgeon through the open chest using a solution of 0.5% bupivacaine mixed with an equal volume of low molecular weight dextran in normal saline, as described by Kaplan *et al.*<sup>1</sup> The third group was given buprenorphine as required, and the fourth group a fentanyl drip. The fentanyl was administered separately from any other intravenous therapy and the rate was controlled by a Dial-a-Flow drip control device. The concentration of the drip was 500 micrograms in a solution of 500 ml of 5% dextrose. In the latter part of the study this was always administered through a 21-gauge butterfly needle.

Premedication and anaesthesia were standardised and the assessment of pain relief was carried out by the nurses half hourly for the first 24 hours. Postoperative minute volume and respiratory rate were measured as frequently as possible during this period and at 24 hours a mixed expiratory Pco<sub>2</sub> was measured and in some cases this was supplemented by an arterial Pco<sub>2</sub>. A subjective assessment of the pain was then obtained from the patients by means of a standard questionnaire using a linear analogue scoring system.

Two patients were lost from the study because they required postoperative artificial ventilation and one patient had to be returned to theatre within a few hours because of continual bleeding. The results therefore are from 10 patients in the group who received papaveretum alone, nine patients in the group who received an intercostal block and papaveretum, 10 patients in the buprenorphine group and eight patients in the fentanyl group. There was

a predominance of men to women in each group. The average mean age in each group was comparable, being almost 60 years of age. Assessment by the nurses proved to be useless because of the impossibility of observing the patients continuously in a normal ward. For the first three groups the numbers of doses administered varied very little. The patients' assessment of the presence of pain showed that the intercostal block and papaveretum were more effective than buprenorphine alone, which in turn was more effective than papaveretum alone. The fentanyl group scored approximately the same as the buprenorphine group but had a much wider scatter. There was no evidence at any time during the 24 hours of respiratory depression as assessed by minute volume and rate, and similarly the mixed-expired PCO<sub>2</sub> measurements were comparable in each group.

As a result of these findings a further trial of post-operative analgesia comparing the effect of an intercostal block plus buprenorphine as required with that of an intercostal block plus papaveretum as required is continuing.

REFERENCE

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**Bronchoscopic assessment of tracheal damage after endotracheal intubation**

D HONEYBOURNE, C BARHAM, J F COSTELLO, L STRUNIN  
Tracheal damage is a complication of tracheal intubation or tracheostomy, but little is known about how rapidly changes occur. Animal studies<sup>1</sup> have shown that progressive damage occurs when the lateral wall pressure exerted by the endotracheal cuff exceeds venous capillary pressure. Studies in vitro have suggested that high-volume low-pressure cuffs are less damaging than the standard low-volume high-pressure cuffs.<sup>2</sup> We have investigated the effects of these two types of cuff in vivo by comparing Portex "blue-line" with Lanz endotracheal tubes.

We studied 28 patients undergoing cardiac surgery who were electively ventilated via an endotracheal tube for some 24 hours after operation. At the time of surgery patients were intubated with one of the two types of cuffed endotracheal tube which were selected randomly. At the time of extubation the tracheal mucosa from main carina to vocal cord level was carefully assessed by fiberoptic bronchoscopy and photographs taken. Tracheal damage was scored by the bronchoscopist according to the degree of oedema, ulceration, and bleeding seen, and also later from the photographs by an independent assessor who was unaware of the type of tube used. Results from both assessors showed significantly less tracheal mucosal damage caused by the low-pressure high-volume type of cuff (Lanz endotracheal tube).

We suggest, therefore, that this type of endotracheal tube should be preferred for those patients who may require intubation for a considerable length of time—for example, because of respiratory failure—as the degree of tracheal damage and risk of long-term sequelae should be appreciably reduced.

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**Lung folding simulating peripheral pulmonary neoplasm (Blesovsky's syndrome)**

C R PAYNE, P JAUQUES, I H KERR  
Five cases are presented in whom the diagnosis of benign pleural thickening with lung folding simulating peripheral pulmonary neoplasm was made. Two patients presented with chest pain, one with dyspnoea, and two were asymptomatic. Radiographic assessment in all cases showed similar appearances, with a peripheral opacity which appeared to lie within the lung and characteristic curvilinear shadows connecting the opacity to the hilum of the lung. These curvilinear shadows are not seen with peripheral pulmonary neoplasms. Volume loss in the affected lobe is common. At thoracotomy, predominantly visceral pleural thickening was noted without significant parietovisceral pleural adhesions. Lung folding had occurred, resulting in the radiographic appearances of an intrapulmonary mass and, after removal of the thickened pleura, the involved lobe expanded to its normal volume and shape. Histology in all cases showed pleural fibrosis with no evidence of malignancy.

Blesovsky<sup>1</sup> was the first to describe the "lung folding" which may occur in association with benign pleural thickening. The aetiology of these large pleural plaques remains uncertain but asbestos has been incriminated,<sup>2</sup> and pulmonary infarction or infection might occasionally be expected to give rise to similar pleural changes.

We feel that the curvilinear shadows probably reflect the mechanical distortion of the lobe by the forcible contraction of the outer pulmonary surface attached to the relatively fixed hilum, resulting in compression of pulmonary tissue along the lines of the intralobar septa. We would emphasise the characteristic radiographic appearances especially of lateral tomography, which are diagnostic and obviate the need for surgery.

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**Cough versus chest physiotherapy in the regional clearance of excessive tracheobronchial secretions**

J R M BATEMAN, S P NEWMAN, KATHLEEN M DAUNT, NÓRÍN F SHEAHAN, D PAVIA, S W CLARKE  
Cough acts as a reserve mechanism for mucociliary action in patients with chronic obstructive lung disease. Chest physiotherapy including cough is effective in helping the removal of excessive secretions from central, intermediate, and peripheral lung regions.<sup>1</sup> In the present study we have evaluated critically the relative roles of cough and chest physiotherapy.

Regional lung clearance was monitored for 1.5 h with a gamma camera (Nuclear Enterprises Mark III) linked to a computer (PDP-1105) after the inhalation of uniform 5  $\mu\text{m}$  polystyrene particles firmly labelled with  $^{100\text{m}}$ technetium. Six patients (mean age  $60 \pm 16$  (SD) years) with stable chronic obstructive lung disease ( $\text{FEV}_1$   $0.9 \pm 0.4$  (SD) l) completed control, chest physiotherapy, and cough studies in a crossover manner. Chest physiotherapy with coughing was administered for 20 min one hour after radioaerosol inhalation. In the cough study the patients coughed for 1 min every 5 min for 20 min. Collected sputum samples were weighed.

Both lung fields were divided into central, intermediate, and peripheral regions and the results from each side combined. The initial regional distribution of radioaerosol was similar for all three studies. The group mean clearance (% initial total lung count) before cough and chest physiotherapy with cough was similar for all three studies. Compared with the control study chest physiotherapy significantly increased ( $p < 0.05$ ) radioaerosol clearance from all three regions, whereas cough was effective ( $p < 0.05$ ) only in the central region [Central region: control  $6.0 \pm 3.5$  (SE)%; physiotherapy  $33.0 \pm 5.0$  (SE)%; cough  $26.0 \pm 5.0$  (SE)%. Intermediate region: control  $3.5 \pm 1.5$  (SE)%; physiotherapy  $20.0 \pm 2.5$  (SE)%; cough  $10.0 \pm 2.0$  (SE)%. Peripheral region: control  $2.0 \pm 0.5$  (SE)%; physiotherapy  $8.5 \pm 1.5$  (SE)%; cough  $3.0 \pm 1.0$  (SE)%]. The weight of collected sputum was greater during physiotherapy (physiotherapy  $19 \pm 5$  (SE)g; cough  $11 \pm 3$  (SE)g).

Our findings demonstrate that cough acts only in central lung regions while chest physiotherapy is effective firstly in moving secretions from peripheral to central regions and secondly in promoting their final removal from the lung.

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#### Effect of an extension tube on the bronchodilator efficacy of terbutaline delivered from a metered dose inhaler

N P KEANEY, S A GOMM, N J P WINSEY, T B STRETTON  
Metered dose bronchodilator inhalers (MDI) are convenient to use and effective even though most of the delivered drug impacts in the oropharynx. It has been suggested that activating the device while this is held a short distance from the open mouth helps to overcome the latter problem.<sup>1</sup> The interposition of a cylindrical dead-space between the mouthpiece of a standard inhaler and the patient's lips should have the same effect. We have tested this possibility in 14 adult patients with reversible airflow obstruction. To do this it was necessary to devise a double-blind investigation so that dose-response curves of a bronchodilator could be prepared. This was done by providing the patient with two apparently identical MDIs, one

of which delivered 125  $\mu\text{g}$  doses of terbutaline and the other placebo. To one or other of the inhalers a tube (spacer) 10 cm long  $\times$  3.2 cm diameter was attached. By taking one puff from each the patient thus received 125  $\mu\text{g}$  terbutaline and neither he nor his immediate observer knew whether this was inhaled through the spacer or without it. The bronchodilator responses to doses of 125, 125, and 250  $\mu\text{g}$  of terbutaline, given at 20 min intervals, were then observed on separate days. One day the subject received the drug via the spacer and the placebo without, and on the other study day the procedure was reversed. The following measurements were made:  $\text{FEV}_1$ , FVC, PEFR, TGV, Raw, and sGaw. These variables were estimated before drug administration, again five and 15 min after inhalation of each dose, and at intervals for five hours after the first dose of terbutaline. The mean ( $\pm$ SEM) control observations for  $\text{FEV}_1$ , TGV, and sGaw were 1.11 (0.1) l, 4.66 (0.23) l, and 0.33 (0.02)  $\text{kPa}^{-1} \cdot \text{s}^{-1}$  on the day when terbutaline was delivered via the spacer and 1.17 (0.09), 4.59 (0.29), and 0.35 (0.02) when the spacer was attached to placebo inhaler. The results obtained at the time of maximum bronchodilation were respectively 1.73 (0.12), 3.76 (0.23), and 0.80 (0.11) when terbutaline was inhaled using the spacer and 1.73 (0.12), 3.76 (0.28), and 0.80 (0.07) without the spacer. The implications of these observations will be discussed.

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#### Pigeon bloom: a further antigen in pigeon breeder's disease

H MACKENZIE, C MCSHARRY, P LYNCH, S W BANHAM, G BOYD  
Pigeon dropping extracts have been investigated extensively as the major source of natural antigen(s) in pigeon breeder's disease,<sup>1</sup> although it is well recognised that individuals may develop bronchioalveolitis in circumstances where contact with pigeon excreta is minimal or absent.<sup>2</sup> Pigeon "bloom" which is a waxy substance coating the birds' feathers and which is readily deposited on hands and clothes during handling of the pigeons, may be important in these situations.

Five pigeon fanciers who described symptoms after attending pigeon shows were selected for study, and two or more precipitin lines were demonstrated in their sera against an aqueous bloom extract. This extract was then used as a sepharose-linked antigen in a radioimmunoassay. Twenty-six sera were tested and a quantitative estimate of IgG antibody to "bloom" extract relative to antibody to pigeon globulin was obtained. Competition and absorption experiments confirmed the different groups of IgG antibody specificities in the fanciers' serum, and although there was a correlation between the two antibody populations, considerable individual variation in their relative levels was apparent.

The existence of a further antigen could explain the rather poor correlation between antibody

pigeon dropping extracts and the disease.<sup>3</sup> Furthermore, the interaction between the various inhaled antigens may itself affect the clinical outcome, and in this respect the potential adjuvant properties of the "waxy" bloom are being explored.

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### Do carcinoid tumours of the trachea occur?

R K FIRMIN, B HEARD, A DEWAR, S C LENNOX Carcinoid tumours of the trachea have been reported infrequently. In the last four years we have resected two tracheal tumours whose pathological diagnosis on light microscopy was carcinoid tumour. As we were intending to report these cases, we also examined the tumours under the electron microscope. To our surprise, neither tumour showed evidence of neurosecretory activity as is found in carcinoid tumours. It seems that one tumour is derived from smooth muscle and the other from glandular epithelium. We feel therefore that a diagnosis of tracheal carcinoid tumour made by light microscopy alone is open to doubt. These cases illustrate the limitation of light microscopy in certain areas of tumour pathology.

### Serial pulmonary function tests in systemic lupus erythematosus

P W IND, H R GRIBBIN, J M B HUGHES, K B ELKON, J R SEWELL Systemic lupus erythematosus (SLE) can affect the respiratory system in a variety of ways and pulmonary function is frequently abnormal. The most dramatic clinical picture is of so-called "shrinking lungs".<sup>1</sup> Gibson *et al*<sup>2</sup> described seven such patients and found diaphragm function to be grossly abnormal in four out of the five in whom it was assessed. They postulated that inability of the diaphragm to generate normal pressures contributed to the shrinkage of lung volumes and the patient's dyspnoea.

Pulmonary function was studied in 117 patients with SLE. Mean ( $\pm$ SD) age and height were 33.0 ( $\pm$ 13.2) years and 163.5 ( $\pm$ 7.8) cm respectively. The most common abnormality was a reduced carbon monoxide transfer factor ( $T_{LCO}$  less than 80% of predicted value) found in 72% of patients. Vital capacity (VC) and total lung capacity (TLC) were reduced in 33% of patients, and  $k_{CO}$  (diffusing capacity corrected for lung volume) was low in 47%.

In seven patients with the most limited pulmonary function showing typical clinical and physiological features of shrinking lungs, serial observations were made over periods ranging from six months to four years. Static lung compliance, maximum lung recoil pressure, and minimum static mouth pressure were low or abnormal. Fluctuations of lung volume were,

in general, accompanied by appropriate changes in minimum static respiratory pressures. Five patients showed a significant improvement in their ability to generate negative pressures against an obstruction at the mouth (mean of -15 decreasing to -36 cm H<sub>2</sub>O) with a mean increase in VC of 96%. In the remaining two patients there was no change in VC, although maximum mouth pressures decreased from -14 and -30 cm H<sub>2</sub>O to -24 and -68 cm H<sub>2</sub>O respectively.

The possible reasons for loss of lung volume in SLE are complex. These serial observations support the notion that inspiratory muscle weakness plays a part.

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### Pulmonary capillary volume (Vc) in rheumatoid disease

E A HILLS, M S GEARY In some patients with rheumatoid disease gas transfer across the lungs is abnormal. Membrane component of gas transfer (Dm) and Vc may be estimated by measuring transfer factor  $T_L$  for carbon monoxide at two or more concentrations of inspired oxygen. Since  $1/T_L = 1/Dm + 1/\emptyset Vc$  by plotting  $1/\emptyset$  against  $1/T_L$  Dm and Vc may be derived ( $\emptyset = \text{ml O}_2 \text{ uptake/ml blood/mmHg}$ ). Dm and Vc were estimated in 48 patients with rheumatoid arthritis and in 48 normal volunteers matched for age, sex, and smoking habits. Volunteers had normal chest radiographs and normal forced expiratory volume in one second and vital capacity. There were no significant differences between rheumatoid and control groups for Dm (*t* test). Mean Vc in rheumatoid male smokers (64.0 ml, SD 16.5) was significantly lower ( $p < .025$ ) than in control male smokers (76.3 ml, SD 18.0). There was no significant difference between rheumatoid and control females. Significantly higher values of Vc (per cent predicted) were found in patients receiving corticosteroids compared with those not receiving corticosteroids or penicillamine ( $p < .02$ ), and lower values were found in patients with nodules than in those without ( $p < .025$ ). Patients with persistently low  $T_L$  for five years had a significantly lower Vc ( $p < .02$ ). It appears that the previously demonstrated abnormality of  $T_L$  in rheumatoid disease is caused by reduction of Vc. This occurs in patients with nodules and seems to be suppressed by treatment with corticosteroids.

### Chest wall mechanics during cough in patients with emphysema and fibrosing alveolitis

D ECONOMIDIS, A J R MORRIS, M GREEN We have previously shown that the lower lateral chest wall moved paradoxically outwards during the expiratory phase of coughing in normal subjects.<sup>1</sup> We predicted that this paradox might be volume-dependent, and we therefore studied six patients with hyperinflation



caused by emphysema (mean TLC 131% predicted) and six patients with fibrosing alveolitis (mean TLC 68% predicted). We measured anteroposterior diameters of the rib cage and abdomen, and lateral diameters of the rib cage at high and low levels using linearised magnetometers, with simultaneous recording of oesophageal (Poe), gastric (Pg), and trans-diaphragmatic pressures ( $P_{di}=P_g-P_{oe}$ ) and volume and flow at the mouth.

During the inspiration preceding a cough the patients all showed a change in shape of the rib cage, which became more circular. In the patients with obstructive lung disease there was little effective  $P_{di}$ , but marked  $P_{di}$  was developed by the patients with fibrosis, compatible with the advantageous curved shape of their diaphragms. During the expiratory phase of the cough both groups of patients showed paradoxical outward motion of the low lateral rib cage, but this was much more marked in the patients with fibrosis than with those with hyperinflation. However, the volume change in the patients with fibrosis was also much greater than in those with emphysema. Thus it is possible that it is the inability of the obstructive patients to achieve rapid volume changes, rather than the configuration of their diaphragm, which is responsible for the relatively uniform motion of their rib cages during the cough. The paradoxical motion of the low lateral rib cage seen particularly in fibrosis may be an important cause of cough fractures.

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#### Radiographic patterns in mycoplasma pneumonia

O C FINNEGAN, S J FOWLES, R J WHITE Previous studies of the radiographic features of mycoplasma pneumonia have given differing conclusions regarding the typical appearances.<sup>1,2</sup> In this survey, the chest radiographs of 65 adults with serologically proven mycoplasma pneumonia were reviewed. The changes were classified according to the extent, localisation, and pattern of consolidation, and other features such as collapse, pleural effusion, and lymphadenopathy were noted. The rate of resolution was examined in relation to the antibiotic therapy received. Two dominant patterns were seen—confluent areas of consolidation indistinguishable from bacterial pneumonia, and nodular opacities. There were also intermediate changes, and sometimes both patterns were seen together. Pleural effusions, collapse, and hilar lymph node enlargement occurred occasionally. Abscess formation was not seen. Complete resolution was almost invariable. There does not appear to be any one radiographic feature which is distinctive of mycoplasma pneumonia.

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#### The present outlook in bronchiectasis

D A ELLIS, P E THORNLEY, A J A WIGHTMAN, M WALKER, J W CROFTON One hundred and sixteen patients with proven bronchiectasis diagnosed at least five years previously were studied to determine the clinical outcome, change in pulmonary function, and degree of social disability. Twenty-two patients had died and the mean duration of follow-up in the survivors was 14 years. The patients who died were characterised by poorer initial ventilatory capacity than the survivors and cor pulmonale was present in 37% at the time of death. The survivors showed a tendency for improvement in symptoms whether treated surgically or medically. Thirty per cent were better than at diagnosis while only 11% were worse. Measurements of  $FEV_1$  and FVC were made at diagnosis and at review. Mild airways obstruction was the predominant abnormality. The change in pulmonary function was expressed as the decline in  $FEV_1$  in ml/yr. The decline in  $FEV_1$  was no greater than expected in 80% of patients and in a further 15% was of the order seen in cigarette smokers with mild airways obstruction. Poor ventilatory capacity was therefore not an important limitation in these patients. Of the survivors 77% had a good work record with less than two weeks loss of work annually from chest illness. The spouses of all married patients were interviewed at home by trained social worker. Fifty per cent reported no social problem but 46% of spouses found the patient's cough distasteful and 29% of couples had experienced difficulties with normal sexual life. Ten per cent of families had moved to ground floor accommodation and 7% of the patients were severely disabled. While the overall prognosis of our patients was good a minority still have physical and social problems as a result of bronchiectasis.

#### Annual decline of lung function indices in pulmonary emphysema

J A HUGHES, D C S HUTCHISON, D BELLAMY, D E DOWD, K C RYAN Cigarette smoking is thought to play an important part in the development of pulmonary emphysema but it is not clear whether abandonment of the habit influences the rate of decline in lung function in this disease. In this study serial measurements of lung function have been measured in order to elucidate the role of smoking.

We have studied 59 male emphysematous patients who had definite radiological evidence of the disease. All were assessed over a period of three years or more (longest: 11 years). None had  $\alpha_1$  antitrypsin deficiency. Their mean age was 52 years (range 25–67 yr); on entry into the study their mean  $FEV_1$  (as % of predicted) was 48% (SD 25), vital capacity (VC) 85% (SD 22). Co transfer 58% (SD 26) and arterial  $P_{O_2}$  9.1 kPa (SD 1.7).

Linear regression coefficients for each variable over time were calculated for each patient and a weighted mean regression coefficient obtained. The annual rate

of decline in FEV<sub>1</sub> was 39 ml, in VC 39 ml, in tco 0.08 mmol min<sup>-1</sup> kPa<sup>-1</sup>, and in arterial PO<sub>2</sub> 0.20 kPa.

The patients were divided into smokers (smoked during the assessment period) and ex-smokers (did not smoke at all during this period). The rate of decline in FEV<sub>1</sub>, VC, and tco was significantly greater in smokers than in ex-smokers. The rate of decline was greater in patients with radiological lesions limited to the upper half of the lung fields than in those with more generalised emphysema and this effect was more marked in the smokers.

#### Medical Research Council (1978-79) survey of notifications of tuberculosis for England and Wales

J DARBYSHIRE, P DAVIES A survey of all new notifications of tuberculosis in England and Wales for the six-month period from 1 October 1978 to 31 March 1979 has been carried out by the Medical Research Council, Tuberculosis and Chest Diseases Unit. The information obtained includes the radiographic characteristics of pulmonary disease, the bacteriological status, and the ethnic origin and country of birth of the patients. The co-operation of the medical officers for environmental health and the clinicians in charge of the patients has been striking and details of over 99% of the 4589 patients notified have been received so far. The results for the full population will be presented. These will include analyses of the ethnic origin and place of birth of the patients, the type of disease (respiratory or non-respiratory) and, if non-respiratory, the site, the radiographic characteristics of pulmonary disease, and the bacteriological status, including information on initial drug resistance.

#### Comparison of radiotherapy alone against radiotherapy and adjuvant 5-fluorouracil and adriamycin in bronchogenic carcinoma

G ANDERSON, T J DEELEY Eighty-one patients with histologically confirmed lung cancer were randomly allocated to receive radiotherapy alone or the same radiotherapy dosage together with adriamycin and 5-fluorouracil. The effects on survival were compared. Radiotherapy was given to the primary tumour and mediastinum using a 4 MEV linear accelerator with two non-opposed fields. Radiotherapy was given as an outpatient with eight treatments over 23 days. The dosages used (in rads) were squamous and adenocarcinoma 3200, undifferentiated and small cell carcinoma 2400, and where malignant cells of unspecified type were present in the sputum 2800. Chemotherapy was given on a day-patient basis as four cycles at 30-day intervals of adriamycin 80 mg/m<sup>2</sup> iv, and 5-fluorouracil 1200 mg iv.

For the whole group survival was significantly better in the adjuvant group ( $p=0.01$  log rank test). Within cell types survival was significantly better in the undifferentiated group receiving adjuvant chemotherapy ( $p=0.03$ ) where median survival was 18 weeks

with radiotherapy alone and 61 weeks with adjuvant chemotherapy. For squamous tumours survival was improved in the adjuvant group ( $p=0.25$ ) and for the other cell types the numbers were too small for analysis. Save for alopecia, the incidence of side effects was small. This form of adjuvant chemotherapy improves survival, is convenient to administer, and is relatively non-toxic.

#### Serum angiotensin-converting enzyme as a biochemical marker in sarcoidosis

P R STUDDY, R BIRD, D GERAINT JAMES Sarcoidosis is a multisystem granulomatous disorder of unknown aetiology, in which various biochemical markers are now being recognised. Serum angiotensin-converting enzyme (SACE) is helpful both for diagnosis and to monitor progress. These data on SACE compare all stages of sarcoidosis with tuberculosis, leprosy, primary biliary cirrhosis, Hodgkin's disease, and inflammatory bowel disease. Freshly drawn blood was allowed to clot, and was spun, separated, and stored at  $-20^{\circ}\text{C}$  until assayed. SACE was measured spectrofluorimetrically using hippuryl-L-histidyl-L-leucine as the substrate. The normal range of  $34\pm 18$  nmol min<sup>-1</sup> ml<sup>-1</sup> was based on values obtained in 80 healthy adult patients; it was significantly increased in 146 adult sarcoidosis patients ( $53\pm\text{SD } 27$ ). Similar values were measured in 34 acute ( $54\pm 27$ ) and in 112 chronic sarcoidosis patients ( $53\pm 28$ ). Steroid therapy reduced SACE activity towards normal, while those not receiving steroid treatment had significantly higher SACE activity ( $57\pm 17$ ) when compared with 35 patients treated with steroids ( $42\pm 30$ ). Seventy-three per cent of the subgroup of 45 untreated patients with clinically or radiologically active disease had SACE activity measured above the normal range ( $75\pm 20$ ); all had extensive pulmonary infiltration. SACE activity was measured in 34 active Hodgkin's disease patients ( $35\pm 14$ ), 31 with primary biliary cirrhosis ( $43\pm 20$ ), 28 with inflammatory bowel disease ( $28\pm 10$ ), 22 with active pulmonary tuberculosis ( $38\pm 12$ ), and 20 with leprosy ( $35\pm 10$ ). The combined false positive rate for these 135 patients was 6%; four of 31 (16%) primary biliary cirrhosis patients had increased SACE activity. Our conclusions were that SACE gave useful diagnostic information in 35% of the total sarcoidosis patients, the highest values were found in those patients with radiological features suggesting extensive pulmonary disease and clinical evidence of activity, and serial SACE measurement is a useful monitor of active sarcoidosis and its response to steroids.

#### Circulating immune complexes in tuberculosis

N MCI JOHNSON, M W MCNICOL, E J BURTON-KEE, J F MOWBRAY The sera of 96 patients, who were either suffering from tuberculosis or who were known to have had the disease in the past, were studied for the presence of circulating immune complexes using

a polyethylene glycol precipitation method.<sup>1</sup> Our routine criteria for the presence of circulating immune complexes in serum are values in the precipitate greater than C<sub>1q</sub> 104 µg/ml, IgG 69 µg/ml, IgM 114 µg/ml (2 SD above the mean for 80 normal subjects).

Circulating immune complexes were detected in 46 (48%) of the patients. Four of the five patients studied before treatment had circulating complexes. Of the patients studied during the first month of treatment, sera of 56% contained complexes. In patients who were near the end of treatment and in those studied after its completion, 30% of sera contained complexes. There was a gradual decline in the incidence of these complexes depending on the length of treatment already received.

The concentrations (in µg/1 ml serum) of C<sub>1q</sub>, IgG, and IgM in the polyethylene glycol precipitates are shown in the following table.

	Control subjects	Tuberculosis patients	
	(n=23)	First month of treatment (n=17)	After treatment (n=17)
C <sub>1q</sub>	38.6 ± 32.6	†103.0 ± 72.0	‡45.2 ± 28.4
IgG	43.0 ± 26.0	* 67.0 ± 44.0	43.0 ± 18.0
IgM	62.8 ± 66.0	*117.0 ± 62.0	‡31.0 ± 35.2

\*Significant increase from control subjects  $p < 0.05$ , †significant increase from control subjects  $p < 0.001$ , ‡significantly lower than in the first month of treatment  $p < 0.01$ , §significantly lower than in the first month of treatment  $p < 0.001$ .

Our results show that a high proportion of patients with active TB have circulating immune complexes. This is not explained by treatment alone. With treatment, there is a tendency for these complexes to disappear. Further work is needed to ascertain whether sequential estimation of circulating immune complexes in TB is of use in assessing the length of treatment needed for each patient.

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#### Alpha one antitrypsin phenotypes in parenchymal lung disorders

C C EVANS, A ELLIS, A DODD The association between emphysema and deficiency of alpha one antitrypsin ( $\alpha_1$ AT) in the serum is well established and caused by the homozygous ZZ phenotype. Recent work has suggested an increased frequency of heterozygote MZ phenotype in subjects with fibrosing alveolitis with and without rheumatoid arthritis.<sup>1</sup> We have studied 389 normal control subjects estimating serum  $\alpha_1$ AT levels by single radial immunodiffusion and determining phenotypes by isoelectric focusing with a pH gradient of 4–5. These methods were applied to the sera of 48 patients with cryptogenic fibrosing alveolitis, 20 with lung fibrosis and rheumatoid arthritis, 36 with asbestosis, 40 with asbestos exposure and no pul-

monary fibrosis, 15 with extrinsic allergic alveolitis, and 21 with mesothelioma. No significant differences were found between the phenotype frequencies in the control subjects and any of the disease states. The mean serum level of  $\alpha_1$ AT in mesothelioma subjects was significantly increased.

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#### Stimulation of mucus secretion in an in vitro rabbit tracheal preparation by normal and cystic fibrosis human serum

A C PEATFIELD, P S RICHARDSON It has been reported that serum from cystic fibrosis patients causes an increase in mucus secretion when applied to the epithelial surface of rabbit tracheal explants.<sup>1</sup> This effect was not observed with normal serum. It was postulated that there are factors in cystic fibrosis serum that promote discharge of mucus and which may be important in the pathogenesis of the disease. Some of our previous results<sup>2</sup> showed that autologous serum stimulated the release of airway mucins into cat trachea, so we were interested to see whether normal human serum would have the same effect and if so, whether the effect of cystic fibrosis serum was the same or larger. A segment of trachea (6 cm approximately) was taken from anaesthetised rabbits cannulated at each end, and placed in an organ bath containing Krebs-Henseleit solution. Two precursors of mucins, <sup>3</sup>H-glucose and sodium <sup>35</sup>S-sulphate, were added to the external fluid. These were taken up by mucus-manufacturing cells and secreted into the lumen from where they were washed out at quarter hourly intervals with Krebs-Henseleit solution. Four aliquots each of normal and cystic fibrosis serum were diluted 1 in 10 in Krebs-Henseleit solution and placed blind into the tracheal segment for three periods of a quarter of an hour.

Cystic fibrosis serum increased secretion of <sup>35</sup>S-labelled mucins relative to control values by a significantly larger amount than normal serum: +498% (range +176% to +1503%, n=12) compared with +292% (range +171% to +476%, n=12),  $p < 0.05$ . There was a corresponding difference for <sup>3</sup>H-labelled mucins but it was not statistically significant. These results confirm a difference between the mucus-promoting properties of cystic fibrosis and normal human sera, but the clinical significance is not clear.

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#### Atopy and bronchial reactivity in cystic fibrosis

M J TOBIN, M X FITZGERALD, O MAGUIRE, D REEN, TEMPANY Conflicting reports exist as to the prevalence and significance of atopy in cystic fibrosis (CF).<sup>1,2</sup> We studied 25 young adults with CF and 25 control

subjects to define the prevalence of atopy, to determine if the genetic pattern of patients with atopic features differed from those without atopy, and to see if atopic status correlated with bronchial reactivity or disease severity. The CF patients had a more frequent personal and family history of atopy compared with control subjects ( $p < 0.05$ ), more positive skin tests ( $p < 0.001$ ), higher mean IgE ( $p < 0.05$ ), IgG<sub>4</sub> ( $p < 0.001$ ), and eosinophil count (374 versus 268/mm<sup>3</sup>,  $p > 0.05$ ). No distinctive HLA pattern was observed in either the total CF group or in those patients with marked atopic features. Inhalation of histamine acid phosphate (400 µg) from a metered dose inhaler produced a greater than 15% fall in FEV<sub>1</sub> in 35% of the CF group and in 4% of the controls, with a mean percentage fall of 15% and 3% respectively ( $p < 0.001$ ). In the CF group a greater than 15% rise in PEFR occurred in 32% after inhalation of the parasympatholytic, ipratropium bromide (54 µg), and in 27% after inhalation of the sympathomimetic, fenoterol (400 µg). Atopic status showed no correlation with bronchial lability, HLA pattern, or disease severity.

The cause of the increased prevalence of atopy in CF remains unknown. It may be an acquired phenomenon resulting from increased antigen access to the IgE producing cells in the submucosa or there may be a genetic link between the genes responsible for atopy and for CF. Likewise, the cause of the increased prevalence of bronchial hyperreactivity is speculative, but it is clear that a significant number of patients derive benefit from bronchodilator treatment.

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**Effect of metoprolol on exercise tolerance in emphysema**

R J A BUTLAND, J A C K PANG, D M GEDDES Patients with emphysema hyperventilate in response to exercise as compared with chronic bronchitis and as a result are more breathless.<sup>1</sup> Hyperventilation may be caused by increased sympathetic activity and this can be blocked by propranolol.<sup>2</sup> We therefore attempted to reduce the hyperventilation in emphysema with  $\beta$ -blockers.

The  $\beta_1$ -blocker metoprolol was first established to be as effective as propranolol in blocking catecholamine-induced hyperventilation in normals. Ten "pink puffers" with emphysema entered a double-blind randomised crossover trial of intravenous metoprolol (7 mg infused over 2 min) or normal saline placebo. Exercise tolerance was assessed by a 12-minute walking test with a rating of perceived exertion followed by a progressive exercise test on a bicycle ergometer. The minute ventilation and heart rate were significantly reduced, both at rest and during the progressive exercise test, by 8.2% (SEM=1.6) and 14.2% (SEM=1.8) respectively ( $p < 0.01$ ). Three of the 10 subjects

achieved a higher workload on metoprolol, there being no change in the other seven. There was no significant difference between metoprolol and placebo in resting or exercise Po<sub>2</sub> and Pco<sub>2</sub>, in the 12-minute walking distance, and in the rating of perceived exertion.

These results indicate that a significant reduction in exercise ventilation in pink puffers with emphysema can be achieved with  $\beta_1$ -blockers. This may improve exercise performance although no benefit was demonstrated in walking distance. The fall in minute ventilation with  $\beta_1$ -blockers does not necessarily imply that sympathetic drive is increased and contributing to the hyperventilation in emphysema but the destruction of the capillary bed which removes 30-50% of circulating noradrenaline on each passage through the lung could account for such an increase.

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**Rehabilitation in chronic respiratory disability: a control study**

A COCKCROFT, M SAUNDERS, G BERRY Thirty-nine men, mostly former coalminers, with chronic respiratory disability took part in the study. After entry they were divided into two groups by a method giving an approximately equal spread of age, smoking habits, and initial performance in a walking test.<sup>1</sup> The treatment group spent six weeks as inpatients in a rehabilitation centre, taking part in a graduated exercise programme. After discharge they were given simple exercises to continue at home. The control group were not encouraged to exercise but at the end of their control period they also went to the rehabilitation centre. The men were assessed at entry, at two months, and at four months. Measurements included weight, spirometry, ventilation, and heart rate during a standard treadmill exercise and 12-minute walking distance.<sup>2</sup>

At two months the treatment group experienced marked subjective benefit. The control subjects felt the same or worse. The walking distance was significantly improved in the treatment group and to a lesser extent in the control group. The difference between the groups was significant when the effects of age, smoking, and initial walking distance were taken into account to reduce variation. At four months the treatment group had maintained their improvement but the control subjects were less far behind. Neither group showed a significant change in FEV<sub>1</sub>, and although the treatment group's FVC improved, there was little difference from the control subjects. Exercise ventilation and heart rate changed little in either group but in a number of men satisfactory results could not be obtained. Both groups had a slight reduction in weight.

Our results confirm the beneficial effects of exercise training in men with chronic respiratory disability.<sup>3</sup>

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### Deposition of pressurised aerosols in the lung using radio-labelled particles

S P NEWMAN, D PAVIA, N F SHEAHAN, F MOREN, S W CLARKE Pressurised metered dose inhalers have been in use for some years, but no direct measurement of aerosol deposition has been made because of difficulties in tagging the particles with a suitable radioisotope. Previous indirect estimates based on metabolic studies suggest that most of the dose is deposited in the mouth and subsequently swallowed.<sup>1</sup>

We have incorporated Teflon particles, labelled with the  $\gamma$ -emitting isotope <sup>99m</sup>technetium (Tc<sup>m</sup>), into pressurised canisters. These particles, mean diameter 2  $\mu$ , standard deviation 0.4  $\mu$  were generated by the spinning disc method,<sup>2</sup> and had aerodynamic properties similar to those of the active drug crystals. The aerosol canisters were activated by a solenoid under computer control, and inhaled volumes, flow rates, and breath-holding periods measured. Assessment was made of the activity in mouthwash and expired air, and the fractions of the dose deposited in the mouth, chest, and stomach were measured in vivo using a scanning whole body counter with a slit collimator. A further count of the chest 24 hours after inhalation enabled deposition in the tracheobronchial and alveolar regions of the lung to be determined.

Five subjects with obstructive airways disease inhaled at a low lung volume ( $22 \pm 4\%$  vital capacity), inhalation being followed by a breath-holding pause of  $3.9 \pm 0.2$  seconds (mean  $\pm$  SD). The inhalation flow rate was  $75.3 \pm 21.4$  l min<sup>-1</sup>, simulating the usual mode of self-administration. The percentage of the dose deposited in the lung was  $9.2 \pm 3.8\%$ , of which  $3.7 \pm 3.8\%$  was deposited in the alveoli and  $5.5 \pm 3.0\%$  in the tracheobronchial region. Initial mouth deposition accounted for  $77.3 \pm 4.9\%$  of the dose.

These results constitute the first direct measurement of the deposition of pressurised inhalation aerosols, and indicate that the particles deposit on both conducting and non-conducting airways.

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### Evaluation of <sup>81m</sup>krypton perfusion lung scans in paediatrics

I GORDON, P HELMS, F FAZIO The <sup>99m</sup>technetium macroaggregates (<sup>99m</sup>Tc-MAA) perfusion lung scan is a well-established method of obtaining regional lung perfusion. The use, instead of particulate matter, of a

short-lived radioactive gas such as <sup>81m</sup>krypton (Kr<sup>m</sup>) (13 seconds half-life) would be very attractive because of the significant reduction in radiation dose and the possibility of frequent repeated perfusion lung scans. The assessment of regional perfusion with intravenous infusion of <sup>81m</sup>Kr has been attempted and the limitations of this method outlined.<sup>1</sup> While the technique is reliable when regional ventilation is normal, it tends to underestimate perfusion defects when regional ventilation is disturbed.

We assessed the value of <sup>81m</sup>Kr perfusion/ventilation scanning in children with congenital heart disease, in whom, apart from dosimetric considerations, the use of intravenously injected macroaggregates might be contraindicated, either for the presence of pulmonary hypertension or of a right to left shunt. <sup>81m</sup>Kr perfusion lung scans were carried out in children with congenital heart disease by continuously infusing <sup>81m</sup>Kr in solution. All the patients had also <sup>81m</sup>Kr ventilation and a <sup>99m</sup>Tc-MAA perfusion scan. The latter was used as a reference technique. In the vast majority of the cases the <sup>81m</sup>Kr perfusion scan provided an accurate index of true pulmonary perfusion, as in these patients regional ventilation is usually not impaired. In the presence of chronic lung disease, however, when regional ventilation was abnormal, continuous intravenous infusion of <sup>81m</sup>Kr no longer provided a reliable assessment of regional perfusion.

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### Clinical ventilation imaging with radioactive <sup>113m</sup>indium

P WOLLMER, M M BARR, J P LAVENDER, F FAZIO simple and reliable method for pulmonary ventilation scanning is an essential complement to the well-established and widely used method of perfusion scanning using <sup>99m</sup>technetium (Tc) microspheres. Ideally the ventilation scan should be performed in multiple views after the perfusion study and should require minimal co-operation from the patient. While continuous inhalation of <sup>81m</sup>krypton (Kr) meets these requirements, it presents a major disadvantage—that is the limited availability of the gas.

Deposition of small radioactive aerosols within the lungs largely takes place by sedimentation to the lower respiratory tract according to regional ventilation. However, bronchial stenosis caused by excessive mucus or bronchial inflammation can induce local turbulence of airflow which increases deposition of particles by impaction in larger airways. This effect can be minimised by keeping low the mass median diameter of the inhaled particles as mainly large particles (with mass median diameter over 1-2  $\mu$ ) tend to deposit by impaction in the proximal airways.

We are currently evaluating a modification of the method proposed by Taplin and Chopra,<sup>1</sup> where the larger particles are removed from a polydisperse aerosol. A solution of <sup>113m</sup>indium (In) albumin

nebulised via a disposable nebuliser in a reservoir settling bag placed in the delivery line between the nebuliser and the patient's mouthpiece. After the nebulisation the patient inhales the aerosol from the bag by tidal breathing. The use of <sup>113m</sup>In (a 394 keV  $\gamma$ -ray emitter) allows the aerosol ventilation scan to be performed after a routine perfusion scan with microspheres labelled with <sup>99m</sup>Tc (which emits 140 keV  $\gamma$ -rays).

Comparison with <sup>81m</sup>Kr ventilation scanning indicates that this simple and potentially widely available aerosol technique provides images of good statistical quality in multiple views and with relatively little central deposition, even in patients with chronic airways disease.

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**Mucociliary clearance in patients with chronic autonomic failure**

P JENKINS, D PAVIA, J R M BATEMAN, S W CLARKE, K M CITRON, R BANNISTER Mucociliary clearance was studied in four patients with chronic autonomic failure and normal ventilatory function. Previous evidence has suggested that autonomic denervation might be expected to impair clearance. However, the four patients in this study showed no evidence of such impairment. A fifth patient was found to have impaired mucociliary clearance but also had chronic bronchitis; the reasons for her exclusion from the present study are discussed.

**Pleural ultrasound in the diagnosis and management of pleural disease**

D J LIPSCOMB, J W HADFIELD, C D R FLOWER, J E STARK Common problems of pleural disease include the recognition of radiographically atypical effusions, the differentiation between fluid, thickening, and tumour, and the selection of the best site for aspiration of loculated effusions. Radiological techniques such as special positioning may not be helpful and are time-consuming and difficult in the sick, immobile, or elderly. The widely available and comparatively inexpensive technique of A-mode ultrasound is useful in resolving these problems. We have studied 30 patients with known diagnoses of pleural effusion, empyema, consolidation, or collapse to gain experience and to validate the technique, and a further 50 patients who posed problems of diagnosis or management. Ultrasound enabled us to distinguish between solid and fluid containing opacities when the distinction was unclear after clinical and radiological examination, and the method was of great practical value in locating the best site for aspiration of loculated or complicated pleural effusions or empyemas.

**Mortality in asbestosis in relation to initial radiographic appearance**

I I COUTTS, J C GILSON, I H KERR, W R PARKES, M TURNER-WARWICK In spite of many epidemiological studies of mortality in asbestos workers there are few data available on the relationship between radiographic abnormality and subsequent progress. Since 1968 lung function tests have been performed at the Brompton Hospital on behalf of the Pneumoconiosis Medical Panel on almost all claimants seeking pensions for asbestosis from South-East England. Between 1968 and 1974, 167 cases were seen in whom the panel subsequently made a diagnosis of asbestosis.

A review of these patients showed that 66 had died by 1 September 1979 and copies of their death certificates have been obtained. Chest radiographs taken at presentation have been read by three readers in random order as part of a larger series using a modification of the 1971 ILO/UC Classification of Radiographs of Pneumoconioses. Interobserver variation was small and for the purpose of this study the median score for profusion of small intrapulmonary opacities has been used and expressed using the four-point scale of the shortened classification. The mean age at death was 61.7 years (range 43-75 yr). The data are summarised in the following table.

Profusion of small opacities	0	1	2	3
Whole group 167 (100%)	41 (25%)	89 (53%)	32 (19%)	5 (3%)
Deaths				
All cases 66 (39.5%)	8 (20%)*	42 (47%)	12 (38%)	4 (80%)
Lung cancer	3 (37.5%)*†	16 (38%)	3 (25%)	1 (25%)
Mesothelioma	0	6 (14%)	1 (8%)	0
Other respiratory disease	2 (25%)	7 (17%)	3 (25%)	2 (50%)
Other causes	3 (37.5%)	13 (31%)	5 (42%)	1 (25%)
Mean age at presentation (whole group) (yr)	53.9	55	58.8	61
Mean age at presentation (deaths) (yr)	54.8	57.7	59.5	63.2
Mean age at death (yr)	58.9	61.2	64.5	65

\*% of deaths in each category.

†% of deaths by cause in each category.

Two-thirds of the deaths were from respiratory causes and 23 (35%) were from lung cancer. The proportions dying from lung cancer were approximately the same in each radiographic category. Mesothelioma accounted for seven deaths (11%). The tumour was thought to arise from pleura in three cases and the peritoneum in four. In only one of these cases was the radiograph classified as being greater than category 1. Eight deaths were attributed to cor pulmonale and these occurred equally among the four radiographic categories. Bronchopneumonia appeared as the cause of death in four patients, three with category 1 radiographs and one with category 2. Asbestosis appeared only twice, both patients having category 1 radiographs.

In this small but defined group mortality was higher in those with definite evidence of small

opacities on chest radiograph but the incidence of lung cancer did not rise with increasing profusion of small opacities nor was the incidence of other respiratory causes of death clearly related to increasing profusion of small opacities on the chest radiograph.

#### Normal and emphysematous lungs studied by computerised axial tomography

P R GODDARD, E M NICHOLSON, J R TODD, I WATT, G LASZLO Computerised axial tomography (CAT) affords a unique method for examining distribution of blood vessels, bronchi, and pulmonary parenchyma. Focal areas of pulmonary destruction caused by emphysema are detected by visual examination with a high degree of resolution. Further, the distribution of absorption coefficients (Hounsfield or EMI numbers) can be used to quantify as well as to detect alterations in the pulmonary parenchyma caused by physiological and pathological processes.

The results from 53 patients with stable chronic airflow obstruction and 19 age-matched controls are presented. Eight supine axial tomograms, from apex to diaphragm, were obtained in each patient and four in each normal subject. Visual assessments were carried out on each tomogram, being scored 0-4 on each side for the presence of abnormal air spaces making a total possible score of 64. Three tomograms were selected from the apex, carina, and base respectively, for computer analysis of "areas of interest". The frequency distribution of EMI numbers was obtained within an area including the whole lung but excluding the thoracic cage and mediastinum. Smaller areas from the upper (ventral) and lower (dorsal) lung fields were also studied. There was a strong negative correlation between the mean EMI number of the whole lung fields and the visual assessments of emphysema score. Both these measurements correlated well with reduced carbon monoxide transfer factor. Normal subjects have higher densities in the dependent portion of the lung reflecting gravitational pooling but this was not present in the majority of patients with emphysema. Computerised tomography is a powerful tool for the study of the regional distribution of abnormalities in diffuse lung disease.

#### Classification of pulmonary embolism

C A WAGENVOORT The incidence of pulmonary thromboembolism in routine hospital necropsy data ranges in various publications from 3-65%. This wide range does not reflect real variations in incidence. The differences are due to varying carefulness of examination but particularly to the way embolism is defined. We have made a classification of pulmonary thromboembolism based on gross and microscopic examination of the lungs, in such a way that it can be easily used by the pathologist in routine necropsies. Terms such as "massive", "unilateral", "recurrent", "acute", and "chronic" thromboembolism have been defined. The standard procedure, definitions, and

classification have been tested in a consecutive series of 100 necropsies. The method may serve as a basis for epidemiological studies on pulmonary embolism, since the results obtained in this way are comparable.

#### Treatment of asthma in a general practice

C D SHEE, D POOLE, I R CAMERON It has recently been pointed out<sup>1</sup> that many asthmatics receive inadequate treatment. Some asthmatics, although correctly diagnosed, may be left with a significant degree of airways obstruction which relatively simple therapy could reverse. We have examined this possibility in a general practice in South-East London. We selected from 13 000 case notes 117 patients aged 16-70 years in whose notes the word asthma had been written. It is reasonable to assume that in these patients treatment would be aimed at reversing the observed airway obstruction and symptoms.

Only 67 (36 females, 31 males) of the 117 patients attended. The mean age was 36 years with a mean FEV<sub>1</sub> of 66% predicted and 18% mean reversibility after inhaled salbutamol. Fifty-one patients (76%) were atopic and 20 (30%) smoked regularly. We grouped patients by FEV<sub>1</sub>; group 1 (n=21) FEV<sub>1</sub> <55% predicted; group 2 (n=22) 56-80% predicted; group 3 (n=24) >81% predicted.

The main interest in this survey was the 21 patients in group 1 who were symptomatic and had an FEV<sub>1</sub> below 55% predicted. Of these one patient was receiving no treatment at all and eight had received no treatment other than a bronchodilator. Thirteen of these patients were skin test positive and only two of these were being treated with sodium cromoglycate. Nine were receiving inhaled steroids and seven oral steroids. Nine were receiving neither form of steroid treatment. These results confirm the suggestion that some asthmatics who are symptomatic and suffering from severe airway obstruction may not be receiving adequate treatment.

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#### Epidemic of asthma deaths: evidence of increased aerobiological challenge

B H DAVIES, J MULLINS, D A WILLIAMS The epidemic of asthma deaths between 1963 and 1967 remains unexplained. Toxicity of bronchodilators, decreased awareness of the severity of the asthmatic attacks, increased severity of asthma, and decreased use of corticosteroids have all been suggested as possible reasons. The death rates in patients aged 5-34 years were particularly increased and evidence that an increased aerobiological challenge occurred during these years has been sought in this study. The aerobiological concentrations of various spores and pollens has been analysed for a 15-year period in Cardiff and related to local and national death rates from asthma during this time. A relationship exists between the hyaline ascospore concentration and death rates dur-

ing the epidemic years, a looser association exists for grass pollen. No relationship exists for *Cladosporium*, smuts, and other spores. It is suggested that increased aerobiological challenge may have existed during the "epidemic" years.

#### Pulmonary involvement in non-Hodgkin's lymphoma

P F JENKINS, M J WARD, P DAVIES, J FLETCHER Non-Hodgkin's lymphoma (NHL) is a relatively common condition in which a variety of intrathoracic manifestations have been described. Much of the available literature consists either of single case reports or else describes the incidence of a particular intrathoracic manifestation in lymphomata of various types. A few thorough descriptions of pulmonary involvement do exist,<sup>1-3</sup> but most authors have dealt with malignant lymphomata in general and have included cases of Hodgkin's disease and, occasionally, of acute leukaemia in their classification. Moreover, histological classifications of the NHL group in these reviews is out of date. Manoharan *et al* recently described the incidence of intrathoracic manifestations in 86 patients with NHL but included a large proportion of cases exhibiting intrathoracic lymphadenopathy as the sole manifestation of intrathoracic involvement.<sup>4</sup>

We have studied 116 cases of NHL using the classification described by Bennett *et al*.<sup>5</sup> In addition, we have included cases of chronic lymphatic leukaemia (CLL) and have placed these in the good prognosis group. The patients were consecutive, non-selected cases referred to a haematology clinic in a district general hospital between 1971 and 1978.

Parenchymal lung involvement occurred in 26% of the 116 patients and pleural disease was found in a further 19%. The varieties of parenchymal involvement included pulmonary infiltration, diffuse nodulation and single or multiple rounded lesions. Pulmonary infiltration occurred almost exclusively in diffuse lymphocytic lymphoma (of all degrees of differentiation) and in CLL. Diffuse nodulation was uncommon and larger rounded opacities were only seen in the undifferentiated lymphomata. Pleural effusion complicated most histological categories but its incidence was low in CLL. Twenty per cent of patients exhibited intrathoracic lymphadenopathy and half of these also had parenchymal or pleural involvement. Parenchymal and pleural manifestations tend to be late complications in NHL and to affect prognosis adversely. They respond poorly to treatment. None of these observations is true with regard to uncomplicated intrathoracic lymphadenopathy.

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#### Sleep apnoea in acromegaly

W H PERKS, P HORROCKS, R A COOPER, S BRADBURY, N BALDOCK, A ALLEN, W VAN'T HOFF, K PROWSE Sleep studies were carried out overnight in a quiet darkened room on 11 patients with biochemically confirmed acromegaly. Continuous recordings were made of airflow at the nose and mouth, thoracic and abdominal movement, ear oxygen saturation, electrocardiogram, submental electromyogram, electro-oculogram, and electroencephalogram. Three patients complained of episodes of daytime sleep and two of these had excessive nocturnal snoring. A further two patients complained of excessive nocturnal snoring but did not fall asleep during the day. These five patients were defined as "symptomatic" and compared to the six "asymptomatic" patients.

In all the symptomatic patients the sleep studies showed definite episodes of sleep apnoea (defined as cessation of airflow at the nose and mouth lasting for at least 10 seconds). Three of the symptomatic patients had more than 30 episodes of sleep apnoea (range 60-187), fulfilling the diagnostic criteria for the sleep apnoea syndrome. The other two patients had seven and five apnoeic episodes respectively. Only two of the asymptomatic patients had episodes of sleep apnoea. One patient had two episodes and the other a single episode of apnoea. Four of the five symptomatic patients were male compared to only one of the six asymptomatic patients. The mean growth hormone levels of the symptomatic group (three of whom had received treatment) during a glucose tolerance test performed at the time of sleep study was 53 mU/l (range 14 mU/l-102 mU/l). The asymptomatic patients (all of whom had been treated) had a mean level of 19 mU/l (range 6 mU/l-87 mU/l). The cardiothoracic ratio measured with a standard postero-anterior chest radiograph was 59% and 62% in two of the patients with the sleep apnoea syndrome, but less than 50% in the remainder.

Sleep apnoea may be a common complication of acromegaly and should be suspected in patients who have excessive snoring or daytime somnolence.

#### Asthma from chloramine-T

M L H FLINDT Seven brewery workers developed asthmatic symptoms after using chloramine-T as a sterilising agent. The case histories, the blood eosinophil, and serum IgE findings, and the results of skinprick tests supported the likelihood of an immunological basis for their illnesses, which had features consistent with type I, IgE-mediated reactions. Although on theoretical grounds it had seemed likely that chloramine-T was acting as a hapten in inducing sensitisation, the results of investigations made so far have not differed from those obtained in the case of antigens presumed complete.



### Hydrocortisone and bronchial beta-adrenergic responsiveness

R N HARRISON, A D MACKAY Corticosteroids have been used in the treatment of asthma for over 20 years yet little is known of their mode of action. As hydrocortisone potentiates the action of various beta agonists on isolated bronchial smooth muscle preparations,<sup>1</sup> an increase in beta-adrenergic responsiveness has been postulated to explain its therapeutic effect. Previous studies in asthmatics have provided some support for the existence of potentiation *in vivo*<sup>2</sup> but further evidence is needed from a study of the effect of corticosteroids on the dose-response relationships of beta agonist bronchodilators. We have therefore looked for an alteration in beta-adrenergic responsiveness in normal and asthmatic subjects after hydrocortisone by measuring its effect on the inhaled salbutamol dose-response curve.

Six mild asthmatic patients who required no regular medication and six normal subjects were studied. Intravenous hydrocortisone hemisuccinate 200 mg or intravenous saline were administered on separate days, at least one week apart, in a double-blind, crossover fashion. Five hours after each injection dose-response curves were constructed from serial measurements of sGaw after cumulative doses of inhaled salbutamol. Baseline measurements of sGaw were made before each injection and before the first dose of salbutamol.

Hydrocortisone produced a 49% increase in sGaw measured five hours after administration to the asthmatic patients ( $p < 0.01$ ). Duplicate measurements on the normal subjects showed a 21% increase in sGaw ( $p < 0.05$ ). Hydrocortisone did not, however, alter the salbutamol dose-response curves in either group.

Our failure to demonstrate potentiation may be the result of our use of the non-catecholamine agonist, salbutamol, as *in vitro* studies have shown that hydrocortisone has a much greater potentiating effect on isoprenaline than on salbutamol.<sup>1</sup> If this applies *in vivo* it would suggest that the structural properties of the agonist are important in the mechanism of potentiation.

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### Changes in effective pulmonary blood flow with prednisolone

C R WINFIELD, W A C MCALLISTER, J V COLLINS Previous evidence that corticosteroids may exert beneficial effects at sites other than the major airways in severe asthma<sup>1</sup> led us to study the effects of intravenous prednisolone in chronic stable asthma. In a double-blind study the effects of a single injection of prednisolone phosphate was compared with placebo

injection in random order in eight patients with stable asthma and in eight normal controls matched for age and sex. "Effective" pulmonary blood flow was estimated using the technique in which a mixture of low concentration of argon, freon 22, and ether is inspired. The concentrations of these gases in the inspired and expired mixture was recorded with a mass spectrometer (Centronics). The difference between the slopes of the expired curves for argon and freon 22 gives an indirect estimate of "effective" pulmonary blood flow. In the normal subjects there was a 38% increase in effective pulmonary blood flow at four hours and 32% at six hours after prednisolone compared with an 8% change with placebo. Similarly, in patients with asthma significant but smaller changes of 23% at four hours compared with 9.6% after placebo were recorded. These effects in both normal and asthmatic subjects suggest changes in pulmonary blood flow with alteration of ventilation-perfusion ratio and this may be one of the ways in which corticosteroids are effective in asthma.

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### Corticosteroids in chronic bronchitis: can the patient's assessment be ignored?

I P WILLIAMS, C R MCGAVIN In a study to examine the methods of assessing the response of patients with chronic obstructive bronchitis to corticosteroids, 20 patients received a week of placebo tablets, followed by three weeks of prednisolone 30 mg daily. Benefit was assessed by a visual analogue scale (VAS), by spirometry and exercise performance. Significant increase in forced expiratory volume in one second (FEV<sub>1</sub>) and in exercise performance were observed after steroid therapy. Changes in forced vital capacity (FVC) correlated both with VAS score and with changes in exercise performance. Changes in FEV<sub>1</sub> correlated with neither. The good correlation between the changes in a ventilatory function test (the FVC) and the patients' assessments of the drug, suggests that the non-specific euphoriant effect of steroids does not eclipse their specific action on ventilatory function. It is suggested that assessment of benefit should include subjective assessment and changes in FVC and exercise performance.

### Does it matter what time of day you give prednisolone?

W A C MCALLISTER, D M MITCHELL, J V COLLINS Cortisol levels in peripheral blood normally oscillate with a clear circadian rhythm. Human corticosteroid binding globulin (CBG) binds cortisol and prednisolone, unlike synthetic corticoids, with high affinity. Angeli *et al*<sup>1</sup> have shown significant circadian fluctuations in CBG binding capacity for both steroids. This finding led us to investigate whether there is a diurnal variation in prednisolone pharmacokinetics and whether it may be related to the circadian fluctuations of FEV<sub>1</sub> and PEF<sub>R</sub> in asthmatics.

A group of six healthy male volunteers on no medication and five asthmatic patients all of whom had been on daily prednisolone for at least three months were studied. The fasted subjects were given 20 milligrams of prednisolone at 8.00 and 20.00 on separate days at least a week apart. Conditions were standardised between night and day except that all subjects slept at night. No food was taken for two hours after the start of the study. For 12 hours after ingestion of the drug blood samples were taken for estimation of plasma prednisolone levels using a radioimmunoassay as described by Chakraborty *et al.*<sup>2</sup> The study was performed on the healthy subjects on at least two occasions both night and day.

Pharmacokinetic data, including area under the plasma concentration time curve (AUC), maximum plasma concentration (C<sub>max</sub>), peak concentration time (T<sub>max</sub>), volume of distribution (V<sub>d</sub>), clearance (Cl), and half-life (T<sub>1/2</sub>), were all calculated and showed no significant difference between night and day for the group as a whole. There was also no difference in the data between normal and asthmatic subjects. We have shown also that equivalent adrenal suppression occurs during day and night and is as marked on 5 as 80 milligrams of prednisolone. It would seem, therefore, that there is no rational pharmacokinetic basis for prescribing prednisolone at any particular time of day, nor is there evidence relating the metabolism of the drug and circadian rhythms of asthmatic physiological changes.

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### Inhaled prazosin in asthma

P J BARNES, P IND, C T DOLLERY Alpha adrenoceptor mediated bronchoconstriction has been demonstrated in asthmatics and several studies have shown that alpha adrenoceptor antagonists decrease airways resistance and inhibit either histamine or exercise induced bronchospasm in asthmatics. But the antagonists used have had either antihistamine activity (thymoxine, phenoxybenzamine) or a direct relaxant effect (phentolamine). Prazosin, the most potent and selective alpha adrenoceptor antagonist available, has no antihistamine or direct action, and we therefore studied the effect of this drug given by inhalation to asthmatics.

Nine asthmatics (six extrinsic, three intrinsic, mean age 35 years, range 25-48 yr) were given prazosin (0.5 mg), salbutamol (1.0 mg) or vehicle double-blind by nebuliser (2 ml over 10-12 min) on separate days. Measurements of FEV<sub>1</sub> and maximum expiratory flow were measured for up to 60 minutes after inhalation

by a Krogh spirometer. There was no significant change in either FEV<sub>1</sub> (1.38±0.66 l baseline and 1.38±0.62 l at 15 min) after inhalation or flow at 70% of TLC (0.14±0.06 l.s<sup>-1</sup> baseline and 0.11±0.04 l.s<sup>-1</sup> at 15 min) after prazosin inhalation. However, all subjects showed a very significant increase with salbutamol in both FEV<sub>1</sub> (mean increase from 1.43±0.70 l to 2.16±0.78 l at 15 min) and V<sub>70%</sub> TLC (0.22±0.09 l.s<sup>-1</sup> to 0.72±0.25 l.s<sup>-1</sup> at 15 min). Prazosin inhalation caused no bronchial irritation and no significant change in heart rate or blood pressure on lying or standing.

The failure of prazosin as a bronchodilator suggests that alpha adrenergic mediated bronchoconstriction may not be important in asthma.

### Action of aminophylline on normal airways

A D MACKAY, C J BALDWIN, A E TATTERSFIELD Inhibition of phosphodiesterase and a resultant accumulation of intracellular cyclic 3'5'-adenosine monophosphate (cyclic AMP) in bronchial smooth muscle has been thought to account for the beneficial effect of theophylline in asthma. Other mechanisms of action must be considered, however, since *in vitro* studies have shown only slight inhibition of human pulmonary phosphodiesterase when the theophylline concentrations were equivalent to therapeutic plasma levels.<sup>1</sup>

We studied the bronchodilator action of aminophylline in six normal subjects using a loading dose of 5.6 mg/kg given intravenously over 10 minutes. This produced a rapid increase in specific airway conductance (sGaw) reaching a peak increase five minutes after injection. sGaw (l.kPa<sup>-1</sup>) increased from a mean value of 1.77±0.11 (SEM) to 2.30±0.16 which was equivalent to 70% of the peak response to 400 mg of salbutamol in the same subjects. Pretreatment with oral propranolol 120 mg caused no change in sGaw after two hours but it halved the response to aminophylline. Further studies with propranolol 40 and 80 mg suggest that this is a dose related effect.

These results show that aminophylline has a bronchodilator effect on normal airways and that this response is partially blocked by propranolol. Since propranolol itself caused no change in sGaw we conclude that these subjects did not have resting beta adrenergic tone to their airways. In the absence of β-adrenergic stimulation it would be surprising if aminophylline could cause such a large and rapid change in sGaw through phosphodiesterase inhibition alone.

## REFERENCE

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