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Proceedings of the Thoracic Society

A meeting of the Thoracic Society was held in Oxford on 6–7 July 1978. Summaries of the papers follow:

Lung crackles in bronchiectasis

A R NATH and L H CAPEL The timing of inspiratory lung crackles in bronchiectasis was compared with the inspiratory timing of the lung crackles in obstructive and restrictive lung disorders. The lung crackles in obstructive chronic bronchitis typically occur early in inspiration, while in fibrosing alveolitis the lung crackles continue to the end of inspiration. By contrast, the inspiratory crackles in bronchiectasis occur in early and mid-phase of inspiration. Further distinguishing features of the lung crackles in the three groups of patients are presented in this study.

Radiological diagnosis of pulmonary oedema

P D SNASHALL, SUZANNE KEYES, BARBARA MORGAN, R J MCANULTY, R G RAWBONE, P F MITCHELL-HEGGS, and J MCIVOR Pulmonary oedema is usually diagnosed by chest radiography but it is often assumed that considerable oedema may exist without radiographic change (Fishman, 1976). We have assessed the sensitivity of the radiograph in detecting pulmonary oedema in large anaesthetised dogs supported in the upright position. We have compared radiographic changes with the gravimetrically measured extravascular lung water.

When we measured the opacity of the radiographs with a densitometer, significant increases of density from baseline were detected when lung water was increased more than 20–30%. Similarly, a radiologist could distinguish baseline from oedema radiographs when lung water was increased by more than 25%. Decreases of lower zone lung volume occurred in most dogs with oedema, and functional residual capacity, measured by helium dilution, fell. There was no consistent change in static lung compliance. With oedema, dogs developed hypoxia due to intrapulmonary shunting, which was greatest in animals with the greatest loss of lower zone volume. We believe that shunting and loss of volume are due to alveolar flooding, which we have histologically shown may occur when extravascular lung water is increased by less than 20%.

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Lung imaging with radioactive aerosols

A P GREENING, F FAZIO, M MINIATI, J E AGNEW, J R M BATEMAN, S W CLARKE, and D PAVIA Continuous inhalation of ^{81m}Kr should be considered the technique of choice for ventilation scanning (Fazio *et al*, 1978). Unfortunately, its application is restricted by the limited availability of the ^{81}Rb——>^{81m}Kr generators (4·6 hours half-life). An alternative, more widely available approach would be lung scanning after inhalation of radioactive aerosols. However, these show variability in deposition due to differences in particle size (smaller particles penetrate deeper into the bronchial tree). In the attempt to control the diameter of the particles the use of ^{99m}Tc-labelled human albumin minimicrospheres (^{99m}Tc-HAMM) with a mean (wet) diameter of 0·8 μ (range 0·2–2·5 μ) has been suggested. In two normal subjects and in six patients with chronic airflow obstruction we have compared the deposition of ^{99m}Tc-HAMM with that of a strictly monodispersed (2 $\mu \pm$ 0·3 μ) aerosol, made of polystyrene particles produced by a spinning disc generator and labelled with ^{99m}Tc (^{99m}Tc-POLY). ^{99m}Tc-HAMM and ^{99m}Tc-POLY were administered with an interval of 24 hours, and images were obtained on a large field of view γ camera. ^{81m}Kr ventilation scans and pulmonary function tests were performed on both occasions and the results confirmed the stability of the respiratory conditions.

In normal subjects the images obtained with ^{99m}Tc-HAMM, ^{99m}Tc-POLY, and ^{81m}Kr were almost identical, showing a uniform distribution of activity to the lung periphery. In the patients the images obtained with both ^{99m}Tc-HAMM and ^{99m}Tc-POLY showed a very inhomogeneous distribution of activity, which was concentrated in "hot" spots scattered throughout the lungs, probably due to areas of bronchial deposition. Despite the very bizarre distribution, the images of ^{99m}Tc-HAMM and ^{99m}Tc-POLY were almost identical, as confirmed by a quantitative computer comparison. The ^{81m}Kr ventilation scan had a more homogeneous, non-spotty appearance.

We conclude that (*a*) radioactive aerosol techniques are reproducible in both normal subjects and patients; (*b*) the ^{99m}Tc-HAMM images are mainly representative of deposition of the larger (2·0–2·5 μ) particles contained in the preparation, the activity being proportional to particle surface rather than diameter; (*c*) aerosol techniques yield, in the absence of airways obstruction, images representative of regional ventilation and can, therefore, be used as a complement to lung perfusion scans for the diagnosis of pulmonary embolism; and (*d*) the bronchial deposition observed in patients with airways obstruction can be used for the early detection of bronchial disease. A more peripheral deposition might be achieved by using polydispersed aerosols with a maximum diameter not exceeding 1·0 μ.

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Fifteen cases of pneumothorax by hydatid cyst

G BROTZU, M PISANO, and A I DESOGUS During 13 years, 15 cases of pneumothorax resulting from rupture in the pleura of hydatid cysts came to our attention. In the same period we observed 206 cases of pulmonary hydatid cyst.

In eight cases the symptomatology was total lung collapse with a tension pneumothorax, which suddenly required the installation of thoracic drainage. In seven cases after a rapid onset there was stabilisation. In three cases the pneumothorax was associated with a pyopneumothorax. Thoracic drainage was used in every case, but only in five was re-expansion of the lung possible. Both radiography and thoracoscopy were used for diagnosis.

The symptomatology at the onset in all cases was chest pain, in 86% fever, and in 80% cough, but never allergic shock. The Casoni and Ghedini reactions were positive in 50% of the cases and eosinophilia was present in 60%.

Pneumothorax by hydatid cyst was correctly diagnosed preoperatively only in five cases.

The surgical procedure was decortication associated in 10 cases with cuneiform resection, in four with simple cystectomy, and in one case a lobectomy was necessary.

A two-surgeon technique for multiple valve replacement

D C T WATSON, H R MATTHEWS, and J B MEADE During a four-year period ending in July 1977, 45 patients underwent surgery for multiple valve replacement using the Bjork Shiley prosthesis. Thirty-six of them had aortic and mitral valve replacement, and a further nine also had tricuspid valve replacement.

The average age for the double valve replacement patients was 49·4 years and the male : female ratio was 15 : 21. All the triple valve replacement patients were women, their average age being 44·5.

The surgery was undertaken on cardiopulmonary bypass using normothermic ischaemic arrest while the aortic and mitral valves were replaced. The average bypass time for double valve replacements was 70·4 minutes and for the triple valve replacements 104·2 minutes. The corresponding ischaemic times were 46·9 and 45·3 minutes.

A two-surgeon technique, which will be described, has achieved a relatively short period of anoxic arrest. It is suggested that the recent introduction of cardioplegic solutions associated with this technique will provide a simple and safe method for multiple valve replacement.

The operative mortality in the double valve group was 5·5% and in the triple group 11·1%. The late mortality and morbidity will be discussed.

Management of penetrating stab wounds of the chest: an assessment of the patients for early operation

F A SANDRASAGRA The efficacy of conservative management of penetrating chest injuries by aspiration or drainage of collections of air or blood in the pleural cavity was established in the second world war and confirmed by subsequent experience in Korea, Vietnam, and in civilian practice. Penetrating stab wounds of the chest are less destructive than combat injuries and respond well to conservative treatment. Nevertheless, some of these patients require early operation for control of haemorrhage or repair of damaged internal organs. Failure of early recognition of this category of patient may be fatal.

Out of a total of 85 patients with penetrating stab wounds of the chest seen in Sri Lanka, 55 were caused by a kris-knife (dagger). Haemothorax, haemopneumothorax, and pneumothorax were the most common complications. These complications were amenable to conservative treatment by aspiration or drainage of the pleural space. Immediate operation was indicated in 30 patients. The indications for surgery were haemorrhage from a major systemic or pulmonary vessel or the heart, cardiac and bronchial tears, and sucking chest wounds. In most cases the need for immediate operation was clinically obvious at the time of presentation. It should have been suspected from the situation of the entry wound, the nature of the weapon used, the size of the haemothorax, and the clinical findings in the others. All 11 deaths occurred in that group in which early operation was indicated, and some of them could have been averted had the need for operation been suspected early.

Seven patients developed an empyema; five were in the group that needed immediate surgery and in the other two infection occurred in a clotted haemothorax. Early repair of the associated visceral injuries and complete evacuation of a haemothorax, either fluid or clotted, could reduce the incidence of empyema.

Pulmonary functional outcome of patients previously treated for thoracic trauma in an intensive care unit

R FEINMANN, B R H DORAN, M C PRESCOTT, and T B STRETTON Ten patients were studied two months to six years after receiving treatment for thoracic trauma in an intensive care unit. All but one patient had been treated by intermittent positive-pressure ventilation for a period ranging from two to 21 days. Observations were made to detect the presence of residual ventilatory defects, defects in gas transfer, and abnormalities in ventilation/perfusion. Four patients were found to have a ventilatory defect, both the vital capacity and FEV_1 being less than 75% of the predicted value. Two patients had restrictive defects, and two had diffuse airflow obstruction. One patient was a known asthmatic, but the aetiology of the other's airflow obstruction remains uncertain: he denied having any symptoms before his accident, was a non-smoker, and a lung scan showed extensive im-

pairment of blood flow to the right lung without equivalent reduction in ventilation. The single breath transfer factor for carbon monoxide was below 75% of the predicted value in the four patients with ventilatory abnormalities, and also in two others. Ventilation/perfusion disturbances were shown by isotopic lung scanning in six subjects, not necessarily those with ventilatory defects shown by spirometry or those with a reduced transfer factor.

Abnormalities in lung function are thus common is this group of patients and may be due to pre-existing disease, to the effects of the trauma that led to their admission to hospital, to pulmonary thromboembolism, or to some aspect of the treatment they received.

Plasma cyclic nucleotides in exercise-induced asthma

J P R HARTLEY, and C J DAVIES The metabolic responses to exercise of normal subjects and patients with exercise-induced asthma have been reported to differ significantly (Soifer *et al,* 1976). It has been suggested that this is due to partial β-adrenoceptor unresponsiveness in asthmatics.

This study has investigated the effect of exercise on plasma cyclic nucleotide levels (3′ 5′ cyclic AMP and 3′ 5′ cyclic GMP) in 10 adults with exercise-induced asthma (>15% fall in FEV_1 after exercise) and five normal individuals. All gave their informed consent. All subjects performed eight minutes of exercise on a cycle-ergometer during which O_2 uptake was measured continuously. Blood samples were taken through an indwelling radial artery cannula before exercise, during the last minute of exercise, and 5, 15, and 30 minutes afterwards. Cyclic nucleotides were analysed as described by Siddle *et al,* 1976.

Plasma 3′ 5′ cyclic AMP increased in the normal subjects (mean maximum increase 26% at end of exercise). In the asthmatics there was little change (mean maximum increase 5%). The difference was significant when the groups were compared by Student's *t* test ($P<0.01$). Plasma 3′ 5′ cyclic GMP altered little, and there was no difference between asthmatics and normals.

In the normal subjects the rise in 3′ 5′ cyclic AMP is probably due to increased circulating catecholamine levels in exercise, and, as catecholamine levels have been shown to be similar during exercise in controls and patients with exercise-induced asthma (Chryssanthopoulos *et al,* 1978) the difference in 3′ 5′ AMP response in asthmatics indicates partial β-adrenoceptor unresponsiveness.

To determine whether this is a fundamental abnormality associated with asthma, or induced by the regular administration of β-agonists in the weeks preceding the test, six normal subjects have repeated the exercise test, with measurement of 3′ 5′ cyclic AMP levels before and after 18 days of regular sablutamol aerosol in a dose of 1600 μg daily. No diminution of 3′ 5′ cyclic AMP response to exercise was found.

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Normal circadian rhythms in peak expiratory flow rate

M R HETZEL, T J H CLARK, and D BROWN Pronounced diurnal variation in peak expiratory flow rate (PEFR) occurs in many asthmatic patients. Diurnal variation in airway calibre has been shown in some normal subjects (Guberan *et al,* 1969; Reinberg and Gervais, 1972). We have attempted to study larger numbers of normal subjects with PEFR measurements at home.

Altogether 221 normal subjects aged 10 to 84 years recorded PEFR (three attempts) on waking, leaving for work, coming home and at bedtime for seven days. Cosinor analysis (Halberg *et al,* 1964) showed a significant rhythm in 145 (65·6%). Mean amplitude ("peak to trough" measurement) was 8·3% of the daily mean (SD 5·2%). There was little variation in amplitude with age and no significant relationship to sex, family history of asthma, atopy, or smoking habit.

Fifteen normal subjects were studied again for five consecutive days at 0930, 1230, and 1730 when flow volume loops were recorded with an Ohio spirometer. Eleven had shown rhythmicity in PEFR at home. No single measurement from the flow volume loop showed periodicity in as many of them, but rhythms were now also detected in the other four normal subjects in some components of the loop.

The computed acrophase (time of daily peak) was compared in the 145 rhythmic normal and 56 asthmatic subjects of whom 33 were studied in hospital and 23 at home. In all cases the acrophase was commonest between 1500 and 1700. This was also true of the estimated acrophase of the other 76 normal subjects whose rhythms were not, however, significant.

Results suggest that circadian rhythms in airway calibre exist in all normal subjects and can often be detected with a peak flow gauge alone. An amplitude of over 20% might be a useful screening test for asthma. Wide diurnal swings in PEFR in asthma appear to result from amplification of this basic rhythm by increased bronchial lability.

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Upper airway function in acromegaly

S HUGHES, and C C EVANS We have previously suggested that the respiratory morbidity and mortality in acromegaly may be due to narrowing of the upper airway (Evans *et al*, 1977). Ten of the subjects previously studied agreed to a further clinical examination, spirometry and flow volume curves, and tomography of the larynx and trachea. Six women and four men were studied, average age 58 years, and only two smoked cigarettes. None had a history of chronic bronchitis, but seven had a significant thoracic kyphosis. None had stridor, but seven had a hoarse voice.

The FEV_1 was reduced in five, and the MEFR:MIFR ratio was increased in a further three, in two of whom the PEFR:PIFR ratio was raised. The MMEF:MMIF ratio was raised in one woman with a kyphosis who was a non-smoker.

Tomograms of the upper airway were normal in only two of the nine subjects studied. There was a paralysis of the vocal cords in one, a retrosternal thyroid compressing the trachea in another, and hypertrophy of the true or false cords was shown in the remainder.

These results add confirmation to the previously discovered abnormalities of the upper airway in acromegaly.

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Significance of antinuclear and DNA-antibodies in cryptogenic fibrosing alveolitis

S T HOLGATE, P HASLAM, and M TURNER-WARWICK The aetiology of cryptogenic fibrosing alveolitis (CFA) is unknown. An autoimmune basis for the disease is suggested by the frequent finding of non-organ specific autoantibodies in the serum (antinuclear, 36·5%; rheumatoid factor, 31·1% (Turner-Warwick and Haslam, 1971)) and an increased prevalence of CFA in the collagen vascular diseases.

Antinuclear and double strand-DNA (DS-DNA) antibodies have been incriminated in pathogenesis of systemic lupus erythematosus (SLE) through deposition of immune complexes (Cochrane and Koffler, 1973). This study was undertaken to investigate the significance of ANA and DS-DNA antibodies in patients with CFA.

Sixty-five patients chosen for study had a mean age of 58 years and a male to female ratio 1·7 : 1. The diagnosis was made by exclusion, but in 20 patients lung histology was also available.

Patients were divided into two categories according to the presence of ANA in their serum (n=34) or not (n=31). Clinical and laboratory features were retrospectively compiled from hospital records at the time of presentation. DS-DNA binding was assayed on stored sera using a standard Farr radioimmune assay. Values found in CFA were compared with healthy controls (50) and with patients with "avian lung" (28), scleroderma (20), and SLE (30).

From many features examined, CFA patients positive for ANA had a longer antecedent history before hospital presentation ($P<0.05$), an increased prevalence of Raynaud's phenomenon ($P<0.05$), and a higher mean ESR ($P<0.05$), serum globulin ($P<0.0125$), and serum IgG ($P<0.025$). There was also a suggestion that lung biopsies from ANA-positive patients (n=7) showed more desquamative than mural change compared with those from ANA-negative patients (n=13).

Serum DS-DNA binding from 50 healthy subjects was 9·0±4·2% (3 SD). Raised DS-DNA binding was found in sera from all patients with SLE (mean binding 31%, range 14–65%), one patient with scleroderma (19%), one patient with avian lung (15%), and 13 patients (22%) with CFA (mean 17%, range 14–28%), nine of whom were negative for ANA. There was a positive correlation in CFA between DS-DNA antibody levels (mostly IgG) and the serum IgA ($P<0.001$).

The presence of serum ANA in fibrosing alveolitis may identify a patient subgroup with less aggressive disease. Raised DS-DNA antibodies are unlikely to have pathogenetic significance and in common with increased serum IgA they probably represent non-specific responses to tissue injury.

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Respiratory disease in welders

S P HAYDEN, J HAYDEN, A C PINCOCK, L E TYLER, and J M BISHOP Welders may have impaired lung function (Challen, 1974) and an increased mortality from pneumonia (Registrar General, 1978). Surveys of welders have usually included shipyard workers, who may have been exposed to asbestos, making interpretation of the results difficult. The findings of such studies have in any case been inconsistent.

In the survey reported here a group of 258 welders and 258 age-matched controls were studied. All worked on the shop floor in the same three engineering factories, situated in the West Midlands. A questionnaire on respiratory symptoms and welding was completed, spirometry and peak expiratory flow tests were performed, and a chest radiograph was obtained.

Results will be presented comparing the welders and controls and discussing the effect of duration of occupation as a welder as a measure of exposure.

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Registrar General (1978). *Decennial Supplement England and Wales 1970–1972. Occupational Mortality*. HMSO, London.

Pleural disease in asbestos workers

P H WRIGHT, A HANSON, L KREEL, and L H CAPEL A distinction is usually drawn between asbestosis (lung fibrosis), which causes loss of lung function, and asbestos-related calcified pleural plaques, which do

not. Although previously described, pleural thickening due to asbestos exposure as a cause of loss of lung function is rarely diagnosed in Britain. It is especially difficult to recognise when a progression from pleural effusion to pleural fibrosis is not seen but the patient presents with established pleural disease. Six cases are described of patients whose disability was clinically thought to be due to pleural restriction. All had abnormal chest radiographs and pulmonary function test results. A characteristic of the pulmonary function test results in this group was a normal or high Kco (transfer coefficient: $Tco/_{Va}$) in the face of a low vital capacity. This abnormality was more characteristic than changes in the compliance curve. The clinical diagnosis was further investigated by performing transverse EMI scans to see if these could be used to distinguish between abnormality of the lung and of the pleura. It is suggested that pleural restriction produces a lung that cannot be fully expanded so pulmonary function testing shows a small lung with a high Kco. It is suggested this might usefully be termed a squashed lung. Other causes of these changes are discussed.

Some aspects of mechanical pulmonary function in acromegaly

B D W HARRISON, K A MILLHOUSE, and J D N NABARRO

Lung function has been studied in 30 patients with acromegaly by spirometry, body plethysmography, and flow volume loops. Lung size has been assessed by total lung capacity (TLC); small airway function by residual volume (RV), TLC ratio, and expiratory flows at low lung volume (MEF_{50} and MEF_{25}); and upper airway narrowing from the flow volume loop (and by laryngoscopy and laryngeal xerography).

Eight patients were excluded from analysis of the results of lung size and small airway function because they had severe kyphoscoliosis and/or clinical or radiological evidence of pulmonary venous hypertension.

In 22 patients TLC was significantly greater than predicted normal in men ($t=3{\cdot}22$, $P<0{\cdot}01$) and women ($t=2{\cdot}22$, $P<0{\cdot}05$). There was a significant correlation between duration of acromegaly and TLC expressed as a percentage of predicted normal ($r=0{\cdot}56$, $P<0{\cdot}01$).

RV/TLC was considered abnormal if more than two standard deviations above predicted. MEF_{50} and MEF_{25} were considered abnormal if less than 70% predicted. Small airway function was considered deranged if two or more of the three indices were abnormal. Eight of the 22 patients had abnormal small airway function that could not be attributed to associated cardiopulmonary disease, skeletal deformity, or smoking history. The duration of acromegaly was significantly longer in patients with small airway dysfunction ($P<0{\cdot}025$).

Four men had evidence of upper airway narrowing that was severe and probably due to a laryngeal myopathy in one. Three had had acromegaly for 10 or more years.

We conclude that the increase in lung size, the small airway dysfunction, and the upper airway narrowing are all related to the duration of acromegaly. The small airway and upper airway abnormalities probably contribute to the mortality and morbidity of acromegaly. This study provides further evidence that acromegaly should be treated early.

Reference values for the lung transfer factor for carbon monoxide

J E COTES, I ASHTON, A M HALL, C HEYWOOD, and M J SAUNDERS

The transfer factor or diffusing capacity for the lung (T1, co, sb) is widely used, but the reference values cited in reports exhibit material variation between laboratories, particularly in the case of female subjects (Cotes and Hall, 1970). In many instances the differences persist after allowance is made for age, stature, and haemoglobin concentration. Aspects of the procedure—for example, the level of alveolar oxygen tension—or the extent to which the subjects are rested before the measurement and technical factors in the design and use of equipment (Cotes, 1963) may contribute to the differences. Other biological factors are the level of habitual activity (Cotes, 1976) and the level of air pollution, including personal pollution by tobacco smoke.

In an attempt to resolve some of the discrepancies the transfer factor and its subdivisions by the single breath carbon monoxide method and the physiological response to submaximal exercise have been measured on some 270 healthy men and women living in areas where the air is clean (Cotes, 1975, for methods). In both sexes significant partial multiple regression coefficients have been obtained on age, stature, smoking, and age multiplied by smoking. In the men the practice of smoking is associated with a higher initial level of transfer factor but a steeper decline with age. In the women the opposite obtains; the smokers have lower values than the non-smokers but their decline with age is also less. The results are now being analysed with respect to cigarette-pack years and to the physiological response to exercise; they are also being compared with those of other authors. The findings will be reported to the meeting.

We are indebted to Mr G Berry for statistical advice.

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Prevalence of chronic bronchitis in Rhodesian Africans

J B COOKSON A prevalence survey of a small township was performed using two questionnaires, both based on that of the British Medical Research Council. The first was put to 9768 subjects aged over 4 years and the second more detailed questionnaire to random selections of these grouped according to their replies. Interviews by the author were used to assess the accuracy of the questionnaires. The overall prevalence of chronic bronchitis was 1·12%. The prevalence was similar in the two sexes and showed no significant increase with age. Rates were much lower than comparable surveys elsewhere. There were fewer smokers than in other surveys and those that did smoke, smoked little; this probably explains the low prevalence in these subjects.

Effects of naturally acquired ("wild") respiratory infection on pulmonary function in healthy people

S A O'CONNOR, D P JONES, J V COLLINS, R B HEATH, and M H LEIGHTON Because it has been suggested that uncomplicated respiratory viral infections may cause detectable abnormalities in small airway function in healthy people we made a six-month prospective study of 28 normal, healthy volunteers aged 18–54 years. At two-week intervals between October 1976 and March 1977 each volunteer performed forced expiratory manoeuvres, and values were calculated for PEFR, FVC, FEV_1, MMF_{50}, and MMF_{75}. Diary cards of respiratory symptoms were completed by all volunteers throughout the study. If symptoms of an infection occurred additional lung function measurements were made for seven days. At such times nose and throat swabs and blood samples were tested for evidence of viral infection. Twenty-eight episodes of symptoms were recorded, and laboratory confirmation of infection was obtained in six. Each of the five respiratory function indices was subjected to an analysis of variance to assess the extent of change after infection. These analyses showed a statistically significant decline in PEFR, FVC, and FEV_1 ($P<0·001$) during the presence of respiratory symptoms compared with asymptomatic periods. A similar change of less significance ($P<0·05$) was found for MMF_{50} with symptoms, but there was no significant change in MMF_{75}.

If it is accepted that PEFR and FEV_1 mainly reflect upper airway function while MMF_{50} and MMF_{75} reflect small airway function, our results suggest that the effects of respiratory infections in healthy people are mainly confined to the upper airways. An alternative explanation is that the tests we have used, MMF_{50} and MMF_{75}, are not sensitive enough to detect the changes in small airway function that may occur in healthy people.

Pulmonary histiocytosis X

F BASSET, B CORRIN, J LACRONIQUE, C ROTH, P SOLER, J-P BATTESTI, R GEORGES, H SPENCER, and J CHRETIEN Seventy-eight collected cases of pulmonary involvement in histiocytosis X disease have been reviewed. The mode of clinical presentation, the radiological changes, and the pathology of the lung lesions are described. The importance of both light microscopic and electron microscopic examination of open lung biopsy material and bronchial lavage specimens is emphasised. The follow-up information has shown that in this series the long-term prognosis is not as favourable as previously thought.

Frozen sections in thoracic surgery

C W EDWARDS The frozen section technique has been in use with various modifications and improvements for over 150 years, and in the past few decades it has been successfully applied to managing surgical cases. Given an experienced pathologist and skilled technical assistance, a rapid diagnosis can usually be reached with confidence. Fatty, necrotic, or calcified specimens are difficult to cut, however, and sampling errors are possible if large quantities of material are submitted. An accurate diagnosis may not be possible with some thoracic tumours, and lymphoid aggregates in the lung or reactive change in the pleura may cause problems. Despite these limitations, it should be possible for most departments to extend their frozen section service if the need is felt.

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Myasthenia gravis: clinical and neurological presentation

GERALD STERN As Thomas Willis first recognised the condition in 1672 and by the end of the nineteenth century Erb, Goldflam, and Jolly had given comprehensive and detailed clinical descriptions, it seems unnecessary to recapitulate the details of this fascinating but still cryptic disorder. It is uncommon—with a prevalence of 3 or 4 per 100 000—and tends to affect women twice as often as men. The salient clinical features remain pathological fatiguability of muscles with a predilection for the extraocular muscles, those of speech and swallowing, and limb girdle muscles, but any muscle or indeed part of a muscle may be affected; weakness of respiratory muscles as a presenting feature is rare but late involvement common. Usually subacute in onset, its natural history is variable and unpredictable, and the degree of involvement can vary from a relentless disease terminating in respiratory failure and death after three or four months to a transient ptosis or diplopia occurring only in bright sunshine or after sustained gaze for brief periods in an otherwise normal life span. Provocative factors commonly include upper respiratory tract infections, emotional crises, and exposure to particular medications, such as curare or quinine. A host of associated disorders may be grouped as haematological —including aplasia of the bone marrow and poly-

cythaemia—and systemic—varying from systemic lupus erythematosus to sarcoidosis. Muscle disorders with pathological fatiguability that can simulate myasthenia gravis include the myopathy of hypothyroidism, polymyositis, penicillamine-induced weakness, and a non-metastatic manifestation of lung cancer. Late in the course of the disease focal muscle wasting with enduring paralysis may occur affecting the limb, extraocular, and, more gravely, the respiratory muscles. About one in eight of the children of myasthenic mothers show a transient neonatal form of the disease that responds promptly to anticholinesterases and is a self-limiting disorder clearing spontaneously in about two months.

Progressive and refractory respiratory failure terminates life in 5–10% of patients with generalised myasthenia gravis. Respiratory failure may be insidious or may occur abruptly, as when a paroxysm of coughing causes a vicious spiral of fatiguability of respiratory muscles. Occasionally excessive doses of anticholinesterase drugs may be responsible, provoking a so-called "cholinergic crisis," and the diagnostic use of a short-acting parenteral injection of edrophonium hydrochloride (Tensilon) may help to determine whether the patient is under or over medicated.

Immunological aspects of myasthenia gravis

C W H HAVARD It is nearly 20 years since Smithers first suggested that myasthenia gravis was an autoimmune disease. He was struck by the similar histological appearance of the thymus in myasthenia gravis to that of the thyroid in Hashimoto's disease. This chronic inflammatory cell infiltration with germinal centre formation, known as thymitis, is characteristic of the thymus in myasthenia gravis. Even when myasthenia is associated with a thymic tumour, and this occurs in 10% of cases, there is usually an area of thymitis adjacent to the tumour. Furthermore, the tumour always has an epithelial component arising in a type of cell that in its early development resembles striated muscle and hence has been called a myoid cell. These myoid cells, although epithelial in nature, have acetylcholine receptors on their surface. Other immunological features of myasthenia gravis that have been known for some time include the circulating antibodies to skeletal muscle and to myoid cells of the thymus that are present in the sera of some patients. The circulating antibody to skeletal muscle does not, however, attach itself to the motor end-plate and is not directly implicated in the production of muscle weakness. The association of other autoimmune diseases with myasthenia gravis has long been recognised. The most common of these are rheumatoid arthritis, SLE, and Graves's disease. More recently, circulating antibodies to the acetylcholine receptor have been reported in over 90% of patients with myasthenia gravis.

There is little doubt now that myasthenia gravis is caused by a reduced number of functioning acetylcholine receptors and that this results from immunological damage provoked by circulating antibodies to the acetylcholine receptor. Great advances have been made in our understanding of myasthenia over the past four years, and this would not have occurred without the contributions of the cobra, the electric eel, and the rabbit.

Cobra venom contains a small protein called bungarotoxin, which binds irreversibly with acetylcholine receptor and leads to paralysis and death. Bungarotoxin can be labelled with radioactive iodine and used as a marker for the receptor molecule. The number of bungarotoxin sites is proportional and probably equal to the number of acetylcholine receptor binding sites. Biopsy specimens of muscles from myasthenic patients disclose that these muscles have less than 30% of the acetylcholine receptors found in normal neuromuscular junctions. Furthermore, there is a factor located in the serum globulins of myasthenic patients that blocks the binding of bungarotoxin to acetylcholine receptors.

The next stage in the saga was the isolation of the acetylcholine receptor from the neuromuscular junction of the electric eel. When the receptor was injected into a rabbit it produced the disease that has now become well known as experimental autoimmune myasthenia gravis. The disease has more recently been induced in several different species by immunisation with syngenetic acetylcholine receptor, and in the baboon the clinical picture closely resembles that of the human condition. Furthermore, the serum of animals immunised with acetylcholine receptors can cause the disease when injected into normal animals, and this suggests that the circulating antibodies to acetylcholine receptors have a pathogenic role. Nevertheless, the thymus has a major part to play because the experimental disease does not occur in thymectomised animals. The role of the thymus is uncertain, but its importance is twofold. It is the primary immunological source of T cells, and secondly it is a source of myogenic cells with demonstrable acetylcholine receptors on their cell surface. It has been proposed that primitive intrathymic cells are induced by abnormal stimuli to differentiate into myogenic cells. Then immunologically competent T cells start an immune reaction against these newly differentiated cells and then leave the thymus to become killer cells infiltrating the neuromuscular junction and cooperating with B cells as helper cells to form antibodies to the acetylcholine receptors in striated muscle.

Radiology of the thymus

LOUIS KREEL In infancy the thymus is normally visible on a chest radiograph. After illness, steroid treatment, or malnutrition the thymus becomes small and is no longer visible but reverts to its former size on recovery or when the steroids are stopped.

In young women a prominence in the region of the left pulmonary artery in otherwise normal individuals is thought to be due to the left lobe of the thymus.

Thymomas larger than 3 cm can usually be shown on chest radiographs supplemented by fluoroscopy. As the thymus lies anteriorly, only minor degrees of rotation will accentuate the tumour, which produces

a sharp angle at its inferior margin where it is in contact with the heart shadow, thus producing a characteristic shape.

Thymomas of 2–3 cm can be shown by thymic venography and mediastinal pneumography as well as by computed tomography. In myasthenia gravis, however, thymectomy is carried out irrespective of small tumours making these investigations superfluous, apart from CT which may be required before radiotherapy.

Thymic metastases spread to the pleura, which are clearly shown on computed tomography.

Anaesthesia for thymectomy

HILARY HOWELLS Myasthenic patients present certain predictable problems to the anaesthetist, which include a liability to postoperative infections and abnormal reactions to neuromuscular blocking agents. Before operation the patient must be stabilised to a satisfactory anticholinesterase regimen and be ready for surgery at a time when he is well rested, free from infection, and has confidence in the hospital environment and the medical team. Both the anaesthetic and surgical managements have been developed at New End Hospital Endocrine Unit and still persist at the Royal Free Hospital.

Anticholinesterase treatment is maintained into anaesthesia. After intravenous induction the patient is intubated and ventilated, without the use of neuromuscular agents, by carefully controlled hand ventilation.

Nitrous oxide, oxygen, and halothane are used during induction and maintenance anaesthesia. Surgical exposure is confined to a partial sternotomy, and fine control of ventilation is necessary to allow adequate surgical access. After surgery, in the well-adjusted myasthenic, the patient is extubated and resumes spontaneous ventilation.

Intensive therapy unit care for the first two days after operation is the rule, during which time a carefully assessed anticholinesterase regimen is established

Elective tracheostomy or controlled ventilation in the postoperative period are used when certain indications are apparent. Both pre- and postoperative chest physiotherapy with daily chest radiographs and pulmonary assessments are essential. Carefully titrated postoperative analgesia is arranged, balanced with adequate ventilatory performance. It is in the postoperative phase that the value of partial sternotomy during operation is apparent.

Myasthenia gravis and thymic tumours

MICHAEL BATES Sixty-five patients with myasthenia gravis and a thymic tumour were reviewed. Forty patients were women (average age 50·4, range 21–68 years) and 25 were men (average age 51·5, range 25–69 years) and they had been operated on by 25 surgeons.

Twenty-five patients had died, nine postoperative (myasthenic crisis 8, cholinergic crisis 1), and 16 late (related to myasthenia 8, unrelated to myasthenia 8).

Most of these postoperative deaths occurred in the early years, and during the past ten years the postoperative management of these patients has greatly improved. The teamwork of neurologist, anaesthetist, and surgeon and the nursing skill available in intensive care units have combined to produce the extremely low mortality rates of many series now reported. Half of the late deaths were due to myasthenia; a certain proportion of cases gain immediate benefit from removal of the thymic tumour, and then the disease again pursues its relentless course, and the patients die of respiratory failure.

These patients have been operated on over a period of 25 years, inevitably a number have been lost to follow-up, and those with limited follow-up are shown here: alive at 7 years (3), at 5 (2), at 4 (4), at 3 (1), at 2 (3), and at 1 (10), total 23. It is reasonable to suppose that possibly half of these patients with a limited follow-up are alive today, and this would add to those who are known to be alive and well but still taking drugs in 1978: alive at 16 years (1), at 13 (2), at 12 (1), at 10 (2), at 8 (1), at 6 (3), at 5 (1), at 4 (1), at 3 (1), and at 2 (4), total 17.

An interesting clinical variation of this disease that is well recognised is the delayed onset of myasthenia after removal of a symptomless thymic tumour. This may occur the day after operation or not for several years, eg:

Male	aged 56	onset of MG 16 months postop	A/W	10 yrs
Male	aged 25	onset of MG 18 months postop	A/W	4 yrs
Male	aged 49	onset of MG 2 months postop	A/W	2 yrs
Male	aged 50	onset of MG 3 months postop	A/W	2 yrs
Female	aged 63	onset of MG 4 months postop	A/W	4 yrs

The second case was a young man of 25 who had a median sternotomy for removal of a symptom-free thymic tumour in May 1972. At operation innocent encapsulated lymphoepithelioma was found. Eighteen months later, on board ship to South Africa, he developed acute myasthenic symptoms and was admitted to Groot Schurr Hospital where tracheostomy had to be performed. Eventually he returned to London, and the mediastinum was re-explored by another surgeon in May 1974, but no residual thymic tissue was found. He is now well but taking Prostigmin.

There have been several theories to explain this atypical clinical course: (1) the disease is present in subclinical state at the time of operation; (2) a distant metastasis may be present; (3) a pleural deposit may be present; (4) thymic tissue may have been left in the mediastinum; and (5) an agent, as yet unknown, may be responsible both for the myasthenia and the thymic tumour.

The great improvement in postoperative care of patients with myasthenia gravis and a thymic tumour, resulting in the low mortality rate, fully justifies an aggressive approach, and it is considered that the

ideal treatment is total thymectomy in conjunction with radiotherapy given either before or after surgery.

Radiotherapy of thymic tumours with myasthenia gravis

ARTHUR JONES The radiosensitivity of many thymic tumours, as shown by the rate of reduction in volume after a given amount of radiation dosage, is well known; it mirrors their lymphocytic component found histologically, and some tumours show pronounced shrinkage after a lesion dose of 1500–2000 rads in 15 fractions in 21 days. In the surgical series studied by Keynes at St Bartholomew's Hospital the presence of a thymic tumour implied a much worse prognosis for thymectomy in myasthenia gravis, both from the difficulty of the operation and from the immediate worsening of myasthenia—and thus the use of radiotherapy as the initial mode of treatment was investigated. Nowadays, megavoltage radiation (either radio-Cobalt or Linear Accelerators) is used exclusively. The tumour-bearing volume is carefully delineated, and treatment is planned to minimise pulmonary irradiation. An attempt is made to administer a tumour dose of 4000–4500 rads in 25–30 fractions in five weeks.

Radiotherapy, however, has problems of its own. Early experience showed it to be important to start with a small radiation dose, as too large an initial dose or too rapid an increase aggravated the myasthenia. Patients were prone to attacks of pyrexia and pulmonary infection, which sometimes precipitated increase of myasthenia and often myasthenic crisis. Mediastinal and pericardial reactions also proved important if uncommon complications of irradiation. They occurred in about one-fifth of 43 cases of thymic tumour irradiated, and varied from retrosternal discomfort with malaise and tachycardia to, in three cases, overt pericarditis. One other patient proceeded to chronic constrictive pericarditis. Such "mediastinopericardial" reactions were clearly conditioned by the presence of radio-responsive tumour actually lying on the pericardium (Jones and Wedgwood, 1960).

Improvement in myasthenia after thymic irradiation proved to be very variable and often took several months to occur; thymectomy was thus postponed for at least two months. Histological studies of thymic tumours removed after such irradiation showed that with dosage of 3500–4000 rads the epithelial elements remained relatively little affected even though the tumour had undergone considerable shrinkage with destruction of lymphocytes. Ablation of the epithelial cells requires higher dosage, and since the incidence of chronic adhesive mediastinitis is very dose-related above 4000 rads this acts as a curb on the cure of such tumours by irradiation alone. The experience of the St Bartholomew's Hospital series indicated that the myasthenia was a more important problem than tumour invasion in the individual patient, and certainly some excellent if unpredictable remissions of myasthenia have been reported.

In this series of 65 cases very few patients were treated with radiotherapy—only four before and four after operation.

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Environmental and constitutional factors determining hypersensitivity to avian antigens in pigeon fanciers

S W BANHAM, P LYNCH, and G BOYD In a survey of 277 pigeon fanciers in Scotland information about contact with pigeons, details of any respiratory symptoms, smoking habit, and other data was obtained. The serum concentration of IgG antibody to pigeon globulin was measured by radioimmunoassay, and values greater than 4 μg/ml were considered to indicate sensitivity to pigeon protein. Factors that influenced the antibody response of this exposed population were then examined.

Three parameters of exposure—number of years keeping pigeons, number of pigeons kept, and hours spent in loft per week—were studied. The percentage of those sensitised was plotted against appropriate intervals of each of these indices, and similarly with the subjects' ages. Age alone and hours in loft did not correlate with sensitisation, but the regression coefficients for years exposed and number of pigeons kept were 0·98 and 0·94 respectively. Atopic state and smoking were also considered, and of 23 people with positive skin test reactions to common allergens, 11 (48%) were sensitised. As reported previously (Boyd *et al*, 1977), only nine of 122 smokers (11%) had levels greater than 4 μg/ml, compared with 28% sensitisation for the whole group.

The number of people sensitised to pigeon material has varied considerably in reported series, possibly due to non-specific reactions produced by the precipitin test used. A significant correlation between degree of exposure and the risk of becoming sensitised was found in this study, in accord with Dixon *et al* (1961) —when quantitative variation in antigen challenge was found to influence the development of a type III reaction in rabbits.

It also confirms the role of these factors in the aetiology of extrinsic allergic alveolitis, as indicated by Pepys (1969). Other external factors exert a major influence on antibody response, however, and the development of clinical disease depends on the interaction of many environmental and constitutional factors.

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Distinction between asthma and chronic bronchitis: a clinicopathological study

B J HUTCHCROFT, R C BUTLER, A GUZ, K D MACRAE, J C SLOPER, J VINTER, and D F WOODROW The definitions of asthma and chronic bronchitis remain unsatisfactory (Fletcher, 1971). In an attempt to improve them typical cases of each disease have been studied by a combination of new and old techniques. The new techniques include IgE concentrations, exercise testing, and ultrastructural and immunofluorescent studies of biopsy specimens of the bronchial mucosa obtained during fibreoptic bronchoscopy. In all, 64 data points were collected from each patient. To test the usefulness of these new definitions, patients with undefined airways disease have been studied by the same techniques. Thirty-two patients with typical asthma and 18 with typical chronic bronchitis were studied, as well as a control population of patients with normal airways. The individual tests that best distinguished between the groups were the higher incidence of skin prick tests in the asthma group, the increased arterial PCO_2, and increased amount of free mucus in the airways of the group with chronic bronchitis, and the increased thickness of the "basement membrane" in the group with asthma. The best of these tests, the incidence of skin prick tests, gave an overlap of 18% between these typical cases. By subjecting the data to multivariate stepwise discriminant analysis this overlap was reduced to 12% using just four of the parameters studied—the incidence of skin prick tests, the presence of a history of postexercise asthma, forced vital capacity, and the blood eosinophil count. Using the criteria from this latter analysis, 64% of 14 patients in the undefined group were correctly placed in the appropriate clinical group. The other 36% were placed in the area where there was overlap between the typical cases. No patient was placed in the wrong group. The results suggest that asthma and chronic bronchitis patients can be separated into two groups, and criteria used can be successful in diagnosing patients with undefined airways disease.

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Can we recognise very severe asthma?

D JONES, I S PETHERAM, J V COLLINS, and M A BRANTHWAITE We set out to define measurable criteria by which patients with asthma who later need assisted ventilation may be distinguished at the outset from other patients acutely ill with asthma. We excluded patients who arrived unconscious and those who suffered sudden cardiorespiratory arrest. We compared 11 patients who had been ventilated with 211 acute asthma admissions.

The ventilated patients exhibited: (*a*) rapid period of deterioration in the preceeding few days, eight within the previous 24 hours; (*b*) tachycardia 110 to 152; (*c*) paradox between 30 and 50 mm Hg in six measurements recorded; (*d*) peak expiratory flow rate (PEFR) unrecordable in four, and less than 60 l/min in three patients; (*e*) variable Po_2, as some had been given oxygen; (*f*) normal or high Pco_2 in all but one patient; (*g*) acidosis in five ((*e*), (*f*) and (*g*) measurements in all 11); and (*h*) initial two- to threefold increase in PEFR in three patients after bronchodilators, followed by decline in PEFR.

Comparison with non-ventilated patients showed that short period of deterioration, pulse 110/min or greater, paradox 30 mm Hg or greater, and PEFR 60 l/min or less, were all highly significant ($P<0.001$).

The following criteria of severity—(1) pulse 110/min or greater; (2) paradox 30 mm Hg or greater; and (3) PEFR 60 l/min or less—applied to our non-ventilated patients (total 195) showed there were only five other patients with this combination who were not ventilated.

We conclude that: (1) patients with asthma needing ventilation have a short period of deterioration; (2) pulse, paradox, and PEFR are all significantly different from non-ventilated patients, but overlap excludes absolute differentiation; (3) initial response to bronchodilators may be misleading; and (4) the criteria pulse 110/min or greater; paradox 30 mm Hg or greater; and PEFR 60 l/min or less may be very helpful in defining those patients with asthma likely to need ventilation.

Pattern of recovery in severe acute asthma

I S PETHERAM, D JONES, J V COLLINS, and D BROWN Varying patterns of airflow obstruction have recently been described in chronic asthma (Turner-Warwick, 1977; Clark and Hetzel, 1977) but there is little information on patterns of recovery in severe acute asthma. All patients admitted with severe acute asthma at Brompton are managed in a uniform way with inhaled and intravenous bronchodilators, and intravenous and oral corticosteroids. Response to treatment is monitored by peak expiratory flow measurements using a Wright peak flow meter every four hours. We have examined the peak flow charts in 201 admissions for (*a*) initial response to inhaled bronchodilator and intravenous aminophylline, (*b*) time taken to achieve 50% of eventual improvement, and (*c*) time taken to reach maximum improvement. We have compared fast responders with slower responders for predictive differences in history of asthma, particularly in the year before admission, steroid consumption, and severity of illness on admission as judged clinically by arterial blood gas tensions and measurements of airflow obstruction.

We have found that (1) in 73% of admissions at least 50% of eventual improvement had occurred by 24 hours and that these patients achieved their maximum PFR sooner ($P<0.001 \chi^2$); (2) there was a highly significant correlation between good initial response to treatment and a shorter time to reach maximum PFR ($P<0.001$); (3) total duration of asthma, steroid consumption, and indices of severity on admission were not useful predictors of speed of response; (4) there was no correlation between the period of deterioration before admission and speed of response

to treatment; and (5) severe morning dipping assessed by the method of Hetzel *et al* (1977) occurred in 46% of quicker responders but only 23% of slower responders.

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Response of asthmatic airways to a single deep inhalation

E M SUGDEN and D J LANE Using a constant volume whole body plethysmograph, breath-by-breath measurements of airways resistance have been made in 21 patients with asthma. Over the first two minutes in the plethysmograph, values declined from an initial high level to a plateau between 0·3 and 0·9 kPa l^{-1} s. The patients then inspired fully to total lung capacity and breath-by-breath measurements were continued for a further 2–3 min. In 10 patients there was a sharp rise in airways resistance to between 0·6 and 1·8 kPa l^{-1} s, which was of rapid onset (within 10 s) and of short duration (about 60 s). The height of the response in a given individual was linearly related to the initial airways resistance. This transient bronchoconstriction could be abolished by prior administration of salbutamol (2 mg by inhalation) but only partially by prior administration of atropine methonitrate (1 mg by inhalation).

Natural history of patients with carcinoma of lung

D M GEDDES Few patients with lung cancer receive no treatment so little is known of the natural history of untreated disease from direct observations. Tumour growth can be measured from serial chest radiographs, however, and from these growth rates a tumour's life can be calculated. Lung cancers grow exponentially so that the time for the tumour volume to double is roughly constant. Measurement of the volume doubling time allows extrapolation back in time to the first malignant cell and forward to the approximate time of death when the total tumour mass is about 1 kg. More than 200 primary lung cancers have been measured in this way, and the mean doubling times and extrapolations based on them are shown in the table.

Histology	*Mean doubling time (days)*	*Years from malignant changes to*	
		diagnosis	*death*
Oat	29	2·8	3·2
Squamous	88	8·4	9·6
Adeno	161	15·4	17·6

Four conclusions can then be made: (1) a tumour is microscopic and causes no symptoms for most of its relatively long life; (2) survival predicted from tumour growth is very similar to that observed in practice, suggesting that treatment has little overall effect on survival; (3) if tumours are selected because they are small and slow growing excellent survival figures can be achieved on the basis of natural history alone; and (4) treatment must be aimed at reducing tumour bulk sufficiently to allow host defences to eradicate the remaining disease; this is likely to be achieved only by an aggressive approach to early disease.

Preoperative bone and liver scanning in patients with carcinoma of lung

T C STOKES, P J ELL, J F STEVENS, and J R BELCHER The mortality in the first year after the apparent successful resection of lung cancer is as high as 30%. This high mortality is due to metastases already established at the time of intervention. To try and identify this group of patients liver and bone scanning was included in the preoperative work-up of patients. A group of patients have now been followed up for four to 16 months, and the incidence of bone and liver metastases appearing has been related to the preoperative scan results.

The liver enzymes gammaglutamyl transpeptidase, AST, and alkaline phosphatase were measured. The hydroxyproline creatinine ratio was measured on a sample of early morning urine as an index of bone involvement.

The alkaline phosphatase is thought to be a poor indicator of bone secondary deposits. Bone pain and radiographic changes are late events.

Nine isolated bone scan abnormalities were detected in a total of 84 scans. Eight of these patients developed clinical and radiological evidence of metastatic bone disease in the first three months of follow-up. In four patients the hydroxyproline creatinine ratio was raised at the time of initial abnormal bone scan. Two out of 45 patients who had tumour resection and normal scan before operation developed clinical evidence of bone metastases three and five months after operation, with concomitant rise of hydroxyproline creatinine ratio.

Four cases of HPOA were detected by bone scanning, and the value of this investigation in differentiating the pain of this condition from that due to secondary deposits is discussed.

In 47 patients who had tumour resections six of the seven patients with liver scan abnormality developed clinical evidence of secondary deposits within six months of resection. Five of 40 patients with normal liver scans developed evidence of secondary deposits within the same period.

It will be shown that raised liver enzymes are a poor indication of liver secondaries, and liver scan should be considered in this small group of patients selected for surgical treatment.

Laboratory profiling in the assessment of prognosis in lung cancer

A L MILLER, P V LONG, J F STEVENS, H A A ISSA, T C

STOKES, and EUNICE LOCKEY In view of the poor survival rates reported for the first year after operation in lung cancer a study was initiated to determine whether a profile of laboratory tests can identify non-survivors either before operation or at their first attendance at a follow-up clinic, usually six weeks after operation.

In addition to the standard biochemical and haematological profiles provided by the Vickers M300 analyser and the Coulter counter, the erythrocyte sedimentation rate was recorded; plasma carcinoembryonic antigen, α-antitrypsin, haptoglobins, and copper were assayed; the activities of lactate dehydrogenase, gammaglutamyl transpeptidase, and heat stable alkaline phosphatase were determined; and the urinary hydroxyproline creatinine ratio measured. Whenever possible two samples were obtained before operation and further samples at each clinic attendance.

One hundred patients will be admitted to the study that began in February 1977. It is now possible to present preliminary findings in nine patients alive and well, without evidence of recurrence, after more than ten months, and in 17 patients who have died during the first year. Interesting differences are seen in several of the parameters measured, both before operation and at follow-up.

Preliminary attempts to establish criteria that discriminate between survivors and non-survivors will be presented; these criteria will be applied prospectively to the remaining patients in the series.

Intrapleural BCG in operable lung cancer

P B ILES and D F SHORE After the report of McKneally *et al* (1976) of the benefit of BCG (Tice) given intrapleurally to patients after resection for lung cancer, we instituted a controlled, prospective randomised study of intrapleural Glaxo BCG in May 1976.

Patients were selected at random to receive (*a*) Glaxo BCG, 1×10^7 viable organisms after surgery, then eight weeks' Isoniazid 300 mg daily starting two weeks later or (*b*) placebo (Lactose) tablets for eight weeks starting two-and-a-half weeks after surgery. Ninety-two patients entered the study, 77 having non-anaplastic cancer. Six of the 38 BCG-treated and nine of the 39 control non-anaplastic cancer patients have died, giving cumulative 18-month survival rates of 77% and 63% respectively. This difference is not significant. Two of the 22 stage 1 non-anaplastic BCG treated patients have died compared with seven of 23 controls, and this trend reaches significance ($\chi^2=4{\cdot}195$, $P<0{\cdot}05$, Log rank test). The survival rate of patients with anaplastic cancer was significantly worse than that of non-anaplastic cancer patients, irrespective of the treatment received ($\chi^2=5{\cdot}05$, $P<0{\cdot}025$ Log rank test). About half of the patients with anaplastic cancer have died, irrespective of the stage of disease at surgery or the treatment received. Half of the BCG-treated patients had a febrile reaction and this was independent of Heaf test response; other complications were similar in both groups.

The limited benefit from Glaxo BCG may be related to the lower incidence and duration of febrile response compared with that reported with Tice BCG, but since five of the 11 BCG-treated patients who died had been febrile other factors may be important. These data suggest that intrapleural Glaxo BCG in the dosage used may have been of benefit in patients with limited non-anaplastic cancer.

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Legionnaire's disease

A C MILLER, S B PEARSON, P JENKINS, J OSMAN, and J M ROWLEY Since June 1976 11 cases of legionnaire's disease have been admitted to hospitals in Nottingham, ten between May and November 1977. One patient on immunosuppressive therapy for systemic lupus erythematosus had few symptoms on admission but deteriorated rapidly and died. The clinical features of the others were uniform, although of varying severity. A five to ten-day period of malaise with increasing cough and breathlessness preceded admission. Pleuritic pain was common (five patients) as were abdominal pain and diarrhoea unrelated to administration of antibiotics (three patients). Sputum production was not a prominent feature. Three patients had pleural friction rubs. Fever, tachypnoea, tachycardia, dehydration, and confusion were associated features. Radiography confirmed lobar consolidation in all cases, initially limited to one lobe in eight patients but subsequently extending to affect other lobes. In some, clearing of the initially affected lobe occurred during this extension. In the nine survivors radiological consolidation persisted for at least seven weeks and in five for 14 weeks. Common findings were lymphopenia, hyponatraemia, and hypoalbuminaemia. Eight patients were mildly uraemic, and one needed peritoneal dialysis. Despite antibiotic treatment eight patients deteriorated, and six needed intermittent positive-pressure ventilation. One of these patients died. Retrograde amnesia was a common finding irrespective of whether they were ventilated. No pathogenic organisms were isolated, and the diagnosis of legionnaire's disease was established by measurements of specific antibody titre (nine patients) or by immunofluorescence studies on post-mortem lung (two patients).

The occurrence of 11 apparently unconnected cases over several months in a relatively small area is so far unique, contrasting with earlier explosive outbreaks over short periods and also with the low incidence of subsequent sporadic cases in large populations. Retrospective study of over 300 other patients presenting during this period with acute respiratory illnesses has not identified any other cases.

Fibreoptic bronchoscopy in the diagnosis of pulmonary lesions in lymphoma and leukaemia

R K KNIGHT, M J PHILLIPS, and M GREEN Pulmonary complications are common in patients with lymphoma and leukaemia and are often a cause of death (Williams *et al*, 1976). In an attempt to elucidate the aetiology of pulmonary lesions that remained undiagnosed by non-invasive techniques, we performed fibreoptic bronchoscopy (Clarke and Knight, 1977) under AP fluoroscopic control in 39 patients (26 with lymphoma and 13 with leukaemia). The alveolar lavage aspirate was spun down and slides prepared and stained with silver techniques, Ziehl-Neelson and standard cytological stains. A sample of this fluid was cultured in the bacteriology laboratory and virus isolation attempted. Brush biopsies, bronchial biopsies, and transbronchial biopsies (TBB) were performed when appropriate. Six patients had fibreoptic bronchoscopy (FOB) performed more than once. In three, diagnoses were obtained at the first bronchoscopy and the second was done for the purpose of reassessment. A further three patients, all with diffuse disease, had three bronchoscopies each in an endeavour to establish a diagnosis.

Fifteen patients had lung shadowing, occupying at least one out of six zones on the CXR. A definite diagnosis was made in nine (60%), and in a further two infection or infiltration by the disease process were excluded and histology was suggestive of alveolar damage due to drug toxicity. Twelve patients had segmental or lobar lesions, for which aetiology was established in eight (66%), and useful negative information obtained in a further one.

In eight cases there were small peripheral pulmonary lesions of less than 3 cm diameter. In only one was a diagnosis obtained, in contrast to a positive rate of 62% for peripheral carcinoma in our hands. The diagnosis rate in small lung lesions would probably be improved by using a two-plane fluoroscopy table to enable the position of the biopsy forceps to be determined more accurately. In a further four cases hilar abnormalities were noted on CXR, and diagnosis was obtained in three (75%).

Several patients had potentially high risk factors including hypoxaemia, thrombocytopenia and/or neutropenia. Two patients with severe hypoxaemia were ventilated with 100% oxygen under general anaesthetic. Those with thrombocytopenia (platelets below 30 000) received a fresh platelet transfusion immediately before FOB. TBB was carried out in all cases without significant bleeding, infection, morbidity, or mortality.

This relatively benign technique has yielded useful information in a worthwhile number of lymphoma and leukaemia patients with pulmonary complications.

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Flow-volume loop: reproducibility of present air- and helium-based tests and an analysis to suggest new indices

J B MACDONALD and T J COLE Maximal expiratory flow-volume loops were performed on air and then breathing an 80% helium : 20% oxygen mixture for three deep breaths (3 B) then for three minutes (3 M). The tests were performed twice daily for five consecutive days on 25 asymptomatic subjects (eight smokers and 17 nonsmokers) using an Ohio dry spirometer and a storage oscilloscope. The standard lung function tests—forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and peak expiratory flow rate (PEFR)—were the most reproducible. Maximal expiratory flow at 50% vital capacity (MEF_{50}) and at 75% vital capacity (MEF_{75}) were passably reproducible. They were as reliable breathing helium as breathing air, with 3 B as reproducible as 3 M. Percentage improvements in MEF_{50} or MEF_{75} after breathing helium (3 B or 3 M), however, were very poorly reproducible—far too unreliable for any of these indices to become a standard test for small airways obstruction despite their alleged sensitivity. Helium isoflow was very poorly reproducible with, on average, more variation within a single subject than between subjects. Thus it is unlikely to become a standard test.

A new application of canonical variate analysis to the data is described. This statistical technique shows which tests or combinations of tests give qualitatively different results and so can be used to see if a new test gives qualitatively different information. Almost all our data variation occurred within four parameters. Thus there are probably only four flow-volume loop features that can be used to discriminate between individuals. The largest parameter (essentially FVC) reflects the width of the loop, while the second parameter (mainly PEFR) records its height. The third and fourth indices are more difficult to interpret: the third is probably related to forced expiratory time and the fourth appears to express the curvature of the trace from PEFR to FVC.

Tidal and maximum flow-volume curves in the assessment of airway narrowing in asthma

R PEREIRA, D HUNTER, and N B PRIDE Airway function in asthmatic patients is usually assessed by tests of forced expiration that cannot reflect directly the difficulties these patients encounter during tidal breathing. We have compared tidal and maximum flow-volume curves in 15 asthmatic patients who were studied sequentially while the severity of their airway narrowing varied either spontaneously or with treatment. These curves can be used to show changes in the capacity to produce maximum flow at all lung volumes and, in addition, other common changes such as changes in total lung capacity, in the volumes used for tidal breathing, and in the proportion of the breathing cycle allocated to inspiration.

Sequential maximum expiratory flow-volume curves showed characteristic changes in FEV_1, and in peak

flow and in maximum flow when 50% and 25% of the vital capacity remained to be expired. Although the relation between FEV_1 and peak flow was approximately linear, this was not the case for the relation between FEV_1 and maximum flow rates lower in the vital capacity. Distinctive patterns of lung emptying reflecting predominant large or small airway narrowing have not so far been recognised on these curves, although it is usual for the change in slow vital capacity after bronchodilation to be large in relation to the change in FEV_1 when asthma is severe. Significant changes in total lung capacity immediately after treatment with salbutamol were uncommon.

When asthma was severe, the proportion of the breathing cycle allocated to inspiration was reduced, and expiratory flow during tidal breathing at rest often reached the maximum capacity for flow over much of the tidal range. After a bronchodilator tidal breathing usually took place at smaller volumes, and the difference between the tidal requirement and the maximum capacity for flow was increased.

These results indicate that improvement in the maximum flow-volume curve is usually associated with changes in the tidal flow-volume curve, which imply a reduction in either inspiratory or expiratory work. They support the use of FEV_1 or peak flow for the clinical assessment of patients, although other indices from the maximum flow-volume curve may be useful when studying mild disease.

Respiratory muscle action and chest wall movement in patients with severe hyperinflation

G J GIBSON and N B PRIDE It has been suggested that with increased ventilation abdominal muscle contraction is co-ordinated to optimise diaphragmatic function, and this is particularly evident in patients with airways obstruction (Grimby *et al*, 1973) where the mechanical advantage of the diaphragm is compromised.

We have studied transdiaphragmatic pressures and chest wall movements in four patients with emphysema and severe hyperinflation during spontaneous breathing and on stimulation by rebreathing CO_2.

During unstimulated tidal breathing in normal subjects subdiaphragmatic pressure (Pab) becomes more positive throughout inspiration as the diaphragm descends. By contrast, in our patients Pab in early inspiration became very much more negative, implying considerable activity of other respiratory muscles. During stimulated breathing this general pattern was maintained, but there was a progressive increase in peak values of transdiaphragmatic pressure (Pdi) later in inspiration, even though in two of the patients Pdi at high volumes was poorly sustained.

The pattern of Pab in early inspiration in our patients could result either from intercostal and accessory muscles raising the rib cage or from relaxation of abdominal muscles that had contracted during the preceding expiration (or from a combination of these mechanisms). The magnetometers showed that while Pab was becoming more negative the AP diameter of the abdomen was increasing, which favours relaxation of abdominal contraction as the main factor. At the same time, in early inspiration the AP diameter of the rib cage in three patients showed a paradoxical decrease; this was exaggerated when breathing was stimulated and is probably also a consequence of abdominal muscle relaxation.

We conclude that, while the diaphragm may be less efficient than normal in patients with hyperinflation, it is able to augment its effect when ventilation is increased. If, as has been suggested, abdominal muscle activity acts to protect the shape and mechanical advantage of the diaphragm in such patients, this must be at the expense of severe distortion of the chest wall.

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Bronchial response to inhaled cigarette smoke in relation to respiratory illness and the bronchial threshold to inhaled histamine

T HIGENBOTTAM, D HAMILTON, C FEYERBAND, and T J H CLARK There is considerable variation between individual smokers in their acute bronchial responses to inhaled cigarette smoke (Guyatt *et al*, 1970). To define the factors contributing to this variation we studied 40 individuals divided, according to their smoking habit and symptoms, equally into five groups: non-smokers; asymptomatic smokers; symptomatic smokers with reduced forced expiratory volumes in one second (FEV_1), asthmatic patients including smokers and non-smokers, and pipe smokers and asymptomatic ex-smokers.

The bronchial responses to smoking an ordinary low tar filter cigarette and a comparable tar and nicotine NSM (new smoking material) cigarette were measured using 12 variables derived from an analysis of the maximal forced expiratory flow volume curve (MEFV). The amount of smoke inhaled from each cigarette was assessed from changes in levels of venous blood nicotine and carboxy-haemoglobin. For each individual the bronchial threshold to inhaled histamine was determined (Higenbottam *et al*, 1978).

In about half the individuals there was a significant change in at least one of the 12 variables from the MEFV after at least one of the cigarettes indicating airway narrowing. There was no difference between the ordinary and NSM-containing cigarettes in the number or magnitude of positive responses to inhaled smoke.

There were large differences between the groups in the proportions of individuals showing a positive response with both asthmatic smokers and non-smokers showing the highest proportion of responders (6 out of 8). By contrast, both groups of asymptomatic and symptomatic smokers showed the lowest proportion of responders. All smoking groups inhaled more smoke per cigarette as judged by blood nicotine and carboxyhaemoglobin than the non-smoking groups.

Differences in bronchial threshold to inhaled histamine between the groups were observed. Symptomatic smokers with an abnormal $FEV_{1.0}$ and asthmatic smokers were found to have a lower threshold to histamine than the other groups.

These results suggest that smokers, even when possessing heightened bronchial reactivity, tolerate those acute irritant effects of inhaled cigarette smoke that might produce acute airway narrowing. In distinction, asthmatic individuals usually remain responsive to these effects. This would further suggest that chronic intermittent acute airway narrowing following smoking is not the prime mechanism involved in the development of airflow obstruction in non-asthmatic smokers.

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Inhaled antihistamines—bronchodilatation and effects in histamine- and methacholine-induced bronchoconstriction

S G NOGRADY and C BEVAN The bronchodilator properties of inhaled antihistamines (Nogrady *et al*, 1978) could be due to specific H_1 receptor blockade or to associated anticholinergic effects. The bronchodilator properties of clemastine, a highly specific H_1 receptor antagonist, and its ability to prevent histamine and methacholine-induced bronchoconstriction were investigated.

Ten stable atopic asthmatic subjects inhaled aerosols of clemastine 1 mg/ml and physiological saline in a 1·0 ml dose from a Hudson nebuliser. Bronchodilatation was assessed at 30 minutes by measurement of specific airways conductance (SGaw) by whole body plethysmography. There was a highly significant 21·9% increase in SGaw with clemastine when compared with saline ($P<0·002$).

All subjects underwent bronchial challenge with increasing concentrations of histamine and methacholine 30 minutes after inhalation of clemastine or saline administered double blind. SGaw was measured at three-minute intervals before each challenge dose. Subjects could tolerate significantly higher concentrations of histamine when treated with clemastine than with saline ($P<0·01$). The parallel shift to the right of the log histamine dose response curve suggests that the protective effect of clemastine is due to specific competitive antagonism to histamine. Clemastine did not protect subjects against methacholine-induced bronchoconstriction, which confirmed that bronchodilatation is unrelated to any anticholinergic properties.

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A double-blind study of the effects of salbutamol metered-dose aerosol on the resting and exercise pulmonary function of patients with emphysema

D BELLAMY, J W REED, and D C S HUTCHISON It is common practice to administer beta-agonist bronchodilator drugs to patients with emphysema despite the view that this disease is characterised by irreversible air-flow obstruction. We have noted that in some patients the vital capacity (VC) may show a substantial increase after inhalation of salbutamol aerosol, together with subjective improvement.

In a double-blind cross-over study either 400 μg (four puffs) of salbutamol or four puffs of placebo from a metered-dose inhaler were administered to 20 clinically stable patients (aged 44–69) with radiological evidence of emphysema. Thirteen of the patients also had chronic bronchitis (MRC criteria), but patients with a history of asthma were excluded. Mean FEV_1 (% predicted) was 43% (range 21–97%), VC 86% (range 53–118%), and Tco 62% (range 25–117%). FEV_1, slow VC, and PEFR were measured every 15 minutes for 90 minutes after inhalation of salbutamol or placebo. At 90 minutes patients performed a standard progressive exercise test on a cycle ergometer.

The effect of salbutamol was measured as the salbutamol response minus the placebo response. Salbutamol produced an increase in the mean FEV_1 of 0·19 l ($P<0·001$) and VC of 0·43 l ($P<0·001$). The difference between the increases in FEV_1 and VC was significant ($P<0·02$). During exercise, the submaximal indices $V_{E0.5}$ and $fC_{0.5}$ increased significantly after salbutamol ($P<0·02$ and $P<0·01$ respectively), $V_E max$ rose significantly ($P<0·04$) but $V_{O_2}max$ and fCmax did not.

The effects on FEV_1 and VC may be brought about by two separate actions—bronchodilatation in larger airways and an increase in the volume of peripheral air spaces. The increase in ventilation on exercise could be mediated by hypoxia due to further impairment of the V/Q relationship or possibly by augmentation of central ventilatory drive.