Thorax, 1977, **32**, 643–652

Proceedings of The Thoracic Society

A joint meeting of the British Thoracic and Tuberculosis Association, the Scottish Thoracic Society, and the Thoracic Society was held on 30 June–1 July 1977 at the George Square Lecture Theatre, University of Edinburgh. Summaries of the papers follow:

Assessment of the bronchoactivity of acute exposure to irritant gases and vapours in humans

R. B. DOUGLAS The bronchoactivity of a number of gases and vapours of industrial importance has been investigated in adults with normal ventilatory indices using the constant volume whole body plethysmograph. The method is also suitable for the assessment of sub-anaesthetic doses of anaesthetics and analgesics.

It is usual practice to express resistance of the airways as specific conductance, which is conductance divided by lung volume. Control values (mean of 10 estimations) were obtained in the box, after which the subject received an acute exposure of 10 breaths of 1 litre each, and the specific conductance was re-measured immediately.

Dose response curves were obtained for the irritants using a randomised double-blind technique. For sulphur dioxide the intercept of the dose response curve at 1 ppm compared favourably with the results of Frank and Amdur (1962) using much longer exposures. The experiments included ammonia which produced copious, watery saliva in all subjects as well as bronchoconstriction. The ketones were also investigated and showed increased irritancy and bronchoactivity with increasing molecular weight. The third member has three isomeric forms and the effects of position of the functional group was successfully examined. Three aldehydes including acrolein were tested, the bronchoactivity falling as the molecular weight increased.

The first anaesthetic investigated was methoxyflurane (Penthrane) 0·35% v/v. The subject remained seated in the plethysmograph and inhaled from a Cyrane Cardiff inhaler through the standard face mask. Breathing was at tidal volume for 1½ minutes and the exhalate was voided externally to avoid contamination of the plethysmograph.

The technique was also successfully applied to the investigation of entonox (50 : 50, 0_2 and N_2O), halothane, and prostaglandin E_2.

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A method of assessing bronchial selectivity of beta-adrenoceptor antagonists in man

H. R. GRIBBIN, C. J. BALDWIN, and A. E. TATTERSFIELD The extent to which beta-blocking drugs act selectively on cardiac rather than bronchial beta receptors should determine their potential danger to asthmatic patients. The introduction recently of many new beta-blocking drugs has highlighted difficulties in assessing accurately this selectivity. Some information can be obtained by giving the drugs to asthmatic patients but this procedure is not without risk. The quantitative assessment of selectivity has relied on studies in the cardiovascular system of animals and man though it is by no means certain that peripheral vascular and bronchial beta receptors have identical characteristics (Vaughan-Williams, 1973). We describe a method in which the bronchial selectivity of these drugs can be assessed quantitatively and safely in normal subjects.

Five normal subjects inhaled increasing doses of salbutamol. The change in airway resistance expressed as specific conductance (sGaw) was plotted against the cumulative dose of inhaled salbutamol to obtain a dose response curve. Similar curves were then obtained two hours after the oral administration of practolol, 100 mg, and propranolol, 40 mg. The displacement of the dose response curve to the right reflects the action of the antagonist at the bronchial beta receptor. The dose ratio calculated for each drug at 50% of maximum airways response was compared to the reduction in exercise heart rate after the administration of each drug in the same subject to assess bronchial selectivity. Our results show that propranolol, 40 mg, and practolol, 100 mg, produce a similar depression of exercise heart rate but a 20-fold difference in their ability to antagonise salbutamol in the airways. This method should provide a useful way of screening new beta-blocking drugs for bronchial selectivity in man.

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Bronchial and metabolic resistance to beta adrenergic bronchodilators

S. T. HOLGATE, W. STUBBS, K. G. M. M. ALBERTI, and A. E. TATTERSFIELD Diminished beta-receptor responsiveness (resistance) after chronic treatment with beta-adrenergic agonists has been demonstrated in a number of human and animal tissues but not in the airways of patients with asthma. We have recently demonstrated that resistance to salbutamol can be produced in the airways of normal subjects taking large doses of inhaled salbutamol (Holgate and Tattersfield, 1976) and we have extended this study to investigate the metabolic effects of this treatment.

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In six healthy subjects, specific conductance (sGaw) was used to follow the bronchodilator effect of intravenous boli of salbutamol sulphate (25 μg) up to a total dose of 300 μg. Five minutes after each injection venous blood was withdrawn through an indwelling catheter for measurement of intermediary metabolites and cyclic nucleotides (3′5′ cyclic AMP and 3′5′ cyclic GMP). Subjects then took inhaled salbutamol (400 μg four times daily) for two weeks. Twelve hours after the last regular dose, sGaw and metabolic dose response curves to intravenous salbutamol were repeated.

After taking regular salbutamol there was a reduction in response to intravenous salbutamol of bronchodilatation (70%), glucose, pyruvate, and lactate (70–90%) and glycerol and ketone (10–35%). This metabolic resistance was not accompanied by a fall in 3′5′ cyclic AMP response to intravenous salbutamol and there was no change in 3′5′ cyclic GMP response.

Inhaled salbutamol in doses used by some asthmatic patients may attain systemic levels sufficient to stimulate metabolic beta-receptors and cause resistance. The finding of metabolic resistance in the presence of normal plasma 3′5′ cyclic AMP responsiveness suggests that resistance does not involve the beta-receptor-adenylate cyclase complex. One possibility is an alteration in the 3′5′ cyclic AMP dependent protein kinase.

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Patterns of diurnal variation in asthma

M. R. HETZEL, and T. J. H. CLARK In a 30-month study of 1169 consecutive admissions for asthma we found that excessive diurnal variation in peak expiratory flow rate (PEFR) could be associated with an increased risk of potentially fatal episodes of unexpected ventilatory arrest. These episodes usually occurred in apparently mild asthma attacks.

During recovery from an attack of asthma, some 20% of patients studied showed no appreciable diurnal variation in PEFR; marked variation occurred in 45% and the remaining 35% had severe early morning falls of more than 50% of the best daily reading. When patients were graded for the severity of the attack this same distribution was seen throughout all grades.

Further analysis was possible in 98 patients who were admitted more than once during the study. Of these 58% always showed marked diurnal variation during recovery from an attack, 16% repeatedly had no appreciable circadian pattern, and the other 26% displayed only diurnal changes on some admissions.

Another group of patients who showed similar excessive diurnal variation in PEFR during their admissions have subsequently kept long-term records of PEFR at home. Although the early morning readings usually improve, significant diurnal variation persists in many patients. Records have occasionally been obtained as a further asthma attack develops. Diurnal variation in PEFR seems to be more prominent in the recovery phase of the attack when we believe the risk of sudden death may be greatest.

Diurnal rhythms in airway obstruction

C. K. CONNOLLY A nomenclature is proposed for the description of diurnal variation of ventilatory function. Peak expiratory flow rate (PEFR) is measured four-hourly. Over a day or waking period four simple patterns are possible: morning dip (m), evening dip (e), midday peak or double dip (p), and midday trough (t); x is used where no pattern is seen. In the p and t patterns the shorter limb must be at least 20% of the longer. Amplitude is measured as percentage fall on the maximum of the day. One day's events can be fully described in the form p70. To describe established rhythms over longer periods the upper case letter is used. The pattern must be seen in 70% of four or more days. Amplitude is taken as the mean of all days in the period observed irrespective of pattern. A period can be described in the form P22.

Patterns in 295 patients with a mean PEFR of 173 l/min in four diagnostic categories, asthma (89), wheezy bronchitis (76), chronic bronchitis (105), and emphysema (25), are described. The incidence of established patterns varied from 64% in asthmatics to 30% in chronic bronchitics. In those showing a pattern, the distribution was as follows: M 42%, P 35%, E 4%, and T one patient. Mean amplitude was significantly greater in asthmatics (28) and wheezy bronchitics (27) than in bronchitics (22), and in M (30) and P (27·6) than in those not showing a pattern, x (22·6). The patterns were recorded starting at two different times in relationship to bronchodilator therapy, at 0600 before therapy and at 0800 in mid-therapy interval. The pattern in asthma was little different, but wheezy bronchitics in the 0600 showed an 80% incidence of pattern but only 26% in the 0800 group, suggesting pattern is much more easily suppressed by therapy in bronchitics than in pure asthmatics.

Corticosteroid response (greater than 30%) was related to M pattern and higher amplitude, and fair corticosteroid response (10–30%) was related to P pattern.

Mucociliary clearance during sleep in healthy subjects

J. R. M. BATEMAN, D. PAVIA, and S. W. CLARKE Many factors such as respiratory viral infection (Camner *et al.*, 1973), drugs (Foster *et al.*, 1976), and smoking (Pavia *et al.*, 1971) may influence the rate of mucociliary clearance from the human lung. Patients with lung disease and increased sputum production often state that expectoration is greatest in the early morning after sleep. Furthermore, it is well known that patients with reversible airways obstruction sometimes complain of 'morning tightness' and exhibit the 'morning dip' phenomenon. A possible factor in both situations may be that of 'sputum retention' during sleep.

For this reason a preliminary study of the effect of sleep upon total lung clearance has been performed first on healthy subjects.

The method utilised the inhalation of 5-micron monodispersed polystyrene particles labelled with

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^{99m}Tc and subsequent whole lung counting over six hours (Thomson and Short, 1969). Four healthy men (mean age 40 years, range 29–52) were studied, of whom two were smokers (18 pack-years). They had normal lung function ($FEV_1/FVC\%$ 82, range 70–91).

Lung clearance was measured with the subjects lying supine both awake during the day and asleep during the night. The onset of sleep varied between 40 and 120 minutes from the time of particle inhalation.

Comparison of the day and night clearance curves demonstrated that the percentage of lung burden remaining was significantly greater during the night study (at 4½ hours post-inhalation $P<0.05$, at 6 hours post-inhalation $P<0.01$).

We conclude that mucociliary clearance slows during sleep at night. These findings may have important implications for patients with chronic bronchitis and asthma.

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Bronchodilatation with ipratropium bromide in severe chronic bronchitics

N. J. DOUGLAS, M. F. SUDLOW, and D. C. FLENLEY Ipratropium bromide (Atrovent, SCH 1000–Boehringer Ingelheim) is an atropine-like drug available in a metered dose inhaler. In chronic bronchitis it has been shown to produce a similar degree of bronchodilatation to salbutamol (*Postgraduate Medical Journal*, 1975).

In a double-blind cross-over study, we administered either 80 μg (4 puffs) of ipratropium or 4 puffs of a placebo from a metered dose inhaler to 21 patients with chronic bronchitis and emphysema who were in a stable clinical condition and had an FEV_1 less than 1 litre. Flow volume curves both breathing air and after 3 breaths of 80% helium 20% oxygen (HeO_2) were recorded before and 90 and 180 minutes after the inhalation of ipratropium or placebo. At 180 minutes the patients inhaled 200 μg of salbutamol and flow volume curves were recorded 15 and 30 minutes thereafter. In six patients measurements of lung volumes and specific airway conductance were made in a body plethysmograph.

One hundred and eighty minutes after the inhalation of ipratropium the FEV_1 rose from 0·58 to 0·73 litres ($P<0.001$) and FVC rose from 1·45 to 1·93 ($P<0.01$). Salbutamol also produced a significant rise in FEV_1 from 0·58 to 0·69 litres ($P<0.001$) and in FVC from 1·50 to 1·84 ($P<0.001$). After ipratropium the FEV_1 was significantly higher than after salbutamol ($P<0.025$) but there was no difference in FVC. When salbutamol was inhaled 180 minutes after ipratropium both FEV_1 and FVC rose to significantly higher levels than after either agent alone ($P<0.01$). There was no correlation between the responses to ipratropium and salbutamol ($r=0.16$). We conclude, therefore, that in patients with chronic bronchitis the response of the individual should be assessed to both a beta sympathomimetic and an atropinic agent separately and in combination.

The plethysmography studies demonstrated that ipratropium resulted in an increase in specific airway conductance from 0·35 to 0·50 sec^{-1} kPa^{-1} ($P<0.02$). The forced expiratory flow rates at 50% VC ($\dot{V}$ max 50) were 10% higher after 3 breaths of HeO_2 than when breathing air and this was not changed by the inhalation of ipratropium. We suggest that in these patients expiratory flow was limited by small airway calibre and that ipratropium acts mainly by dilating the large central airways.

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Ipratropium bromide, salbutamol, and prednisolone in bronchial asthma and chronic bronchitis

I. LIGHTBODY, C. INGRAM, J. S. LEGGE, and R. N. JOHNSTON Eleven patients with bronchial asthma and 10 with chronic bronchitis were treated for three-day periods with aerosols of ipratropium bromide (40 μg four times daily) or salbutamol (200 μg four times daily) by random allocation, then the alternate drug, next both drugs together, and finally both drugs with prednisolone, 10 mg three times daily, in a single blind controlled trial. The effects of these four treatment periods were assessed clinically by measuring the FEV_1, $FEF_{25-75\%}$, $FEF_{75-85\%}$, FEF_{50}, and FEF_{75} nitrogen slope and progressive exercise testing on a bicycle ergometer.

Both drugs produced similar degrees of improvement though salbutamol was more effective in patients with bronchial asthma. The combination of salbutamol +ipratropium bromide in those with asthma and chronic bronchitis more than doubled the gain in FEV_1 obtained with each drug. Prednisolone helped only those with asthma.

Observation on the management of severe bronchial asthma

N. J. COOKE, G. K. CROMPTON, and I. W. B. GRANT A retrospective analysis of 419 consecutive admissions for severe bronchial asthma to one respiratory intensive therapy area in 279 patients from 1970 to 1974 is reported.

Heart rate is one of the most useful clinical indicators of the severity of asthma. The majority of admissions with a heart rate of less than 110 per minute had had symptoms for several days, whereas most of those with a heart rate of more than 150 per minute had had symptoms for 24 hours or less. There

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were 143 (34%) admissions of patients under 20 years of age. These accounted for 51% of admissions with a heart rate of 130/150 per minute and 56% of those with a heart rate of over 150 per minute. More than 50% of admissions from general practitioners with a heart rate on admission to hospital of over 130 per minute had either received no systemic corticosteroid therapy or had not been advised to increase their maintenance dose.

All patients in hospital were treated with a salbutamol aerosol administered by intermittent positive-pressure ventilation every 2–4 hours for at least 24 hours, and very large doses of corticosteroids, intravenously or by mouth, were given in every case. Orotracheal intubation and artificial ventilation were required on seven occasions. There were only two hospital deaths (0·5% of all admissions).

It was concluded that (1) most dangerously severe attacks of asthma tend to develop very rapidly, (2) in this respect young people are particularly at risk, (3) in patients with severe asthma general practitioners are apt to be too slow in prescribing systemic corticosteroids in adequate dosage, and (4) prompt admission to a respiratory intensive therapy unit will ensure the survival of the vast majority of patients with severe asthma.

Respiratory centre output in asthma

C. P. MUSTCHIN, R. C. GODFREY, and J. B. L. HOWELL The respiratory responses of asthmatic subjects to rising inspired carbon dioxide induced by rebreathing have been studied (a) serially during recovery from severe asthma, and (b) during an asthmatic attack provoked by antigen or histamine inhalation in mild untreated asthmatics. The two responses measured were ventilation and the inspiratory dP/dt max as a measure of central respiratory drive.

In group A, with severe bronchoconstriction, the rate of increase of dP/dt max in response to CO_2 was high and fell progressively over succeeding days with clinical improvement. The corresponding ventilatory responses were variable. In group B, after an induced mild attack, both the dP/dt max and ventilatory response increased.

The increased dP/dt max response in both groups is interpreted as evidence of an increased ventilatory drive during the asthmatic attack. This view is supported by the rising ventilatory response in the induced mild attacks, when the increase in airway obstruction was unlikely to have significantly limited the ventilatory response.

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Rebound hypoxaemia after cessation of oxygen therapy in patients with asthma

M. RUDOLF, J. A. MCM. TURNER, and K. B. SAUNDERS In patients with chronic hypercapnic respiratory failure, it has been shown that, after cessation of oxygen therapy, arterial oxygen tensions (Pa_{O_2}) may fall to values below control (pre-oxygen therapy) levels (Rudolf *et al.*, 1975). It is not known whether or not a similar rebound hypoxaemia occurs in patients who do not have carbon dioxide retention. We have accordingly measured the changes in arterial blood gases in a group of eight asthmatics during a control period breathing air, followed by one hour of oxygen therapy and then a further period again breathing air.

Mean Pa_{O_2} increased from a control value of 8·5 kPa (64 mmHg) to 29·8 kPa (224 mmHg) at the end of the oxygen breathing hour. On cessation of oxygen, mean Pa_{O_2} fell to reach a value not significantly different from control by 6 minutes, and then continued to fall to reach levels significantly lower than control by 30 and 45 minutes, when it was 7·7 kPa (58 mmHg). Mean arterial carbon dioxide tensions did not alter significantly throughout the period of the study. The undershoot in Pa_{O_2} is thought to be due to the persistence of changes in ventilation:perfusion ratios brought about by the period of oxygen breathing.

We have also observed a similar rebound hypoxaemia in patients with acute myocardial infarction, and we belive that an undershoot in Pa_{O_2} on cessation of oxygen breathing is a common occurrence irrespective of the presence of underlying pulmonary disease.

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Some aspects of obstructive bronchopulmonary diseases in Poland

M. ZIERSKI, J. LEOWSKI, and P. SAWICKI In Poland, as in many other countries, chronic nonspecific bronchopulmonary disease is a major health problem.

Investigations were performed from 1968 to 1975 in some population groups, according to age, sex, occupation and social factors in polluted and non air polluted areas in the country and were in some areas repeated in the same populations during the next 5 years. The results of those studies revealed that about 23% of the population aged 20–70 years produce syndromes of cough and expectoration. Among irritant factors smoking plays an important role, having a greater effect than other extrinsic factors such as air pollution and occupation. Despite the higher frequency of these syndromes in men (about 30%) than women (about 15%) not the sex but other environmental factors have influenced these differences between the sexes. Airways obstruction was noted in about 8%; the mean FEV_1 values were lower in females than in males. There was a relationship between giving up smoking and higher regression, lower incidence of exacerbations, and fresh symptoms of bronchitis. In some areas longitudinal investigations have allowed an estimation of the risk factors influencing the incidence of chronic nonspecific bronchopulmonary disease and more precise definition of the dynamics and classification of the chronicity of bronchopulmonary disease with and without obstructive syndromes.

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Tests of small airways function in working coal miners

R. G. LOVE, J. BURNS, E. COPLAND, and D. C. F. MUIR As part of the epidemiological research of the National Coal Board analysis is being made of the effects of underground environmental conditions on the lung function of coal miners. However, it is not at present known whether long-term exposure to coal dust causes miners to exhibit increased evidence of small airways disease in early middle age. It is intended that results of tests of small airway function, such as closing volume and forced expiratory flow at low lung volumes, be related to the measured dust exposures of about 200 working coal miners, aged 33–46 years, whose occupational and medical histories have been studied for a period of 15–20 years. The usefulness of such measurements in the study of industrial lung disease is discussed.

Pathophysiology of byssinosis

F. G. WARD, and G. B. ROOKE Byssinosis is a condition predominantly seen in cotton workers in the processing of raw cotton from the picking of the raw cotton to the production of cotton yarn for weaving. The clinical features and the theories of aetiology are considered. Most of the evidence suggests that the aetiological agent is in the debris rather than the cotton fibre which varies from 16·7 to 6·2 microns and is about 3 cm long. Cotton fibres are largely trapped in the nasal hairs. Simple mechanical irritation is unlikely as a cause since much higher dust concentrations of jute and sisal are not associated with the true picture of byssinosis. The aetiology is obscure but three main theories are usually put forward: (1) hypersensitivity to a dust component; (2) bacterial or fungal contamination producing an endotoxin or proteolytic enzyme; and (3) a specific chemical substance, or substances, which causes airways narrowing either directly or via histamine release. The chief physiological change is a fall in FEV_1 but many consider that the small airways are affected.

Very little has been published concerning the pathology, partly because the uncomplicated disease is seldom fatal and it is difficult to separate the effects of chronic bronchitis and emphysema. The striking feature macroscopically is that in an established case there is often nothing to find. We studied 43 cases *post mortem*. The changes seen on microscopy were consistent with those found in so-called 'asthmatic bronchitis' and were more marked in the larger bronchi. Emphysema is not a consistent feature.

Effect of x-radiation upon the lungs of patients with emphysema

C. BEVAN, and J. E. COTES We have recently reported a reduction in breathlessness on exertion and increase in daily activity in selected patients with emphysema after deep *x*-ray therapy (Axford *et al.*, 1977). In six patients for whom serial measurements were available the irradiation reduced the slope of the inspiratory and expiratory volume pressure relationship measured between 20% and 80% of vital capacity. For expiratory compliance the mean values were 8·90 and 5·43 l kPa^{-1}, average reduction 42%, and for inspiratory compliance 6·18 and 4·47 l kPa^{-1}, average reduction 24%. The maximal recoil pressure at the end of inspiration was initially on average 0·695 kPa (range 0·47–0·78 kPa). The increase after treatment was small in three of the patients (range 0·05–0·10 kPa) but in the others it was relatively large (range 0·29–0·37 kPa) and associated with material hysteresis. The latter patients were those who on clinical grounds were judged to have achieved the greatest increase in daily activity as a result of treatment. However, the physiological changes were both greater than might have been predicted from the morbid anatomical findings in similar but more disabled patients and less than would seem to be required to explain the clinical improvement.

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Enhancement of bronchial clearance by hypertonic saline aerosol in chronic bronchitics

D. PAVIA, M. L. THOMSON, and S. W. CLARKE The radioaerosol method (Thomson *et al.*, 1974) was used to measure the effect of hypertonic saline aerosol on the rate of clearance of secretions from the lung. Seven patients (5 male) with chronic obstructive lung disease were investigated. The mean (±SD) age and height of the patients was 60·7±9·5 years and 1·70±0·11 metres respectively. All were cigarette smokers who had smoked on average 23·8±26·2 pack-years. The mean (±SD) ventilatory indices together with the percentages of predicted (Cotes, 1975) in parentheses were: forced vital capacity, FVC 2·84±0·72 litres (80±22%); forced expiratory volume in 1 second, FEV_1 1·41±0·52 litres (54±28%); and FEV_1/FVC 50·0±14·9% (71±22%).

Two trial runs were done in each patient. In both runs 5·0±0·7 μm polystyrene particles tagged with ^{99m}Tc were inhaled under controlled conditions by the patients, and their subsequent clearance was monitored for six hours by whole-lung counters. Scanning was also done by a gamma rectilinear scanner. The treatment run was identical with the control run save that 30 minutes after inhaling the radioaerosol the patients inhaled an aerosol of hypertonic saline (1·21 M NaCl) for 11 minutes from an ultrasonic nebuliser.

Although the initial distribution of the radioaerosol along the airways was the same in both runs, whole-lung clearance over the first 50 minutes was twice as fast ($P<0·01$) after treatment (38·4%/h) as in the control (19·1%/h). The mean weight of sputum produced (10·67 *v* 14·31 g; $P<0·10$) and its radioactive content ($151·6\times10^3$ *v* $246·4\times10^3$ gamma counts; $P<0·05$) was higher in the treatment than in the control run. However, the number of coughs in the two runs (113 *v* 121) was similar.

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Total body and exchangeable potassium in cor pulmonale

A. D. HOWIE, K. BODDY, M. MADKOUR, D. DAVIES, M. MAHAFFEY, A. I. PACK, and F. MORAN Potassium depletion has been reported in cor pulmonale based on measurement of exchangeable potassium (K_e). However, when total body potassium (TBK) was measured directly by whole-body counting we were unable to confirm the findings obtained with K_e.

TBK and K_e have now been measured simultaneously in patients with this condition. Conclusive evidence was obtained, by sequential measurements of K_e at 20, 40, and 68 hours post-administration of potassium 43, that equilibration is slow and K_e increases significantly up to 68 hours. Values obtained at shorter intervals will, therefore, be underestimates of K_e (especially at about 20 hours) and apparent deficiencies of potassium using this method require careful interpretation. In our group of patients, neither the measured K_e (68 hours) nor TBK was significantly different from the expected normal values.

Upper gastrointestinal abnormalities in chronic lung disease

M. BEELEY, B. COCKING, P. GRECH, and D. A. HARRISON The prevalence of acute gastric ulcers at necropsy in patients with emphysema is 10 times that in patients dying from other causes (Flint and Warrack, 1958). Twenty per cent of patients treated in the Respiratory Unit at Massachusetts General Hospital developed upper gastrointestinal haemorrhage requiring blood transfusion and a further 20% had frank or occult blood in the stool (Bendixen *et al.*, 1965). Bleeding in patients with chronic lung disease may be massive and is then associated with a high mortality (Bourgeois *et al.*, 1964).

The suggestion that reflux of duodenal contents into the stomach is a major factor in gastric ulceration is gaining acceptance and such reflux has been demonstrated in a high proportion of patients with chronic lung disease (Beeley and Grech, 1971). This paper examines the concept that reflux of duodenal contents into the stomach occurs with unusual frequency in patients with chronic non-specific lung disease and searches for resulting atrophic gastritis which is known to be associated with gastric ulceration.

Seventeen patients with chronic bronchitis (Medical Research Council, 1966) in whom barium meal examinations excluded gastric ulcer were subjected to a radiological test for duodenogastric reflux (Grech, 1970) and to gastroscopy with multiple mucosal biopsies (Gear *et al.*, 1971). When the biopsy results from each of four biopsy sites were correlated with reflux using the Exact test, it was found that there was a statistically significant relationship between reflux in the erect position and the presence of chronic gastritis on the antral lesser curve, mid-lesser curve, and high-lesser curve biopsies ($P=0{\cdot}044$ in each case). The patients, who fell into 'gastritis' and 'non-gastritis' groups, were compared with reference to other factors known to be associated with gastritis.

This study provides a possible explanation for the special tendency of patients with chronic lung disease to gastric ulceration and may therefore be relevant to their clinical management.

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Twelve-minute walking distance, spirometric measurements, and subjective estimates of disability in patients with obstructive and restrictive ventilatory defects

C. R. MCGAVIN, M. ARTVINLI, H. NAOE, and G. J. R. MCHARDY In 44 patients with obstructive ventilatory defects and 18 with restrictive ventilatory defects we have compared subjective estimates of disability with the distance walked in 12 minutes (12MD), with perceived exertion (PE) (Borg, 1970) in the walking test and with the results of pulmonary function tests (FEV_1, FVC, and carbon monoxide transfer factor, TLco). Subjective estimates of disability were obtained from a series of simple questions, from the question on dyspnoea in the MRC Questionnaire on Respiratory Symptoms (1966), and from the point marked by the patient on a structured diagram of everyday activities, scaled in proportion to their oxygen cost.

Patients' estimates of how far they could walk before stopping or in 12 minutes were not related to the distance they covered. In the whole group, 12MD was well related to estimates of disability from the diagram and of dyspnoea from the questionnaire. In each subgroup, the estimates of disability from the diagram correlated well with 12MD but less so with FEV_1 and FVC, and 12MD correlated better with FVC than with FEV_1. There was a significant correlation between 12MD and TLco in the restrictive group. In each subgroup, PE was significantly negatively correlated with 12MD. In 15 patients who stopped during the 12-minute walk, the distance to the first stop was well correlated with the total distance covered.

Simple exercise tests may be more valuable than spirometry as estimates of respiratory disability.

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Breathing patterns at rest, during progressive exercise, and during CO_2 rebreathing in patients suspected of having disproportionate dyspnoea

B. D. W. HARRISON, A. C. MACFIE, M. RUDOLF, J. FREEMAN, and P. MARCHANT In a study to assess the relative value of the breathing pattern at rest, during progressive exercise on a cycle ergometer and during CO_2 rebreathing, in diagnosing disproportionate dyspnoea (DD) we present the preliminary results in 10 patients with this diagnosis, 10 normal subjects, and 15 patients with organic lung or heart disease.

All the patients with DD and five patients with organic disease were assessed by a psychiatrist. The psychiatric assessment confirmed the referring clinicians' diagnosis in 13 patients, suggested a psychosocial contribution to the symptom of breathlessness in one, and indicated that the psychiatric history was possibly not relevant to the symptom of breathlessness in another.

At rest the breathing pattern was quantified by analysing the breath-to-breath variation in tidal volume. During exercise and CO_2 rebreathing the pattern was quantified using the correlation coefficient of the tidal volume–minute volume relationship (Hey *et al.*, 1966).

At rest five patients with DD, one with ischaemic heart disease, and one with sarcoid had patterns more irregular than the normal subjects. During progressive exercise five patients with DD had patterns more irregular than the limits found in the other groups, and seven patients with DD and two with sarcoidosis had patterns more irregular than the normal subjects. During CO_2 rebreathing only three of the 10 DD patients had definitely irregular breathing patterns.

This study suggests that the breathing pattern during exercise is probably of more value in providing objective evidence for the diagnosis of disproportionate dyspnoea than the breathing patterns at rest or during CO_2 rebreathing.

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Percutaneous transthoracic needle biopsy of lung from periphery to hilum

I. I. RUBIN Transthoracic needle biopsy has a definite place among chest diagnostic techniques. Despite many good reports, it has been slow to become established as a routine procedure in certain conditions. This may be owing to fear of complications or seeding, or because before the days of good image intensification and before the days of cytopathology the results were limited.

In our series of over 60 cases the diagnostic yield has been over 90% with no mortality and no serious morbidity. There has been about a 25% incidence of small pneumothorax and occasionally some streaking. Specimens have been obtained from all parts of the lung, including the hilar area. We do not limit biopsy to peripheral lesions. Contrary to some, we believe that biplane fluoroscopy is essential, particularly when viewing deeper lesions. We find the procedure technically rewarding as do an operator and his team in accurately locating a lesion and then placing a needle or needles in it.

The procedure is carried out under biplane fluoroscopy with local anaesthesia, using a pointing needle and then an 18- or 20-gauge spinal needle and a 15-millilitre Luer lock syringe. The tumour can usually be felt as the needle penetrates. The needle is then attached to the syringe, which is rotated clock- and counter-clockwise with firm negative pressure on the barrel. The needle and syringe are withdrawn with continual negative pressure. Slides are prepared from the material blown out. Any larger pieces are saved for histological study. The contents of the needle and syringe are washed with saline and saved for culture or for spinning down. When further tissue is required it is obtained by cutting, but we have found this to be unnecessary since adopting a good technique for saving blown-out tissue for histology.

BTTA short-course chemotherapy study; patterns of biochemical change in patients on rifampicin and pyrazinamide-containing regimens

J. H. ANGEL, and A. R. SOMNER Serial estimations of blood urea, uric acid, and liver function tests have been performed on serum from patients in the current short-course chemotherapy study. The results before the start of chemotherapy are compared with those obtained after one month and two months on chemotherapy in patients on one regimen containing rifampicin plus isoniazid, and in patients on two different regimens containing rifampicin plus isoniazid plus pyrazinamide. The incidence of clinically significant adverse effects from these various regimens is also compared.

A study by the British Thoracic and Tuberculosis Association of the treatment of lymph node tuberculosis

I. A. CAMPBELL The aims of this trial were to study the chemotherapy of lymph-node tuberculosis in a prospective, controlled manner, comparing two regimens of 18 months' chemotherapy, and to attempt to assess the value of surgery. Chemotherapy consisted of isoniazid with either rifampicin or ethambutol plus an initial supplement of streptomycin. These two regimens were randomly allocated to 19 patients who had previously undergone excision of the lymph nodes, 56 patients who had undergone diagnostic biopsy, and 33 patients who had had no surgery at all.

The majority of patients were of Indian or Pakistani origin (80%). *Mycobacterium tuberculosis* was the only organism grown. Progress during treatment was uneventful in 65% of patients. Fresh nodes appeared during treatment in 12%, existing nodes enlarged in 13%, and fluctuation developed in 11% of patients. Discharge and/or sinus formation was infrequent (7%), as was breakdown of a surgical scar (4%). Excision or

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aspiration after the start of chemotherapy was performed in 19% of patients.

In the period up to the end of chemotherapy no difference emerged between those patients who received rifampicin with isoniazid and those who received ethambutol with isoniazid. Satisfactory results were obtained in 98% of the patients by the end of treatment although 13% still had slight node enlargement. The relative merits of excision plus chemotherapy, diagnostic biopsy plus chemotherapy, and chemotherapy alone are discussed. Follow-up is planned for 18 months after the end of treatment.

Infecting agents in pneumonia

R. J. WHITE Ninety-six adult patients with primary pneumonia have been investigated for evidence of bacterial, virus, and mycoplasma infection. Sputum and blood were cultured for bacteria. A throat swab for virus culture was taken when the illness was of short duration, and complement fixation tests against viruses and mycoplasma were done on paired sera.

Evidence of bacterial infection was found in only 16 patients, some of whom also had rises in virus antibody. Forty-nine of the patients had a fourfold rise in antibody or a single high titre against virus or mycoplasma. Influenza A and *Mycoplasma pneumoniae* accounted for the majority, but parainfluenza, respiratory syncytial virus, Q fever, and psittacosis were also identified.

In 36 patients no organism was identified, and the possible reasons for this are discussed. The clinical and pathological features of bacterial and viral pneumonias have been examined and suggestions are made for a more rational approach to antibiotic therapy.

Aetiology of unresolved pneumonia

S. R. BULMER, and D. LAMB Pulmonary opacities on a chest radiograph suggest a carcinoma of the lung but firm histological diagnosis cannot always be obtained before operation. Occasionally non-tumour lesions are resected. Of these one of the largest groups comprises unresolved pneumonia in which there is no evidence of any tumour obstructing the drainage of the associated airway. Such cases form the basis of this presentation. We have reviewed those seen in the Edinburgh University pathology department over a 10-year period. In the main, the histological appearances of the lesions show an intra-alveolar exudate which has undergone organisation. Within the area of organisation there is evidence of aspirated foreign material in a significant number of cases. It appears that aspiration of food or gastric contents is a significant factor in the aetiology of some 'unresolved pneumonias'.

Corticosteroid treatment and the prognosis of cryptogenic fibrosing alveolitis

A. J. JOHNSON, R. M. HONEY, M. TURNER-WARWICK, and K. F. W. HINSON A long-term retrospective study of 220 cases of cryptogenic fibrosing alveolitis has been undertaken. Two hundred and seven cases have been traced to death over a 20-year period (140) or have been followed for a minimum of two years and are still alive (67). The mean age at presentation was 57·6 (range 19–85) years which is similar to previous studies (Livingstone *et al.*, 1964; Stack *et al.*, 1972). However, the sex distribution is somewhat different from these reports, 67% of the cases being male. One hundred and forty patients (68% of the population) have died and 80% of these deaths occurred within five years of presentation, emphasising again the high mortality of this disorder. Of all deaths, 40% were due to cryptogenic fibrosing alveolitis.

Corticosteroids were administered to 143 patients, and in 127 of these an assessment of response was made six weeks after treatment was begun. A strong association ($P<0.01$) was found between the response to early corticosteroids and the duration of survival. Of those with a 'good' response, 56% were alive five years after presentation compared with 31% with minimal or no improvement. Conversely, 23% with a good response died within two years of presentation whereas 56% of patients with a minimal or no response died within this period. The predictive value in terms of survival in relation to early steroid response is of obvious clinical importance. The factors relating to corticosteroid response, particularly the semiquantitative analysis of histology and radiographic features, have been studied systematically and are reviewed.

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Studies in chronic allergic bronchopulmonary aspergillosis: immunological findings

J. L. MALO, J. LONGBOTTOM, J. MITCHELL, R. HAWKINS, and J. PEPYS Precipitin tests by two different methods, double-diffusion (DD) and counterimmunoelectrophoresis (CIE), and measurements of total and specific IgE against *Aspergillus fumigatus* were made in 50 patients with chronic allergic bronchopulmonary aspergillosis and in three control groups—atopics with a positive immediate prick test to *A. fumigatus* but no evidence of allergic aspergillosis, atopics with a negative prick test to *A. fumigatus*, and non-atopics.

Precipitins were found in 84% and 78% of the patients with aspergillosis by the DD and CIE methods respectively. Precipitins were also found in 6 out of 27 (22%) patients with a positive prick test to *A. fumigatus* but no evidence of aspergillosis and in 1 of 24 patients with a negative prick test to *A. fumigatus*.

The means of specific and total IgE values were significantly higher in the group of patients with aspergillosis than in the three other groups of patients. The increase in specific but not total IgE showed a statistically significant correlation with positive precipitin tests in the patients with aspergillosis. Total IgE but not specific IgE values were significantly

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higher ($0.02 < P < 0.05$) in patients who had had a transient radiographic shadow in the previous three months. Positive precipitin tests were also significantly correlated with the number of transient shadows in the past and with the interval of time since the last transient shadow.

Effect of smoking on circulating antibody levels to avian protein in pigeon breeder's disease

G. BOYD, M. MADKOUR, S. MIDDLETON, and P. LYNCH In a survey of farmers (Morgan *et al.*, 1973), a higher proportion of those with positive precipitin reaction to *M.faeni* were either non-smokers or ex-smokers and fewer of those who smoked had positive responses. Survey data from 256 pigeon fanciers aged 16–76 years who were all in frequent, regular contact with pigeons, were examined to determine whether a similar reaction occurred to the inhaled antigens in this type of extrinsic allergic alveolitis. One hundred and thirty-seven were cigarette smokers and 119 were non-smokers or ex-smokers. Circulating antibody to pigeon 7S globulin was measured in each individual using radioimmunoassay (Nielsen *et al.*, 1974), and the levels in each group were then compared using a non-paired Student's *t* test. Significantly lower levels of antibody were found in the group of smokers ($P = 0.001$). The survey data were also analysed to examine the influence of chronic bronchitis and also the contribution of dusty occupations upon the antibody response but no differences emerged. From a total of 256 fanciers 78 were found to be sensitised to pigeon 7S globulin, of whom 21 were smokers and 57 non-smokers. Statistical analysis, however, failed to reveal any significant difference between circulating antibody responses in these groups.

Pigeon fanciers who smoke appear less likely to become sensitised to pigeon antigen than those who do not smoke but, where sensitisation occurs, the intensity of the antibody response is probably unaffected by smoking habits.

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Effect of injection of irradiated autologous tumour cells with adjuvant BCG into patients with resectable bronchial carcinoma

B. H. R. STACK, N. MCSWAN, J. M. HENDERSON, D. PARRAT, D. J. HOLE, W. G. S. SPILG, C. R. GILLIS, R. G. WHITE, and M. A. TURNER Preoperative tests of immunological function were performed in 52 patients with resectable bronchial carcinoma. There was no difference in the incidence of positive tuberculin reactions between patients and controls but the incidence of a positive DNCB test after sensitisation was only 52% compared with 100% in controls. The patients had depressed lymphocyte transformation ratios for PPD but not for PHA compared with controls.

In a pilot study, 15 patients were randomly allocated between treatment (8) and control (7) groups. Suspensions of irradiated cells from the patients' own tumour mixed with BCG were injected intradermally into the thigh region of treatment group patients on the day of operation and two weeks later. There was some overall increase in the tuberculin reactivity of the treatment group two weeks after the operation ($P = 0.08$). This was accompanied by an increase in total leucocytes ($P = 0.09$). There was no change in total lymphocytes in the treatment group but a significant fall was found in the control group ($P < 0.05$).

Because of local ulceration, the technique of administering BCG was changed. In a further 37 patients, it was administered by a multiple puncture technique in the deltoid region of the arm in all patients one week before operation and in the treatment group at weekly intervals on three occasions after the operation. In these patients, suspensions of irradiated autologous tumour cells were injected at weekly intervals into the deltoid region of the arm which had been treated with BCG the previous week. Tests of cell-mediated immunity were carried out before operation and during the postoperative period.

No significant difference was seen between the treated and untreated groups with regard to any of the immunological tests described.

Relationship of mediastinal node metastases and cell type to five-year survival in patients operated on for lung cancer

G. L. BAUM, I. RUBENSTEIN, J. KALTER, Y. LIEBERMAN, and Y. PAUZNER The survival rate in 202 patients operated on for lung cancer in the five-year period, 1 January 1966 to 31 December 1970 was related to the cell type of the cancer and to the presence of metastases in hilar or mediastinal lymph nodes, or both. The resection was primary in 151 of the 202 patients. The five-year survival rate for the whole group was 27·8%. Out of 44 patients with large-cell tumour, 40·8% survived 5 years, as did 19·2% of the patients with adenocarcinoma. The five-year survival rate in patients with other cell types of cancer was proportionately smaller. Surprisingly, adenocarcinoma was the commonest type of lung cancer encountered.

The survival rate at five years for all cell types was down to 11·1% when mediastinal node metastases were present compared with 31% when only hilar nodes were metastasised and 36% when there were neither mediastinal nor hilar metastases. The survival rate in cases of large-cell tumour and adenocarcinoma with mediastinal node metastases was clearly worse than in those with hilar node metastases or no metastases. In cases of epidermoid cancer the distinction was not so clear. The group of small-cell tumours was too small to judge. Nevertheless, five out of 45 cases with mediastinal node metastases survived

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five years. This raises some doubt whether the presence of mediastinal node metastases should in itself be regarded as a contradiction to resection of the primary carcinoma. In large-cell tumours, however, it is significant that despite a 52% survival rate in 25 cases without metastases only one out of ten cases with mediastinal node metastases survived 5 years. Three out of twelve cases of epidermoid cancer with mediastinal node metastases survived for this period.

Aspiration and mortality in 344 road accident deaths

E. HOFFMAN Two patterns of aspiration emerged from this prospective study—early inhalation, mostly within 24 hours, confirmed at necropsy and, later, 'silent' aspiration suspected on clinical grounds.

Early aspiration was found in 123 (35·8%) of the 344 deaths. Of these, 68 died instantly, 24 within one hour, 24 within 24 hours, and 6 survived longer. Inhalation of blood was found in 114, vomit in 18, and in one case chips from a shattered windscreen led to suffocation at the accident site. Inhaled blood originated from three sites. It was found in 73·1% of maxillofacial fractures, 27·8% of lung injuries, and 25·1% of skull fractures. In the pathologists' opinion aspiration was the cause of death in 7 (2%), contributory in 27 (7·8%), and irrelevant in 89 (25·8%).

Later aspiration in hospital, though rarely witnessed, is usually due to inhalation of oropharyngeal secretions or vomit in the unconscious, or in patients whose defence mechanisms are impaired. Pathologists reported that 43 (28·2%) of the 152 hospital fatalities died of pulmonary oedema or pneumonia. Clinical analysis showed that most of these lung complications were probably due to aspiration, as conditions predisposing to inhalation were often present. On admission 27 were unconscious, 16 had an obstructed airway, and 9 vomited. Other factors included an early onset of lung complications, advanced age, and predominance of head and/or chest injuries.

This survey showed that aspiration is an important contributory cause of mortality both at the site and in hospital. Preventive measures at the site include the education of the general public and police in the maintenance of a clear airway and positioning of the unconscious. In hospital prevention of aspiration should be the prime consideration not only in traumatic cases but also in a variety of medical and surgical conditions.

The mortality of lung complications is high. Early management depends on the type of case. The aspiration variety of shock lung should be treated by immediate mechanical ventilation. Bacterial pneumonia is usually due to a mixture of aerobic and anaerobic bacteria and requires a combination of suitable antibiotics.

The Thoracic Society Prize 1978

A competition will be held for a prize of £250 to be judged on the content and presentation of original papers accepted for the Society's meeting at Oxford on 6–7 July 1978. Candidates should have made the principal contribution to the work to be reported and be under the age of 35 years at the time of the meeting. They need not be members of the Thoracic Society. Only original material, not previously presented at any national or international scientific meeting or in a scientific journal, will be considered. Further details may be obtained from the Honorary Secretary, Dr. J. E. Cotes, MRC Pneumoconiosis Unit, Llandough Hospital, Penarth, S. Glam. CF6 1XW, or from any member of the Society.

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