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Clinical assessment of the protective value of dust respirators in extrinsic allergic alveolitis

D J HENDRICK, R MARSHALL, JENNIFER A FAUX J M KRALL Six subjects with budgerigar fancier's lung, pigeon breeder's lung, or mushroom worker's lung underwent identical paired inhalation provocation tests lasting 20 minutes to five hours (mean 2·3 hours) using a natural method of antigen exposure. For one test of each pair, the subjects were protected by the use of industrial respirators which incorporate electrostatically charged, resin-impregnated merino wool filters. The "unprotected" challenges provoked late responses of mild to moderate severity, characteristic of extrinsic allergic alveolitis. These were monitored by methods described previously to the Society[1] using four subjective and six objective monitoring parameters. A monitoring score of 1 was allowed for each parameter showing a significant change. A combined monitoring score of 32/57 was associated with the "unprotected" challenges—that is 56% of the maximum score possible. The respirators successfully protected four of the subjects from any suspicion of a positive response. The remaining two subjects reported symptoms of minimal severity, but there was no objective confirmatory evidence of positive reactions. The combined monitoring score associated with all six "protected" challenges was 2/60 (3%), while that associated with corresponding control challenges was 3/73 (4%). We conclude that respirators of this type can offer substantial, and in most cases complete, protection against single exposures to environmental dusts that may provoke extrinsic allergic alveolitis.

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Bronchial disease in ulcerative colitis

TIM HIGENBOTTAM, G M COCHRANE, D TURNER, W M SEYMOUR, T J H CLARK Inflammatory bowel disease and ulcerative colitis in particular are well recognised as having associated systemic complications. Until recently, the lungs have been considered free from involvement, although there have been reports of patients with alveolitis[1,2] which has been attributed to salazopyrin therapy. Further case reports have described another variant of lung disease associated with ulcerative colitis in which patients developed a suppurative bronchitis unrelated to therapy.[3] Ten patients, described in detail, all developed a productive cough and in some exertional dyspnoea after the onset of ulcerative colitis. Eight were non-smokers and two longstanding ex-smokers. Four underwent bronchoscopy for intractable coughing and this revealed a bronchial epithelial abnormality with features of chronic inflammation resembling the changes usually found in ulcerative colitis. Coughing was relieved in seven by a beclomethasone diproprionate aerosol after salbutamol and sodium cromoglycate had failed. A survey of patients attending an inflammatory bowel clinic and medical clinics revealed an increased prevalence of chronic productive cough compared with general medical patients without bowel symptoms. This difference could not be explained by smoking habits. The bronchial mucosa may share a similar inflammatory pathology to the colonic mucosa in patients with ulcerative colitis, suggesting a common pathogenesis. The bronchial epithelial changes cause a range of pulmonary disorders of which bronchitis may be the most common and the earliest form of presentation.

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Idiopathic pulmonary haemosiderosis

P H WRIGHT, P W N KEELING, R E POUNDER, I S MENZIES, M BUXTON-THOMAS, L KREEL Seven patients who had been diagnosed as having idiopathic pulmonary haemosiderosis (IPH) at the Brompton and London Chest Hospitals were reviewed and investigated. Three had abnormal jejunal biopsies and improved subjectively and objectively after six months of gluten withdrawal. Only one of the three complained of gastrointestinal symptoms, but two of the four patients with normal jejunal biopsies complained of food intolerance. A range of routine blood tests did not identify the patients with abnormal jejunal mucosa, although tissue typing showed an excess occurrence of HLA B8. Isotope and CT scans of the lungs showed different distributions of disease but the patients with coeliac disease did not show a consistent pattern. These findings suggest a connection between

coeliac disease and IPH, although the lung disease may not be identical in such patients.

Is there a genetic component in bronchial carcinoma in smokers?

M R HETZEL, M LAW, E E KEAL, T P SLOAN, J R IDLE, R L SMITH It is now widely accepted that many chemical carcinogens require oxidative metabolism by tissues to generate reactive metabolites which constitute the proximate carcinogens.[1] Ability to form oxidative metabolites of polycyclic hydrocarbons in cigarette tar may, therefore, influence individual susceptibility to bronchial carcinoma. The metabolic oxidation of many drugs and other chemicals is under the control of a single gene locus and displays polymorphism in the population.[2] Two phenotypes exist in British whites, dominant extensive metabolisers (EM) and recessive poor metabolisers (PM) comprising 91% and 9% of the population respectively. We tested the hypothesis that inherited oxidative capacity influences susceptibility to bronchial carcinoma in smokers by comparing the phenotype frequencies with those obtained from a previous study of 258 healthy British whites.[3] In 106 smokers (76 men, 30 women; mean age 63 years ±SD 9 years) the diagnosis of bronchial carcinoma was confirmed by histology (92 cases) or sputum cytology (14 cases). Cell types were squamous (39 cases), large cell undifferentiated (22), small cell (30), adenocarcinoma (11), undifferentiated (three), and bronchioalveolar cell (one). Patients were phenotyped by urinary measurement of debrisoquine metabolism.[2] The incidence of PM patients (two in 106 cases) was significantly lower than expected for a random population. The 95% limits for PM frequency (0·2–5·3%) were significantly lower ($2p=0·0069$) than for the random population (5·7–12·7%). The PM phenotype (some 10% of the population) therefore appears to enjoy a four to fivefold lower incidence of bronchial carcinoma. Taking the United Kingdom as a whole, this may be relevant to an estimated two million smokers who are phenotypically poor metabolisers.

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Are we taking enough notice of pollution?

J R BELCHER While accepting the importance of smoking in the aetiology of new growth of the bronchus (NGB), the following evidence suggests that more notice should be taken of the importance of pollution. (1) There is a rising incidence of NGB among non-smokers in the USA.[1] (2) The wide variation in the incidence of NGB in different parts of the USA is not related to cigarette consumption. Paper making, oil and transport industries, and certain chemical industries may be important. The difference is not wholly accounted for by rural/urban differences. (3) Rural/urban differences are important. (The incidence of NGB in Northern Ireland is almost half that in Liverpool). (4) British emigrants to New Zealand,[2] Australia, and South Africa take the British incidence of NGB with them, and the later in life they emigrate, the greater the difference in incidence from that in the local population. (5) In the Far East the incidence of NGB is rising rapidly in both men and women. This is not related to smoking habits but may well be related to a rapid increase in the number of petrol-driven vehicles. (6) It has been shown that cooking on kerosene stoves in Hong Kong is a major factor in the incidence of NGB in women. (7) The incidence of NGB in the younger age groups of women in the United Kingdom is, if anything, falling. Is this because of the Clean Air Act?

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Gallium 67 scan in the diagnosis and staging of bronchial carcinoma

R PANNIER, I VERLINDE, I PUSPOWIDJONO, J P WILLEMOT, M DE PONDT Gallium 67 (^{67}Ga) scan was used as a routine procedure in the evaluation of the lung and mediastinal status in 75 patients suspected of having a bronchial carcinoma. The results obtained allow us to draw the following conclusions. (1) Gallium 67 scan is of great value in the assessment of metastatic mediastinal invasion in the presence of proven bronchial carcinoma. Patients with a negative mediastinal ^{67}Ga scan may be spared mediastinoscopy and submitted at once to thoracotomy if otherwise suitable for surgery. Mediastinoscopy should still be performed when the ^{67}Ga scan is dubious or positive because of the possible uptake of ^{67}Ga in non-carcinomatous diseased tissue. (2) In the presence of a peripheral coin lesion larger than 2 cm a negative ^{67}Ga scan almost excludes malignancy. (3) A negative ^{67}Ga scan is of great value in the differential diagnosis of suspected hilar images. (4) ^{67}Ga scan should always be performed in patients with a clinical image suspected of bronchial carcinoma and negative X-ray findings. (5) When carcinoma is suspected the ^{67}Ga scan is of great value in evaluating the retrocardiac area. (6) In elderly patients, where more invasive procedures should be avoided, a positive ^{67}Ga uptake at the site of an X-ray image suspicious of carcinoma adds greatly to the probability of bronchial malignancy.

Respiratory drive during exercise in normal subjects and patients with obstructive or restrictive lung impairment

R SERGYSELS, A VAN MEERHAEGHE, G SCANO, R WILLEPUT, R MESSIN, A DE COSTER Fifteen healthy subjects, 15

patients suffering from chronic obstructive lung disease (COLD), and 12 patients suffering from interstitial lung disease (ILD) performed a progressive exercise test on a bicycle, increasing the power output by 30 watts/3 min. The following parameters were measured: CO_2 production ($\dot{V}CO_2$), ventilation ($\dot{V}E$), respiratory frequency (f), tidal volume (Vt), Vt/TI (mean inspiratory flow), TI/T.TOT (TI, inspiratory time/T.TOT respiratory time for one cycle), and finally PO.1 (the occlusion pressure at 0·1 s at end-expiratory level). PO.1/VE(I) and PO.1/VCO2(D) were considered respectively as indexes of thoracic impedance (I) and respiratory drive per unit CO_2 output (D). When compared to normal subjects at a given $\dot{V}CO_2$ max, VE showed a "rapid shallow breathing" pattern (RSB). I and D correlated with FEV_1 in COLD (I, $p<0·001$; D, $p<0·05$) and with VC% or static lung compliance in ILD (I, $p<0·001$; D, $p<0·05$). In patients, D showed no correlation with PaO_2, $PaCO_2$, and PH measured at maximum power output. However, $f/\dot{V}CO_2$ at max power output correlated slightly with FEV_1 in COLD and with VC% in ILD. These results suggest that increased D during exercise in COLD and in ILD is related more to lung and/or chest wall afferent reflexes than to chemoreceptors. "RSB" appears to be a mechanical adaptation to increased impedance related to airflow limitation (COLD) or decreased lung compliance (ILD).

Respiratory muscle weakness and ventilatory control in myotonic dystrophy

D E SERISIER, F L MASTAGLIA, G J GIBSON Patients with myotonic dystrophy are often hypersomnolent, prone to CO_2 retention, and unduly susceptible to sedation. Since the ventilatory response to CO_2 is frequently reduced, apparently out of proportion to the degree of weakness, an abnormality of central respiratory control has been suggested.[1] Undue tendency to CO_2 retention is also a recognised feature of patients with paralysis or severe weakness of the diaphragm.[2] Evidence on diaphragm structure and function in myotonic dystrophy is conflicting, with occasional clinical and pathological reports suggesting marked involvement.[3] The present study was designed to assess whether the abnormalities of respiratory control in myotonic dystrophy could be attributed to dysfunction of the diaphragm. Eighteen patients unselected by respiratory symptoms were studied and compared to 20 control subjects. Lung and respiratory muscle mechanics were assessed by measurement of lung volumes, maximum voluntary ventilation, and maximum static respiratory (mouth) pressures; control of ventilation was assessed by resting mixed venous PCO_2, ventilatory response to CO_2 during rebreathing and the tidal breathing pattern; function of the diaphragm was assessed by measurements of the change in vital capacity between erect and supine postures, movements of the chest wall and transdiaphragmatic pressures during tidal breathing, full inflation manoeuvres, and maximum inspiratory efforts. The results indicated marked weakness of the respiratory muscles in the majority of patients, often unsuspected from the degree of overall skeletal muscle weakness. The diaphragm appeared to share in the generalised respiratory muscle weakness but there was no evidence of disproportionate involvement of the diaphragm. The ventilatory response to CO_2 correlated with indices of peripheral mechanical function such as vital capacity and maximum static pressures. A high prevalence of irregularities of resting tidal breathing was observed and remains unexplained.

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Attenuation of respiratory arterial pH oscillations in patients with chronic airways obstruction: relationship to carbon dioxide retention

G M COCHRANE, J G PRIOR, C B WOLFF Respiratory oscillations in alveolar PCO_2 ($PACO_2$) are carried into arterial blood and detected by the carotid bodies.[1] Carotid body denervation may be associated with elevation of $PACO_2$,[2] and alteration of $PACO_2$ profiles (as in tube-breathing) modifies ventilation in man.[3] These studies raise the possibility that respiratory PCO_2 oscillations play a role in the control of breathing. By monitoring arterial pH oscillations (which reflect arterial PCO_2 ($PaCO_2$) oscillations) in vivo, we have investigated whether or not attenuation of respiratory arterial pH oscillations is associated with a rise in mean $PaCO_2$. We studied 14 patients with chronic obstructive bronchitis (FEV_1 range 0·5–1·5 litres BTPS), four patients with features of both chronic obstructive bronchitis and chronic asthma (FEV_1 range 0·3–1·6 litres BTPS), and six patients with predominantly emphysema (FEV_1 range 0·9–1·3 litres BTPS). Arterial blood gas tensions were measured in vitro. Respiratory arterial pH oscillations were measured in vivo with a fast response pH electrode, sampling blood from the non-dominant radial artery. Arterial pH oscillations were characterised by the slope of the descending limb ($\Delta pH/\Delta t$) rather than the amplitude which varies with respiratory period. $\Delta pH/\Delta t$ in patients with chronic obstructive bronchitis or mixed chronic obstructive bronchitis/chronic asthma ranged from zero to $5·03\times10^{-3}$ pH units $.s^{-1}$. In these patients, $PaCO_2$ ranged from 4·76–8·27 kPa, and was related to $\Delta PH/\Delta t$: $PaCO_2 = -453\ (\Delta pH/\Delta t) + 7·34$ kPa: ($r=-0·663$, $p<0·01$). In patients with emphysema ($PaCO_2$ range 4·67–5·99 kPa), $\Delta pH/\Delta t$ ranged from zero to $2·14\times10^{-3}$ pH units $.s^{-1}$. There was no significant relationship between $\Delta pH/\Delta t$ and $PaCO_2$. Our findings are consistent with attenuation of arterial pCO_2 oscillations being one mechanism in the development of hypoventilation in patients with chronic obstructive bronchitis. It appears, however, that hypo-

ventilation does not occur in patients with emphysema despite attenuation of arterial PCO_2 oscillations.

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Vagal control in acute respiratory failure

D MURCIANO, F VIAU, F PLANTE, B LOCHON, J-P DERENNE, R PARIENTE Acute respiratory failure in patients with chronic respiratory diseases is characterised by changes in the pattern of breathing without gross modification of minute ventilation. Respiratory frequency is high and tidal volume is small when compared to the chronic state. In order to elucidate whether vagal influence was responsible for these changes, we studied patients in acute respiratory failure. They were all intubated or tracheotomised. Minute ventilation, occlusion pressure, and blood gases were measured before and after fibroscopic administration of xylocaine in the airways. After xylocaine minute ventilation decreased slightly and inspiratory time was unchanged. The main effect was a marked prolongation of expiration resulting in a decreased respiratory frequency. On the other hand, occlusion pressure, mean inspiratory flow, and tidal volume increased slightly. It should be noted that this improvement of breathing pattern developed in association with a decrease in PaO_2 and an increase in $PaCO_2$. In conclusion, vagal influence might be partly responsible for the changed breathing pattern during acute respiratory failure. The changes observed in arterial blood gases may be related to xylocaine-induced bronchodilatation.

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Ventilation and perfusion scanning in the selection of patients for lung resection

H R MATTHEWS, L K HARDING, R M CAYTON The coexistence of chronic pulmonary disease and carcinoma of the bronchus poses a difficult problem of management with regard to predicting survival and respiratory reserve after lung resection for operable tumours. Older techniques designed to solve this problem are not satisfactory and the decision as to how much lung can be removed is still generally based on subjective clinical assessment. The resulting errors of judgment lead either to the "respiratory cripple" or to leaving in place tumours that could actually be removed. Logically the question that needs to be answered is how much lung will be removed that is actually contributing to gas exchange. To measure this objectively we have used ventilation and perfusion (V/Q) scans with quantitative analysis to determine the percentage contribution to both ventilation and perfusion made by the upper, middle, and lower zones of each lung in such patients. Taken with conventional lung function tests this enables us to estimate the functional effect of lung resection and the respiratory reserve after operation. A typical patient, a man aged 55 years, presented in 1978 with chest pain, dyspnoea, and recent haemoptysis. Investigations revealed an obstructive ventilatory defect and a non-occlusive well-differentiated squamous carcinoma at the junction of the left upper and lower lobes. He was orthopnoeic and considerable doubt existed as to whether he would tolerate left pneumonectomy. Scans showed that ventilation was distributed 61% to the right lung and 39% to the left, but perfusion was 78% to the right and only 22% to the left. He therefore had only 1/5 matched ventilation/perfusion on the left side and an increased dead space. As a result left pneumonectomy was performed. Two years later he is fully ambulant and well. On the basis of our overall experience with this method we feel that it merits wider investigation. It is simple, non-invasive, and readily available, and brings a degree of objectivity to an important decision that is otherwise largely intuitive.

Transbronchial needle aspiration: a new diagnostic technique

G BUIRSKI, P CALVERLEY, N J DOUGLAS, D LAMB, M MCINTYRE, M F SUDLOW, H WHITE Needle aspiration of tissue to obtain cytological specimen is a well-known and simple procedure. We use this technique routinely for aspiration of enlarged lymph nodes with excellent results, and have recently extended this technique to obtain specimens through the fibreoptic bronchoscope using the NK Key Med injection needle. Forty consecutive patients, all with bronchoscopically visible lesions thought to be tumour, were studied. Bronchial brushings, biopsies, and needle aspirates were obtained from each lesion. The aspirate was smeared onto a glass slide and immediately fixed. The needle aspirates were reported by an independent cytologist to whom no other histological evidence was available. Other specimens were sent for routine pathological analysis. We found that the needle aspiration technique produced good specimens, with minimal trauma to the lesion, and little haemorrhage. In 26 of the 40 patients a positive diagnosis of bronchial carcinoma was obtained using the combined methods of brushings and biopsy (biopsy alone produced 25/40+ve; brushings alone produced 16/36+ve). Needle aspiration alone gave a positive diagnosis in 31 cases. There was no discrepancy in cell type, using the WHO classification, between the various techniques. When all the methods were combined the diagnostic rate was increased to 88% (35/40). Of the nine patients with positive needle aspirate but negative biopsy, five had peripheral upper lobe lesions such that adequate bronchial biopsy was difficult. We conclude that transbronchial needle aspiration is an effective and accurate way of obtaining diagnostic

material. It should increase the diagnostic rate for tumours. The needle is less rigid than the biopsy forceps and has the advantage of reaching lesions at maximum flexion of the bronchoscope tip. To extend the value of this technique we are currently assessing its use in the investigation of peripheral lesions under fluoroscopy, as a staging procedure by aspiration at the main carina[2] and by suitable modification to aspirate subcarinal nodes.

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Prognosis of peripheral lung tumours

T TREASURE, J R BELCHER After resection for lung cancer, the prognosis is stated to be related inversely to tumour size in both central and peripheral lesions.[1–4] In the case of central tumours where this measurement can only be made on resected specimens, this is not altogether surprising since increasing size of tumour implies involvement of mediastinal structures and inevitably the prospect of surgical cure seems less likely. Peripheral tumours on the other hand are, as a group, the most amenable to complete anatomical resection, and there is agreement that small peripheral tumours, without evidence of distant metastases or mediastinal lymph node involvement, offer the best prospect of surgical cure.[2 5] Peripheral tumours are also an interesting group to study in this respect since they can be measured on the preoperative chest radiograph and this measurement correlates well with the measurement of the resected specimen.[4] This is of considerable importance in practice because the patient must be accepted or rejected for surgery on this type of information. We reviewed over 300 peripheral tumours subjected to resection. A preliminary study revealed that tumours in the largest group (over 6 cm diameter) did better than those one size smaller (4·6–6·0 cms). Others have reported no long-term survivors in this group.[1 3] We describe the results in this series of peripheral tumours in relation to size and cell type. As a result of our findings we would be reluctant to deny the chance of potentially curative resection to this group of patients on the grounds of tumour size alone.

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Survival of patients with malignant mesothelioma

M R LAW, B E HEARD, M E HODSON The case notes of 65 patients with a histological diagnosis of malignant (diffuse) mesothelioma have been studied, and the biopsy or necropsy material or both reviewed. Histological classification into three groups has been made: epithelial, mixed, and sarcomatous. Of the 65 patients, 15 gave no history of exposure to asbestos dust and their mean survival from onset of symptoms to death was found to be longer than that of the 50 exposed patients. A review of malignant mesotheliomas recorded in the medical literature for other purposes has been carried out and supports this observation. In addition it was found in the present study that the survival of patients with epithelial tumours was longer than those with sarcomatous tumours; mixed tumours held an intermediate position. Differing clinical features of patients with various histological types, and of the exposed and unexposed groups, are discussed.

Circulating adrenaline, histamine, and cortisol in nocturnal asthma

P J BARNES, G A FITZGERALD, M J BROWN, C T DOLLERY The mechanism of nocturnal wheezing remains uncertain. Factors such as allergen exposure, posture, timing of medication, sleep, and plasma cortisol levels do not show a close correlation with the fall in peak expiratory flow (PEF) at night. Urinary catecholamine excretion shows a circadian variation with a reduction at night corresponding to the fall in PEF.[1] We studied five men (aged 22–35 yr) with extrinsic asthma under laboratory conditions after a 48-hour synchronisation period. Venous plasma adrenaline, cyclic 3′5′ adenosine monophosphate (cAMP), histamine, and cortisol were measured four hourly during a 24 hour period. PEF showed a circadian variation with highest values at 1600 (256±62 l min^{-1}; mean±SEM) and lowest at 0400 (138±71 l min^{-1}). Plasma adrenaline showed this same circadian pattern with peak levels at 1600 (0·62±0·15 nmol l^{-1}) and trough levels at 0400 (0·25±0·05 nmol l^{-1}) and correlated significantly with PEF ($r=0·97$ $p<0·001$). Plasma cAMP gave an identical pattern with a significant correlation with PEF ($r=0·98$, $p<0·001$) and reflected circulating adrenaline levels. Circulating histamine gave an opposite pattern with levels of 6·01±1·06 nmol l^{-1} at 1600, rising to a peak at 0400 of 22·9±2·09 nmol l^{-1}, and was inversely correlated with PEF ($r=-0·94$, $p<0·001$) and with plasma adrenaline ($r=-0·90$, $p<0·001$). Plasma cortisol was out of phase by 4 h with a trough value at 2400 and so did not correlate with PEF ($r=-0·16$, $p>0·1$). A slow dose adrenaline infusion (0·01 μg/kg/min) at 1600 and 0400 reduced the plasma histamine levels and caused a rise in PEF. The marked rise in circulating histamine at night correlates significantly with the fall in PEF and may reflect release of bronchoconstrictor mediators from pulmonary mast cells. It is possible that the fall in circulating adrenaline has a permissive action on mast cells by reducing tonic beta adrenergic receptor stimulation. Although the

trough in plasma cortisol precedes that of PEF by 4 h, this may also play a role in view of the delayed action of corticosteroids. It is likely that a combination of factors is responsible for nocturnal asthma and these may act at the level of the mast cell.

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Response to inhaled salbutamol in thyrotoxicosis

R N HARRISON, A E TATTERSFIELD Thyrotoxicosis has many features of sympathetic overactivity yet when it complicates asthma there is said to be an increase in bronchodilator and corticosteroid requirements.[1] We have therefore examined a group of thyrotoxic patients to see if the disease is associated with changes in bronchial adrenergic sensitivity. The cardiorespiratory response to increasing doses of salbutamol was measured in nine untreated thyrotoxic patients and repeated at least three months later when they were clinically euthyroid. There was no difference between mean baseline FEV_1 or sGaw before and after treatment. Mean (±SEM) vital capacity increased from 4045 (±275) ml to 4285 (±350) ml after treatment ($p<0.05$). sGaw was poorly reproducible particularly when patients were toxic and there was a wide variation in airway responsiveness within the group on each occasion. When data from all patients were pooled the mean dose-response curve to salbutamol after treatment was displaced to the left of the pretreatment dose response curve ($p<0.001$) indicating an increased airway response to salbutamol after treatment. Resting heart rate was higher before treatment ($p<0.001$) but did not increase further in response to any dose of salbutamol. These results suggest that bronchial adrenergic responsiveness may be diminished in untreated thyrotoxicosis. This is surprising on theoretical grounds since beta-receptor density is thought to be increased in the disease.[2] The findings would, however, explain the detrimental effect the disease has on asthma. Drug metabolism may be increased in thyrotoxicosis so we measured the time course of the bronchodilator action of a single 400 μg dose of salbutamol in a further five untreated toxic patients. The mean maximum increase in SGaw (57%) occurred at one hour and had fallen to 14% by four hours. The overall time course is similar to previous reports on normal subjects.

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Dose-response comparison of the administration of ipratropium bromide from a metered dose inhaler and by wet nebulisation

S A GOMM, N P KEANEY, L P HUNT, T B STRETTON The inhalation of bronchodilators by wet nebulisation has become a common method of treating patients with airways obstruction. Few studies have compared the effect of administering equal doses of a drug delivered from a metered dose inhaler (MDI) and by wet nebulisation. A cumulative dose-response study was performed on two consecutive mornings by inhaling 72 μg of ipratropium bromide either from a MDI or a Wright nebuliser in 10 patients with stable reversible airways obstruction. The drug was administered in doses of 18, 18, and 36 μg from a MDI and in 9, 9, 18, and 36 μg doses as a wet aerosol at 30 minute intervals. The following measurements were made: PEFR, FEV_1, FVC, TGV, Raw, sGaw, and pulse rate before drug administration, at 30 minutes after each dose, and at intervals for five hours. The mean (±SD) control observations for FEV_1 were 1·49 (0·59) l before using the MDI and 1·52 (0·58) l before wet nebulisation. There was no significant difference in the mean maximum post-bronchodilator values, which were 2·09 (0·90) l and 1·97 (0·84) l respectively, indicating a valid basis for comparison of the two modes of administration of ipratropium bromide. On each day, cumulative administration of 72 μg ipratropium bromide produced highly significant dose-dependent increases in PEFR, FEV_1, FVC, and sGaw ($p<0.001$). However, statistically significant changes in response to each of the dosage increments above 18 μg were not obtained. There was no difference between the MDI and Wright nebuliser in any of the indices of the cumulative dose-response relationships at 18, 36, and 72 μg. After the cumulative 72 μg dose, significant bronchodilatation persisted for 3·5 hr by MDI and for 1·5 hr by wet nebulisation ($p<0.001$). By fitting an exponential model of the form $y=A-Be^{-cx}$ to the mean values of sGaw and FEV_1 an estimate was made of the dose of drug required for each method of administration to achieve 99% of the bronchodilator response. For the MDI these doses were 58 and 78 μg for sGaw and FEV_1 respectively, and by wet nebulisation they were 54 and 82 μg respectively. The administration of a cumulative 72 μg of ipratropium bromide from a MDI and by wet nebulisation produced comparable peak bronchodilatation. Allen and Campbell[1] reported that 120 μg of ipratropium bromide (MDI) was required for prolonged bronchodilatation, and by analogy a similar recommendation may be made for the administration of ipratropium bromide by wet nebulisation.

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Local IgA production

R A STOCKLEY, S C AFFORD, D BURNETT Immunoglobulin A (IgA) protects epithelial surfaces from bacterial invasion and the majority present in lung secretions is locally produced. Soutar[1] suggested that failure of "local" production with normal systemic production is associated with morbidity in patients with bronchitis. The assessment of local IgA production is complex since the IgA in secretions consists

of both "locally" produced and serum-derived components. Most conventional techniques attempt to allow for the serum-derived component by the use of formulae that estimate the degree of protein transudation from serum.[1] However, Stockley *et al*[2] suggested that the use of such formulae could lead to errors, particularly in the presence of inflammation, suggesting a reduction in local IgA production where none exists. The present study describes a technique of thin layer chromatography associated with crossed immunoelectrophoresis that enables a more direct assessment of secretory IgA which is dependent upon its greater size (11S) compared to serum IgA (7S). Both 11S and 7S IgA were measured in sputum from 16 patients with active chest infection and 17 in the stable clinical state. The average amount of 11S IgA was greater in the infected samples (14·6% of a standard serum, SD±5·7; non-infected=6·0%, SD±4·9; $p<0·001$). Similarly the amount of 7S IgA was increased in infection (26·6%, SD±27·9; compared to 3·5%, SD±3·3; $p<0·001$). However, there was no difference between the proportion of IgA present as the 11S component (infected=48·1% total SD±·27·1; non-infected 64·0% SD±22·3). Secretory piece concentrations accurately reflect the 11S IgA in infection though it is present in excess in non-infected samples probably as free secretory piece. This is emphasised in patients with systemic IgA deficiency. The results suggest a rise in local IgA production in the presence of infection, and the techniques provide a useful method for the study of the components of the secretory IgA system.

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Anergy in sarcoidosis: a possible explanation

J D WILLIAMS, M SMITH, B H DAVIES Cutaneous anergy and depression of systemic immune responses are characteristic of sarcoidosis. Peripheral blood lymphocyte responsiveness to plant mitogens is reduced and this correlates with cutaneous anergy.[1] The presence of hyperglobulinaemia and reduction in T cell numbers suggests an imbalance of suppressor cell function. T cell bearing receptors for the Fc portion of IgG (Tg) have been shown to be suppressive in controlling immune responses,[2] and only function after interaction with immune complexes, suggesting an important role for the IgG Fc receptor in the regulation of the immune response. We measured the level of circulating immune complexes in 24 patients with sarcoidosis by the Raji cell assay, and the number of Tg cells by rosetting with ox red blood cells sensitised with IgG ambo receptor. The patients with low levels of immune complexes (<40 units AHG equivalent) had normal numbers of Tg cells (13–25%). All the patients with increased complexes, however, had decreased numbers of Tg lymphocytes. Immune complexes were isolated from the sera of several patients by precipitation with polyethylene glycol 6000. The incubation of these complexes with T lymphocytes isolated from the peripheral blood of normal individuals resulted in a fall in the percentage of Tg cells. After the interaction of normal lymphocytes with immune complexes and their subsequent stimulation with the mitogen phytohaemagglutinin, there was a 50% fall in the degree of stimulation. These findings suggest that immune complexes and suppressor cells may play a critical role in producing the altered immunologic reactivity in sarcoidosis.

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Asbestos pleural disease: a case for compensation?

MARK G BRITTON In 1973 a report by the Industrial Injuries Advisory Council[1] suggested that "all pleural abnormalities which can be ascribed to exposure to asbestos should be covered by the definition of pneumoconiosis" and thus eligible for compensation providing disability was also proven. Reluctance to implement the above recommendations has been caused partly by the lack of definitive evidence that pleural changes alone can give rise to disability. Various types of benign asbestos pleural disease are reviewed and the possible evolution of diffuse pleural thickening are discussed with reference to a case history. The lung function tests on 88 asbestos workers with various types of asbestos-related disease are analysed with respect to pleural disease. The results for the groups are as in the following table, confirming a highly significant decrease in lung function with increasing pleural abnormality ($p<0·001$). The data for each group are also considered with respect to the degree of pulmonary fibrosis present.

Disease category	*Vital capacity*	*Transfer factor*
	% of predicted	*% of predicted*
No pleural disease	92·8	72·0
Pleural plaques (mild)	86·6	71·2
Pleural plaques (moderate)	80·4	65·1
Diffuse pleural thickening (mild)	77·3	66·3
Diffuse pleural thickening (moderate/severe)	60·0	73·5

Several workers with moderate to severe diffuse pleural thickening without evidence of asbestosis showed significant disability. It is suggested that these workers should be encompassed within the terms of the National Insurance (Industrial Injuries) Act 1965 by adding "diffuse pleural thickening due to exposure to asbestos" to the list of prescribable diseases, and they would thus become eligible for compensation from the Department of Health and Social Security.

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Lung en cuirasse: restrictive pleurisy associated with asbestos exposure

G M STERLING, A HERBERT Various pleural reactions to asbestos, including benign plaques, mesothelioma, and pleurisy are well recognised but it is only recently that diffuse pleural thickening causing lung restriction in the absence of apparent underlying lung fibrosis has been described.[1] We report a further six patients with this condition in whom physiological tests showed a restrictive defect on spirometry (mean FVC=53% predicted, mean FEV_1/FVC ratio=72%) with generally reduced lung volumes (TLC=64% predicted) and low carbon monoxide transfer factor (T_{LCO}=58% predicted) but normal transfer coefficient (K_{CO}=97% predicted). Pulmonary compliance, measured in four subjects, was low and maximum inspiratory pressure was high, excluding impaired diaphragmatic contractility as a cause of the restrictive defect. The low compliance can be explained by restricting visceral pleural thickening, rather than lung fibrosis, though there is probably some overlap between pure restrictive pleurisy and typical asbestosis, in which there is usually some pleural involvement.

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Lung en cuirasse: histopathology of restrictive pleurisy with asbestos exposure

A HERBERT, G M STERLING The histopathology of the cases of restrictive pleurisy discussed in the preceding paper are described. Pleural biopsies taken at thoracotomy demonstrate dense fibrosis of parietal and visceral pleura which can extend to involve cortical interlobular septa and perivascular connective tissue. The superficial layers of parietal and visceral pleura show active granulation tissue organising haemorrhagic exudate in the pleural space. The clinical impression that the lungs themselves are normal is born out by normal lung parenchyma in the biopsies: however asbestos bodies are present in sections of these otherwise normal lungs. The necropsy findings in one case demonstrate restrictive pleural fibrosis dominating the pathological picture in a man who, unlike the other patients in the group, was exposed to an exceptionally large amount of asbestos dust. Although fibrous pleurisy, particularly with recurrent effusion, is now accepted as a manifestation of asbestos exposure its association with a restrictive lung abnormality is not well recognised. The relationship between chronic fibrous pleurisy and mesothelioma is also discussed. The conditions may coexist and benign fibrous pleurisy can precede mesothelioma. Both conditions can occur in people who have been exposed to small amounts of asbestos insufficient to cause pulmonary fibrosis. The essentially benign nature of the pleurisy does not preclude the subsequent development of mesothelioma.

Final fall in concentration of bolus gas in closing volume test

J ROELANDTS, M VERHAMME, M DEMEDTS Different authors have described a final fall in the concentration of the bolus gas (phase V) after the terminal rise (phase IV) in the single breath closing volume test. It was attributed to the dead space gas preceding the bolus during inspiration. In subjects presenting a phase V we verified this hypothetical mechanism by the following experiments. First, the effect on phase V of a bolus distributed to the lower parts of the lungs (instead of to the upper ones) was examined. This was achieved on the one hand by inhaling the bolus not at residual volume but at very high lung volumes, and on the other hand by inhaling the bolus at RV in reversed posture, which was inverted again at TLC before the full expiration. In both situations a downward plateau with a reversed phase IV was found, as expected, but also an upward phase V. This indicates that the latter originates from a zone with a high concentration of bolus gas, that is, the dependent ones, and not from the zone receiving the dead space gas. Secondly, we examined whether phase V was accompanied by changes in the oesophageal pressure gradient. It appeared that the gradient was abolished and phase V occurred during abdominal muscular effort at the end of the expiration. The latter may cause gas to be expired again preferentially from the dependent lung zones. Finally the occurrence of a phase V depended on posture and muscular effort, indicating that it is mainly caused by the non-gravitational effect of very forceful muscle contraction when approaching RV, on the distribution of pleural pressure.

This work was supported partially by a grant from the FWGO.

Mechanisms of phases III and IV in single breath washout curves

M VERHAMME, J ROELANDTS, M DEMEDTS It is still a matter for dispute to what extent phases III and IV are determined by intraregional or inter-regional inhomogeneities. In our approach to the problem we measured in nine young healthy subjects: (a) simultaneous single breath washout curves with bolus (Helium) and resident gas methods, and (b) inter-regional distributions of boli inhaled at RV and of RVr/TLCr (the regional RV/TLC ratio) using ^{133}Xe and a gamma camera. These measurements were performed in different postures without and with body inversion between inspiration and expiration. Our study was based on the assumption that major changes occurring in phases III or IV or both after body inversion would indicate that they were determined predominantly by inter-regional concentration differences and gravity dependent emptying patterns. We found that body inversion always caused an inversion of phase IV with both the bolus and resident gas methods. Changes in phase III were less consistent. With the bolus method, inversion between both lateral decubitus postures always caused reversal, but between prone and supine posture generally no clear reversal. With the resident gas method, an upward phase III was maintained after body inversion especially between

prone and supine postures. Scintigraphic measurements after ^{133}Xe ratios between the uppermost and lowermost lung zones: (a) for the bolus showed 2·53± 2·11 in supine and prone posture and 3·14±1·32 in both lateral postures, and (b) for RVr/TLCr 1·32± 0·19, respectively 1·53±0·38. Body inversion decreased this ratio to 83·4±27·9% of its control value in supine-prone postures and to 88·4±31·4% in the lateral postures. In conclusion, phase IV depends predominantly on inter-regional concentration differences and gravity dependent emptying patterns. Phase III with the resident gas method is determined primarily by non-gravitational factors. Phase III with the bolus method can be explained by an interaction of intra and inter-regional concentration differences, the latter being more important in the lateral than the prone or supine posture.

Exercise testing in pulmonary sarcoidosis

C G INGRAM, PATRICIA REID, R N JOHNSTON Twenty patients with proven pulmonary sarcoidosis, mainly stages 2 and 3, were assessed with standard respiratory function tests and exercise studies on a bicycle ergometer to measure the change in single breath carbon monoxide transfer coefficient (KCO) during exercise. The increase in TLCO with exercise was plotted and an "exercise slope" derived. The results of these measurements in normal subjects were compared with patients at different stages of disease. A minimum of three exercise tests were performed in each patient with a maximum of 11 (average five) over periods of seven months to two years. Twenty-five normal subjects on exercise testing showed an "exercise slope" value of 0·0051 (SD 0·0006). When first studied nine patients had a normal TLCO at rest and a normal exercise response. Eight patients had a normal TLCO at rest, but an abnormal response to exercise. No patients had an abnormal resting TLCO but a normal exercise response. Three patients had an abnormal resting TLCO and an abnormal exercise response. During the evolution of the disease there has been an overall decline in the "exercise slope". The serial exercise studies have been related to changes in the chest radiographs, to changing doses of prednisolone in 15 patients, and to progress in the five patients who did not receive prednisolone. One patient showed completely normal tests at rest and on exercise despite considerable changes in the chest radiograph. The implications of these results in assessing the progress of pulmonary sarcoidosis are illustrated and discussed.

Respiratory sensitisation in cimetidine workers

M B DALLY, I I COUTTS, P S BURGE, J V HUNTER, R C PAGE, R HAWKINS, A J NEWMAN TAYLOR Three individuals, employed in a factory making cimetidine tablets, reported rhinitic reactions when exposed to cimetidine tableting dust. Provocation testing produced no reactions to tablet excipients, but reproduced their nasal symptoms when cimetidine powder was added. Reactions were most severe at 1900 to 2000 in the evening. A prevalence survey was carried out in those exposed to cimetidine dust in the factory employing the index cases. Work-related respiratory reactions were defined on the basis of responses to a standardised interviewer-administered questionnaire. Spirometric measurements were made, together with skin prick tests with five common inhalant allergens and a 10% (w/v) cimetidine solution. Before the study employees were divided into three ranked exposure categories. Eighty-seven per cent of those eligible took part, and the questionnaire was satisfactory in relation to repeatability and validity. Of 21 subjects with daily exposure, work-related respiratory symptoms were reported in 13, including seven with asthma. In those exposed more than once a week but less than daily, four out of 18 had symptoms, including one with asthma, while three out of 15 exposed less than once a week had symptoms of rhinitis. In nearly all of those with positive responses, the onset of symptoms followed the start of cimetidine exposure, the intervals ranging from weeks to months. No relationship was found between atopy (defined on skin prick testing) and symptoms, and no skin reactions were elicited by cimetidine. Lung function showed a small but significant group decrease in FVC in those with daily exposure, but neither this observation nor the occurrence of symptoms could be attributed to the effects of smoking. Specific acquired hypersensitivity to inhaled cimetidine dust appears to occur, but the mechanism and outcome are yet to be determined.

Optimal dose of salbutamol respirator solution in asthma: comparison of three doses

E H WALTERS, A COCKCROFT, T GRIFFITHS, K ROCCHICCIOLI, B H DAVIES Salbutamol solution, administered by nebuliser or other techniques, is usually given in a dose of 5 mg. Little evidence exists that this is the optimal dose for bronchodilatation or that this dose is without side effects. We studied 12 patients with asthma with increasing doses of salbutamol, 1·5 mg, 3·0 mg, 7·5 mg, and placebo. Salbutamol was administered twice daily for four days in a double-blind manner. Measurements of ventilatory capacity, pulse rate, and tremor were recorded. There was a significant dose-related response for FEV_1 and PEFR measured either as peak volume compared to baseline or as the average response found from the area under the response curve by trapezoidal integration. There was a significant dose-related response in pulse rate, and palpitations were experienced in four patients with 7·5 mg inhaled salbutamol. Tremor was similarly related to dose. A correlation with plasma levels of salbutamol was attempted which showed a highly significant dose-related increase with drug absorption evident after a 3 mg dose. Salbutamol solution appears to produce satisfactory bronchodilatation and fewer side effects at a dose of 3 mg.

Cardiovascular response to intravenous aminophylline in normal subjects

A D MACKAY, P D SPURRIER, A E TATTERSFIELD In acute asthma aminophylline is often given as an intravenous bolus over several minutes for rapid relief of symptoms and Mitenko and Ogilvie[1] recommended a loading dose of 5·6 mg/kg. Adverse effects continue to be reported in patients receiving aminophylline and although cardiovascular factors are often implicated there has been little systematic study of these. We studied the cardiovascular response of six normal subjects to aminophylline 5·6 mg/kg given via a peripheral vein over 10 minutes as recommended by Piafsky and Ogilvie.[2] The subjects attended on two occasions when blood pressure (BP) and heart rate (HR) were measured at intervals before and for 30 minutes after intravenous injections of firstly saline and subsequently aminophylline (5·6 mg/kg) each given single-blind over 10 minutes. On each day the subjects also received either oral propranolol 80 mg or placebo double-blind 1·5 hours before the saline injection. Both BP and HR were measured with the subject lying and tilted to 70°. BP was measured by sphygmomanometer and HR from the electrocardiogram. After saline there was no change in systolic pressure on tilting but an increase in mean arterial pressure. Aminophylline produced a fall in supine systolic BP (5 mmHg) and a larger fall (13 mmHg) on tilting with a small fall in mean arterial pressure. Heart rate increased on tilting after both saline and aminophylline, by 15 and 22 beats/min respectively. Propranolol caused a fall in systolic BP but then blocked the postural fall produced by aminophylline and mean arterial pressure rose on tilting. The increase in HR on tilting was only slightly reduced by propranolol. Aminophylline appears to cause relaxation of vascular smooth muscle in either veins or arterioles and this effect is blocked by propranolol. The postural fall in BP after aminophylline might account for some of the adverse reactions to aminophylline, particularly those at home where patients are less likely to remain supine.

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Effect of a single dose of isoprenaline or salbutamol on airway epithelial goblet cells in the rat

M A BALDWIN, D LAMB, D P EVANS There is well-documented evidence for the production of an increased number of goblet cells in the airway epithelium by chronic irritation. In experimental animals sulphur dioxide, tobacco smoke, nitrogen dioxide, and ammonia have all been used as chronic irritants to induce such an increase. In 1973 Sturgess and Reid[1] first reported an increase after repeated injections of isoprenaline, a beta-adrenoceptor agonist. We have studied the response of the rat airway epithelium to a single intraperitoneal injection of isoprenaline, salbutamol, other adrenergic agonists and antagonists, and cholinergic agonists. The single dose regimes with isoprenaline and salbutamol produce an increase in goblet cells with a maximum at around 24 hours after injection. We have used this model to investigate the dose-response relationship and the effect of isoprenaline on goblet cells at sites other than the lung. The increase in goblet cells occurring within 24 hours of injection produces a valuable model for the study of the origins of goblet cells, particularly as there is an absence of the inflammatory effects inherent in the exposure to irritants. The significance of the possible pharmacological effects of isoprenaline and salbutamol are discussed.

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Modifying effects of ketotifen, clemastine, and disodium cromoglycate on allergen and histamine dose-response relationships in the nose

M J PHILLIPS, S OLLIER, R J DAVIES The nasal mucosa is an easily accessible target organ for allergen and histamine challenge, and its response may be followed conveniently by measurement of nasal airways resistance (NAR) using a technique of anterior rhinometry. The modifying effects of various therapeutic agents on these dose-response relationships can be studied and an evaluation of their antihistaminic and "anti-allergic" activities carried out. Ten patients with allergic rhinitis received nasal provocation challenges with increasing concentrations of allergen, and a further 10 had provocation tests with increasing concentrations of histamine. Dose-response relationships for allergen or histamine were established for each patient when off all treatment. Identical challenges were carried out on four subsequent occasions, with one-week intervals separating allergen challenges and three-day intervals separating histamine challenges. Each of these latter provocation tests was preceded by nasal administration of ketotifen, clemastine, disodium cromoglycate, or normal saline given in a randomised double-blind fashion. Allergen was given in two concentrations—first a tenfold dilution of the standard solution and then the standard solution. The mean percentage inhibition of the nasal response was 45·6% after ketotifen, −0·18% after clemastine, and 5·9% after disodium cromoglycate. The inhibition of the nasal response after ketotifen was statistically significant at the 5% level. The mean inhibition of the response to the standard allergen solution was 8% after ketotifen, 29% after clemastine, and 21% after disodium cromoglyate. These differences were not statistically significant. Differences between the effects of the drugs on nasal histamine provocation tests were found.

Assessment of the use of antibiotics for the treatment of chest infection in a district general hospital

F M MOSS, M W MCNICOL, D A MCSWIGGAN, D L MILLER A 28-day survey of all antibiotic prescriptions for inpatients in Central Middlesex Hospital showed that

chest infection was the most common indication for therapeutic prescription of antibiotics (108 patients, 25% of all therapeutic antibiotic prescriptions). The reason for each prescription was determined by a brief interview with the prescriber. Subsequently we collated the prescriber's clinical observations, and the laboratory and chest X-ray evidence to produce an "infection score". Items included were fever, leucocyte count, patients' general condition, presence of diabetes, long-term steroid therapy, qualitative assessment of sputum, qualitative assessment of respiratory function, and chest X-ray changes. All chest X-rays taken on the day of prescription or the preceding day were reviewed independently. The appropriateness of each prescription was assessed by the "infection score". We considered that 29 (30%) of the prescriptions were inappropriate because there was not enough evidence to support the diagnosis of chest infection. In 13 patients the score was zero. A significantly higher proportion of patients over 80 years of age received antibiotics inappropriately. The most frequent reason for the misdiagnosis of infection was misinterpretation of chest X-rays showing pulmonary oedema. The antibiotics given were in general appropriate for the prescriber's diagnosis. Ampicillin, the most frequently prescribed drug, accounted for 60% of the prescriptions. Our experience suggests that policies intended to reduce the unnecessary use of antibiotics must take into account the need for a more discerning approach to the diagnosis of infection.

Effect of carbimazole on exercise tolerance in chronic airways obstruction

R J A BUTLAND, J A C K PANG, D M GEDDES A reduction in thyroid function lowers the metabolic rate and consequently the minute ventilation. The induction of hypothyroidism might, therefore, improve the exercise performance of patients with chronic airways obstruction. Previous studies using radio-iodine claimed such a benefit but were uncontrolled and produced the clinical features of myxoedema. In this study we attempted to reduce thyroid function to a lesser degree to avoid hypothyroid symptoms and observed the effect on exercise tolerance. Ten patients with severe dyspnoea and chronic airways obstruction (FEV_1= 0·65±0·07 litres (SEM), FVC=2·59±0·29) entered a randomised double-blind cross-over trial between carbimazole 80 mg daily and matched placebo. The patients took carbimazole or placebo for two months, then placebo for one month to allow thyroid function to return to normal, and finally the cross-over drug for two months. Assessment of thyroid function, lung function, and exercise tolerance was performed monthly. The free thyroxine index after two months of carbimazole (C) was 64±10·5 compared with 89± 3·8, on placebo (P) ($p<0·01$). The normal range is 50–140. Serum tri-iodothronine was reduced (C= 2·01±0·14, P=2·30±0·05 nmol/l, $p<0·05$) and thyroid stimulating hormone was raised (C=14·28±6·07, P= 2·67±0·28 mU/l, $p<0·02$). There was no significant difference in the 12-minute walking distance (TMD) (C=705±74 m, P=719±40 m), the rating of perceived exertion during the TMD (C=13·3±0·5, P= 13·5±0·4), the oxygen cost diagram score (C=52·5± 3·9, P=51·8±2·5), the dyspnoea grade (C=3·5±0·3, P=3·7±0·1), the resting arterialised capillary blood gas tensions (PaO_2: C=9·8±0·4 kPa, P=9·3±0·3 kPa, $PaCO_2$: C=4·5±0·3 kPa, P=4·8±0·2 kPa), or the resting minute ventilation (C=12·0±0·8 litres, P= 12·7±0·6 litres). During a progressive exercise test to exhaustion on a cycle ergometer, there was no significant difference in the minute ventilation, heart rate, blood gas tensions at exhaustion, or the total work done (C=80±17 watts, P=88±12 watts). There were no symptoms or signs of hypothyroidism. Lung function (FEV_1, FVC, TLC, KCO) was unchanged. Thus a 28% reduction in the free thyroxine index produced no symptomatic or objective benefit in exercise tolerance in patients with severe airways obstruction. These results provide no support for the use of carbimazole in chronic airways obstruction.

Week-to-week reproducibility of the 12-minute walking test and its use in assessing the effects of oral steroid treatment in chronic airways obstruction

J F O'REILLY, J M SHAYLOR, B D W HARRISON We assessed the repeatability of the 12-minute walking test at fortnightly intervals and then used this and other tests to assess the effects of 30 mg prednisone daily, given in a double-blind, placebo-controlled fashion in 10 patients, aged 52–70 yr, with chronic airways obstruction. After initial tests patients received two weeks' placebo prednisone in addition to their usual treatment. The tests were repeated and then patients received in random order either two weeks' active prednisone or placebo prednisone followed by a two-week cross-over treatment period. The tests were repeated when the treatment changed and at the end of the study. Like others we found the 12-minute walking distance to be very reproducible on any one day with mean variation of 3·1%. Tests performed two weeks apart show more variability with coefficients of variation ranging from 0·2–44% (mean 10·6%). Three patients showed coefficients of variation of greater than ±10%. Eight patients walked further after active predisone than the mean distance walked when not receiving active prednisone. This extra distance was small and within the expected range on placebo in all but two patients, who were two of the patients showing the greatest variability of walking distance. These results will be discussed and compared with the results of standard lung function tests and the patients' subjective assessment of their condition.

Hyperventilation in exercise-induced asthma

P M TWEEDDALE, D J GODDEN, I W B GRANT Exercise has long been recognised as a potent means of inducing bronchoconstriction, though the most effective form of exercise has been in dispute.[1] The hyperpnoea of exercise has recently been simulated by isocapnic hyperventilation.[2] A modification of this technique has

been studied and comparisons made with treadmill exercise. Six male and four female patients were studied, their ages ranging from 13 to 37 years. All had a history of exercise-induced asthma and seven were atopic. Isocapnic hyperventilation was performed twice on one day, and both hyperventilation and treadmill exercise, in random order, on a second day. Temperature and humidity of inspired air, and minute ventilation were closely matched for each patient. The forced expiratory volume in one second (FEV_1) was measured before and after each stimulus, and the fall in FEV_1 was used to compare responses. Statistical analysis was by paired *t* test. Bronchoconstriction was induced on all four occasions in nine patients, but on only two occasions (both on the same day) in the tenth. The mean fall in FEV_1 after the first hyperventilation was 1·00 litre (SD 0·25) equivalent to a 36% fall in FEV_1. Responses to the second hyperventilation on the first day, and those to hyperventilation on the second day were of similar magnitude, as were responses to treadmill exercise. None of the differences between these responses was statistically significant. Isocapnic hyperventilation is a satisfactory and reproducible substitute for exercise in the provocation of asthma. It has recently been suggested that relative heat exchange within the airways during exercise provides the initial stimulus to bronchoconstriction,[2] and that this is markedly ventilation dependent. The technique of isocapnic hyperventilation enables the minute ventilation to be kept within a predetermined range and was also preferred by most of our patients.

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Management of large hiatus hernias

M MEREDITH BROWN Large hiatus hernias often cause no symptoms, and many are found by chance as by routine chest radiography. Others cause significant disability and serious complications may occur. There is often hesitation in referring these patients for operation, as many are old and frail, and because the difficulties of repairing any large hernia lead to the suspicion that it may be unsuccessful. With adequate preparation and proper technique this suspicion proves ill founded. Disabilities may be summarised as follows: (1) the hernia may contribute to dyspnoea; (2) spasm after distention may cause severe mediastinal pain, often mimicking angina; (3) dyspepsia may be a significant disability but symptoms of reflux are seldom important. Complications may threaten life: (1) *incarceration*, with obstruction of the gastric outlet, leads to repeated vomiting and dehydration demanding urgent gastric drainage and intravenous therapy; (2) *haemorrhage* may be acute with haematemesis or malaena, but is more often insidious and the resulting anaemia may be severe and contribute to dyspnoea; (3) *peptic ulcer* in stomach or duodenum, may perforate or bleed, but oesophageal ulceration is not expected; (4) *carcinoma* may arise in the herniated stomach, usually at the cardia, and dysphagia in a patient with a large hernia should always arouse a suspicion of this complication. Although an acute complication may demand an urgent intervention, it is clearly preferable to carry out an elective operation after proper preparation. This will include a careful assessment of the patient's respiratory and cardiovascular systems and up-to-date full barium studies. Endoscopy is less essential though it may be appropriate to perform a fibreoptic gastro-oesophagoscopy as the first stage of the operation. Anaemia should be corrected and recognised infection treated. The essentials of the surgical treatment of the uncomplicated large hiatus hernia are reduction and repair. Fundoplication alone is insufficient and prevention of reflux is not the primary aim. The logic of the direct transthoracic approach needs no apologist. Reduction of the contents seldom presents a problem. The peritoneal sac must be excised and its neck closed, as in the repair of any hernia. The greatly enlarged hiatus must be reduced leaving a gap comfortably admitting the oesophagus. The weak muscles of the posterior margin may be reinforced with fascia lata. Such an operation can be carried out with an acceptable risk and reasonable prospects of success and may be confidently recommended.

Bolus obstruction of the "normal" oesophagus

D GLADSTONE, C E DREW Bolus obstruction of the oesophagus is defined as the impaction of food or other semi-solid material in the oesophagus in the absence of any obvious distal abnormality. Four cases are described showing various facets of this condition. All the patients were women, 57 to 82 years of age. The obstruction was caused by meat in three cases and in the fourth it followed ingestion of normacol. One patient suffered two episodes of bolus obstruction and one suffered rupture of the upper oesophagus just before oesophagoscopy. The danger and the misleading findings of contrast radiography are outlined, and possible reasons for the condition discussed.

Corticosteroid resistance in chronic asthma

J CARMICHAEL, I C PATERSON, P DIAZ, A B KAY, G K CROMPTON, I W B GRANT Some patients with chronic asthma in whom airflow obstruction can be dramatically relieved by bronchodilator aerosols fail to derive any benefit from systemic treatment with corticosteroids even in high dosage. These patients are difficult to treat, and are responsible for a disproportionately high percentage of the total attendances at asthma clinics and of admissions to hospital. Fifty-eight patients exhibiting the phenomenon of "corticosteroid-resistance" were compared with an equal number of "corticosteroid-responsive" chronic asthmatics in respect of age, sex, smoking habits, duration of symptoms, family history of asthma, atopic status, diurnal variations in peak expiratory flow rate (PEFR),

and bronchial reactivity to inhaled methacholine. The two groups of patients were also compared in respect of certain laboratory findings, including lymphocyte and eosinophil counts, immunoglobulin concentrations, monocyte complement receptors, and neutrophil superoxide anion production. In the clinical studies, the only statistically significant differences observed between the two groups were a more frequent family history of asthma, a longer duration of symptoms, and a more marked degree of bronchial reactivity in the corticosteroid-resistant asthmatics. These patients were also much more liable than corticosteroid-responsive patients to experience nocturnal or early morning wheeze, and to exhibit wide diurnal variations in PEFR. Similar patterns are, however, observed in untreated chronic asthmatics, and are more liable to persist in those who prove to be corticosteroid-resistant. Since most "morning dippers"[1] are corticosteroid-resistant, wide diurnal fluctuations in the severity of asthma may not be a biological characteristic of corticosteroid-resistance but merely an expression of unrelieved airflow obstruction. A similar hypothesis may also explain the more marked degree of bronchial reactivity observed in such cases. The corticosteroid-resistant chronic asthmatics appeared to differ from corticosteroid-responsive patients in that the administration of prednisolone was not associated with the decrease in monocyte complement receptors and the inhibition of casein enhancement which was the "normal" response to this drug in corticosteroid-responsive patients. Details of these findings will be reported in a separate communication. The main purpose of this paper is to draw attention to the clinical phenomenon of corticosteroid-resistance. Further studies to elucidate its causes are in progress.

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Corticosteroid-resistant chronic asthma and monocyte complement receptors

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It has been suggested that blood monocytes or tissue macrophages or both may play a central role in the mechanism of action of the anti-inflammatory effects of glucocorticosteroids.[1] A number of ways in which steroids affect monocyte function have been suggested, one of which is inhibition of monocyte complement receptors.[2] Since an appreciable number of patients with bronchial asthma are resistant to treatment with oral prednisolone we have attempted to determine whether there are differences between corticosteroid-resistant and corticosteroid-responsive patients in terms of (1) monocyte complement rosettes and (2) chemotactic factor-induced complement receptor enhancement (CRE).[3] Monocyte complement receptors (MCR) and enhancement of MCR by a monocyte chemotactic factor (casein) (CRE) were measured in corticosteroid-resistant and corticosteroid-responsive chronic asthmatic patients. In newly diagnosed patients who subsequently responded to corticosteroids the percentage of MCR and CRE was lower after seven days of oral prednisolone and returned to pre-treatment values when prednisolone was withdrawn. The MCR and CRE in corticosteroid-responsive asthmatics receiving prednisolone was significantly lower than in corticosteroid-resistant asthmatics taking prednisolone. However, there was no significant difference in MCR and CRE between non-responders taking prednisolone and non-responders receiving other forms of treatment. These results suggest that one of the effects of systemic corticosteroids in asthmatics who respond to this form of treatment is a decrease in both the percentage of MCR and the degree of CRE. Since these changes were not found in corticosteroid-resistant chronic asthmatics, such patients may have a defect in the expression and mobilisation of complement receptors on the monocyte cell membrane.

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