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A joint meeting of the Belgische Vereniging voor Pneumologie (Société Belge de Pneumologie) and the Thoracic Society was held in Bruges on 20–21 April 1978. Summaries of the papers follow:

Electron microscopy of the normal and damaged pulmonary alveolus

BRYAN CORRIN The electron microscopy of the normal alveolus is described with emphasis on function, particularly gas exchange, surfactant secretion, phagocytosis, and the metabolic processing of circulating vasoactive substances. The ultrastructural features of alveolar regeneration after cytotoxic injury are described together with the contribution of electron microscopy to our understanding of the pathology of the adult respiratory distress syndrome.

Electron microscopy of cancer of the lung

BRIAN E. HEARD and ANN S. DEWAR The typing of lung tumours pathologically is based currently on appearances in paraffin sections observed by light microscopy, and a widely used classification is that of the World Health Organisation (1967). However, electron microscopy is bringing to light much new information on the structure of these tumours, which will have to be incorporated in future classifications. In this paper the authors describe some ultrastructural findings in their own series of lung tumours and discuss the impact of findings of this type on present concepts based on observations made over the years by light microscopy.

Electron microscopy of muscular evaginations

DONALD HEATH When smooth muscle cells shorten on collapse or constriction, bulbous evaginations project from their surface in the gaps between attachment points on the plasma membrane for myofilaments. On electron microscopy such evaginations have a clear cytoplasm devoid of organelles and myofilaments. In ultrastructural studies of pulmonary vascular pathology the observer who does not recognise such evaginations for what they are may be perplexed. Examples of this phenomenon induced by hypoxia and pyrrolizidine alkaloids are shown in the pulmonary trunk and pulmonary veins respectively.

Comparison of the diagnostic contribution of scanner and conventional radiology

MICHEL COLLARD, M. F. SERVAIS, and ALAIN BRIQUET In a double-blind study, physicians made a thoracic diagnosis from computerised tomograms (EMI CT 5005—exposure time: 18 s) and from good standard radiographs. It is important to distinguish the true diagnostic value of this new method for thoracic lesions.

1 *Degenerative pulmonary diseases* The computerised tomogram is more spectacular than conventional radiology in pulmonary fibrosis and emphysema.

2 *Infectious diseases* In pneumonic consolidation or collapse, either lobar or segmental, one is able to visualise a nodular lesion amid a dense lesion. The contribution of the scanner is interesting in cases of mixed lesions involving a pleural component with a parenchymal lesion.

3 *Neoplastic processes* Small pulmonary tumours and an objective diagnosis in neoplastic lesions (adenocarcinoma, etc) are still difficult to establish. However, early pleural tumours are diagnosed much earlier, as are pleural effusions.

4 *Metastatic lesions* Metastatic deposits that cannot be seen on conventional radiographs can be visualised on computerised tomograms (the vast majority of these are subpleural). The true indication is the formal exclusion of all neoplastic lesions when a surgical operation has to be done.

5 *Mediastinal pathology* The differentiation of various elements in the mediastinum is sometimes difficult except for large structures (eg, thymus, and mediastinal lymphoma).

Computerised tomography is a very useful method in the study of the lung parenchymal and pleural pathology. However, in many cases, traditional radiology also permits an excellent approach to a similar problem.

Computerised tomography in the pathology of the pleura and thoracic walls

M. OSTEAUX and L. JEANMART In the thoracic field where conventional radiology is efficient, it seems reasonable to limit computerised tomography (CT) to specific information. The following theoretical advantages of CT can be recognised:

—Suppression of the superpositions without tomographical shadow, this being due to the point-to-point mathematical reconstruction of the picture
—Great sensitivity to small density variations
—Ability to measure the density and deduce the composition and eventually the nature of some components, either normal or due to a lesion

—Representation of the total extent of the structures from the wall to the mediastinum, due to the flexible expression of the picture through the play of the centre and the window
—New topographical approach to the thorax by means of axial sections, this often constituting a decisive factor in the topographical understanding of complex lesions and giving a new view in 'black' areas for conventional radiology: periphery, 'corners'.

The limitations of the method are:
—Rather poor definition in comparison with standard radiology
—Long scanning times, impairing definition of mobile structures
—Rather thick slices (involving densitometric problems when dealing with small structures).

The contribution of CT is then analysed in two fields where it seems considerable: pleural lesions, which are poorly demonstrated by conventional radiology, and parietal pathology, where CT proves to be the diagnostic method of choice.

Conventional radiology shows the pleura and its lesions very poorly. The intrinsic pleural contrast is indeed very small and besides the peripheral situation is unfavourable in ordinary radiology. Tiny effusions can be demonstrated. Metastases can be observed which are otherwise absolutely invisible. In particular, in the follow-up of neoplastic diseases it may be observed that the occurrence of pleural effusions without condensation in standard radiology is due to small-sized pleural metastases which so far had escaped. The pulmonary tumours, primary as well as secondary, are very often bound to the pleura by thin opaque tracts, which could represent a lymphatic extension of the disease.

The sternopericardiac ligament with its bilateral pleural reflection is particularly well delineated. In the case of unilateral subatelectasia, the mediastinum tips entirely over around its posterior insertions. The inclination of the sternopericardiac ligament proves to be an early sign of subatelectasia. CT proves to be the method of choice in the study of parietal extension of intrapulmonary lesions or vice versa. The primary tumour formations of the wall in areas inaccessible for clinical examination are perfectly shown, in the same way as adenopathies of lymphomatous or metastatic origin.

As an original contribution of the technique, the neoplastic or inflammatory invasion of the muscles, of the subcutaneous tissue, and of the cartilages is clearly represented.

A few questions about fibreoptic bronchoscopy

PAUL VAN DE CALSEYDE and ROBERT PANNIER There is today an increased tendency to advocate more generalised use of fibreoptic bronchoscopy under local anaesthesia. In relation to this the authors wish to raise a few questions:

1 Is local anaesthesia the best procedure for bronchial exploration?
—On the basis of 30 years' experience with different methods of anaesthesia, both local and different types of general anaesthesia, it seems that local anaesthesia is not always the most appropriate method.
—Even for fibroscopy, general anaesthesia with the jet technique, which provides good relaxation of the patient, should be used for the examination of children, elderly patients, patients under stress, nervous people, and all patients in whom endoscopy may take a long time.

2 Is fibreoptic bronchoscopy actually the best technique for endoscopic intervention?
—Firstly, as with the rigid bronchoscope, considerable practice is needed to obtain good results.
—Except for minor indications, because of a better general view of the bronchial tree, and a better control of unexpected situations, such as bleeding, bronchorrhoea, and hypersecretion, the first endoscopic examination should be performed with a rigid bronchoscope under general 'jet' anaesthesia. It should then necessarily be completed by a guided fibroscopy through the rigid tube. In a well-relaxed patient the superiority of the fibrescope over the classical bronchoscope complete with a good set of optical instruments is real except for the basal segmental bronchi.

3 Does fibreoptic bronchoscopy permit serial examination?
—At first it should be remembered that the fibreoptic bronchoscope is a very frail instrument.
—Secondly, attention has recently been drawn to the danger of microbial or viral contamination by way of fibroscopy.
—Thirdly, proper sterilisation of the fibrescope is a long-lasting and complex procedure ($\pm$60 h). Therefore, unless one has several fibreoptic bronchoscopes, serial examination is to be avoided.
—Finally, the authors wish to stress the need to continue the current practice of classical bronchoscopy in order to produce a number of well-trained bronchoscopists able to handle the removal of foreign bodies which should, in principle, not be attempted with fibreoptic bronchoscopes.

Comparison between the positive biopsy rates in lung cancer achieved with the rigid bronchoscope and with the fibreoptic bronchoscope

J. WEBB and S. W. CLARKE The advent of fibreoptic bronchoscopy (FOB) in a chest hospital where a large number of rigid bronchoscopies were being done enabled a direct comparison between the two techniques to be carried out. The positive biopsy rate achieved in lung cancer has been used as a method of assessing the relative efficiency of the two techniques. A retrospective survey of all the bronchoscopies done at the Brompton Hospital over a one-year period (July 1974–June 1975) has been carried out. The following details were obtained from the patients' notes: the findings at bronchoscopy, the biopsy results, and the final diagnosis.

Altogether 273 FOBs and 325 rigid bronchoscopies (RBs) were carried out, and a final diagnosis of lung cancer proved histologically or cytologically was made in 95 of the FOB series and in 168 of the rigid series. The diagnosis was made from the bronchial biopsy obtained at bronchoscopy in 68 of the 95 cases in the FOB series (72%) and in 83 of the 168 in the rigid series (51%). The difference between those two biopsy rates was highly significant ($P<0.001$). The percentage positive biopsy rates in the presence of visible tumour that was accessible to biopsy was 91% in the FOB series and 84% in the RB series.

We believe that patient selection was not a cause for the difference between the two groups for the following reason. The anatomical sites of the tumours were recorded from the diagram on the FOB reports. In the 68 positive biopsies in the FOB series, 23 were assessed to have been outside the range of the RB. Of these 23 cases, 14 were at segmental level in the left upper lobe, six at segmental level in the right upper lobe, one in the apical segment of the right lower lobe, one in the apical segment of the left lower lobe, and one in the left lower lobe bronchus had been inaccessible to biopsy at a previous RB. If 23 is subtracted from 68 positive biopsies, the biopsy rate would be 45/95=47%. This figure is not statistically different from the 51% achieved in the RB series. It is reasonable to infer that this is evidence that the two groups were comparable and that the difference in the biopsy rates was due entirely to the increased biopsy range of the FOB.

Metastatic sites in early death after lung cancer resection

PH. DE FRANCQUEN, P. ROCMANS, R. PARMENTIER, and P. VANDERHOEFT Fifty patients operated on for lung cancer (1968–77) died during the first postoperative month. Resection had been performed when mediastinoscopy was negative and when no distant metastasis was detected pre- and peroperatively. Necropsy findings were compared with preoperative investigations to assess the value of these investigations. The group includes 25 curative and 25 reductive resections (local malignant extension macroscopically resected).

Besides expected intrathoracic residues, 10 distant metastases were detected in nine patients (1 curative and 8 reductive). Two patients presented cervical nodes invaded by oat-cell carcinoma. The hepatic metastasis in two of the three patients could be detected only by direct exploration and were oat-cell carcinoma. The four adrenal metastases ranged from 10 g to 220 g. Three were adenocarcinoma; the last one was large-cell carcinoma with simultaneous liver metastasis. A renal metastasis from squamous-cell carcinoma was discovered in one patient.

The incidence of distant metastasis in early necropsies after curative surgical resection was reported as 25% (Matthews *et al.*, *Cancer Chem. Rep.*, **4**, 63, 1973) and 26% (Winstanley, *Thorax*, **23**, 327, 1968) compared, in our series, to 4% after curative resection and 32% after reductive resection. Some undetected metastases could be discovered by more sophisticated investigations. An improvement of the five-year survival rate can be expected by a better staging of lung cancer.

Porcine glutaraldehyde-preserved valves for mitral and aortic replacement

F. DEROM, G. PRIMO, J. L. LECLERC, G. BERZSENYI, J. BLEYN, and F. DEUVART More than 1000 glutaraldehyde-preserved porcine aortic and mitral heterografts have been implanted in these surgical services since October 1974.

The main purpose of this paper is to present specific surgical problems and short-term and long-term follow-up of these valves according to the date of their implantation. The surgical aspects will be discussed regarding possible problems, drawbacks, and advantages during surgery, using these valves.

The main topic of this paper, however, will be the study of emboli, incidence of endocarditis, and incidence of haemodynamic problems related to valve dysfunction.

The reason why the porcine heterograft is the valve of choice of these two departments is discussed and arguments are presented in order to justify this policy.

Surgical treatment of adenoid cystic adenoma of left main bronchus and trachea by left pneumonectomy, resection of 7·5 cm of trachea, and direct reanastomosis of right lung

G. STALPAERT, G. DENEFFE, and R. VAN MAELE A young woman of 23 years, the mother of one child, had presented during the last three years with periods of recurrent acute bronchitis. During the last few months dyspnoea and stridor necessitated medical observation. At bronchoscopy stenosis of the trachea and complete obstruction of the left main bronchus was found. On 22 November 1977 an exploratory thoracotomy was performed, which revealed an afunctional left lung and complete obstruction of the main bronchus. Positive adenopathy was not found. Biopsy revealed an adenoid cystic adenoma. A left pneumonectomy was performed, closing the trachea with tumoral tissue covered with a pericardial flap.

Two weeks later a right thoracotomy was performed with liberation of the whole trachea and the right lung. The tumour invaded the trachea from the carina up to 7 cm in the trachea on the left side; 7·5 cm of the trachea was resected with the aid of extracorporeal circulation. Biopsies of the right-stem bronchus and the trachea were negative. An end-to-end anastomosis was very easy. The anastomotic line was covered with a big flap of pericardium.

Postoperatively artificial ventilation was used for several days. Spontaneous respiration returned after one week with efficient coughing. The follow-up of this patient is described. To our knowledge, this is the first time this kind of operation has been successfully performed.

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Treatment of severe attacks of asthma in intensive care units: 12 years' experience

A. DE COSTER, A. CORNIL, A. DE TROYER, J. P. THYS, J. P. DEGAUTE, and M. ECTORS During the past 12 years, 120 patients with acute bronchospasm have been admitted to our intensive care unit. Forty-three patients were in a comatose state I to III; three patients were admitted twice. Forty-two patients were admitted with severe mental disturbance (disorientation, agitation) or sometimes very severe exhaustion and fatigue. In more than 50% of the patients in each group, the clinical history was in agreement with atopic asthma. Besides the well-known factors liable to induce asthmatic attacks, some more unusual ones have to be considered such as desensitisation procedures, skin diagnostic tests, and inhalation provocation tests.

The clinical signs of an acute asthmatic attack are well known. In the ECG, besides tachycardia and myocardial ischaemia, right auricular P waves are very frequent and usually reversible. Auricular fibrillation and ventricular premature beats as well as ventricular fibrillation (1 case) and cardiac arrest (4 cases) are not uncommon.

In comatose patients, $Paco_2$ is always high, and pH values sometimes reflect an important acidosis with a respiratory but also a metabolic component. Usually, low values of Pao_2 are easily corrected to normal levels.

In comatose patients, intubation and artificial ventilation were needed for the treatment of 38 acute attacks of bronchospasm (for 46 admissions). Two patients died. In patients with mental disturbances only, medical treatment was useful in 12 attacks (for 42 admissions) but artificial ventilation was needed in all the other cases. Three patients in that group died. The problems of artificial ventilation when dealing with very high airway resistance as well as the complications of such treatment are discussed.

In conclusion, the authors try to give a practical scheme based on their experience, for the treatment of such patients.

Prevention of histamine-induced bronchoconstriction by inhalation of the antihistamine clemastine

S. G. NOGRADY and C. BEVAN Ten stable atopic asthmatic subjects had baseline measurement of specific airways conductance (SGaw) performed by whole body plethysmography on two separate days. Measurements were repeated 30 minutes after inhalation of 1 ml of saline or clemastine 0·1% administered double blind in random sequence from a Hudson nebuliser. Subjects then inhaled five tidal breaths of increasing concentrations of histamine from 0·1 to 325 mg/ml administered at three-minute intervals from a similar nebuliser. SGaw was measured at each of the 12 concentration increments and the test terminated when it had fallen by more than 50%.

Mean baseline SGaw rose by 30·9% with clemastine but only by 7·9% with saline. After histamine challenge there was a sharp fall in SGaw in all subjects on saline treatment day but when treated with clemastine no fall in SGaw could be elicited in five subjects. The remaining five subjects exhibited a fall in SGaw but the log histamine dose-response curve was shifted significantly to the right. These subjects could tolerate without a fall in SGaw a mean histamine concentration of $3{\cdot}4 \pm 4{\cdot}1$ mg/ml when treated with saline and $32{\cdot}2 \pm 24{\cdot}6$ mg/ml when treated with clemastine ($P < 0{\cdot}05$). There was no significant difference between the slopes of the log dose-response curves to histamine on clemastine and saline treatment days.

These findings suggest that the antihistamine clemastine given by aerosol inhalation is a bronchodilator and significantly protects against histamine-induced bronchoconstriction. The similarity of slope of the log dose-response curves suggests that this effect is due to competitive inhibition of H_1 receptors rather than a nonspecific bronchodilator action.

Comparative study of bronchial reactivity and atopic status in asthma and rhinitis

W. J. STEVENS, R. L. LINS, and P. A. VERMEIRE Bronchial reactivity to histamine was determined by inhalation of serial dilutions of histamine (0·125 mg/ml –32 mg/ml) in patients with asthma (n=44) and rhinitis (n=52). Each group was subdivided into allergic and non-allergic based on history, skin testing, RAST, and, if necessary, specific bronchial provocation. Rhinitis patients had no pulmonary symptoms. In addition, patients with both asthma and rhinitis (n=43), allergic as well as non-allergic, were also studied. Healthy individuals (n=15) without history of asthma or rhinitis served as a control group. For each individual, PD_{15}, defined as the histamine concentration that induced a 15% fall of FEV_1, was calculated based on the first decrease in $FEV_1 \geqslant 15\%$.

Bronchial reactivity was highest in patients with allergic asthma (PD_{15} 0·22 mg/ml) and non-allergic asthma (PD_{15} 0·52 mg/ml); the difference between both groups was not significant (Student's *t* test). In the rhinitis group, allergic patients were more reactive than non-allergic patients (PD_{15} 1·08 *v* 4·00, $P < 0{\cdot}05$). The PD_{15} of patients suffering from both asthma and rhinitis was 0·78 for allergic patients and 1·78 for non-allergic patients (not significant). All asthmatic patients (allergic and non-allergic) were far more reactive than patients with rhinitis (allergic and non-allergic) (PD_{15} 0·59 *v* 2·08, $P < 0{\cdot}001$). Allergic patients (rhinitis, asthma, rhinitis and asthma) were more reactive than non-allergic patients (PD_{15} 0·59 *v* 1·43, $P < 0{\cdot}005$). All patient groups tested differed significantly from controls. In patients allergic to house dust mite there was

no correlation between PD_{15} of histamine and PD_{15} of house dust mite. Although there were significant differences in the mean total serum IgE levels between groups, IgE could not be correlated with the degree of bronchial reactivity.

In conclusion, our data show that bronchial hyperreactivity, which is a common abnormality in patients with asthma, is also present, although to a lesser extent, in rhinitis patients.

In patients with asthma and rhinitis, bronchial hyperreactivity is less than in asthma without rhinitis. Finally, bronchial reactivity is higher in allergic patients.

Effect of H_1- and H_2-receptor antagonists on antigen bronchial challenge

NOEMI M. EISER, A. GUZ, J. MILLS, and P. D. SNASHALL

Histamine, a powerful bronchoconstrictor, is released in immediate allergic reactions. However, H_1-receptor antagonists have not been useful in treating asthma. We have previously demonstrated that only H_1-receptors exist in normal human bronchi. Using H_1- and H_2-receptor antagonists, we have now investigated the role of histamine receptors in bronchial challenge with antigen in nine stable allergic asthmatic patients.

Seven patients were challenged with *Dermatophergoides farinae*, one with *Aspergillus fumigatus*, and one with rat urine. Five breaths of antigen were inhaled from a Hudson nebuliser attached to a breath-actuated dosimeter. The response at 10 min was monitored by specific airways conductance in a body plethysmograph. Increasing concentrations of antigen were given until a definite response occurred. A cumulative log dose-response curve was then constructed. On separate days the challenges were repeated following intravenous injections of (*a*) an H_1-receptor antagonist, chlorpheniramine (20 mg), (*b*) an H_2-receptor antagonist, cimetidine (200 mg), and (*c*) chlorpheniramine with cimetidine.

An analysis of variance was used to compare the responses of the group as a whole. The dose-response curve was shifted progressively to the right by cimetidine, chlorpheniramine and cimetidine with chlorpheniramine. Thus in asthmatics the bronchial response to the immediate allergic reaction is mediated by both H_1 and H_2-receptors.

Pitfalls and refinements in the assessment of an oral antiallergic agent

E. M. LUMB, G. J. R. MCHARDY, D. M. CLARKSON, M. V. SHOTTER, and A. B. KAY A problem in assessing new drugs in asthma is the choice of relevant sensitive measurements which need to be made over prolonged periods to overcome the heterogeneity and variability of the disease. Sodium nivimedone (BRL 10833), which acts similarly to sodium cromoglycate (DSCG) (Coulson *et al.*, 1977), given at an oral dose of 200 mg thrice daily, was compared with placebo in a six-week double-blind cross-over trial. Twenty-four non-smoking, atopic, asthmatic outpatients, aged between 16 and 32, who had not taken local or systemic corticosteroids during the preceding three months, took part in the study. The subjects recorded symptoms and bronchodilator use each day and measured peak expiratory flow rate (PEFR) thrice daily. In the 12 subjects who received placebo during the first three weeks (group 1), we compared the final week on placebo with the final week on sodium nivimedone; there was a significant improvement in PEFR, both overall and at specific times of day, whether or not allowance was made for prior bronchodilator use. Symptom scores improved and bronchodilator use decreased, but not significantly. In contrast, patients who received sodium nivimedone during the first three weeks (group 2) showed no improvement in these variables when drug was compared to placebo. In general, an objective improvement (PEFR) was associated with a subjective improvement (diary card scores) in group 1 patients. There was no clinical or laboratory evidence that sodium nivimedone in the doses given had any untoward effect.

These studies indicate:

1 that sodium nivimedone may have an effect in asthma similar to that of DSCG (Bernstein *et al.*, 1972),

2 that evaluation of compounds with similar activities in a double-blind cross-over study must take into account the order of treatments, and

3 that response to treatment is best assessed by frequent serial measurements. In a prolonged study these are more easily handled by a system of computer data processing (Clarkson *et al.*, in press).

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Serum angiotensin converting enzyme in sarcoidosis and other granulomatous disorders

P. STUDDY, R. BIRD, and D. GERAINT JAMES Patients with active sarcoidosis have been shown to have a high level of serum angiotensin I converting enzyme activity (SACE).

SACE is a dipeptidase that cleaves the substrate hippuryl-l, L-histidyl-l, L-leucine. The product can be measured spectrofluorometrically by tagging L-histodyl with o-phthaldialdehyde. The results are tabulated.

Patients with severe parenchymal lung infiltration had the highest SACE concentration. After corticosteroid treatment SACE concentrations fall to normal, and rising concentrations may herald a relapse. SACE concentrations are normal in four other chronic granulomatous disorders—namely, Crohn's regional

ileitis, primary biliary cirrhosis, Hodgkin's disease, and active tuberculosis.

Condition	Number of patients	Mean activity SACE (nmol/min/ml ±SD)	P= significance
Healthy controls	26	34± 8	
Acute sarcoidosis	12	49±16	<0·002
Chronic sarcoidosis	62	50±27	<0·001
Sarcoidosis—steroids	31	43±21	<0·02
Sarcoidosis—no steroids	43	55±24	
Primary biliary cirrhosis	31	44±20	NS
Inflammatory bowel disease	26	31± 9	NS
Hodgkin's disease	5	47± 9	NS
Tuberculosis	18	30±11	NS

Prognostic factors in sarcoidosis: a computerised study

E. NEVILLE, P. STUDDY, A. N. WALKER, and D. GERAINT JAMES The computerised data on a series of 818 patients with histologically proven sarcoidosis were analysed for prognostic factors. Disease outcome was assessed in two ways: (1) chest *x*-ray resolution; and (2) evidence of complete remission of sarcoidosis at two years.

Each clinical feature was examined and resolution or remission was expressed as a percentage. The mean of these two figures was considered as a prognostic index for sarcoidosis. Results are tabulated in order of prognosis:

Feature	Chest resolution No.	%	Acute sarcoidosis No.	%	Prognostic index %
Erythema nodosum	147/231	64	210/251	84	74
Hilar lymphadenopathy	268/458	59	334/458	73	66
Irish	33/ 60	55	42/ 65	65	60
Female	243/426	57	307/500	61	59
Age 31	178/350	51	254/392	65	58
Overall	349/700	50	467/818	57	54
English	268/527	51	341/602	57	54
Age 30	162/360	45	211/417	51	48
Peripheral lymphadenopathy	85/185	46	109/220	50	48
Male	106/274	39	160/318	50	45
West Indian	25/ 72	35	43/ 79	54	45
Hilar adenopathy infiltration	59/150	39	77/150	51	45
Pulmonary infiltration	35/ 92	38	31/ 92	34	36
Lupus pernio	7/ 24	29	5/ 33	15	22
Bone	4/ 21	19	4/ 31	13	16
Cor pulmonale	0/ 18	0	0	0	0

Pulmonary and hepatic granulomas associated with phenylbutazone treatment

E. G. LEBACQ and V. DESMET Phenylbutazone treatment induces various hypersensitivity reactions besides numerous toxic manifestations. Granuloma formation may be the result of such reactions (Goldstein, 1963; Guckian and Perry, 1966).

This report deals with a woman, 45 years old, who presented in 1974 with dyspnoea, generalised rash, and fever following phenylbutazone treatment at the total dose of 16 g over one month.

Chest *x*-ray revealed diffuse shadows in both lungs. Liver and spleen were enlarged, and no palpable lymph nodes were noted. Tuberculin reaction was positive. No acid-fast bacilli were detected. The main laboratory data included an inflammatory reaction and an elevated alkaline phosphatase. No autoantibodies were found, and various serological tests were negative. Lung and liver biopsies were performed, showing a granulomatous reaction with epithelioid nodules, scattered epithelioid cells, and numerous inflammatory cells.

Prednisone was administered for six weeks, after which the chest radiograph and clinical findings were normal. The treatment was discontinued, and a Kveim test carried out at that time was negative.

Various diagnoses such as tuberculosis, sarcoidosis, and mycosis capable of inducing granuloma formation in the lung and liver were discarded on clinical and biological grounds. Intradermal and patch-tests with aqueous solutions of phenylbutazone gave a similar inflammatory reaction in the patient and the controls. No serum precipitins against phenylbutazone could be demonstrated.

In July 1977, a challenge test with oral phenylbutazone, 300 mg per day for three days, gave rise to a generalised rash without visceral involvement. Skin biopsies revealed signs of acute inflammatory reaction and vasculitis. By immunofluorescent technique, deposits of IgG and complement were demonstrated in the biopsy specimens.

It is felt that type III hypersensitivity to phenylbutazone might be involved in this reaction and that epithelioid granulomas may be induced by immune complex deposition in the tissues, as suggested for sarcoid granulomas (Ghose *et al.*, 1974).

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Arterial oxygen tension and histamine provocation in asthmatics

TERENCE T. CHAPMAN It would seem reasonable to expect a direct relationship between the arterial oxygen tension and ventilation as measured by the forced expiratory volume. However, it has already been established that bronchodilators can cause a fall in Po_2 in obstructive lung disease. This investigation was designed to measure any changes in arterial Po_2 after bronchoconstriction induced by histamine inhalation in asthmatic patients.

Ten consecutive cases were examined. Two were taking steroids alone, one combined with cromoglycate

and one cromoglycate only. All had been shown previously to be hyperreactive to histamine inhalation. An indwelling needle was inserted in the brachial artery, and blood samples were taken at the beginning and end of each investigation and also as described below. The patients were given an initial inhalation of distilled water through the nebuliser. This was followed by eight inhalations of histamine, 0·03 mg/ml. The inhalation dose was doubled until either a maximum dose of 0·5 mg/ml was reached or there was a fall of 20% or more in the forced expiratory volume. Between each inhalation test spirometry was carried out and a blood sample was withdrawn.

The six patients who were not taking steroids or cromoglycate had an average Po_2 increase of 16·5% in association with a fall in the FEV_1. There was no significant change in the patients on steroids. After the bronchodilator there was a fall in Po_2 in all cases. The mid-expiratory flow rates followed the same changes as the FEV_1. The mechanism of the blood gas changes is discussed.

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Effects of nitroglycerin on transfer factor for carbon monoxide

B. NEMERY, A. FRANS, C. VERITER, and L. BRASSEUR

At rest and during exercise, nitroglycerin (NTG) relaxes the peripheral capacitance vessels and decreases the venous return (Mason and Braunwald, 1965; Detry *et al.*, 1974; Goodman and Gilman, 1975). The present study was designed to determine the effects of this blood redistribution on the pulmonary capillary blood volume, estimated by measuring TLCO by the single breath method.

Eight normal subjects were studied at rest in several positions (sitting, supine, and supine with the legs passively held up) and during moderate upright exercise.

At rest, the control data were obtained after a resting period of 30 minutes in the studied position, after which NTG was administered sublingually (3 mg). The measurements were repeated 3, 8, 15, 30, 45, and 60 minutes after NTG intake and indicated a significant decrease of both TLCO and KCO (transfer factor per litre alveolar volume). In all positions, the maximal decreases were observed after 8 minutes (10–15%) and the decreases remained significant up to 60 minutes (6–10%). Peripheral effects, however, were different: the increase in heart rate (HR) was more important in sitting position (30%) than in supine position (15%) and was abolished after 15 minutes.

The changes of TLCO and KCO cannot be attributed to accumulation of carbon monoxide due to the repeated measurements, as this effect was taken into account.

A moderate exercise (600 kgm/min) was performed during 40 minutes. The control data were collected 5, 10, and 15 minutes after the start of the exercise and NTG was then administered. Three and eight minutes after NTG intake, a slight (5% and 3%) but significant decrease of TLCO and KCO was observed. 15 minutes after NTG intake no significant change was found. After the end of the exercise, repeated measurements (1/2, 3, 5, 10, and 15 minutes) again showed significantly lower values (4–9%) with respect to values obtained after an exercise of identical intensity and duration.

The similarity of the decreases of TLCO and KCO in both sitting and supine position contrasts with the discrepancy between the peripheral effects (increase of HR) of NTG in both positions. Thus the decrease of the pulmonary capillary blood volume can be due to a peripheral venous pooling but might also be partly the result of blood redistribution within the pulmonary circulation.

In exercising subjects, the factors that cause a decrease of TLCO and KCO after NTG are also present, but they are partly or totally counterbalanced by the haemodynamic effects of exercise. This cancelling effect disappears after the end of the exercise.

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Usefulness of ventilation-perfusion scanning for evaluation of the sequelae of thoracic injuries

J. SCHMERBER, Th. MANDERLIER, P. KINNAERT, M. THIRION, J. P. DE KOSTER, and A. SCHOUTENS

In preliminary study the authors review about 20 patients who suffered a thoracic injury. These patients were studied by ventilation-perfusion scanning (^{133}Xe) after stabilisation of the pleuropulmonary and costal lesions. This technique seems to be very useful to appreciate local sequelae of thoracic injuries and helps to discriminate these sequelae from previous chronic bronchopulmonary pathology. This investigation is compared with the other classical methods such as radiography, spirometry, and pulmonary perfusion scanning. Examples of the above described technique are reported.

Effect of aminophylline on FEV_1 in patients with nocturnal asthma

A. A. AL-KHADER and R. B. COLE

Asthmatic patients who develop wheezing attacks in the early hours of the morning are commonly met with in clinical practice, and the potential seriousness of these nocturnal deterioration is emphasised by figures which show that the majority of respiratory arrests and hospital deaths due to asthma occur between midnight and 0800 hours (Hetzel *et al.*, 1977). There is

present little firm evidence to indicate the most effective method for preventing nocturnal asthma.

In a double-blind trial the effects of two preparations of aminophylline (aminophylline suppositories BPC 720 mg and phyllocontin tablets 450 mg) were compared with similar placebo preparations in 10 patients whose complaint was asthma which woke them from sleep. Using a vitalograph, FEV_1 was measured in each patient at three-hourly intervals from 1900 hours to 0700 hours on four different nights, the preparation being administered immediately after the 2200 hours measurement.

On the nights when a placebo was administered the FEV_1 showed a steady and statistically significant fall between 1900 hours and 0400 hours followed by a slight rise at 0700 hours. Aminophylline had a statistically significant effect in reducing or reversing this fall in FEV_1 in every patient, suppositories and tablets being equally effective. Neither preparation caused important side effects.

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Hypothalamopituitary-adrenal function in asthmatics whose oral steroids have been stopped or reduced

B. D. W. HARRISON, LESLEY H. REES, RUTH M. CAYTON, and J. D. N. NABARRO Hypothalamopituitary-adrenal function has been studied by measuring plasma immunoreactive ACTH and plasma cortisol levels during insulin hypoglycaemia tests (IHT) in 11 asthmatics in whom oral steroids had either been stopped or were being reduced. All were taking inhaled beclomethasone.

Seven patients whose oral steroids had been stopped 15–37 months previously showed normal cortisol responses to IH, and there was a significant correlation between the rise of ACTH during IH and the rise of cortisol. In three of the patients the ACTH response was unexpectedly small.

Serial synacthen and IHTs were performed in five asthmatics as oral prednisone was reduced to between 0 and 3 mg/day from doses ranging from 5 to 10 mg/day, which had been taken for between six and 17 years.

The results from this part of the study showed:

1 There was evidence of impaired ACTH and cortisol responses to IH when patients were receiving only 3 mg prednisone/day.

2 There was progressive improvement of ACTH and cortisol responses to IH as the dose of prednisone was reduced below 3 mg/day.

3 One patient showed a normal ACTH response and a subnormal cortisol response during her first IHT, indicating recovery of hypothalamopituitary function before recovery of adrenal function. This is the expected recovery sequence, and in such patients a normal synacthen test is valuable.

4 Two patients had lower cortisol responses during the IHT than during synacthen tests performed one and two months earlier. In these patients the ACTH response was subnormal. This suggested that the adrenal recovery was in advance of hypothalamopituitary recovery, the reverse of the expected sequence, and in such patients a normal synacthen test would be misleading.

Saudi Arabia and acclimatisation to desert heat: observations after a two-year sojourn

P. G. ARBLASTER An abundance of oil reserves, an indigenous population of some millions, and exceptional leadership have raised the Kingdom of Saudi Arabia to a premier place in world politics and finances. A position perhaps uniquely difficult, for sudden wealth is arguably a greater cultural shock than is sudden poverty.

The Middle East has for centuries been the cradle of western civilisation. Saudi Arabia, however, though served by Red Sea and Gulf ports, had no major river to nurture a sophisticated or settled society. Political and functional unification of the area was therefore delayed and would probably have been impossible but for the sterling qualities of the ruling family and the founder of the Kingdom, King Abdul Aziz bin Saud.

Nearly 750 million Moslem pilgrims visit Mecca each year, and Saudi Arabia exercises leadership for Islamic tradition, culture, and temperance. In contrast and at the same time, she is the only large country notable for the introduction of water, telex, and colour TV in the span of one decade.

Her climate is that of the desert and therefore characterised by unrelenting heat (often greater than 38°C) and dryness (vapour pressure less than 10 mmHg (dew point of 50–60)). The critical problem for man and beast is to avoid or limit heat gain.

Typical exposure factors could be the sun radiating 800 kc/M^2/hr in an ambient atmosphere of 40°C and vapour pressure of 10 mmHg. In a man of 1·5 M^2 this will produce a possible heat gain of 680 kc/hr. The adaptability of man is unique, however, his greatest asset is his ability to cool by loss of water vapour. The latent heat of cooling of 1·0 g of H_2O=0·6 kc and thus 680 kc could be lost by the evaporation of about 1000 g/hr—thus maintaining homeothermal state.

Acclimatisation could ameliorate the problems of excessive heat, but these appear to be limited to possible limitation of sweating and reduction of its saline content, raised lactase production, raised aldosterone concentrations, and non-specific changes in mental resilience.

Adaptation, which implies genetic variance, was illustrated by outlining certain features in animals indigenous to the desert. Particular attention was given to the unique and highly efficient features of the camel.

A knowledge of the limitations of adaption, which causes mental and physical breakdown and loss of acclimatisation, have direct bearing on standards that should be laid down for mental and physical work,

sleep, and optimum growth and development. Knowledge of such limitations is of maximum importance in view of the increasing numbers of people in desert areas and with increasingly improved international travelling.

Mesotheliomas in Turkey

I. BARIS, P. C. ELMES, F. D. POOLEY, and A. SAHIN The central uplands of Turkey are covered with snow in winter and are hot and dry in summer. Agriculture is based on small village communities, and there are a few small mines but little industry. Over the whole area recent survey radiography revealed a high incidence of three pleural diseases, which are independently and patchily distributed. The diseases are calcified pleural plaques, a fibrosing pleurisy, and malignant diffuse mesothelioma. Epidemiological follow-up studies have shown that by itself the pleural plaque disease does not shorten life but the other two diseases do. In two villages 50% of the deaths are due to mesothelioma and occur between 30 and 60 years of age. These villages are about 70 km apart and around each are other villages which are structurally and economically identical but where no pleural disease occurs. One affected village is based on an ancient rock cave settlement, the other is not. But in both, the tuf (volcanic) rock is hollowed out for storage chambers and is used for building. This tuf rock is friable and contains submicroscopic fibrils of a zeolite mineral, which is also found in the street dust and agricultural soil. Although the other villages use the rock in the same way the content of fibrous minerals seems to vary. Detailed studies to confirm the association between exposure to these fibres and mesothelioma are planned.

IgE-mediated hypersensitivity to the Chironomid *Cladotanytarsus lewisi* ('green nimitti') as an important cause of bronchial asthma in the Sudan

A. B. KAY, M. O. GAD EL RAB, J. STEWART, and H. H. ERWA Hypersensitivity to Chironomidae (non-biting midges) has been a problem in the Sudan since about 1927 (Lewis, 1956). The trouble is probably due to the working of dams, which have produced lake-like conditions on parts of the Blue and main Niles where breeding has evidently increased (Lewis, 1956). The periods of midge outbreaks, which in some years reach plague proportions, are most often during the dry season when the Nile discharge is minimal (Lewis, 1957). The exact number of individuals who suffer from bronchial asthma is uncertain, but it is probably many thousands, especially at Khartoum and Wadi Halfa where the midges sometimes appear in such vast numbers as to hinder or prevent work and recreation (Lewis, 1956). We have undertaken studies to determine whether there is an immunological basis for this hypersensitivity.

Sixteen Sudanese with bronchial asthma associated with hypersensitivity to the Chironomid, *Cladotanytarsus lewisi* ('green nimitti'), were investigated. All patients gave a positive immediate-type skin reaction to an extract of the midge and the majority had markedly elevated concentrations of circulating IgE. Serum from all patients passively sensitised human lung fragments *in vitro* for the release, by the 'nimitti' antigen, of histamine and slow-reacting substance. This tissue-sensitising activity could be removed by immunoabsorption with an anti-IgE. These results indicate that this widespread and important hypersensitivity in the Sudan is IgE-mediated and so is potentially treatable by desensitisation.

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Evaluation of spirometers: a study on the Monaghan M403, the Pneumoscreen, the Spirotron, the Vicatest, and the Vitalograph spirometers

A. M. J. WEVER, M. G. BRITTON, J. WEVER-HESS, K. H. VAN DER PLAS, and D. T. D. HUGHES A study was done comparing each of the five spirometers with the Stead-Wells spirometer in 100 subjects, using the forced vital capacity (FVC) and the forced expiratory volume in one second (FEV_1) as parameters.

The Stead-Wells spirometer is a water-sealed spirometer and is recommended as a reference spirometer by the American Commission on Environmental Health and Respiratory Physiology (Committee recommendations, 1975). The Vicatest and Vitalograph spirometers are volume-displacement dry spirometers. Both instruments showed a very good linearity over their entire volume ranges; their FVC and FEV_1 readings showed a very good correlation with the readings of the Stead-Wells spirometer. The maximum capacity of the Vicatest spirometer is only 5·6 litres (ATPS), however. The Monaghan, the Pneumoscreen, and the Spirotron spirometers are flow-integrating 'electronic' spirometers. The volumes recorded were found not to be entirely linearly related to flow.

The FVCs and FEV_1s measured by these three spirometers also showed good correlations with the readings of the Stead-Wells spirometer, but to a lesser extent than did both dry spirometers, especially with regard to the FVC. Although volume-displacement spirometers are less compact than flow-integrating spirometers, the former spirometers need no special attention with regard to calibration, and they give no problems of reproducibility and drift. The flow-integrating spirometers depend considerably on electronics. This is not a disadvantage in itself, but measuring flow still remains more difficult than measuring volumes.

Therefore, for routine assessment of ventilatory function, we prefer the modern volume-displacement dry spirometers, preferably fitted with registration and calculating devices.

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Evaluation of a new technique for the measurement of total lung resistance and elastance

A. J. MORRIS, N. SIAFAKAS, and M. GREEN Computation of total lung resistance and elastance from measurements of transpulmonary pressure, flow, and volume during tidal breathing is well established. Methods have entailed measuring pressure differences at points of equal volume and flow, or fitting a straight line to a 'closed loop' plot of flow or volume against transpulmonary pressure.

A new method using a root mean square analysis has recently been described (Gillard *et al.*, 1975). In addition, a machine has been marketed (Auprem 91A, Jaeger and Deckers Medical, Brussels), which uses this method to derive the 'best fit' relationships between flow, volume, and pressure by applying an error minimising process to a series of at least three continuous breaths and giving a digital display of resistance and elastance.

To evaluate this machine we programmed a PDP-11 computer to calculate directly for each breath root mean square values for resistance and elastance from oesophageal pressure and volume. We compared the Auprem with the computer simultaneously in five normal subjects and in three patients with lung disease, breathing at FRC, high and low lung volumes, with added resistances at the mouth and at fixed frequencies of 20 and 40 cycles per minute, and obtained 112 paired values for resistance and elastance.

There was a highly significant correlation of the results from the two systems ($r=0{\cdot}96$ for resistance; $r=0{\cdot}84$ for elastance). However, the Auprem gave values higher than the computer (mean 25%) for both resistance and elastance. When identical signals were fed into the two systems, these differences were minimised. It appeared, therefore, that these discrepancies were largely due to the different means of measuring pressure, volume, and flow in the two systems rather than to the methods of computation.

We conclude that the root mean square method gives consistent and reproducible results and has the advantage of allowing continuous digital analysis of resistance and elastance.

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Regional volumes and static elastic characteristics in healthy and emphysematous lungs

M. DEMEDTS, J. CLÉMENT, P. DEVOS, J. COSEMANS, and K. P. VAN DE WOESTIJNE We measured (1) regional distributions of inspired ^{133}Xe (V_r/TLC_r %) at four overall lung volumes (0, 25, 50, and 75% VC), and (2) static expiratory pressure ($Pst_{(1)}$)-volume (V) curves at various oesophageal levels in healthy subjects and in patients with isolated emphysema.

V_r/TLC_r% varied sequentially in both healthy subjects and in patients with emphysema; the apico-basal volume differences were larger in the latter. Exponential and second-degree polynomial functions were fitted on the $Pst_{(1)}$-V curves (above the inflection point). The polynomial fit was significantly better than the exponential in both groups. The vertical oesophageal pressure gradient was not influenced by lung expansion, implying that alveoli located at different vertical heights in the lungs are submitted to a varying pressure difference with changing lung volume (Pardaens *et al.*, *Journal of Applied Physiology* 1975, **39**, 191). This, in conjunction with non exponential $Pst_{(1)}$-V characteristics, may explain the sequential regional lung expansion. These results are qualitatively different from those of Milic-Emili *et al.* (*Journal of Applied Physiology*, 1966, **21**, 749).

Bronchial response to inhaled cigarette smoke

TIM HIGENBOTTAM, DAVID HAMILTON, COLIN FEYERBAND, and TIM CLARK It is generally believed that cigarette smoke, when inhaled, like dust and sulphur dioxide, produces airway narrowing by means of a vagal reflex (Nadel and Comroe, *J. Appl. Physiol.*, 1961, **16**, 713). However, in two large studies, only a proportion of smokers showed evidence of acute bronchoconstriction after smoking (McDermott, *J. Physiol. (Lond.)*, 1962, **162**, 53; Guyatt *et al.*, *Am. Rev. Resp. Dis.*, 1970, **101**, 44).

This failure of response may represent differences in susceptibility or may simply reflect variation in degree of inhalation of smoke or variation of irritant qualities of the smoke inhaled.

To test these possibilities we performed two studies. In the first, we varied the number of cigarettes smoked on each occasion and, in the second, we varied the tar yield of the cigarettes smoked and included a new smoking material blended cigarette. To estimate the degree of smoke inhalation the change in venous blood nicotine was determined. Each study was performed twice—the first using measurements from a forced maximal exhalation and the second measuring changes in airway resistance using a whole body box plethysmograph.

We found no relationship between measurements of ventilatory capacity or airways resistance and either the number or type of cigarette smoked nor between the measurements and changes in venous blood nicotine. It appeared that individual subjects in each study responded in the same way to each type of bronchial challenge.

Our results suggest that the response to cigarette smoke is idiosyncratic and raises the possibility that the type of response in any given individual may determine the future development of chronic obstructive bronchitis.

Transfer factor in patients with emphysema and lung fibrosis

A. FRANS, CH. FRANCIS, D. STANESCU, B. NEMERY, J. PRIGNOT, and L. BRASSEUR T_{LCO} and K_{CO} were compared in two groups of patients with pulmonary emphysema (E) and diffuse interstitial lung disease (DILD). The diagnosis of DILD was based on clinical, radiological, functional, and histological data and, in some

patients, on the presence of specific precipitins. The diagnosis of E was based on clinical, radiological, and functional criteria. TLCO and KCO values were expressed as percentages of predicted values for males (1) and females (2). In E, TLCO and KCO are equally decreased (TLCO=51·6%, SD=11·5%, KCO=54·6%, SD=9·0%, n=23, P not significant); the total lung capacity (TLC) was normal or increased. In DILD, TLCO is more decreased than KCO. In six patients with normal TLC, however, there was no significant difference between TLCO (55·5%, SD=14·2%) and KCO (59·8%, SD=14·6%); in the 17 others, with a restrictive syndrome, TLCO (41·6%, SD=13·9%) was significantly ($P<0.001$) more decreased than KCO (61·2%, SD=18·3%). It seems therefore that the relatively less important diminution of KCO in those patients is linked to the presence of a restrictive syndrome.

This could be partly explained by the fact that their TLCO and KCO were expressed as percentages of expected values established at normal alveolar volumes (VA′) (Frans *et al.*, 1975; Salorinne, 1976). It is well known indeed that TLCO increases and KCO decreases when VA′ increases (McGrath and Thompson, 1959); we confirmed this finding in 21 healthy subjects; if their TLCO and KCO measured at submaximal VA′ were expressed as percentages of the same indices estimated at maximal VA′ the two following equations were derived:

$$TLCO\ (\%) = 109{\cdot}9 - 0{\cdot}8156\ (VA') + 0{\cdot}0071\ (VA')^2 \quad (n=118),$$

$$KCO\ (\%) = 365{\cdot}5 - 5{\cdot}159\ (VA') + 0{\cdot}0251\ (VA')^2 \quad (n=118),$$

where VA′ is expressed in pc of maximal VA′. Therefore TLCO and KCO measured at submaximal VA′ are under and overestimated respectively when they are expressed in function of predicted formulas (Frans *et al.*, 1975; Salorinne, 1976).

We recalculated the predicted values of TLCO and KCO for the 17 patients with a restrictive syndrome taking into account these two equations and their actual VA′ (expressed in pc of predicted TLC); when TLCO and KCO are expressed in function of these new theoretical values the differences between TLCO (47·8%, SD=15·9%) and KCO (43·6%, SD=14·6%) are minimised.

In conclusion, we suggest that (1) TLCO and KCO are equally discriminant for patients with normal TLC; (2) in patients with DILD and restrictive syndrome, the expression of TLCO and KCO in pc of predicted values established at normal VA′ is erroneous; and (3) theoretical values established at submaximal VA′ would be useful, otherwise, KCO is particularly misleading in patients with DILD: in our series, seven of them had normal KCO despite hypoxaemia at rest and during exercise.

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Use of carbon monoxide to monitor pulmonary haemorrhage

A. GREENING and J. M. B. HUGHES Using radioactive carbon monoxide ($C^{15}O$) and external counting, we were able to show that an elevated pulmonary diffusing capacity (DLCO or DLCO/VA (KCO)) in Goodpasture's syndrome was caused by a stagnant pool of blood, presumably extravascular (Ewan *et al.*, 1976). We have now monitored 27 cases of lung haemorrhage with serial measurements of diffusing capacity using the single-breath method of Ogilvie *et al.* (1957) or our own rebreathing technique. All measurements were corrected to a standard haemoglobin concentration of 14·6 g/dl, using the pulmonary diffusion equation of Roughton and Forster (1957). Apart from Goodpasture's syndrome (70% of our cases) we found lung haemorrhage associated with pulmonary haemosiderosis, systemic lupus erythematosus, polyarteritis nodosa, leukaemia (with thrombocytopenia), and pulmonary oedema. We excluded cases where bleeding appeared to come from the bronchi.

A striking finding in these cases was the transient nature of the bleeding. In several patients more than one episode of haemorrhage was documented but the duration of each episode rarely exceeded 48 hours. Carbon monoxide can combine only with intact haemoglobin, so that the elevated DLCO reflects only recent bleeding.

In capillary haemorrhage, haemoptysis is slight or absent, in contrast to bronchial bleeding. With extensive haemorrhage, lung volumes fall, but the diffusing capacity for carbon monoxide is much more sensitive and specific than, say, the vital capacity. There is a good correlation between the rise and fall of the diffusing capacity and changes on the chest radiograph, but the rise of DLCO may precede the *x*-ray changes by 24 hours. Serial testing is particularly valuable. The patient may have a baseline below the predicted value, and a 50% rise above this level would be consistent with haemorrhage.

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Ventilation distribution after induced bronchoconstriction in normals and in subjects with early lung disease

M. MARCQ, L. GEPTS, and A. MINETTE We studied the effect of induced bronchoconstriction on single-breath He (bolus method) and N_2 (resident method) washouts in six normal subjects (group 1) and in five heavy smokers (group 2) with ventilation distribution abnormalities as assessed by an increased slope of the N_2 alveolar plateau (phase III). Expired He and N_2 con-

centrations were measured simultaneously with a mass spectrometer before and after an aerosol of 1% acetylcholine. This was inhaled during a period of time sufficient to produce at least a 20% decrease in end-tidal FEV_1.

In subjects of both groups, the N_2 and He phases IV/VC ratios were either increased or decreased; substantial changes were observed in all subjects of group 2 but only in two of group 1. In general, the changes in He and N_2 phases IV/VC were parallel except in two subjects. In one subject of group 1, the He phase IV/VC decreased markedly but the N_2 phase IV/VC remained unchanged. In one subject of group 2, the N_2 phase IV/VC was much smaller than the He phase IV/VC obtained before inhalation of acetylcholine, and the difference was exaggerated after bronchoconstriction, the N_2 phase IV/VC decreasing and the He phase IV/VC increasing markedly.

The slope of N_2 phase III increased to variable degrees in all subjects except in one of group 1 and in one of group 2. In the subject of group 1, there was nevertheless a marked increase in N_2 closing capacity to total lung capacity ratio (CC/TLC). The slope of He phase III was less frequently altered after acetylcholine than the N_2 slope.

The most consistent finding after induced bronchoconstriction was a marked reduction in the height of He phase IV, particularly in normal subjects who also had larger heights before inhalation than subjects of group 2. In two subjects of group 1 and in one of group 2 there was even a reversal of the He phase IV after acetylcholine. In one subject of group 1, the only subject studied with unchanged spirometry even after three minutes' inhalation of acetylcholine, the only changes we observed were a marked increase in the N_2 CC/TLC and a substantial reduction in the height of He phase IV.

We conclude that in order to evaluate present or provoked peripheral changes in bronchial calibre and/or bronchomotor tone the simultaneous measurement of bolus and resident gas washouts is a useful and sensitive tool. One should not only measure both phases IV/VC but also the slope of resident gas phase III and the height of the bolus phase IV. The latter index, when reduced after bronchoconstriction, represents greater uniformity of distribution of inspired gas at residual volume, probably as a result of increased mean and ranges of opening and closing airway pressures (Engel *et al.*, 1976). The fact that the He phase IV sloped downward in three of our subjects after acetylcholine might be interpreted as either due to preferential distribution of the bolus in the lower lung or the result of first in, first out sequence of ventilation, not necessarily vertically orientated.

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Low frequency breathing at rest and during exercise in severe chronic obstructive lung disease

R. SERGYSELS, R. WILLEPUT, D. LENDERS, J.-P. VACHAUDEZ, W. SCHANDEVYL, and A. HENNEBERT In 12 patients suffering from severe chronic obstructive lung disease (COLD), spontaneous breathing (SB) was compared to low frequency breathing (LFB) at rest and during exercise (40 watts).

At rest, LFB induced without change in ventilation ($\dot{V}$) a significant improvement in alveolar ventilation, $\dot{V}A$ ($+1{\cdot}55$ l, $P<0{\cdot}025$), Pa_{O_2} ($+4{\cdot}6$ mmHg, $P<0{\cdot}025$), and Pa_{CO_2} ($-4{\cdot}7$ mmHg, $P<0{\cdot}001$).

During exercise LFB induced a significant decrease in $\dot{V}$ (2·92 l, $P<0{\cdot}005$). Therefore improvement in gas exchange was minimal compared to the one obtained at rest: $\dot{V}A$: ($+1{\cdot}54$ l, $P<0{\cdot}05$); Pa_{O_2} (0 mmHg NS); Pa_{CO_2} ($-1{\cdot}9$ mmHg, $P<0{\cdot}05$). Hypoventilation during LFB was explained mainly by expiratory flow limitation when both respiratory frequency and end expiratory level are lowered during exercise. This suggests that SB with high respiratory frequency allows recruitment of lung units within phase time constants and therefore expiratory flows exceeding the one recorded at isovolume during LFB and during a forced vital capacity.

These data indicate that, in the management of severe COLD, LFB during walking or climbing stairs may be inappropriate.

Lung function in adolescent boys

J. E. COTES, I. ASHTON, and C. HEYWOOD A comparison of the respective reference values (Cotes, 1975) shows that a young adult male has a larger lung and a higher transfer factor than a lad of the same stature. To investigate the mechanism, repeat measurements of lung function were made on 168 young people three years after a cross-sectional study in which they first took part when aged 8–16 years (Cotes *et al.*, 1973). Among the males were 21 who, at the time of of the second study, were in the age range 17–19 years. The results were expressed in the form of log log regression relationships of lung function on stature, sitting height, leg length, and fat-free mass, the latter obtained by the methods of Durnin and Rahaman (1967) from measurements of body mass and skinfold thickness.

For the subjects who at the time of the second study were in the age range 11–16 years the relationships were almost identical with those obtained in the first study. For those aged 17–19 years the lung function relative to stature exceeded that predicted by the relationships for the children except in the case of the K_{CO} when the values for these subjects were in line with prediction. In the case of the vital capacity the discrepancy was reduced to insignificant proportions by using sitting height instead of stature as the reference variable, but in the case of the transfer factor and the residual volume the discrepancy persisted and was not materially reduced by including fat-free mass or leg length as additional reference variables.

It is concluded that during adolescence the lung grows relative to stature, sitting height, leg length, and fat-free mass. There is need for additional reference variables to describe the changes.

We are indebted to Mr. G. Berry for statistical advice and to Dr. K. M. Laurence for an introduction to the subjects.

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A case of acute hypercalcaemia followed by a prolonged pulmonary uptake of ^{99mTc}-pyrophosphate. Discussion on the demonstration and evolution of pulmonary calcifications secondary to hypercalcaemia

A. SCHOUTENS, G. BERKENBOOM, P. MARTIN, C. GILLET, and J. SCHMERBER-VEREERSTRAETEN A 42-year-old woman took orally 500 000 IU vitamin D and 9 g Ca (gluconate and lactate). This was followed by brief but intense metabolic disturbances: alkalosis, hypercalcaemia up to 19 mg per 100 ml, hyponatraemia over a period of two or three days; moderate renal insufficiency over a period of 12 days. An uptake of ^{99mTc}-pyrophosphate (^{99mTc}PPi) by the lungs was documented on the 21st day; a faint uptake was still present at five months. A pulmonary scan with ^{99mTc}-microspheres showed a diffuse heterogeneity of the perfusion; a diffusion test and the radiographic study of the lungs were normal.

The whole body retention of PPi at 24 hours post-injection was very high (90% of the injected dose) during the first month, depressed during the second month with a progressive return towards stable values over the subsequent three months.

The relative pulmonary uptake of ^{99mTc}PPi was high and stable during two months and decreased thereafter.

This observation shows that a brief hypercalcaemia can be followed by tissue metabolic abnormalities over a period of at least three months, with the demonstration of persistent uptake of ^{99mTc}PPi by the lungs at five months.

A review of the literature indicates:

1 The ^{99mTc}-pyrophosphates and related compounds are able to demonstrate metastatic calcifications in the lungs and the stomach at a time when the *x*-rays are normal.

2 The most common causes of metastatic calcification of the lungs are: malignant bone disease; chronic renal failure; hyperparathyroidism; and hypervitaminosis D.

3 Few and controversial data are published concerning the reversal of pulmonary calcifications.

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Immunoglobulins, complement, and arylsulphatase in sputum from chronic bronchitis and other pulmonary diseases

LESLEY S. TURNBULL, LINDSAY W. TURNBULL, J. W. CROFTON, and A. B. KAY The immunoglobulins IgG, IgA, IgM, and IgE and the individual complement (C) components C3 and C4 were measured in the sputum and serum from 26 patients with chronic bronchitis, 20 asthmatics who were skin test positive, 6 who were skin test negative, 7 patients with bronchiectasis, 15 with bronchial carcinoma, and 5 with pneumonia. Apart from raised serum concentrations of IgE in skin test positive asthmatics, the serum concentrations of immunoglobulins G, A, and M were, in general, similar for all patient groups. In all subjects except those with bronchiectasis, sputum IgG was present in small amounts whereas IgM was usually undetectable. IgA (7S) was detected in all of the sputum samples examined, three of the bronchiectatics having particularly high values. Appreciable amounts of IgE were found in the sputum from many chronic bronchitics and skin test positive asthmatics but in only a few in the other groups. Sputum C3 and C4 concentrations were low or undetectable in all groups.

When the immunoglobulin or complement concentrations were expressed as a sputum to serum ratio, high values were obtained for IgA in all patient groups. Compared to the other diseases, IgE ratios were elevated in chronic bronchitis and IgM ratios in bronchiectasis. Arylsulphatase IIB was also measured in sputum and was considerably higher in bronchiectasis than in the other pulmonary disorders, consistent with the greater inflammatory changes in this condition.

These data support our previous findings on an association between IgE and chronic bronchitis (Turnbull *et al.*, 1977).

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Alveolar lipoproteinosis—report of a case

W. WIJNS, J. LULLING, J. STEYAERT, F. MEERSSEMAN, and J. PRIGNOT In alveolar lipoproteinosis, an uncommon condition first described in 1958 by Rosen *et al.*, the alveolar spaces are filled by a PAS-positive proteinaceous material rich in lipid while septa appear normal.

An additional typical case, first mistaken for pulmonary sarcoidosis, is reported.

A definite diagnosis was obtained by pulmonary biopsy during fibreoptic bronchoscopy. Clinical, radiological, and functional remission occurred without aggressive treatment. The functional data regularly followed include: lung volumes (spirometric and plethysmographic), blood gases, diffusion, and occasionally exercise tolerance test and closing volume. Clinical, pathological, and radiological features of the disease are reviewed.

Evaluation of treatment is difficult because of the rarity of the disease and the occurrence of spontaneous remissions. Pulmonary lavage as described by Ramirez and Campbell (1965) should be used only in acutely ill patients. Such technique has provided abundant material for histochemical and ultrastructural studies.

Although the pathogenesis of alveolar lipoproteinosis remains uncertain, most authors support the concept that the alveolar filling is related to an insufficiency of pulmonary macrophages to clear surfactant.

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Averill A Liebow Pulmonary Pathology Collection

The Department of Pathology, University of California, San Diego School of Medicine, La Jolla, California, is happy to announce that since January 1977 the Averill A Liebow Pulmonary Pathology Collection has been formally established as a permanent teaching collection within the department at La Jolla. This collection comprises nearly 10 000 cases of pulmonary pathology that have been gathered over some 40 active years by the late Dr Averill A Liebow, Professor Emeritus and former Chairman, Department of Pathology, UCSD School of Medicine. They include original histologic material, appropriate photomicrographs, radiographs, and clinical histories, along with Dr Liebow's personal consultation letters on the individual cases. In addition to the role of this collection in departmental research and teaching activities, it is our intent to make this material available to investigators and scholars interested in pulmonary pathology. We also hope to keep the collection active by continued receipt of interesting cases, which will be reviewed by the Curator of the collection. Those desiring more information about ways in which the collection can be utilised, or interested in submitting cases, should write to Drs Jerrold L Abraham (Curator), Kurt Benirschke, or Colin Bloor, Department of Pathology, UCSD School of Medicine, La Jolla, California 92093. We are pleased to acknowledge the encouragement and support of the Division of Lung Diseases, National Heart, Lung and Blood Institute, NIH, in maintaining the activity of the collection.