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A joint meeting between the Thoracic Societies of Great Britain and France was held in Paris on 8–10 June 1979. Summaries of the papers follow:

Fibre-related diseases

J BIGNON All fibres structures with a length/diameter ratio $\geqslant 2$, may be pathogenic in man. Asbestosis, pleural fibrosis, and respiratory and extrarespiratory carcinoma have been observed with asbestos and other mineral fibres and could be observed with man-made fibres. The dose-effect relation is still unknown, especially for low levels of exposure. The diagnosis of respiratory disease due to inhalation of fibres is established by X ray, the International Classification of pneumoconioses being a valuable tool. Thoracoscopy may contribute to the diagnosis of pleural lesions. We do not know which are the most important physical or chemical parameters of fibres and what their biological effects are on cells. The mechanisms underlying the pathogenic effect of fibres are still unknown. As well as inhalation the ingestion route could be implicated.

Biologically relevant fibres: their definition and measurement

F D POOLEY All fibrous particles if they are of a respirable size are in some way or other biologically relevant. The fibrous particles formed by certain minerals appear to be more significant than others mainly because they are implicated in the production of cancer. Fibres formed from other minerals are mainly implicated in the production of fibrosis and pleural plaques.

The minerals and materials that can break down and form respirable dust particles of a fibrous nature can be divided into three groups as follows: (1) man-made mineral fibres—these include glass fibre slag, rock wools, and ceramic fibre; (2) asbestos mineral fibres—formed from the minerals chrysotile, amosite, crocidolite, anthophyllite, tremolite, and actinolite; and (3) other naturally occurring fibres, including dust particles formed from such minerals as zeolite, sepiolite, attapulgite, halloysite, rutile, and others.

Research into diseases of the respiratory system precipitated by fibrous dust is concerned mainly with establishing which properties of the fibrous dust formed by the various materials and minerals can be correlated with the disease type. To obtain this information sophisticated measurement and analytical techniques have to be used to distinguish between particles of the various minerals which may be contained in dust fractions that have been sampled from air or extracted from the biological material. The size and chemical characteristics of the dust formed by various minerals and materials can then be established and their concentrations by number and mass determined for correlation purposes.

Dose response relationships from epidemiological data

P C ELMES The object of borrowing this technique from the pharmacologist is to predict safe limits for occupational or environmental exposure. The pharmacologists, however, measure at predetermined dose (exposure) levels that cover the range of dosage they wish to use. We are expected to extrapolate down towards zero from observations made at unacceptably high levels of risk. To this statistical difficulty are added the following errors of measurement: (1) past dust analyses that do not include all the relevant fibre sizes, are usually gross underestimates, and do not specify the type of asbestos in use; (2) response in terms of death is inaccurate because there are other causes of mesothelioma, lung cancer, and lung fibrosis besides asbestos; and (3) response in terms of morbidity is inaccurate because there are other causes of the breathlessness, radiographic changes, basal crackles, clubbing, and lung function abnormality usually attributed to asbestos. For these reasons current dose response studies are grossly inaccurate and tend to overestimate the risks at low levels of exposure. The only method available of measuring the risk in given occupational situations is to wait 40 years and see.

Thoracoscopy in pleural mesothelioma

C BOUTIN, P FARISSE, J R VIALLAT, P CARGNINO, and R CHOUX Pleural mesothelioma accounted for 20% of the cancers in our series of 198 chronic pleural effusions. Thoracoscopy through a single opening was carried out under general anaesthesia with a cold light thoracoscope of 7 mm diameter. Biopsy specimens were taken under visual control for optical and electron microscopic examination. In a series of 33 mesotheliomas, 24 patients with pleural effusion underwent 30 thoracoscopies. In 23 patients the macroscopic lesions were compatible with the diagnosis of mesothelioma. We have compared the endoscopic aspects of mesothelioma and metastatic pleural effusions.

	Metastatic effusions	*Mesothelioma*	*Total*	P
"Grape-like" nodules	3	9	12	<0·001
Thickening	26	6	32	NS
Nodules and masses	44	5	49	NS
Mixed appearance	13	3	16	NS
Lymphangitis	6	0	6	NS
Non-specific	14	1	15	NS
Total	105	24	129	

The most specific appearances were yellow-white almost translucent grape-like nodules arising from the parietal pleura (nine patients). Another typical

pattern was dense pleural thickening (six patients). In the remaining patients the lesions observed were less specific.

The biopsy was positive in 29/30 thoracoscopies (96·6%). Talc poudrage was carried out in 10 patients: their mean survival was 458 days. In ten matched mesothelioma patients who underwent pleurectomy the mean survival was only 395 days. It is concluded that in mesothelioma pleural effusions, thoracoscopy is a safe and efficient procedure to help reach a precise diagnosis. Surgery should be preserved for mesothelioma without a pleural effusion.

Environmental mesothelioma in Kappadocia (Turkey)

I BARIS A clinical and radiological survey has shown that calcified pleural plaques and pleural and peritoneal mesothelioma are endemic in some areas in Turkey. These diseases seem to be associated with natural deposits of mineral fibrous rocks. In some areas there are asbestos deposits, but in other villages, such as Karein or Tuskoye where the incidence of mesothelioma is very high, the mesothelial diseases might be related to fibres other than asbestos, such as zeolite fibres.

Use of the international X-ray classification of pneumoconiosis ILO/UC for the diagnosis of fibre-related respiratory disease

A HIRSCH and L DI MENZA The object of the ILO/UC International Classification of pneumoconioses and the general instructions for its use in asbestos respiratory diseases have been set forth. The ILO 1979 classification has been used in four groups of asbestos exposed subjects: two groups in hospital and two groups at work. All subjects were investigated by a standardised questionnaire on occupational history, PA and lateral chest radiographs, and, for most of them, ferruginous bodies were counted either in sputum or in bronchoalveolar lavage. The most frequent radiological signs were parenchymal fibrosis, pleural thickening, pleural calcification, and diaphragmatic straightness. The fibrosis and diaphragmatic straightness were related to the intensity of the exposure. On the other hand, all the radiological signs were related to the length of the exposure. Up to 20–29 years after the onset of exposure the commonest radiological sign was diaphragmatic straightness followed by fibrosis, pleural thickening, and calcification in decreasing order of frequency. Only two signs, pleural straightness and fibrosis showed increased frequency after 10 years of exposure.

Animal experimental data on fibres

J C WAGNER In 1956 we decided to use intrapleural inoculation as a method for investigating the potential of various dusts to produce pleural mesotheliomas in rats. Four pleural tumours developed—two after crocidolite, one with chrysotile, and one tumour was found in a quartz-inoculated animal, subsequently shown to be a lymphocytic sarcoma.

These experiments were then undertaken on a much larger scale using SPF Wistar rats, kindly provided by ICI, Alderley Park, Cheshire. We then repeated the experiment using standard rats. The results of the two studies were identical. Of the rats inoculated with crocidolite, 65% produced mesotheliomas and to our surprise a slightly higher incidence was obtained with a specially prepared sample of super-fine chrysotile from Canada. Unlike the usual chrysotile materials, this sample contained many straight fibrils of very small diameter. In conjunction with Dr Mearl Stanton at NIHS in Bethesda, Maryland, we then tested a large number of mineral fibres of different types, and it became obvious that the finer the fibre, the higher the mesothelioma rate. We are still uncertain of the critical length of fibre, but any straight mineral fibre of a diameter of less than 0·5 μm is capable of producing mesotheliomas. In addition, we have followed diameters down to 0·10 μm, and the rate with the finer fibres is greater than with those of 0·5 μm.

In inhalation studies we have been able to produce asbestosis, pulmonary carcinomas, and mesotheliomas, the mesothelioma rate being considerably less than that of the carcinomas.

Behaviour of asbestos fibres in the respiratory system as shown by animal experiments

L LE BOUFFANT, S BRUYERE, H DANIEL, and G TICHOUX Two main factors determine the fate of asbestos fibres in the respiratory system—their mineral nature and their size characteristics. A comparative study of the evolution of polydisperse chrysotile and amosite fibres was made in rats by determining the mineral content of the lungs by X ray diffraction. More rapid clearance was observed in the case of chrysotile in comparison with amosite. In addition, the rate of chrysotile clearance seems to be strongly influenced by the size factor; a rate of clearance up to 95% was found after two months with particles of 0·3 μm average length. Morphologically, chrysotile fibres in the lungs disintegrate progressively into elementary fibres by dissociation of fibre clumps under the action of tissue media.

The two varieties of asbestos also differ in their chemical behaviour in the lung. A mixture of chrysotile and amosite fibres about 20 μm in length were observed after two months. Changes had occurred in the chrysotile lattice, with almost total disappearance of the electron diffraction pattern, while the amosite lattice remained unchanged.

The evolution of chrysotile fibres in organic media was studied in vivo with microchambers with semi-permeable walls. There was a progressive decrease in magnesium content (21·2% after one month), while silica, retained in the fibre skeleton, hardly decreased (0·8%). Chemical testing under mild conditions showed a close parallel between the mg content and intensity of X ray diffraction (7·36 Å and 3·68 Å).

The transport of chrysotile and amosite from the lungs to the tracheobronchial nodes, the parietal pleura, and the diaphragm also varied with the two asbestos varieties.

Fibre counts with the electron microscope showed that chrysotile was more rapidly eliminated from the lungs than amosite. In the lymph nodes fibre concentrations for both varieties were increased; the rate of increase was larger with amosite, which is not chemically attacked. In the diaphragm the two types of fibres also accumulated, but in this case to a greater extent for chrysotile. This last result confirms observations made on human lungs.

Interaction of fibres with human and animal cells

M C JAURAND and J BIGNON In-vitro studies were carried out to compare the biological activities of various fibres. The fibres used in this experiment were UICC asbestos fibres (A chrysotile, crocidolite) and palygorskite (or attapulgite); glass fibres, quartz, and nemalite were used as reference. The reactivity of three drugs containing attapulgite fibres was also studied. Asbestos fibres and palygorskite were either untreated or acid treated with oxalic acid 0·1 N; chrysotile was also treated with SO_2. The haemolytic activity was measured by determining the percentage of haemoglobin released by incubating particles with red blood cells (RBC). The reactivity on alveolar macrophages was determined by measuring the percentage of LDH and β-galactosidase (β-gal) released by incubating particles with alveolar macrophages.

Chrysotile and palygorskite were highly haemolytic; crocidolite and glass fibres poorly haemolytic. Acid treatment modifies the reactivity on RBC: when treated, chrysotile and palygorskite were less haemolytic, but the activity of crocidolite was increased.

The fibres also had different effects on alveolar macrophages: crocidolite fibres were cytotoxic (both enzymes released) while chrysotile fibres induced a selective release of β-gal. Acid-treated chrysotile became cytotoxic, and this toxicity was very similar to that obtained with quartz. Preliminary results on acid-treated crocidolite showed that the fibres caused a small release of β-gal.

Treatment with SO_2 did not modify the toxicity to any extent. The drugs analysed were haemolytic and cytotoxic.

Animal experiments elsewhere have shown that chrysotile and crocidolite fibres injected in the pleural cavity induced mesothelioma in about 45% of rats. Glass fibre induced about 15% and acid-treated chrysotile induced no mesothelioma. A relationship may be proposed between in-vitro and animal experiments for chrysotile fibres (untreated: carcinogenic and haemolytic; acid treated: not carcinogenic and non-haemolytic), but such a relationship would not obtain for crocidolite or glass fibre.

Assessment of health risks of exposure to mineral fibres: contribution of measurements in environmental and biological samples

P SEBASTIEN, G BONNAUD, and J BIGNON Using an analytical electron microscope, it is possible to identify, size, and count mineral fibres in some environmental and biological samples. Data obtained in two fields of investigation are reported.

General urban and environmental pollution

Levels of asbestos in air were measured in a general urban environment (Paris) inside buildings sprayed with asbestos and in the vicinity of an asbestos plant and were found to be respectively in the ranges (10^{-9} g/m^3): 0·1–7, 1–800, 5–3000. In 1977 42 wines (French and foreign) were investigated; 15 were positive for chrysotile fibres with concentrations ranging from $2–64\times10^6$ fibres/litre. Large quantities of attapulgite fibres have been found in four drugs commonly used for treating gastrointestinal diseases. These findings have been used by the administration for setting up safety standards.

Retention of asbestos fibres in the respiratory system

Monitoring fibres in biological specimens for the assessment of past exposure is more reliable than an occupational history.

Amphibole fibres are found in lung parenchyma more readily than chrysotile.

Interstitial fibres (in lung parenchyma) are longer and more numerous (about 100 times) than intra-alveolar fibres (recovered by lung washing).

Ninety-nine per cent of the fibres encountered at necropsy or after operation in lung parenchyma are thinner than 0·33 micron, whereas length is related to the type of exposure; aspect–ratio values are in the range 20–1000.

Chrysotile (short fibres) is the only asbestos fibre found to any extent in parietal pleura, whatever the respective amounts of amphiboles and chrysotile in lung parenchyma.

These data must be considered with the results of epidemiological and experimental investigations for a better understanding of asbestos-related diseases.

Obstructive lung disease in flax-scutchers

P MORERE, P PASQUIS, G NOUVET, G PARIS, and L BENCE Flax scutching (separation of the textile fibre from the whole plant) is an important cause of occupational dust inhalation in France (the first EEC flax producer), and especially in Normandy which produces two-thirds of French flax. Seven flax factories were randomly selected in the Rouen region and the 122 employees were studied clinically, radiologically, and spirographically. Dust concentration was measured at each working post with a distinction between particles smaller than 5 μm and larger particles. Dust particles were also identified both chemically and microscopically (for the vegetable debris).

About one out of two workers complained of respiratory symptoms according to the international criteria defining chronic bronchitis; 54 out of 119 were dyspnoeic.

A mixed or obstructive pattern on spirometry was observed in 54 of the 119 people examined. The obstructive picture was not related to age; on the contrary, when pure, it was more frequent in young people. It was not more prevalent on Mondays as in

byssinosis, but was, however, directly related to the amount of dust inhaled. This dust consists of mineral dust (25 to 40%) containing silica and vegetable dusts. The vegetable debris contains flax fibres, as well as oleaginous (olive) seeds, and Cladosporium and Alternaria spores representing potentially potent antigenic material.

Correlations between chest radiography, clinical data, and lung function tests (flow–volume curve) in asbestos workers

M BEDU, CL MOLINA, A TOURREAU, J MAILLET, and J C CHEMINAT This study concerns 61 asbestos workers four years after they stopped working in very dusty asbestos conditions. Flow–volume curve showed a decreased flow at low lung volumes, particularly in old subjects with a high dust index. In 13 subjects (21%) with a normal chest radiograph, we observed a decrease in flow. This is interpreted as airways obstruction, and is an early effect of asbestos exposure. This obstruction affects the small airways because the Vmax is density independent in the last portion of the VC. Flow–volume curves breathing a helium oxygen mixture were no more sensitive than those breathing air. This test would appear to be sufficient to monitor exposed workers in epidemiological studies, and this could prevent repeat chest X ray examinations that may be dangerous.

Lung fibrosis after inhalation of fibrous attapulgite

H SORS, A GAUDICHET, P SEBASTIEN, J BIGNON, and P EVEN Attapulgite (A) and sepiolite (S) are amphiboloid fibrous clays extracted in France, Spain, and the USA and largely used in all developed countries in the petroleum, oil, cement, plastic, painting, agricultural, and pharmaceutical industries, and for animal bedding. A and S are fibrous aluminium and magnesium silicates with remarkable absorbing, water retentive, and cation-exchanging properties. Pronounced lung fibrosis was observed in a 40-year-old mining engineer after two years of a moderate occupational exposure to attapulgite during breaking, milling, drying, sieving, and conditioning operations. The patient was free of symptoms but chest radiography showed typical lung markings. Lung volumes and DLCO were slightly reduced, and arterial blood gases essentially normal. Alveolar lavage fluid (ALF) was cell rich (6×10^5 cells/ml) with a normal proportion of macrophages, lymphocytes, and PMN leukocytes (81, 17, and 2% respectively), without ferruginous bodies, but with 42 000 mineral particles/ml, a number similar to that observed in heavy exposure to asbestos fibres. Electron microscopy showed fibrous particles shorter than the usual asbestos or glass fibres (length 0·4 to 4·4 μm with a length/diameter ratio of 21 ± 20). The fibre shortness probably accounted for the absence of ferruginous bodies. After filtration on nucleopore (0·4 μm) the fibres in ALF were studied by X ray diffraction (crystalographic structure) and X ray energy spectrometry (scanning electron probe chemical microanalysis). Both the chemical composition (Si02 60%, $A1_2O_3$ 12%, Mgo 8%, Fe_2O_3 6%) and the X ray microdiffraction diagram were similar to those of mineral attapulgite. The increasing world production of A and S ($1\cdot5\times10^6$ tons/year) and its very large use, particularly as a pharmaceutical digestive absorber, mean that special attention must be paid to the fibrosis and cancer hazards of this new fibrous material.

Methods and interest of preoperative primary lung carcinoma staging

C SORS, G GONNOT, H LONGEFAIT, L TOTY, and P HERTZOG Preoperative staging of lung carcinoma includes evaluation of (*a*) local and regional extension of the tumour and lymph glands and (*b*) metastatic spread.

Clinical or paraclinical examinations may specify local size and extension adequately but standard radiographs or tomograms sometimes conflict with other data. Preliminary surgical exploration may provide decisive information for or against definitive surgery. Discovery of recurrent laryngeal nerve paralysis does not strictly contraindicate surgical intervention, though like recent rhythm disorders or phrenic paralysis it makes the intervention more hazardous and less likely to succeed. On the other hand oesophageal invasion shown by dysphagia or superior vena caval compression confirmed by angiography exclude surgery.

Bronchial endoscopy gives useful information in the case of a proximal tumour. A tumour may be suspected from bronchial rigidity but before deciding that surgery is impossible the diagnosis must be confirmed by multilevel biopsies and convincing histology.

The methods used to show metastases in the pulmonary vascular tree (angiography/^{99m}Tc scan) show only a functional slowdown so proof of anatomical invasion requires selective angiography.

Fixation scans are relatively specific. In particular, we find ^{67}Ga scans valuable because of their selective fixation to neoplastic pulmonary tissue and metastases. In 19 out of 23 cases of cancer we could define precisely the extent of the tumour and ganglion damage. These results were confirmed each time by surgery.

Mediastinoscopy is of interest and, in a series of 261 patients, picked up 125 cases of previously undetected adenopathy. It helps in topographical diagnosis of mediastinal disease, but does not distinguish between inflammation and neoplasia, unless histological examination is carried out.

Bone and brain metastases can presently be detected by scans, but the latter show only metastases greater than 2 cm in diameter. With abdominal metastases contrast X-ray examinations are usually negative. Liver scans are subject to important errors in interpretation, as illustrated in our figures, which show that 35% of the results are conflicting. Biological testing, alkaline phosphatase, gammaglobulin, bilirubin, amylase, and cortisol are significant only if abnormal. Abdominal ultrasonography is valuable though the interpretation is difficult and laparaoscopy

gives only a limited view of possible lesions. We have performed exploratory laparotomies before surgery and found this method preferable to all the others and it presented no additional surgical risk. In 175 patients we discovered eight primary abdominal cancers and 35 hepatic, peritoneal, ganglionic, or adrenal metastases.

In evaluating the thoracic spread of the tumour or metastases, tomodensitometry cannot replace the present proved methods; it is only a supporting method.

Chemotherapy of non-small cell disseminated bronchial cancer

P LAMY Fifty-one patients suffering from non-small cell bronchial cancer with metastasis were divided at random into two groups: 33 patients received BACFON polychemotherapy and 18 patients received no chemotherapy. Overall there was no significant difference between the two groups (total mean survival time (MST): 22 weeks with treatment and 18 without), but a significant difference could be observed if there was an early response (MST: 38 weeks) compared to no response (MST: 15 weeks). Similar results were obtained when radiotherapy was added (MST: 34 weeks) compared to chemotherapy without radiotherapy (MST: 22 weeks).

Management and treatment of lung cancer: possible use of lasers

P HUGH-JONES, J COSTELLO, and W WHIMSTER Most lung cancers arise within a bronchus. Small cell cancers disseminate so early that their treatment, in future, is likely to be by multiple chemotherapy, though the main tumour mass must first be removed with minimum damage to the patient.

A laser beam projected through a quartz fibre bundle down a fibreoptic bronchoscope can deliver non-ionising radiation of great, but controlled, intensity directly to the tumour mass without damage to the surrounding tissue (as may occur with surgery or x-irradiation).

Lasers have successfully been used for treating skin, bladder, brain, and other cancers. In some cases the laser energy is differentially concentrated into the tumour by prior absorption of dye into the malignant cells damaged by their own hypoxia, and by then using a laser of complementary colour to the dye. With this possibility for human lung cancer we have made preliminary experiments on the skin of hairless mice using a pulsed ruby laser and a Neodymium-YAG laser.

The preliminary results show that if the dose of laser energy is reduced so as just not to burn the skin or to produce obvious naked eye effects, then histological examination shows damage to epithelial and subepithelial tissues, especially sweat glands, with little cellular reaction. We hope to proceed with further experiments on tumour-bearing mice, with and without dye absorption, before considering the use of lasers bronchoscopically.

Radiotherapy and combined radiochemotherapy in the treatment of inoperable primitive epidermoid lung carcinoma

P LAVAL, J P KLEISBAUER, P RATHELOT, R POIRIER, and A BETTENDORF The study is based on 564 patients with primitive lung carcinomas (mean age 64±9 years). They were treated during 1970–7 and included 356 cases of epidermoid carcinoma (mean age 63±9 years). We selected the patients where high energy radiotherapy (cobalt 60, Betatron) alone or in combination with chemotherapy had been the chosen treatment—109 patients representing 30% of the epidermoid carcinomas and 19% of the total. Eight patients were excluded from the study (five for unexplained death and three for lack of documentation).

An analysis of the survival time (S_1-death) for the remaining 101 patients was assessed from the beginning of treatment and based on age, TNM classification, and modality of the treatment. The results were compared with those found in a series of 27 cases where a better prognosis could be expected (early diagnosis, smaller lesions, therapeutic possibilities) (S_1-death: 3 years: 13–4 years: 5–5 years: 9).

Two points are emphasised: (1) Correct indications such as age, Karnofsky, and minor lesions should enable the choice of treatment as a palliative or curative measure; (2) a long-term and regular follow-up should be made with particular mention of tolerance, intercurrent infections, thrombovascular manifestations, and immunological response during treatment. Particular attention is drawn to problems in the long-term management of patients other than those due to the tumour—namely age, debility, and cerebrovascular and cardiovascular disease aggravated by the chronic hypoxaemia often present.

Chemoimmunotherapy in the treatment of inoperable lung cancer: results of a randomised trial

B SERROU, J B DUBOIS, H POURQUIER, H PUJOL, PH GREILLIER, and F B MICHEL A randomised trial was performed in patients with inoperable but non-metastatic lung cancer as judged by bone marrow biopsy and bone, cerebral, and hepatic scanning. The patients were randomly assigned to two groups; one received two courses of irradiation for five days separated by an interval of three weeks; the other received the same irradiation associated with chemo-immunotherapy, including adriamycin, vincristine, 5 FU, CCNU, and BCG. After 12 months, the results show a highly significant difference in survival in favour of the group treated both by radiotherapy and chemoimmunotherapy (49·3% versus 29·9%: $P < 0{\cdot}001$). At 18 months there were no survivors in the group treated by radiotherapy alone compared to 35·5% in the group receiving chemotherapy. These results are encouraging and favour the use of early chemotherapy in patients with inoperable lung cancer.

Pulmonary hypertension and chronic airways obstruction

M J BOYD, I P WILLIAMS, N BROOKS, A M HUMBERSTONE, G L LEECH, C W G TURTON, and F J C MILLARD In chronic lung disease non-invasive assessment of pulmonary hypertension (PHT) from clinical examination, electrocardiography, and radiology is insensitive and unreliable. Rise in pulmonary artery end-diastolic pressure (PAEDP), however, results in a prolonged right ventricular isovolumic contraction time, defined as the time interval from tricuspid valve closure (TVC) to pulmonary valve opening (PVO). This interval can be obtained non-invasively by M-mode echocardiography of the tricuspid and pulmonary valves. We have determined the TVC–PVO interval from high speed echocardiographic recordings (200 mm s^{-1} paper speed) in 17 patients with chronic lung disease. Direct measurement of PAEDP by cardiac catheterisation on the same day showed a range of PAEDP from 15 to 45 mmHg. The linear correlation between $\log_{10}$ measured PAEDP and TVC–PVO interval is high ($r=0{\cdot}92$). It is concluded that echocardiography is a useful non-invasive technique for the quantitative assessment of PHT in chronic lung disease.

M-mode echocardiography was used to investigate pulmonary artery pressures in 29 patients with chronic airways obstruction. Readings could not be obtained in 12 patients because of chest hyperinflation or deformity. The pressure was significantly higher in subjects with widespread radiological emphysema than patients with bronchitic symptoms and without widespread radiological emphysema. A negative correlation ($r=-0{\cdot}56$, $P=<0{\cdot}025$) was found between the pulmonary pressure and the diffusion constant for carbon monoxide (KCO). When the distribution and degree of hypoxia was considered it did not seem likely that a ventilation perfusion mismatch was affecting the KCO significantly. It is suggested that the KCO may be reduced in patients with widespread emphysema because of structural damage at the alveolar capillary membrane, and that this damage may be of more importance than previously suspected in the development of pulmonary hypertension.

Comparative study of alterations of respiratory function tests in chronic pulmonary thromboembolism and primary pulmonary hypertension

J BRUNE, A EMONOT, TH WIESENDANGER, C MUNSCH, and P GALY Changes in respiratory function were studied in 25 patients with primary pulmonary hypertension and in 24 patients with pulmonary thromboembolism (PTE) of the main arterial trunks. Pulmonary pressures were measured in all cases of pulmonary hypertension and in 12 cases of PTE. Lung scans using ^{133}Xenon ventilation and ^{99m}technetium perfusion were performed on all patients.

There was no significant difference between the two diseases with respect to Pa_{O_2} measurements, alveolar-arterial oxygen gradient, acid-base balance, carbon monoxide diffusing capacity DLCO over alveolar volume (DLCO/VA), alveolar-arterial carbon dioxide gradient, and mean pulmonary artery pressures. The photoscans, however, were of great value. Although there were no ventilation abnormalities, perfusion was totally different in the two. In PTE there were wide zones of vascular cutoff, while in pulmonary hypertension the overall aspect was heterogeneous with a diffuse spotty appearance but no large filling defects. These scintiphotographic differences illustrate the different topographies of the two types of vascular obstruction.

Pressure flow relations in the pulmonary circulation in patients with obstructive airways disease

H C MIDDLETON, M D PEAKE, and P HOWARD Mean pulmonary artery pressure (PAP) and cardiac output (CO) were measured in 12 patients with severe obstructive airways disease and mild hypoxaemia by a floating catheter technique. Most patients had severe emphysema. At rest PAP was $1{\cdot}44\pm0{\cdot}64$ kPa ($10{\cdot}8\pm4{\cdot}8$ mmHg) and CO $5{\cdot}44\pm1{\cdot}85$ l/min. Mean Pa_{O_2} was $8{\cdot}91\pm0{\cdot}63$ kPa. On light exercise PAP rose to $3{\cdot}7\pm1{\cdot}32$ kPa ($27{\cdot}9\pm9{\cdot}8$ mmHg) and CO to $9{\cdot}8\pm2{\cdot}41$ l/min. A linear regression drawn through these results has a slope of 1·2 l/min/kPa ($R=0{\cdot}59$). Mean Pa_{O_2} did not change significantly.

Patients with chronic obstructive airways disease complicated by oedema and chronic hypoxaemia were divided into two groups: (1) those showing evidence of pronounced deterioration of Pa_{O_2} and (2) stable Pa_{O_2}. Patients with a poor prognosis have a pronounced rise of PAP on exercise and a very small increase in CO. The more stable patients (36 patients) have a linear relation between PAP and blood flow on exercise with a slope of 0·98 l/min/kPa ($R=0{\cdot}5$). This was not significantly different from the group above.

Pressure flow relations in the pulmonary circulation were similar for emphysematous patients and in the early phases of cor pulmonale. Mechanical factors in the lung probably determine PAP at this stage rather than hypoxaemia. Hypoxaemic patients who deteriorate are a distinct group. The effects of hypoxaemia are then additive in several ways to mechanical effects on the pulmonary circulation.

Exercise rehabilitation in chronic obstructive airways disease

I P F MUNGALL and R HAINSWORTH In view of the known spontaneous variation in the results of exercise studies and respiratory function tests (Mungall and Hainsworth, 1979) frequent assessments were undertaken during a trial of exercise rehabilitation. Respiratory function tests, a 12-minute walking test, and submaximal exercise performance were measured in 10 patients with chronic obstructive airways disease at two-weekly intervals on six occasions during each of three periods: before training, during (12 minutes of daily exercises), and after. Results of the last four assessments from each period are compared (table).

The results of exercise tests showed no consistent changes in the regression lines of heart rate or minute

ventilation on oxygen uptake. Samples of arterial blood withdrawn at rest on the last day of each period of the study showed a small but significant reduction in the difference between alveolar and arterial oxygen tensions during the training period.

	Before training	*During training*	*After training*
FEV_1 (l)	1·54± 0·06	1·60± 0.06*	1·59± 0·07
Forced vital capacity (l)	2·79± 0·09	2·83± 0·10	2·79± 0·10
Total lung capacity (l)	7·14± 0·16	6·86± 0·18	7·04± 0·20
Transfer factor (mmol/min/kPa)	43·30± 1·80	46·60± 2·10	52·00± 2·10*
Distance walked in 12-minute test	961·00±19·00	1049·00±22·00*	1028·00±26·00*

*Significantly different from value before training $P < 0.05$ by paired t test.
Results are means ±SE.

These results have shown that during a programme of simple exercise training patients with obstructive airways disease could walk further in a 12-minute walking test. They also showed significant improvement in the FEV_1, transfer factor, and the difference between alveolar and arterial oxygen tensions.

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Swimming exercise training for patients with serious chronic respiratory failure

C SORS, Y LANUSSE, B DAUTZENBERG, and J MUGICA A progressive exercise training programme was carried out on 28 patients with severe chronic obstructive pulmonary disease (COPD). They were divided into three groups: (*a*) emphysema, (*b*) COPD with a fall in the arterial oxygen tension during exercise, and (*c*) COPD with no fall in the arterial oxygen tension during exercise.

The training lasted eight to 16 weeks and took place in a swimming pool with patients wearing fins and fighting against counterweights that pulled them backwards. Their heart rate was maintained at 70–80% of that corresponding to maximum oxygen uptake. The patients whose arterial oxygen tension fell during exercise were given oxygen at 8 l/min. Measurements at rest and during ergometric bicycle exercise were made before and after the training programme. All patients improved subjectively. In group 2 the fall in the arterial oxygen tension associated with exercise disappeared. The only measurable improvements are indicated ($P<5\%$) in the table with the standard deviation of the change.

	Group 2		*Group 3*	
	Before	*Change with training*	*Before*	*Change with training*
VO_2 max (ml/min)	970·0	+305·0 (±180·0)	1·310	+265·0 (±92·0)
Max work load (watts)	71·0	+ 18·0 (±10·4)	86·6	+ 24·7 (±15·9)
FEV_1(l)	0·722	+ 0·250(±0·119)	1·346	+ 0·421 (±0·475)
VC(l)	2·071	+ 0·557(±0·321)	2·531	+ 0·681 (±0·632)
SaO_2% (at rest)	87·6	+ 4·2 (±2·0)	92·3	+ 1·2 (±1·6)

Physical training is the only technique that has proved to be objectively beneficial in chronic respiratory failure. Training in a swimming pool gave excellent results, but the respective roles of posture and immersion remain unclear. Eight of our patients carried out the same level of exercise with the same cardiac output on both the bicycle and in the swimming pool. The arterial oxygen tension was significantly higher in the case of the swimming pool exercise (=+1·57%). These results confirm that special training in a swimming pool can benefit patients with COPD.

Frequent and prolonged measurement of peak expiratory flow rate in workers exposed to (1) electronic soldering flux fumes containing colophony (pine resin) and (2) isocyanate fumes. A comparison with history and bronchial testing. A study to define the usefulness of peak expiratory flow rate records for the diagnosis of occupational asthma

P SHERWOOD BURGE, I M O'BRIEN, and M G HARRIES Peak expiratory flow rate (PEFR) has been measured hourly from waking to sleeping in 29 workers with respiratory symptoms exposed to the fumes of soft-soldering fluxes containing colophony (pine resin). Thirty-nine records of mean length 33 days have been analysed and the results compared with the occupation history and bronchial provocation testing in the same workers. From plots of daily mean, maximum, and minimum PEFR recurring physiological patterns of asthma emerge. The most common pattern is for asthma to increase with each successive work day. Some workers have an equivalent deterioration each work day.

Regular recovery patterns taking one, two, and three days are described. The combination of a three-day recovery pattern and a late asthmatic reaction on Monday results in Monday being the best day of each week. Blind assessment of these records has shown them to be specific and sensitive, provided the worker was not taking corticosteroids or sodium cromoglycate during the recordings, and provided that bronchodilator usage was kept constant on days at home and at work. The results of the PEFR records correlate well with bronchial provocation testing, and provide a suitable alternative to this for the diagnosis of mild to moderate occupational asthma. The records are of particular use for screening symptomatic workers whose symptoms appear unlikely to be related to work.

Similarly PEFR has been recorded hourly or two-hourly from waking to sleeping in workers with respiratory symptoms exposed to isocyanate fumes at work. Twenty-three recordings averaging 33 days duration have also been documented in 20 workers. Each worker has also been admitted for bronchial

provocation testing to toluene di-isocyanate (TDI) or diphenylmethane di-isocyanate (MDI) fumes or both. A final assessment of work-related asthma made from subsequent work exposure has been compared with the results of bronchial provocation testing and blind subjective assessment of the peak flow records. Both techniques were specific and sensitive.

Physiological patterns of occupational asthma were defined from the records of PEFR. The most striking finding was the slow recovery from work-induced asthma. This commonly took several days to start and in one worker took 70 days to complete after leaving work. Several workers developed a pattern resembling fixed airways obstruction after repeated exposure at work. The consequences of these findings for the documentation of symptoms of occupational asthma are discussed and recommendations made for the recording of PEFR in workers in general.

UK beryllium case registry

W JONES WILLIAMS, S NOSWORTHY, and W R WILLIAMS

We present a detailed analysis of 38 cases of beryllium disease occurring in Britain between 1945 and 1978. Most (35) were examples of chronic disease of which two followed acute disease. One had acute disease with complete recovery, and one had skin involvement only. The patients (eight women) were aged 20–69 years.

The occupations included the fluorescent lamp industry, beryllium metal/alloy, ceramic, and experimental work. The duration of exposure in the chronic cases ranged from four weeks to 25 years. Twenty-three patients developed the disease at variable times (five weeks to 14 years) after termination of exposure. Among the presenting symptoms dyspnoea and weight loss were conspicuous. Bilateral miliary or nodular radiological shadowing was common. Twenty-five out of 27 patients had microscopic evidence of sarcoid type granulomas while tissue analysis in 12 patients showed that four contained up to 20 μg of Be/100 g of tissue. Beryllium urine analysis was positive in six of 21 tested. Sixteen of 20 showed a positive beryllium skin patch test without any complications. Five out of 10 showed a positive beryllium macrophage migration inhibition (BeMIF) and eight of nine a positive beryllium lymphocyte transformation. Interestingly, 98% were Mantoux-negative. In 13 cases tested the Kveim test was negative and is thus of value in distinguishing the disease from sarcoidosis. Most patients required steroids. Twelve patients have died at intervals of three to 29 years after diagnosis, most from cor pulmonale.

We are grateful to the many clinicians and pathologists who allowed access to their notes and material. Supported by Health and Safety Executive Research Grant.

Epidemiological study of chronic respiratory disease among talc millers

P LEOPHONTE, P FERNET, J PINCEMIN, J L MOUSSET, and A DELAUDE

A cross-sectional study among 176 talc millers included a CECA questionnaire on chronic bronchitis, clinical examination, spirometry (Vitalograph), and a lung radiograph (size 35×35 cm). We used ILO standards and "blind" reading by two skilled physicians. Dust measurements were used to calculate a total dust score for each worker by adding the different score values for each place of work throughout their working life. A computer was used for data processing.

We distinguished CB (chronic bronchitis) in 9·7% of patients, FRS (functional respiratory symptoms) in 29·6%, and NFS (no functional symptoms) in the remainder. CB and FRS were more frequent after the age of 50. Functional symptoms increased with tobacco consumption ($P<0.05$), adverse weather conditions, previous illness, and dust exposure.

There were 46 patients with pneumoconiosis (26·6%); 10 with heavy radiological shadows (5·6%). Pneumoconiotic workers had more functional symptoms (41%) than non-pneumoconiotic workers (26%). Nine of the 10 pneumoconiotic workers with extensive radiological shadows are below the mean standard values for VC and FEV_1 though within the normal range. The patients with mild pneumoconiosis had VC and FEV_1 values similar to non-pneumoconiotic workers. Dust exposure intensity and duration were the main risk factors for pneumoconiosis.

In conclusion the prevalence of CB in talc workers is the same as that observed in other industrial groups, but the prevalence of pneumoconiosis is high and respiratory symptoms are relatively frequent. The main risk factors were dust exposure intensity and age.

Effect of "dose" of cigarette smoke (cigarettes per day, tar per day, and tar per cigarette) on respiratory symptoms and respiratory function of 18 400 male civil servants

TIM HIGENBOTTAM, T J H CLARK, M SHIPLEY, and G ROSE

Habitual cigarette smoking is associated with development of symptoms of chronic expectoration and reduction in airway function. To examine the relative risks of differing smoking habits and the fate of ex-smokers we reanalysed the data obtained during a previous large-scale screening study of 18 400 male civil servants (Reid *et al*, 1974). Specific questions relating to respiratory symptoms and smoking habits together with measurements of FEV_1 and FVC were collated as well as information about daily tar consumption.

Altogether 3437 non-smokers, 6684 ex-smokers, and 7575 current cigarette smokers were compared. The prevalence rates of respiratory symptoms, particularly chronic expectoration, were strongly associated with current daily cigarette consumption and estimated tar exposure each day. Clinically significant symptoms such as dyspnoea appeared unrelated to cigarette consumption and were rare (less than 5% in all age groups). In asymptomatic smokers in all age groups there was a small reduction in FEV_1 (of about 0·4 l for 20+ cigarettes a day), which was strongly related to

both daily cigarette consumption but not estimated tar exposure. Stopping cigarettes led to an apparent reversal of these effects, which was maximal in ex-smokers of greater than 13 years' standing.

The major effects of smoking appear to be to produce a minor potentially reversible fall in FEV_1, and to increase the prevalence of a productive cough. These effects of cigarette consumption may or may not be a precursor to development of severe disabling disease in a minority of smokers. Screening smokers for early signs of airways obstruction is unlikely to separate those at risk from the much larger population with minor airways obstruction, which may be more simply detected by measurement of FEV_1 or predicted from estimates of daily cigarette consumption or tar exposure.

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Haptoglobin group and pulmonary carcinoma

A BETTENDORF, R FAVRE, J COLONNA, R POIRIER, J P KLEISBAUER, and P LAVAL For some time the relation between cancer and hereditary factors has been widely accepted. A control group (1455 patients) has been compared with patients with pulmonary carcinoma (318 patients) to study the possible role of a genetic factor expressed through the haptoglobin phenotype.

The frequency of the Hp1 gene was less in the carcinoma patients while the frequency of the Hp2-2 phenotype was increased. It is concluded that if indeed a genetic factor exists there is no evidence that it has a primary role.

Necessity of blood theophylline measurements to determine a correct therapeutic dose: correlations with spirometry

F RUFF, GENEVIÈVE MENILLET, MARIE-LOUISE COUSSA, MARIE-CHRISTINE SANTAIS, J-C SALTIEL, and J CHRÉTIEN When oral theophylline is prescribed it is necessary to consider whether the dose is adequate and whether it is safe. Plasma theophylline concentrations have been measured with a micromethod using high performance liquid chromatography (Waters Inc), with a modification (Ruff *et al*, 1978) of the Bates' method. Only 200 μl of total blood are necessary so it is possible to make several determinations. With an oral theophylline given three times a day, determinations are useful around the fourth hour and before the next theophylline ingestion.

It is now well established that the plasma theophylline concentration has to be between 10 and 15 μg/ml to be useful. This has been correlated with spirometry. To avoid complications, a plasma theophylline concentration under 20 μg/ml is necessary.

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Metabolic effects of intravenous aminophylline at therapeutic plasma levels

D A JONES, P G M MORGAN, J V COLLINS, and J MORLEY Although intravenous aminophylline is often used in the treatment of severe asthma, there are few detailed reports of its metabolic consequences in man. Animal studies indicate that aminophylline administration is associated with increased catecholamine and insulin release. Some studies in man have suggested similar changes at unknown plasma aminophylline levels (Ensinck, 1970; Tickner *et al*, 1977). Such altered hormone release is thought to occur as a result of inhibition of the inactivation of cyclic 3′, 5′-adenosine monophosphate (cyclic AMP) of aminophylline.

We investigated the metabolic consequences of intravenous aminophylline administration in 10 healthy fasting volunteers. Each subject was seated under standard conditions for the duration of the experiment, an indwelling needle inserted into a forearm vein, and basal venous blood samples were withdrawn for measurement of plasma cyclic AMP, insulin, glucose, Na^+, K^+, and triglycerides. Increasing doses of intravenous aminophylline based on body weight were administered so as to show a dose-response effect when plasma concentrations varied between 0·9 ($\pm$0·2 SD) and 10 ($\pm$1·7 SD) μg/ml, and subsequent doses of aminophylline brought the final plasma concentrations to 15·7 ($\pm$2·1 SD) μg/ml. Blood samples were taken 20 minutes after each dose for assay of cyclic AMP, insulin, etc.

We found no significant differences between any of the measurements as a result of the increasing plasma aminophylline concentrations. We therefore conclude that, unlike salbutamol (Neville *et al*, 1977), intravenous aminophylline giving plasma concentrations within the accepted therapeutic range has no severe metabolic consequences in normal subjects. Furthermore, we question whether aminophylline exerts its bronchodilator effects solely via the mechanism of changes in intracellular cyclic AMP.

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Double-blind cross-over study of slow release oral salbutamol and aminophylline at night for prevention of nocturnal asthma

A J FAIRFAX, W R MCNABB, H J DAVIES, and S G SPIRO Sustained release bronchodilator preparations such as salbutamol "spandets" and Phyllocontin are often prescribed for nocturnal symptoms of asthma. There are no data for plasma concentrations of either drug in the early morning in asthmatic subjects and therapeutic levels for salbutamol are unknown.

We compared plasma concentrations after two Ventolin spandets (16 mg salbutamol) and two Phyllocontin (450 mg aminophylline) in an outpatient double-blind cross-over study. The drugs were given at midnight to 14 chronic asthmatics aged 14–71 (mean 41·2 years), all with documented regular nocturnal falls in PEFR$\geqslant$15%. Each drug was given for one week and compared with two weeks' placebo. On the last day of each treatment week the patients were admitted to hospital overnight for plasma concentrations at 0600. Seven patients were also admitted for 15-hour salbutamol infusions to determine the time course of plasma concentrations on a known effective dose of salbutamol (May *et al*, 1975).

In the outpatient study the mean morning PEFR was significantly higher ($P=<0{\cdot}002$) in the two-week period on active drugs (245 l/min$\pm$7·0 SE) than in the placebo fortnight (218 l/min$\pm$7·2 SE). The evening PEFR showed no statistical difference during the four-week trial. Comparing morning PEFR values for each drug, both salbutamol ($P<0{\cdot}01$) and aminophylline ($P=<0{\cdot}05$) gave higher values than placebo. Plasma samples six hours after medication gave a mean salbutamol level of 18·7 ng/ml ($\pm$4·5 SD) and a mean aminophylline level of 7·0 μg/ml ($\pm$2·9 SD). Plasma concentrations with continuous intravenous salbutamol (8 μg/kg/hr) reached a plateau by six hours. The mean level at 15 hours was 20·3 ng/ml ($\pm$3·2 SD).

In conclusion, salbutamol levels at 0600 were similar to those achieved during an infusion at a rate known to be therapeutically effective. Aminophylline given at night produced early morning levels in the lower therapeutic range.

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Intravenous salbutamol and aminophylline in asthma —a search for synergy

P D J HANDSLIP, A DART, and B H DAVIES Synergism between B_2 adrenergic stimulants and phosphodiesterase inhibitors has been shown in vitro for histamine release from human leucocytes (Lichtenstein and Margolis, 1968). Synergism has not been conclusively shown between such drugs in their reversal of airways obstruction (Campbell *et al*, 1977; Dyson and Campbell, 1977). In an attempt to show such an interaction we have constructed dose response curves to salbutamol and aminophylline when given separately and in combination.

The patients were 10 well-controlled asthmatics requiring regular inhaled salbutamol, who showed a greater than 15% improvement in FEV_1 after inhalation of 200 μg salbutamol. Each patient recorded PEFR and asthma score for two weeks before investigation. The studies were performed on fasting subjects who had received no bronchodilator therapy for at least eight hours.

On three consecutive mornings each patient was given increasing intravenous doses of salbutamol, aminophylline, or a combination of the two. FEV_1 values were initially recorded until consecutive values were identical. The first drug bolus was then given, and FEV_1 recorded every two minutes until it had fallen back to baseline or a new steady state was achieved. The next bolus was then given. On the fourth morning the response to placebo injection was recorded.

A mean improvement of 13% was produced by 75 mg of aminophylline. Corresponding improvements for 75 μg of salbutamol and a combination of 75 mg aminophylline and 75 μg salbutamol were 18·4% and 20% respectively. Similarly, all other doses used (25, 50, 100, 150, and 200 mg/μg) showed less than complete addition when the drugs were given in combination. The data were also analysed for latency of onset and duration of effect of each bolus.

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Effect of beta-adrenergic blockade and stimulation on respiration

M RUDOLF, J TURNER, G SUMMERS, M ULLAH, C GOOD, and N STANLEY Previous work has suggested that the ventilatory response to CO_2 in normal subjects can be stimulated by salbutamol and depressed by propranolol (Leitch *et al*, 1976; Mustchin *et al*, 1976). Propranolol crosses the blood-brain barrier and is believed to act directly on the medullary chemoreceptor. Other less lipid soluble beta-blockers (oxprenolol and sotalol) might be expected to cause less depression and, in combination with salbutamol, might allow clinically useful central respiratory stimulation while inhibiting undesirable peripheral side effects.

Accordingly a double-blind study was performed on eight subjects; each received on four separate days either placebo, 80 mg propranolol, 80 mg oxprenolol, or 120 mg sotalol by mouth followed after two hours by an intravenous infusion of salbutamol (10 μg/min). Measurements were made of ventilation ($\dot{V}$), CO_2 output ($\dot{V}CO_2$), mixed venous carbon dioxide tension ($P_{\bar{v}}CO_2$), and ventilatory and occlusion pressure responses to progressive hypercapnia before and two hours after drug ingestion, and 15 minutes after starting salbutamol infusion.

None of the beta-blockers altered any of the respiratory measurements. Salbutamol infusion in the absence of beta-blockade produced a 20% increase in ventilatory response to CO_2 and 25% increases in $\dot{V}$ and $\dot{V}CO_2$; $P_{\bar{v}}CO_2$ remained unchanged. No significant changes in $\dot{V}$ or $\dot{V}CO_2$ occurred when salbutamol was given in the presence of beta-blockade.

Our results fail to show any impairment of CO_2 responsiveness by any of the beta-blockers, a finding in agreement with a recent study when propranolol was found to have no effect on the chemical drive to breathing (Patrick *et al*, 1978). Augmentation of resting ventilation by salbutamol is attributable entirely to increased metabolic CO_2 production. Combinations of salbutamol and beta-blockers that allegedly do not cross the blood-brain barrier fail to produce any useful increase in central respiratory drive.

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Clinical implications of the dose independent pharmacokinetics of prednisolone

W A C MCALLISTER, J V COLLINS, and J MORLEY

Prednisolone is commonly used in treating respiratory disease, but only recently have methods been developed for measuring plasma concentrations. In this study we have assessed whether plasma prednisolone concentration varies in direct proportion to dose—that is, if it shows linear kinetics.

Five healthy male volunteers were given single oral doses of 5, 10, 20, 40, and 80 mg of prednisolone in random order with intervals of at least a week between each dose. Subjects fasted overnight and took the tablets at 0800 h. They remained fasting for three hours and refrained from alcohol for 24 hours before and after ingestion. Samples were taken at 0·5, 1, 2, 3, 4, 6, 8, 10, and 24 hours, and plasma was frozen immediately for further assay.

The prednisolone concentrations were measured using a radioimmunoassay as described by Chakraborty *et al* (1976). The area under the plasma concentration time curve was estimated by the Spline-Akima method (Fried and Zietz, 1973) using digital high-speed computer. The areas under the curve were a linear function of the dose administered. Peak plasma concentrations were a linear function of dose. These results may be taken as evidence that prednisolone obeys linear kinetics.

There are several clinical implications that follow from this finding. Firstly, there is a directly proportional relation between plasma prednisolone concentration and dose given. Secondly, the plasma half-life remains the same throughout the dose range. There is, therefore, a predictable increase in plasma prednisolone concentration without lengthening of the half-life at increasing doses. Thirdly, because of its linear kinetics adverse interactions with other drugs are less likely to occur. These facts are borne out by long clinical experience with prednisolone. Finally, variations in clinical response are therefore likely to be due to individual response characteristics of the patient and their disease, rather than to the drug kinetics. This may also be true for the development of side effects, and we are currently studying this problem.

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A radioactive in-vivo assessment of antismoking cigarette filters (MD-4)

NOIRIN F SHEAHAN, D PAVIA, J R M BATEMAN, and S W CLARKE The MD-4 filter has been widely marketed in Britain since 1976 as an antismoking aid whereby the smoker's nicotine dose is gradually reduced over a two-month period. The product consists of four staged, ventilating filters that have proved in vitro to reduce the transmission of smoke. However, no complete in-vivo study has been reported. We have monitored the effect of the filters in a group of smokers using the radioactive gas ^{81m}krypton to trace the entry of smoke into the lung.

^{81m}Kr, a short-lived ($T\frac{1}{2}$=13 s) gamma emitting, inert gas, was carried in air into a cigarette chamber designed so that smoke drawn through the cigarette was evenly laden with ^{81m}Kr. As the subject smoked through an MD-4 filter his whole lung radioactivity, monitored with a scintillation counter, rose proportionately to the amount of smoke entering the lung.

Twelve volunteers smoked cigarettes through the filters and also one cigarette without, in a single-blind cross-over fashion. Smoking parameters were not controlled. The mean whole lung radioactivity for the 12 was reduced by 24%, 37%, 57%, and 63% for filters 1 to 4 respectively, compared to a predicted reduction of 30%, 60%, 70%, and 80% established by the in-vitro study. In the case of filter 1 only the observed reduction was not statistically significant.

The fact that no significant reduction was seen for filter 1 is interesting when one considers that many low tar cigarettes achieve this state (on in-vitro investigation) by about the same degree of ventilation as this filter. In the case of the other filters we conclude that the amount of smoke reaching the lung is reduced, but less so than the manufacturers predict.

Significance of the increased $Paco_2$ observed after administration of pure oxygen to patients with acute exacerbations of chronic respiratory failure

J PH DERENNE, M AUBIER, D MURCIANO, E TOUATY, B FLEURY, M FOURNIER, G DECROIX, and R PARIENTE Acute exacerbations in patients with chronic respiratory failure (CRD) are characterised by severe hypoxia and hypercapnia. The hypoxemia is difficult to correct because the administration of oxygen is often responsible for a pronounced increase in $Paco_2$. This fact is commonly attributed to depression of the respiratory

centre secondary to the removal of the hypoxic stimulus. These patients are considered to be insensitive to carbon dioxide, respiratory control being essentially dependent on a hypoxic stimulus.

We tested this hypothesis on 22 CRD patients by studying their ventilatory response during the first 15 minutes after the administration of pure oxygen. The changes in ventilation were compared to the changes in P_{ACO_2}.

We observed a rapid (mean 72 sec) initial fall in ventilation (ΔV_1) followed by a slower secondary rise (ΔV_2). Minute ventilation was stable after 12 minutes. Mean values for ΔV_1 and ΔV_2 were $21{\cdot}3 \pm 2{\cdot}7\%$ and $14{\cdot}1 \pm 2{\cdot}4\%$ of control ventilation ($P < 0{\cdot}002$). As a result the final ventilation was slightly but significantly less than control ($9{\cdot}4 \pm 0{\cdot}6$ l/min against $10{\cdot}3 \pm 0{\cdot}5$ l/min, $P < 0{\cdot}002$).

There was a linear correlation between ΔV_1 and ΔV_2 ($r = 0{\cdot}67$, $P < 0{\cdot}001$). ΔV_1 represents the hypoxic influence on the respiratory centre, and ΔV_2 is probably an index of the hypercapnic stimulus.

In three subjects minute ventilation was greater on oxygen than on air, but in all 22 patients P_{ACO_2} increased. The average increase was 24 mmHg (range 6–75 mmHg). It was striking that the linear correlation coefficient between change in ventilation and P_{ACO_2} was close to zero ($r = 0{\cdot}06$). Since V_{CO_2} was not significantly modified and since VT and V were little affected by oxygen, the hypercapnia seems to reflect a primarily aggravated ventilation–perfusion mismatch.

Effects of methacholine inhalation in asthmatic subjects on single breath analyses and semi-quantified ^{81m}krypton ventilation scans

D HONEYBOURNE, J W REED, J F COSTELLO, and P HUGH-JONES Patients with acute or induced asthma develop changes in the distribution of ventilation and hence in the ventilation-perfusion balance in their lungs. We compared a mass-spectrometer analysis of a single expirate in such patients (West *et al*, 1957) with the changes seen in the lungs on isotope scanning to determine whether the single breath test reflected the changes in the development of ventilation and blood-flow.

Ventilation scans were performed before and after inhalation of methacholine using ^{81m}krypton, which reflects the ventilation rate per unit volume (Fazio and Jones, 1975). The counts in the gamma camera were stored on a computer and later retrieved and the lung images divided into six areas. The percentage of the total count per unit area was then derived and the pre- and post-methacholine images were compared. The methacholine was nebulised via a Bennett ventilator and inhaled by the patient. The dose of methacholine had been previously assessed to be that which would produce a fall of FEV_1 of at least 20%.

We found a significant change in the slopes of the respiratory exchange ratios and the Argon alveolar plateaus after methacholine indicating a deterioration in the ventilation-perfusion ratio and the inequality of ventilation. The krypton scans showed changes in the percentage of counts per unit area, the upper zones particularly showing a fall in ventilation rate per unit volume in most cases. We conclude that changes in single breath tests in these patients were reflected topographically on the ventilation scans.

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Bronchial histamine receptors in normal, atopic, and asthmatic subjects

NOEMI M EISER, K D MCRAE, and A GUZ Bronchial hyperreactivity to non-specific stimuli is one of the hallmarks of bronchial asthma. Its cause is unknown. This study investigates the possibility that different patterns of H_1- and H_2-histamine receptors may confer different degrees of bronchial reactivity in normal, atopic, and asthmatic subjects. Bronchial challenge with histamine acid phosphate was performed on 18 non-asthmatic and 18 asthmatic subjects. In each group were nine non-atopic and nine atopic subjects. Five breaths of histamine were inhaled from a Hudson nebuliser attached to a breath-actuated "dosimeter." The nebuliser was washed and dried after each dose. The bronchial response was monitored by specific airways conductance measurements in a body plethysmograph. Every three minutes a further dose of histamine was given, double the previous concentration, until a definite response occurred. On separate days histamine challenge was repeated 10 minutes after intravenous injections of either saline; placebo; cimetidine, 200 mg and 400 mg (H_2-receptor antagonist); chlorpheniramine, 20 mg (H_1-receptor antagonist); or cimetidine 200 mg with chlorpheniramine 20 mg.

Intra- and inter-subject comparisons were made with an analysis of variance. A similar pattern of response emerged in all four groups. The histamine response was slightly enhanced by placebo injection, and slightly diminished by cimetidine 200 mg. Neither result achieved significance at the 1% level. Both cimetidine 400 mg and chlorpheniramine, however, significantly shifted the histamine dose-response curve to the right, though the effect of the cimetidine was small in comparison with that of chlorpheniramine. The combination of chlorpheniramine with cimetidine produced a similar shift to that seen with chlorpheniramine alone.

These results suggest that both H_1- and H_2-receptors are present in human bronchi, but that the H_1-receptor predominates. Both types of receptor appear to mediate bronchoconstriction. Since the pattern of histamine receptors in normal, atopic, and asthmatic subjects is similar, the cause of bronchial hyperreactivity in asthmatics remains obscure.

Spirometry induced bronchoconstriction

A D MACKAY, C P MUSTCHIN, and G M STERLING Bronchoconstriction in asthmatic patients after a maximum respiratory manoeuvre is well documented, but there is some discrepancy in reports of its frequency. It has been seen commonly in patients studied using the whole body plethysmograph (Gayrard *et al,* 1975) but relatively rarely using spirometry (Ginemo *et al,* 1972), perhaps in part because of the timing of measurements. Spirometry requires a maximum respiratory manoeuvre, however, and is the method usually used in epidemiological and pharmacological research.

We have seen a young asthmatic patient who showed a profound and reproducible fall in forced expiratory volume in one second (FEV_1) with rapidly repeated measurements—for instance, 10 seconds apart. This fall had not appeared with conventional longer intervals between successive measurements. We therefore decided to re-examine the phenomenon by spirometry.

Eighteen atopic asthmatics, 18 non-atopic asthmatics, ten chronic bronchitics (MRC criteria) with airways obstruction, and 17 normal subjects performed a series of pairs of FEV_1 measurements, with the first and second measurements separated by initially 10 seconds, then 30 seconds, and finally 60 seconds. At least three minutes elapsed between each pair of FEV_1 measurements. Two further pairs of FEV_1 measurements were made at the interval that had produced the greatest fall in FEV_1 ("key interval") to examine the consistency of the response. A correlation with bronchial lability on exercise testing was sought in 18 asthmatic patients. In all patients a further pair of FEV_1 measurements was performed after inhalation of 200 μg salbutamol.

Both atopic and non-atopic asthmatics showed a slight fall in FEV_1 with successive measurements. This was not seen in the normal subjects or chronic bronchitics. Considering the three pairs of measurements at the "key interval" the second FEV_1 was significantly less than the first ($P<0.005$) for both the atopic and non-atopic asthmatic patients. The means and standard errors are shown below:

	Atopic	*Non-atopic*
1st FEV_1	2·66±0·27	1·88±0·17
2nd FEV_1	2·54±0·26	1·78±0·16

A fall in FEV_1 on the second of the two successive measurements is common in patients with asthma. The small size of the fall, however, is unlikely to interfere seriously with spirometry results in clinical testing. Some patients show a larger response and should be excluded from pharmacological trials. Salbutamol diminished or abolished the response. The fall in FEV_1 on rapidly repeated measurements did not correlate with the results of exercise testing.

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Prevalence of functional respiratory symptoms in relation to asthma in young adults

A ARNAUD, P DOR, A BARRE, and J CHARPIN The aim of this study was to estimate the frequency of respiratory symptoms in a population of young male adults, and to analyse the replies to questions relevant to the epidemiological identification of asthma. This study, lasting 10 months, was carried out on 28 000 army recruits in the south of France, 90% of whom were aged between 18 and 21. A self-administered questionnaire taken from the European Coal and Steel Community questionnaire was used under the supervision of a doctor.

Only 0·8% of the completed questionnaires were judged inadequate while over 95% gave unequivocal answers. Fourteen per cent of the subjects said that they had had "wheezing in the chest," 9% had "episodes of shortness of breath with wheezing in the chest," and 6% had "asthma." A positive reply to all three questions was given by 3·4%.

The high prevalence of "wheezing in the chest" may be explained by the highly statistically significant relation between this symptom and smoking. A high prevalence of nasal symptoms was also observed (blocked nose, running nose, repeated sneezing) and was also statistically linked with smoking. In 5% of the population nasal symptoms were related to grass pollen allergy. These results suggest that, in young adults, symptoms that may be mainly attributed to asthma or allergy should be considered in the light of the subject's smoking habits.

Histamine release in experimentally induced asthma and urticaria

M G HARRIES, I M O'BRIEN, and P S BURGE Histamine was assayed by a fluorometric technique in venous plasma after asthma induced by exercise and food and after urticaria induced by heat, food, and aspirin. Seventeen subjects with asthma and six normal controls were exercised by running. Fall in FEV_1 after exercise in asthmatics was 39% (±17 SD) on placebo and 19% (±11 SD) after pretreatment with 40 mg of sodium cromoglycate given by inhalation. Samples were taken through a catheter every five minutes after exercise of 30 minutes and then every 10 minutes for a further 30 minutes. The mean rise in plasma histamine 10 minutes after exercise was 0·21 ng/ml (±0·4 SEM), thereafter plasma histamine fell below control levels in all cases reaching a minimum of −1·5 ng/ml (±0·57 SEM) after 25 minutes and −0·75 ng/ml (±0·51 SEM) after 60 minutes. The rise in histamine in whole blood was 31·25 ng/ml (±4·3 SEM) reaching a peak 10 minutes

after exercise at a time when the absolute basophil count was at its peak of 241 (±49/mm³ SEM).

Five subjects with asthma induced by foods were each challenged at least twice and showed a readily reproducible asthmatic response but a change in plasma histamine of no greater than 0·2 ng/ml (±0·22 SEM) throughout the challenge despite a fall in FEV_1 of greater than 30% on each occasion.

By contrast, three subjects with urticaria only, one induced by heat, one by chocolate, and one by aspirin, showed rises in plasma histamine of 12 ng/ml, 6·1 ng/ml, and 16·2 ng/ml respectively. In each case the rise in histamine was concomitant with the rash both in timing and degree.

Discharge of mast cells or basophils as shown by a rise in blood histamine is not necessarily associated with an asthmatic reaction, rather it is associated with the development of urticaria.

Relationship of month of birth with asthma and allergy

JOHN MORRISON SMITH and V H SPRINGETT Analysis of the month of birth of 1715 children with asthma shows clear evidence that a higher proportion (54·8%) were born between May and October when compared with the population of England and Wales (50·2%). The distribution of month of birth for patients with hay fever and for patients with positive skin reactions to grass pollen does not account for the finding. This is in keeping with previous work (Morrison Smith, 1970). Of the children with positive skin reactions to *Dermatophagoides pteronyssinus*, a higher proportion (56·2%) are born between May and September. These findings differ from previous reports by Björkstén and Suoniemi (1976) and Pearson *et al* (1977).

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Clinical and immunological features of patients with cryptogenic fibrosing alveolitis and associated digital vasculitis

MARGARET E HODSON, PATRICIA L HASLAM, S G SPIRO, and MARGARET TURNER-WARWICK The clinical features of 12 patients with cryptogenic fibrosing alveolitis (CFA) who also have digital vasculitis (DV) will be described. The vasculitis did not improve in the 10 patients who were treated initially with steroids, but five cases responded to immunosuppressants and four to penicillamine. Two patients had some features of scleroderma, two of polymyositis, and five had a polyarthritis. Ten patients had none of the generally accepted clinical features of scleroderma and in particular three patients had no associated features.

Detailed immunological studies on this group of patients will be reported and contrasted with findings in a group of patients with CFA and no associated DV or other systemic features ("lone" CFA). There was no significant difference in the prevalence of immune complexes shown by Clq binding in the group with DV (50%) and the group without (41%). A raised IgM (66%), however, was found in the DV group compared with 35% in the group with "lone" CFA ($P<0·01$). The finding of six speckled or nucleolar antinuclear antibodies (ANA) in the group with DV, five of which were in patients with no features of scleroderma, is of considerable interest. The overall incidence of ANA in CFA is 36·5%, but of speckled and nucleolar ANA is only 6·2% (Haslam and Turner-Warwick, 1971). The immunoglobulin class, RNAase, and DNAase sensitivity of the ANA in the group of CFA with DV will be reported. A high incidence of speckled ANA was also found by Sharp *et al* (1972) in patients with "mixed connective tissue disease" who were liable to Raynaud's phenomenon leading to gangrene of multiple digits.

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Pulmonary function in Crohn's disease

P PASQUIS, P BAPTISTE, PH DENIS, R COLIN, and R LEFRANCOIS Pulmonary function has been studied in 28 patients with Crohn's disease (14 men, 14 women; mean age 32). The ileum alone was affected in 10 patients and the colon in 18 with distal involvement in seven cases. The age at onset of colitis, sex, length of history, and disease activity index (Best, 1976) were similar whatever the predominant site of involvement.

The following parameters were measured in each patient: lung volumes, functional residual capacity (FRC) determined both by plethysmographic and helium dilution methods, lung compliance, pulmonary diffusing capacity using a steady state method, and arterial blood gases at rest.

The patients fell into three groups: (1) 10 patients in whom lung function was unaffected; (2) six patients in whom lung compliance and pulmonary diffusing capacity were decreased ("fibrosis"); and (3) 12 patients in whom FRC was increased ("hyperinflation"). The three groups did not differ according to age and sex but fibrosis and hyperinflation were significantly more frequent in the 18 patients with colonic involvement than in the 10 patients with ileal involvement ($P<0·05$). Fibrosis patients were significantly younger at the onset of colitis ($P<0·05$) than patients in the other two groups, and the frequency of smoking was greater ($P<0·05$). Hyperinflation patients were investigated during an attack of colitis, and their disease activity index was significantly greater ($P<0·001$) than the index of the other two groups. Repeat lung function investigations remained unchanged in four fibrosis patients after several weeks or months whereas it was normal after remission in eight hyperinflation patients.

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Immune complexes in sarcoidosis

N MCI JOHNSON, M W MCNICOL, E J BURTON-KEE, and J F MOWBRAY The sera from 50 patients with sarcoidosis have been examined for the presence of immune complexes using polyethylene glycol (PEG) precipitation followed by single radio-immuno diffusion (SRID) to measure Clq, IgG, IgM, or IgA (Nydegger *et al*, 1974). Serum Clq, C_3, and immunoglobulin concentrations were estimated by SRID. CH_{50} was measured by standard functional assay using sensitised sheep red cells.

Immune complexes were detected in 29 patients (58%). No correlation could be found between the presence of these complexes and the length of history, stage, or activity of disease, or steroid therapy. In patients with extrathoracic sarcoidosis, especially skin or joint disease, complexes were commonly found.

Rheumatoid factor was detected in 14 patients, in 13 of whom circulating complexes were also detected. Although there was no correlation between the presence of rheumatoid factor and length of history or stage of disease, 12 of the 14 patients suffered from active disease.

CH_{50} and the serum concentrations of Clq, C_3, IgG, IgM, and IgA did not differ significantly from those of a control group. Our findings will be compared with those of previous studies using different methods (Gupta *et al*, 1977, Daniele *et al*, 1978), and the significance of immune complex and rheumatoid factor in sarcoidosis will be discussed.

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Plaque-forming response of rabbit lymphoid tissues to sheep erythrocytes after intratracheal immunisation

M FOURNIER, F VAI, D CHOUDAT, E TOUATY, and R PARIENTE An experimental model was developed in the rabbit to isolate lymphocytes from spleen, bronchoalveolar spaces, bronchi, and tracheobronchial lymph nodes. The immune response to sheep erythrocytes after intratracheal immunisation was investigated using a haemolytic plaque assay as a function of time after immunisation and as a function of the dose of antigen administered. The overall kinetics of response were similar to those observed in other animal species with a maximum at the fifth day after immunisation. The number of specific antibody forming cells per 10^6 lymphocytes depended on the lymphoid tissue studied, with a constant decreasing order: hilar lymph nodes, bronchi, spleen, and alveolar spaces. The specific response increases with the dose of antigen administered, the spleen becoming the most responsive tissue with the highest doses.

Weight loss and thyroid function in emphysema

D M GEDDES, D C LINCH, S J SKEATES, and P R DAGGETT The emphysematous pink puffer tends to be underweight and is often thought clinically to be thyrotoxic. We have therefore studied the hypothalamic-pituitary-thyroid axis, urinary catecholamines, and dietary intake in 11 patients with emphysema (type A) and compared them with matched chronic bronchitics (type B).

Serum thyroid hormone levels, ^{131}I neck uptake, catecholamine excretion products, and diet were all within the normal range for both groups. The TSH response to injected TRH was significantly less in type A than type B patients (table) and nine of the 11 had subnormal responses. In the absence of pituitary or thyroid disease the most likely explanation for these findings is an abnormality of catecholamines. A flat TRH test has been reported during dopamine infusion (Besses *et al*, 1975) and in association with phaeochromocytoma. The pulmonary circulation inactivates circulating dopamine and noradrenaline (Gillis and Roth, 1977) as well as other vasoactive amines. In emphysema the pulmonary circulation is severely attenuated, so excess catecholamines may reach the systemic circulation. If this explanation is correct it could also apply to other clinical features of emphysema, such as weight loss and increased respiratory drive.

Time (min)	*Type A*	*Type B*	P
0	< 0·5	1·8∓1·4	< 0·01
20	2·0∓1·5	6·8∓4·6	< 0·01
40	2·2∓2·4	6·9∓5·2	< 0·01
60	1·4∓1·5	5·2∓5·5	< 0·02

Serum TSH mU/L ± SD after 200 mg TRH IV.

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Thoracoabdominal motion and pressures during tidal breathing

N J BRENNAN, A J R MORRIS, and MALCOLM GREEN We have studied chest wall configuration during tidal breathing in five normal subjects, five patients with emphysema, and five patients with pulmonary fibrosis. We measured anteroposterior diameters of the ribcage (RC_{AP}) and abdomen (ABD_{A-P}), and lateral diameters of the ribcage at high (RC_{HL}) and low (RC_{LL}) levels, using linearised magnetometers, with simultaneous

recordings of oesophageal (Poe) and gastric (Pg) pressures, and volume (V) at the mouth.

In normal subjects inspiratory and expiratory movements of about equal magnitude occurred in all diameters in phase with volume. In patients with emphysema ABD_{AP} and RC_{AP} increased in phase with volume but RC_{HL} and RC_{LL} paradoxically decreased during inspiration, reflecting distortion of the ribcage configuration. In contrast, patients with restrictive lung disease increased RC_{LL} and ABD_{A-P} during inspiration while RC_{HL} and RC_{AP} excursions were considerably reduced.

It appears that in emphysema, the diaphragm, which is low and flat, tends to pull the low lateral ribcage paradoxically inwards during inspiration, while in restrictive lung disease the normal curvature of the diaphragm is maintained, and its action results both in lower ribcage expansion and in diaphragm descent with outward abdominal displacement.

These findings suggest that movement of the chest wall over the tidal range depends on its configuration, and that different groups of respiratory muscles act at different lung volumes. Thus at low lung volumes (restrictive lung disease) tidal ventilation is effective with diaphragmatic activity alone. In the normal range there is a diaphragmatic and intercostal component to tidal ventilation. At high lung volumes (emphysema) ribcage expansion is achieved by intercostal and accessory muscle activity while the diaphragm has a paradoxical action on the ribcage thus reducing its effectiveness.

Pulmonary abscess due to Torulopsis Glabrata

J COLONNA, MME M L CHATOT, A BETTENDORF, R POIRIER, J P KLEISBAUER, and P LAVAL After a case of pulmonary infection due to *Torulopsis glabrata* we reviewed published reports and found ours to be the ninth reported case to date. *T glabrata* is a yeast member of the Cryptococcacae family and occasional commensal of the upper respiratory and digestive tract, lower urinary tract, and vagina. Identification is possible using morphological and biochemical criteria.

Treatment of this frequently fatal disease relied previously on amphotericin B but the more recent utilisation of flucytosine has dramatically changed the prognosis. The occurrence of this yeast will undoubtedly increase as the use of corticosteroids and antibiotics becomes more widespread.

Electron microscopic study of diagnosis of anaplastic bronchogenic carcinomas presumed to be oat cell carcinomas

F BLANCHON, B MILLERON, F CHATELET, J ROLAND, G AKOUN, and H BROCARD Bronchogenic oat cell carcinoma is difficult to diagnose when undifferentiated or very poorly differentiated. Electron microscopy has shown the presence of secretory granules in the cell cytoplasm of oat cell carcinoma. Since chemotherapy can lead to complete remission in oat cell carcinoma we have compared histological features on electron microscopy with the results of treatment.

The 20 bronchogenic carcinomas selected for study had histological features on bronchial biopsies suggesting a possible diagnosis of oat cell carcinoma. The samples were then submitted to electron microscopy. The study investigated the correlation between the presence of secretory granules and the therapeutic results.

This study showed secretory granules on electron microscopy, both when optic microscopy had suggested a probable oat cell carcinoma and also when the diagnosis was an undifferentiated carcinoma. The response to chemotherapy suggests that undifferentiated carcinomas with secretory granules show the same response to chemotherapy as carcinomas diagnosed as oat cell carcinomas on optic microscopy.

Comparison of histological results from needle biopsies and surgery

M C PEARSON and R GOLDING Needle biopsy is an accepted technique in the preoperative diagnosis of malignant lesions in the thorax. To assess if this method could accurately predict specific malignant cell types, biopsy and surgical results were compared.

Between 1973 and 1978, needle biopsies were performed on 316 patients at the London Chest Hospital. Tissue was obtained in all cases. Subsequently 117 (37%) patients underwent surgery, and these comprise the group under review.

The histological report of the biopsy was compared with the surgical specimen with the following results.

Malignancy reported—(a) same specific cell type reported in both biopsy and surgical specimens 55%; (b) different cell types reported on biopsy and surgical specimens 9%; and (c) cell type unspecified on biopsy specimen 18%.

No malignancy reported—18%.

As it has been suggested that patients with oat cell carcinoma should not undergo resection but should receive chemotherapy (Fox and Scadding, 1973) the incidence of this cell type in the potentially operable group of patients has been reviewed. An accurate preoperative diagnosis of oat cell carcinoma was made in six patients while the biopsy diagnosis was either incorrect or missed in five patients. Though this group of patients is small, it is considered that on the evidence available a thoracotomy should not be denied to a patient who is potentially operable on the basis of a needle biopsy diagnosis of oat cell carcinoma. Where no malignancy was reported on the biopsy specimen, however, 14 (12%) patients were shown to have malignant lesions at thoracotomy. Though this technique will indicate a specific cell type correctly in only 55% of patients, it does have an 88% accuracy in determining a preoperative diagnosis of malignancy.

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Value of sequential fibreoptic bronchoscopy in the therapeutic assessment of small (oat) cell carcinoma

P G MORGAN, P HARPER, R L SOULAMI, D G GEDDES, M E HODSON, and S G SPIRO Survival data after chemotherapy or radiotherapy to small cell carcinoma of the bronchus have shown that patients who achieve a complete remission as judged by clinical examination and radiological techniques are most likely to survive longest. A continuing problem in the treatment of this disease, however, is tumour recurrence at the original primary site. To assess the validity of clinical and radiological findings we have performed sequential bronchoscopies on 16 patients whose small cell carcinoma was originally diagnosed at bronchoscopy. The patients were given a 14-week induction course of combination cytotoxic chemotherapy and then underwent another bronchoscopy. Ten patients had clinical or radiological evidence suggesting a complete response, and the remaining six had only partial regression of tumour (50% decrease in two diameters of measurable tumour mass). Of the ten complete responders, two had tumour visible at the original biopsy site. Of the remaining seven, three had abnormal mucosal appearances; histology showed no evidence of small cell carcinoma, but subsequently all three patients died from recurrence at this primary site. In the remaining four complete responders there was no visible abnormality, histology was normal, and to date tumour has not recurred. Of the six partial responders, tumour was visualised and identified histologically at the primary tumour site.

We would recommend that fibreoptic bronchoscopy is mandatory in assessing the response of small cell carcinoma to treatment and, further, it should be performed at any critical stage in the treatment of the disease when it is considered that the patient is failing to respond to treatment.

Sterilising activity of isoniazid and pyrazinamide in combination with rifampicin in experimental tuberculosis of the mouse

J GROSSET, CH TRUFFOT, C BOVAL, and J FERMANIAN Two hundred and fifty female Swiss mice, 28 days old, were inoculated intravenously with $1{\cdot}1\times10^6$ cfu of *Mycobacterium tuberculosis*, H37Rv strain, subcultured in Dubos liquid medium. After 14 days without treatment all mice were treated for three months with 25 mg/kg isoniazid (H) plus 10 mg/kg rifampicin (R) given six days a week by mouth. At the end of the third month the mice were randomly allocated to three different continuation regimens—namely R alone, RH, or RH+150 mg/kg pyrazinamide (Z) given six days a week until the end of the sixth month. After a follow-up of six months without treatment the mice were killed and their lungs and spleens cultured on Löwenstein-Jensen medium to assess the sterilising effectiveness of each regimen.

The number of culture-positive animals did not differ significantly for any continuation regimen: 35 out of 53, 31 out of 52, and 32 out of 55 respectively with the R, RH, and RHZ regimens. There is no evidence that H and Z contributed to the effectiveness of the R in the continuation phase of chemotherapy in mouse experimental tuberculosis. It is not possible to say whether the same conclusions apply to chemotherapy in man.

Day hospital for patients with respiratory disability—assessment after one year

P LEVI VALENSI, H DEHU, D SAINFEL, B GRANDSIRE, and J F MUIR In 1977 we opened an outpatients department of five beds for patients with chronic obstructive lung disease to be used for diagnostic procedures and to improve control of treatment. Patients with less severe respiratory disabilities, such as asthma, come for diagnostic reasons (24·4%) and the more severe patients for control (75·6%).

This outpatient facility has not decreased the numbers of outpatient consultations, but it does permit increased activity in the unit, with the same number of nurses, doctors, and equipment (2225 patients in 1976—3091 in 1978). Although it costs more than an ordinary consultation it appears to be of benefit psychologically and with better follow-up there should be fewer admissions to hospital.

Immotile cilia, bronchiectasis, and abdominal situs inversus

J J LAFITTE, O FABIOCCHI, A B TONNEL, C VOISIN, E PUCHELLE, and M MAZZUCA Kartagener's syndrome includes situs inversus, chronic sinusitis, and bronchiectasis. Afzelius *et al* (1975) showed that the syndrome was related to cilial immobility and suggested that the lack of dynein arms was the basis of the ciliary dysfunction. We report a case of a woman with bronchiectasis, sinusitis, and abdominal situs inversus. This association is similar to Kartagener's syndrome.

Ultrastructural studies of cilia from the nasal and bronchial mucosa showed a lack of dynein arms with complete disorganisation of the outer doublets in numerous cilia. In addition extra tubules were observed in several cross sections of cilia and the orientation of respiratory cilia was found to be random. The rate of transport of radioactive amberlite particles in the tracheobronchial tree was reduced.

In our case two main abnormalities were associated; one corresponds to the lack of dynein arms described by Afzelius (1976) and the other is a complete displacement of the axoneme components. This could be due to a defect of radial spokes (Sturgess *et al*, 1979). Our findings indicate the complex congenital pathology of ciliary structures which can underly chronic sinobronchial disease.

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Immotile syndrome in infants and children

A GRIMFELD, G TOURNIER, P JOUANNET, J P BISSON, J L SALOMON, A BACULARD, and J GERBEAUX As shown by Afzelius (1976) and Pedersen (1976), the Kartagener syndrome is related to an ultrastructural defect resulting in immotility of cilia. Ultrastructural investigations showed first a lack of dynein arms and later a lack of central radial spokes (Sturgess *et al*, 1979). Both these structures are considered necessary for the movement of cilia. Another important fact also mentioned by these investigators was the occurrence of similar defects in the cilia of patients without situs inversus.

The purpose of the present study was to examine the motility and ultrastructure of respiratory cilia in children with subacute or relapsing suppurative bronchitis of unknown origin, whether or not it was associated with situs inversus.

The first group studied consisted of six children, two girls and four boys aged from 2 to 11 years. Five had situs inversus, of whom two were siblings. The one child without situs inversus, a 4-year-old boy, belonged to a sibship with Kartagener syndrome. The second group contained five children with chronic suppurative bronchitis of unknown aetiology but without situs inversus or a family history of Kartagener syndrome.

The mucosal samples were collected through bronchial brushing or biopsy. They were placed immediately in cell culture media (INRA-Menezo-B2 Api system SA) and studied within three hours by light microscopy (Nachet NS 400 magnification ×40). Ciliary movements were checked with a movie camera under interferential light (Bolex movie camera 16 mm H 16 SBM- speed 24 and/or 50 pictures/second). Another sample was immediately fixed (6·5% glutaraldehyde in buffer Söresen) and prepared for electron microscopic study.

All six children in the first group had definite ciliar immotility while all five patients in the second group had normal cilial motility. Cilial ultrastructural defects were also observed, both the hereditary defects as previously described but also possible acquired abnormalities.

The results suggest that bronchial ciliary motility should be investigated through light microscopy when investigating infants and children with chronic or relapsing suppurative bronchitis. The examination is simple and fast with well-trained technicians. Ultrastructural cilial defects should be looked for as well and to complete the studies, scintigraphic analysis of mucocilial clearance is suggested.

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Use of potentiating agents in megavoltage therapy for localised carcinoma of the lung not treated by surgery

R A GUERIN A five-year survival of 20% without local recurrence, or metastases, or both, was obtained after radiation therapy alone. This figure is slightly inferior to the survival rate of surgically treated tumours. Failure is mostly due to the appearance of metastases after radical treatment despite additional chemotherapy, immunotherapy, or both. Experience has shown that certain cancers controlled locally by radiation therapy can recur three, five, eight years or more later. Two thirds of squamous cell carcinomas are sterilised with doses of 60 gray (Gy) (1Gy=100 rads).

A dose of 80–90 Gy has a greater curative effect on tumours usually unresponsive to doses of 60 Gy. But this level of radiation results in significant damage to normal tissue with unacceptable complications. Even with such doses, quiescent cells and hypoxic cells remain unresponsive. These cell populations are both clonogenic later. Megavoltage therapy must therefore be associated with chemical and physical radiosensitising agents (for example, hyperthermia and drugs of the nitro-imidazole group).

Treatment protocols should fully exploit the biological effects of chemotherapy—recruitment, cell synchronisation, and synergistic lethal effect.

The biological effects of neutrons on hypoxic cells should also be explored, as most of the latter respond to neither X nor γ therapy. Overall, new treatment strategies must seek to complement the specific biological effects of radiotherapy with chemotherapy and radiosensitising agents (chemical, or physical, or both). The goal is a 10% growth rate in the cure of squamous cell carcinomas.