Thorax, 1979, **34**, 414–429

Proceedings of the Thoracic Society

A Meeting of the Thoracic Society was held in London on 1–2 February 1979. Summaries of the papers follow:

Drug-induced oesophageal injury

H R MATTHEWS, F J COLLINS, S E BAKER, J STRAKOVA

Oesophageal injury from therapeutic agents has been reported with increasing frequency and with an increasingly wide range of drugs since 1970. We report a recent case of oesophagitis due to emepronium bromide (Cetiprin) at the Queen Elizabeth Hospital, Birmingham, and review all the reported instances of oesophageal damage caused by this and other drugs.

A 15-year-old school girl developed severe pain and difficulty on swallowing two months after starting emepronium for mild urinary incontinence. A barium swallow was normal but endoscopy showed severe ulcerative oesophagitis at the level of the aortic arch. There was no other oesophageal abnormality. Special radiological and manometric studies established a connection between the drug and the oesophageal lesion, and complete healing occurred on withdrawal of the drug.

Forty-one other cases of oesophageal damage due to eight different drugs have been reported, with nine drug-related deaths. The clinical and pathological features of these are reviewed in the hope of avoiding further instances of yet another iatrogenic disease.

Immediate and late consequences of heroin-induced pulmonary oedema

W W ADDINGTON, A S BANNER, E V SUNDERRAJAN, M K AGARWAL, and J RODRIGUEZ

The arterial and mixed venous ($P_{\bar{v}}O_2$) blood gases and haemodynamic state of six patients with heroin induced pulmonary oedema (HIPO) were evaluated by Swan-Ganz catheterisation within three hours of admission to hospital. The FIO_2 was 1·0. The mean and range of the group as a whole and the data of the two patients who died are shown:

	Mean	*Range*	*Died*
pH	7·33	6·89–7·47	6·89, 7·02
Pao_2 (mmHg)	192	34–349	34, 65
$Paco_2$ (mmHg)	40	29–65	29, 65
HCO_3 (mEq/L)	20	13–26	13, 16
$P_{\bar{v}}O_2$ (mmHg)	42	23–59	23
BP (mmHg)	123/70	60/40–150/100	60/40, 140/100
RA (mmHg)	5·3	2–10	5, 10
PA (mmHg)	27/10	20/4–40/15	25/4, 30/15
PCW (mmHg)	9·5	5–16	10, 16

Hypoxaemia was due mainly to increased venous admixture and the haemodynamic data are typical of non-cardiac pulmonary oedema. The two patients who died were different from the survivors in having severe metabolic acidosis, a very low $P_{\bar{v}}O_2$, and, in one patient, systemic hypotension.

In a separate group of seven patients, referred because of productive cough and dyspnoea, bronchograms were performed at least nine months after an episode of HIPO. The chest radiographs were minimally abnormal and did not suggest significant airway disease. In every patient extensive bronchiectasis was recorded. Generalised bronchiectasis was found in four patients while in the others findings were confined to the lower lobes. Abnormalities consisted of varicose or cylindrical bronchiectasis or both in all patients and cystic changes in three. Pulmonary function tests showed airflow obstruction, restriction, and impaired co transfer.

In summary, the immediate consequences of HIPO are non-cardiac pulmonary oedema, severe hypoxaemia, metabolic acidosis, and death. A late consequence is bronchiectasis, which may be a common finding in symptomatic heroin addicts months to years after recovery from HIPO.

Clinical, radiological, and pulmonary function assessment in 13 long-term survivors of paraquat poisoning

G R FITZGERALD, G BARNIVILLE, R T N GIBNEY, and M X FITZGERALD

Death from ingesting the herbicide paraquat usually results from severe hypoxaemic respiratory failure, secondary to characteristic diffuse intra-alveolar fibrosis. We studied 13 patients (11 adults and two children) who had survived a recorded episode of paraquat poisoning for at least one year to determine the prevalence of residual pulmonary disability. Of the 11 adults, five (all non-smokers) had no clinical, radiological or functional evidence of pulmonary disease. A further four patients (all smokers) were considered normal on clinical and radiological criteria but had a mild deficit in pulmonary function, as evidenced by slight reduction in FEV/VC ratio and/or marginally reduced arterial oxygen tensions in the resting recumbent position, the latter values improving on exercise. This physiological deficit could reasonably be attributed to the effects of cigarette smoking, but a paraquat effect could not be ruled out. The remaining two adult patients had pronounced arterial hypoxaemia. Both were known to have respiratory disability antedating paraquat poisoning, but one patient showed new and persistent pulmonary infiltrates that could be ascribed to permanent paraquat lung damage. Finally, two young children had normal clinical, radiological, and simple pulmonary function indices. We conclude that most patients surviving an episode of paraquat

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poisoning have no clinically significant residual pulmonary damage. Based on serial radiological studies before and after paraquat poisoning in one patient, there is some evidence to suggest that permanent lung damage can occur occasionally.

Pulmonary vasoconstriction and oedema caused by tricyclic antidepressants in animals

G W GILL, GWENDA BARER, and D E SHIERS Fatal respiratory changes resembling those of the respiratory distress syndrome have occurred after amitriptyline overdose (Lindström *et al*, 1977). The tricyclic antidepressant compounds are concentrated in the lung and only slowly removed. We have found in animals that amitriptyline, iprindole, and imipramine in large doses cause pulmonary vasoconstriction, bronchoconstriction, and oedema.

Twenty-eight anaesthetised open-chested cats on artificial ventilation had one lobe of lung separately ventilated and perfused at constant flow with blood drawn from the right atrium. Lobar inflow and bronchial and left atrial pressures were measured. Amitriptyline (2–5 mg), iprindole (2–5 mg), and imipramine (1–6 mg) caused large often long-lasting rises in inflow pressure and smaller rises in bronchial pressure; left atrial pressure hardly changed. The inflow pressure was delayed until the fall in systemic pressure was maximal, suggesting that it might be secondary to release of a vasoactive substance in the lung. We used inhibitory drugs to investigate this possibility, but the experiments were not entirely satisfactory since repeated doses of tricyclics showed tachyphylaxis. Nevertheless, pulmonary vasoconstriction and oedema still followed doses of iprindole when an antihistamine, an α-adrenoreceptor blocker, a serotonin blocker, and prostaglandin synthetase inhibitors had been given (chlorpheniramine, phentolamine, methysergide, aspirin, indomethacin, and flurbiprofen). The reaction is intrinsic to the lung as we observed pulmonary hypertension and oedema after all three tricyclic drugs in isolated rat lungs perfused with blood.

The reaction is probably not due to platelet aggregation as an in vitro test showed that these drugs caused deaggregation of platelets aggregated by ADP.

Investigation of these acute changes may help explain the slow progressive changes after concentration of the drugs in the lung in cases of poisoning, which are increasing in number.

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Occupational asthma, rhinitis, and urticaria in a research establishment breeding locusts

P S BURGE, G EDGE, I M O'BRIEN, M G HARRIES, and J PEPYS Locusts are now widely used in schools for teaching biology and in universities for research. Frankland (1953) described occupational asthma in two scientists from each of two research establishments. We describe a prevalence study in one of these establishments, where the two original cases were still working 24 years later. The study lasted six weeks. A respiratory questionnaire was administered by one of three interviewers who also recorded FEV_1 and FVC before and after 200 μg salbutamol by inhalation. Workers were skin prick tested to six common environmental antigens as well as antigens derived from locusts, and blood was obtained for antibody estimations.

The workers were divided into four exposure groups depending on their current job: (1) workers handling insects in the laboratory, (2) field workers, (3) other laboratory scientists, and (4) administrators, etc. Group 2 workers were seen only if they were in England during the survey. This included two thirds of group 2 workers, and is likely to be an unbiased sample of them. All but one of groups 1, 3, and 4 workers were seen.

Work-related respiratory disease was defined as breathlessness, wheeze, or tightness in the chest that improved during a weekend away from work. It was largely confined to group 1, where 28% were affected. Work-related rhinitis was more widespread, with 41% of group 1 workers affected. Clinical sensitisation was present in three workers before employment at the centre; 16 of the remaining 20 workers were sensitised within the first three years of employment. Atopy (one or more positive skin prick tests to common environmental antigens) was found to predispose to respiratory disease, particularly in group 1 workers, where 47% of atopics and 18% of non-atopics were affected. FEV_1 was reduced in those with work-related asthma compared with the normal workers.

Specific antilocust antibodies correlated with exposure and disease. Positive skin prick tests were found in 43% of group 1 workers and 27% of group 4 workers. Of 100 consecutive patients in our allergy clinic 28% also had positive skin prick tests to locust antigens. There are probably cross-reacting antigens between insects and mites, which might lead to continued symptoms in affected workers after occupational exposure has ceased.

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Tuberculin-negative tuberculosis in children with positive cultures for M tuberculosis

P STEINER, M RAO, MINERVA S VICTORIA, H JABBAR, and M STEINER Results of repeated 5 TU PPD-S tuberculin tests on 200 children with culture-proved *M tuberculosis* infection showed that 28 initially were negative reactors to the Mantoux test. Seventeen of them had extensive or overwhelming tuberculous disease at the initial testing. Seven of these patients were reactive to 250 TU PPD on admission, and all of the survivors (15) subsequently became positive reactors to 5 TU PPD-S after receiving antituberculosis treatment. Eleven patients who did not have life-threatening or serious forms of tuberculosis were

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negative reactors to 5 TU PPD, 250 TU PPD, and the non-tuberculous mycobacterial antigens, PPD-A (Avium), PPD-B (Battey), PPD-G (Gause) on admission and remained non-reactors to these antigens. These patients were retested monthly until discharge from hospital (three to six months).

There was an explanation for the negative reactor state of only two of these 11 children—one had leukaemia and the other sarcoidosis. There was no ready explanation for the persistent negative reactor state in the remaining nine children. It is concluded that a small percentage of children (4·5%) with non-threatening forms of tuberculosis may be negative tuberculin reactors despite no apparent cause. In such instances other procedures must be used, such as lymphocyte transformation, biopsy, and culture, to establish the diagnosis of tuberculosis.

Geographical distribution of mycobacteria other than M tuberculosis in the eastern United States

H GRUFT, J FALKINHAM, and B PARKER The epidemiology of *Mycobacterium intracellulare* infection is still unknown. Because the frequency of skin sensitivity to PPD-B in the USA is higher in the south-eastern coastal region, it has been suggested by Gruft, Katz, and Blanchard that the micro-organism resides in the ocean and estuaries of the southeastern USA and is transmitted to man via wind-blown water droplets formed during wave formation and rain.

To test this hypothesis we surveyed fresh, brackish, and ocean waters in the eastern USA. Samples were collected from lakes, inland rivers, brackish rivers, sounds, bays, and ocean waters off the Atlantic coast from Maine to Florida and along the Gulf of Mexico from Florida to Louisiana.

To date about 90% of the 850 strains of acid-fast bacilli isolated have been identified; the relation between their distribution and several other variables has been studied.

The acid-fast bacilli isolated from Gulf coast and southern Atlantic coast samples were predominantly members of the *M avium-intracellulare-scrofulaceum* (MAIS) complex (82% and 70% respectively). Non-MAIS mycobacteria were found in the waters of Florida and the northeastern USA in 76% and 89% of the samples, respectively. No bacilli from Runyon's group I or IV were isolated from any samples. Although only 30% of ocean waters of high salinity were positive for acid-fast bacilli, 40% of the positives contained MAIS. MAIS also predominated in brackish waters—especially those with 1 to 2% salinity—while the other mycobacteria predominated in other waters.

Studies are currently under way in our laboratory to examine the tolerance of these water isolates to salt and to detect any characteristic that may reflect special preference for any ecological niche.

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Beta-adrenergic responsiveness in asthmatic and atopic non-asthmatic subjects

J E HARVEY and A E TATTERSFIELD The development of diminished bronchial beta-adrenergic responsiveness, or resistance, from excessive bronchodilator aerosol usage, has been suggested as a possible cause for the increase in asthma mortality in the 1960s (Connolly *et al*, 1971). Most clinical studies in asthma have not supported this suggestion. The development of resistance to the bronchodilator effects of inhaled salbutamol, however, has been clearly shown in normal subjects taking large doses of regular beta-agonists (Holgate *et al*, 1977).

Using a similar technique and dosage schedule to Holgate *et al* (1977) we have now studied eight atopic, asthmatic subjects and six atopic subjects with no clinical or symptomatic evidence of asthma. Specific airway conductance was measured in the body plethysmograph, and dose-response curves to inhaled salbutamol (10–600 μg) were constructed. After baseline studies the subjects took regular, inhaled salbutamol, increasing from 100 μg four times a day during the first week to 500 μg four times a day during the fourth week. Dose-response studies to inhaled salbutamol were repeated after each week.

In contrast to the findings in normal subjects, we found no reduction in the response to salbutamol after the month of salbutamol treatment, either in asthmatic or atopic subjects. We also studied the responses to histamine inhalation and the protection afforded by inhaled salbutamol to histamine challenge during the control period and again during the fourth week of salbutamol treatment. Neither group showed any suggestion of salbutamol resistance after four weeks' treatment.

Studies of diurnal peak expiratory flow rate patterns before and after four weeks on salbutamol showed no significant changes in either group. There was, however, a consistent fall in baseline FEV_1 in the final week of the study, in both the asthmatic and the atopic group, though salbutamol responsiveness was maintained.

These studies show no evidence of diminished beta-adrenergic responsiveness in either asthmatic or atopic non-asthmatic subjects after large doses of inhaled salbutamol. The difference between these results and those obtained in normal subjects suggests differences in beta-receptor function.

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Effect of ipratropium bromide (Atrovent®) and terbutaline (Bricanyl®) on mucociliary clearance and pulmonary function in chronic obstructive bronchitis

D PAVIA, J R M BATEMAN, NÓIRÍN F SHEAHAN, and S W CLARKE The effects of regular administration (two puffs four times a day for seven days) of a synthetic anticholinergic ipratropium bromide (Atrovent®), and a

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beta$_2$-adrenergic, terbutaline (Bricanyl^R), on lung mucociliary clearance and as bronchodilators were ascertained in a controlled, double-blind, cross-over study in seven patients (six male, one female) with chronic obstructive bronchitis.

The mean (±SD) age and height of the study group were 62·9 (±8·9) years and 1·70 m (±0·08) respectively. Six were current cigarette smokers and one was an ex-smoker with a mean (±SD) tobacco consumption for the group of 53 (±23) pack-years. The mean±SD pulmonary function indices for the group with the percentage of predicted values in parentheses were FEV_1: 1·22±0·58 l (44±15%); FVC: 2·56±0·52 l (73±20%); FEV_1/FVC: 44±14%; and PEFR: 174±91 l min^{-1} (37±20%). The mean (±SD) increase in FEV_1 after the inhalation of two puffs (1 mg) of isoprenaline administered from a metered dose inhaler was 30 (±24)%.

Two puffs from a metered dose inhaler of either Atrovent^R-placebo (propellants only), Atrovent^R (40 μg), Bricanyl^R-placebo (propellants only), or Bricanyl^R (500 μg) were administered four times a day for one week each, and mucociliary clearance was measured by radioaerosol tracer (Pavia *et al*, 1978) as well as pulmonary function at the end of each treatment period and after a control period (seven days) in which no treatment was given. On the mornings of the measurements, after the placebo and drug periods, one final dose of treatment was given about 135 min before the start of the test.

Comparable improvements in pulmonary function were noted for both bronchodilating agents, which were statistically significantly greater compared to the respective placebos. There was no statistically significant difference between the five mean mucociliary clearance curves for the group; however, there was a significantly ($P<0·05$) greater penetration towards the periphery of the lung of the tracer radioaerosol (polystyrene particles, diameter: 5±0·8 μm) in the test after the ipratropium administration compared to the other four.

We conclude that in chronic obstructive bronchitis both Atrovent^R and Bricanyl^R are equally effective in reversing bronchoconstriction and do not alter the rate of clearance of lung secretions. With Atrovent^R, however, there was enhanced penetration of particles, suggesting the two drugs have a different site of action. Scrutiny of the maximum flow-volume curves, however, failed to differentiate this difference further.

These results were confirmed when the total number of patients studied were increased to 12 for the Atrovent^R and nine for the Bricanyl^R.

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How cardioselective are the new beta-blocking drugs?

A D MACKAY, H R GRIBBIN, C J BALDWIN, and A E TATTERSFIELD Many of the new beta-blocking drugs are claimed to be cardioselective and therefore relatively safe for patients with asthma. It has, however, been difficult to assess cardioselectivity accurately in man since previous methods did not allow bronchial beta-blockade to be measured quantitatively. Gribbin *et al* (1977) described a method for assessing bronchial beta-blockade in man in a quantitative manner, and we now describe the results with four new beta-blocking drugs—atenolol, acebutolol, labetolol, and bevantolol.

Bronchial beta-blockade was assessed by carrying out salbutamol dose-response studies in six normal subjects, measuring the change in specific airway conductance (sGaw), after increasing doses of inhaled salbutamol. These were then repeated after two different doses of each beta-blocking drug and the shift to the right of the dose response curve was used as a measure of the amount of bronchial beta-blockade. To assess cardiac beta$_1$-receptor blockade we carried out steady state exercise at 70% of the previously determined maximum work load in the same subjects after the same dose of each drug. All studies were carried out at the same time of day and at least four days apart. The first studies on practolol and propranolol were extended to include atenolol, 50 and 100 mg, acebutolol, 100 and 200 mg, labetalol, 150 and 300 mg, and bevantolol, 75 and 150 mg.

Our studies showed that all four drugs in both doses caused considerably less bronchial beta-blockade than 40 mg of propranolol. Practolol, atenolol, and bevantolol produced a similar degree of bronchial beta-blockade and less than acebutolol and labetalol. Atenolol and bevantolol also produced the greatest reduction in exercise heart rate.

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Gribbin, H R, Baldwin, C J, and Tattersfield, A E (1977). A method of assessing bronchial selectivity of beta-adrenoceptor antagonists in man. *Thorax*, 32, 643–652.

Response in asthmatic patients to ambient sulphate air pollution

ANNE HERSEY COULSON, R DETELS, R G FREZIERES, and R KATZ The relationship between respiratory symptoms, peak flow, and use of medicines in 34 individuals with atopic asthma diagnosed by a physician and changes in levels of ambient air pollutants and pollens was studied. Members of the asthma panel all lived within four miles of a monitoring station of the Southern California Air Quality Management District in an area historically exposed to relatively high levels of sulphate and particulate pollutants and relatively low levels of oxidant pollutants. Total particulates, sulphur dioxide, nitric oxide, nitrogen dioxide, oxides of nitrogen, carbon monoxide, pollens, and moulds were continuously measured. Levels of sulphates were measured five days a week during the study period. Climatic variables including temperature, humidity, precipitation, barometric pressure, and wind direction and speed were collected continuously.

Panel members used portable Wright peak flow meters three times each day and maintained a daily diary of day and night symptoms, and use of medicines from August 1977 to April 1978. Correlations of symptoms and medicines with peak flow were poor;

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between symptoms and use of medication, reasonable; and between day and night symptoms, good. The correlation of symptoms, changes in medication and peak flow with changes in level of each pollutant were analysed for each panelist. The mean symptom score of panel members on days falling in the highest and in the lowest tertile of sulphate levels were compared. Eleven of the 34 panelists responded to sulphates; four reported symptoms only and seven reported symptoms plus peak flow and/or medication level changes that correlated with levels of sulphate pollutants. All but one of these responded primarily to changes in sulphates with few correlations to changes in other pollutants. The results of this study suggest that at least seven of the 34 asthmatic patients followed were sensitive to changes in levels of sulphates.

Tracheobronchial clearance in asthma

J R M BATEMAN, D PAVIA, NÓIRÍN F SHEAHAN, J E AGNEW, and S W CLARKE Airway obstruction in asthma arises from smooth muscle contraction, mucosal oedema, and mucus plugging (Dunnill, 1971). Little attention, however, has been focused on the role of mucociliary clearance and mucus plugging in asthma. The present study has been designed to assess tracheobronchial clearance of lung secretions, firstly, in patients in remission from asthma and, secondly, in patients with mild asthma.

The method used the inhalation of uniform 5 μm polystyrene particles permanently labelled with the radionuclide ^{99m}Tc (half life 6 h) and subsequent whole lung counting at 30-minute intervals over an initial six-hour period (Thomson and Short, 1969). A final count was made at 24 hours to determine alveolar deposition of the radioaerosol and thus enable calculation of tracheobronchial clearance over the 24 hours. The data from five patients with asthma in remission (asymptomatic and requiring no treatment for one to six months) and five patients with mild asthma (symptomatic and requiring regular treatment) have been non-parametrically compared with that from matched normal control subjects.

Pulmonary function was determined for each asthmatic and control subject and only three indices (FEV_1, PEFR, and $MMFR_{25-75}$) expressed as a percentage of predicted values were significantly reduced in the mild asthmatic group when compared with the control group ($P<0.01$).

In the table the group mean clearance of deposited radioaerosol from the tracheobronchial tree is expressed as a percentage of the total 24-hour clearance for the asthma remission, the mild asthmatic, and respective control groups for the first six hours after radioaerosol inhalation. Clearance of radioaerosol was significantly less for the mild asthmatic group when compared with the respective control group ($P<0.05$). Tracheobronchial clearance over the same period in the asthma remission group was similar to the respective control group.

We conclude that mucociliary clearance is impaired in mild asthma but normal when patients are in complete remission. This finding implies that mucociliary slowing may be an important factor in the pathogenesis of asthma.

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Tracheobronchial clearance of deposited radioaerosol over the initial six-hour period expressed as a percentage of the total 24-hour clearance

	Mean (%)	*Range* (%)
Asthma remission	76	60–89
Control group	72	55–91
Asthma mild	56	49–64
Control group	81	63–100

Physiological comparison of adult PiM and PiMZ phenotype subjects from a random population

R J KNUDSON, M D LEBOWITZ, D J MCDONAGH, and S P NATHAN For plethysmographic studies of lung mechanics and pulmonary diffusing capacity, 62 subjects were drawn from a randomly selected population sample. Data obtained from the 24 subjects of PiMZ phenotype were compared by age group with data from 38 PiM subjects matched for sex, age, and smoking history. Comparison of mean values for lung volumes, lung elastic recoil, maximum expiratory flow, diffusing capacity, and the occurrence of frequency dependence of dynamic compliance showed no differences between phenotype groups.

For comparison, previous data obtained from a highly select group of normal subjects of the PiM phenotype have been included. A plot of the rate of loss of recoil per year of age was obtained. From this figure it is apparent that the present subjects, viewed either collectively or by phenotype, lose elastic recoil at a greater rate than those previous subjects studied. Despite the greater loss of elastic recoil in the present subjects there is no evidence of an accelerated effect of age on the PiMZ subjects when compared to the PiM subjects, nor was there evidence of an increased effect of smoking. From these data it appears that the PiMZ phenotype per se is not a risk factor in development of emphysema.

Clinicopathological correlations in chronic cor pulmonale complicating chronic bronchitis and emphysema after treatment with long-term domiciliary oxygen therapy

D LAMB, P M A CALVERLEY, R J E LEGGETT, R BULMER, and D C FLENLEY Clinicopathological relations are reported in 15 patients suffering from chronic hypoxaemia (PO_2 breathing air 45–58 mmHg), with CO_2 retention and pulmonary hypertension (mean pulmonary artery pressure 20–50 mmHg) along with secondary polycythaemia (red cell mass 23–86 ml/kg).

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All suffered from irreversible airways obstruction and hyperinflation of the lungs due to chronic bronchitis and emphysema, complicated by chronic cor pulmonale, and 12 were treated with long-term domiciliary oxygen for three to 72 months before death. Oxygen for 12-15 hours in the 24-hour day, at a flow rate of 2/1min was provided to raise the day time arterial oxygen tension to over 60 mmHg. At necropsy most of the patients had right ventricular hypertrophy, as shown by the ratio of the weight of the left ventricle plus septum to that of the right ventricle of between 1·0 and 2·7, and this hypertrophy appeared to persist despite partial reversal of pulmonary hypertension by the long-term oxygen treatment. Despite these homogenous abnormalities in clinical pattern and respiratory function, which were allegedly typical of the "blue and bloated" types of patients, at necropsy there was considerable variability in the extent of bronchial gland hypertrophy (Reid index 25–69%), and also in the extent of panlobular and centrilobular emphysema.

There was no definite pathological evidence of oxygen toxicity, and the alveolar to arterial oxygen tension gradients were not increased during long-term oxygen treatment, suggesting that progressive pulmonary fibrosis from oxygen treatment is not a major hazard in these patients undergoing this treatment over prolonged periods. The possibility of reversing the pulmonary vascular changes resulting from chronic hypoxaemia in these patients will also be discussed.

Nature of chronic lung disease in highland Papua, New Guinea

H R ANDERSON At Goroka, in the eastern highlands of Papua, New Guinea, 46 men and 24 women with evidence of chronic lung disease underwent clinical, lung function, and other investigations. Forty-three patients had an FEV_1 of less than 50% predicted, and 19 had cor pulmonale. All subjects were found to have chronic obstructive lung disease which closely resembled that seen in European populations. Compared with a series from London and Chicago, however, the highland subjects were 10 years younger and had more normal values for total lung function capacity and transfer factor. Previous reports that highland chronic lung disease has a restrictive component due to pulmonary and pleural fibrosis were not confirmed.

Epidemiological studies have been unable to relate highland chronic lung disease to tobacco smoking. Exposure to domestic wood smoke appears to be the most probable cause though the evidence for this and for other possibilitites, such as acute respiratory infections, remains inadequate.

Corticosteroid trials in patients with chronic airflow obstruction

J WEBB, T J H CLARK, and CLAIR CHILVERS Patients with chronic airflow obstruction inadequately controlled with bronchodilators are often given a course of corticosteroids to reverse the airflow obstruction. These trials of corticosteroids vary in both duration and dose, since the time course and dose-response characteristics of the response of airflow obstruction to treatment with corticosteroids is not well defined. We have performed a trial with 40 mg prednisolone a day for three weeks with an initial week on placebo in 19 patients with chronic airflow obstruction in order to study the time course of response to corticosteroids. Each patient recorded the peak expiratory flow (PEF) twice daily for the four weeks, and in addition short tetracosactrin tests were performed before and after the trial in eight patients, and the recovery of the basal cortisol and ACTH levels were observed for five days after the last dose of prednisolone in a further seven patients.

The PEF of the 19 patients were submitted to an analysis of variance that showed a highly significant difference in PEF over the four weeks ($P<0·01$) and a highly significant difference between morning and evening PEF. These morning and evening differences in PEF remained constant throughout the four weeks. Individual response to prednisolone was assessed by comparing the PEF during week 1 on placebo and the PEF during weeks 3 and 4 while on prednisolone. Response or lack of response to prednisolone was assessed in two ways: (1) using a 10% increase in PEF as a response criterion and (2) carrying out a *t* test on the data with a significance level of 1%. The same 13 responders were identified using both criteria, and their mean response was 28%. The maximum response occurred on the eighth day of treatment. The individual responses were assessed by eye, and in 12 patients the maximum response of PEF occurred within eight days and in the remaining patient 11 days. The morning and evening difference in PEF remained constant throughout the four weeks in the 13 responders.

The basal cortisol and response to tetracosactrin was normal before treatment (mean cortisol 381 nm/l, 881 nm/l). The basal level and tetracosactrin response within 24 hours of the last dose of prednisolone were both abnormal and highly significantly different from the pretreatment levels (75·6 nm/l $P<0·01$; 207 nm/l $P<0·001$). The basal cortisol and ACTH levels in a further seven patients both rose simultaneously to normal levels within four days.

The following conclusions can be drawn: (1) 13 patients, considered as a group, reached a new improved level of PEF after eight days of treatment. In individual patients the time taken to reach the new level did not exceed 11 days. Six patients failed to respond to corticosteroid treatment; (2) basal cortisol and ACTH levels were depressed after three weeks on 40 mg of prednisolone a day and rose to normal levels within four days; and (3) prednisolone did not significantly decrease the morning dip in PEF.

Factors contributing to the clinical grade of breathlessness in coalworkers with pneumoconiosis

A W MUSK, CAROL BEVAN, M J CAMPBELL, and J E COTES Factors underlying the capacity for exercise have been

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investigated in 125 coalworkers with pneumoconiosis, first investigated in 1969 (mean age 52 years) and followed up in 1978. Investigations included the BMRC questionnaire on respiratory symptoms, anthropometry, spirometry, measurements of transfer factor, lung mechanics, and the physiological response to exercise.

Multiple regression and discriminant function techniques were used to describe the clinical grade of breathlessness and the symptom limited maximal oxygen uptake in 1978 and the change in clinical grade of breathlessness between 1969 and 1978 in terms of the other variables. About 40% of the variance in the symptoms limited maximum oxygen uptake and in the clinical grade of breathlessness could be described by the anthropometric, spirometric, and gas transfer variables. Measurements of pulmonary compliance, conductance, and recoil pressures did not add significantly to the predictive value of the pulmonary function tests. A deterioration in breathlessness in previously healthy subjects was presaged by a relatively low symptom limited maximum oxygen uptake, high exercise ventilation, low FEV_1 and relative to the FEV a high airways conductance, the latter combination possibly reflecting narrowing of the small lung airways. An increase in breathlessness was associated with a gain in body mass and increase in the questionnaire score for bronchitis. The progressors were then heavier, had a lower Kco and FVC, and a higher V-isoV but similar specific conductance, closing volume, and bronchitis score compared with those whose breathlessness remained the same or was reduced. These findings may be of use in designing means of reducing the progression of exercise-related symptoms in coalminers with pneumoconiosis.

Ventilatory control in the obesity-hypoventilation syndrome

M LOPATA, R A FREILICH, E ONAL, J PEARLE, and R V LOURENCO We investigated the causes of impaired ventilatory control in six patients with the obesity-hypoventilation syndrome (OHS) by assessing the response to CO_2 rebreathing of the three major components of the respiratory control system: (1) neural drive, assessed by moving average diaphragmatic EMG (EMG_{di}); (2) muscle output, assessed as pressure developed at the mouth 150 msec after airway occlusion ($P_{0.15}$); and (3) minute ventilation (V_T). The linear regression of EMG_{di}, $P_{0.15}$, and V_T, vs end tidal CO_2 ($PACO_2$) in the OHS patients were compared with those from patients who had recovered from OHS, and from obese, as well as non-obese controls. In the OHS patients the mean V_T vs $PACO_2$ response was less than that in the obese and former OHS subjects. The EMG_{di} response to CO_2 in the OHS patients did not differ from the other groups, while in only three was the $P_{0.15}$ response reduced. The coupling of neural to muscular and muscular to ventilatory events was assessed as the ratio of the slopes of EMG_{di} to $P_{0.15}$ and $P_{0.15}$ to V_T, respectively. Three OHS patients had impaired neural-muscular coupling with normal muscular-ventilatory transfer. Monitoring of thoraco-abdominal motion by respiratory magnetometers showed that abdominal end tidal position was displaced outward during CO_2 rebreathing in these three patients. Normal neural-muscular coupling with impaired muscular-ventilatory transfer was present in the other three OHS patients, in whom end tidal abdomen position moved inward during rebreathing. We conclude that the impaired ventilatory response to CO_2 seen in patients with OHS is secondary to mechanical limitations to breathing, due either to impaired diaphragm efficiency or abnormal lung and/or chest wall mechanics.

Influence of hyperinflation and inspiratory muscle strength on mouth occlusion pressure in chronic airflow obstruction

H R GRIBBIN, G J HEINZ III, I GARDINER, and N B PRIDE Measurements of mouth occlusion pressure (MOP) at the start of inspiration reflect changes in pleural pressure and have been used as an index of respiratory centre output which is independent of the mechanical properties of the lung. The measurements used have been either $P_{0.1}$ (pressure at 0·1 s after start of occluded inspiration) or dP/dt/max (maximum rate of rise of mouth pressure at the start of occluded inspiration). In chronic airflow obstruction, however, the chest wall is hyperinflated and the inspiratory muscles are at a potential mechanical disadvantage so that a given amount of neuronal activity may produce less change in MOP than in a normal subject. This was recognised in the original description of the method (Whitelaw *et al*, 1975).

We have studied 12 patients with chronic airflow obstruction of similar severity (FEV_1: range 0·7–1·0 l, mean 0·9±0·1 l) but with varying degrees of hyperinflation (TLC as % predicted; range 103%–161%, mean 128±16%) all of whom were eucapnic. The $P_{0.1}$ responses expressed as $P_{0.1}$ (60) ($P_{0.1}$ value at a PCO_2 of 60 mmHg) and the slope of the $P_{0.1}$ response, $\triangle P_{0.1}/\triangle PCO_2$ were compared with TLC as % predicted and diaphragm contour. A weak negative correlation existed between $\triangle P_{0.1}/\triangle PCO_2$ and TLC as % predicted ($r=-0.49$, $P=0.1$). Maximum inspiratory mouth pressures at lung volumes from RV to TLC were obtained in six of the patients and were reduced compared with normals (max insp mouth pressure at FRC=−36±10 cmH_2O). No relationship between maximum inspiratory mouth pressure and $P_{0.1}$ responses emerged.

In spite of hyperinflation considerable adaptation of inspiratory muscle function is present, although maximum pressures are reduced. This does not appear to influence $P_{0.1}$ responses but it is still not clear whether ventilation is similarly unaffected.

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Thoracoabdominal motion and pressures during coughing

A J R MORRIS, N SIAFAKAS, and M GREEN We have studied chest wall configuration during voluntary coughs in seven normal subjects. We measured antero-posterior diameters of the rib cage (RC_{A-P}) and abdomen (ABD_{A-P}) and lateral diameters of the rib cage at high (RC_{HL}) and low (RC_{LL}) levels using linearised magnetometers, with simultaneous recordings of oesophageal (Poe) and gastric pressures (Pg) and volume (V) and flow (V) at the mouth. During thoracic gas compression preceding the cough Poe and Pg rose abruptly and continued for 80–120 ms after opening of the glottis. During the cough Poe fell as flow diminished, but Pg remained slightly raised for longer. Transdiaphragmatic pressure (Pg–Poe) was raised, indicating activity of the diaphragm during this expiratory manoeuvre.

The chest wall diameters decreased abruptly during compression, except RC_{A-P} which enlarged due to distortion of the rib cage. When the glottis opened, RC_{A-P} and RC_{HL} diminished, but RC_{LL} and ABD_{A-P} held their positions constant in three subjects and actually began to enlarge in four subjects, despite continued expiration.

The two adjacent lateral diameters (RC_{HL} and RC_{LL}) therefore moved in opposite directions relative to each other during the early part of expiration. This distortion of the lower region of the rib cage may be due to outward abdominal pressure. Positive abdominal pressure tends to expand the lower rib cage at low lung volumes when there is a substantial area of apposition of the diaphragm on the rib cage. We conclude that this distortion and paradoxical movement may be the mechanism of cough fractures. This is consistent with the observation that cough fractures are peculiarly common in pregnant women (Savage, 1956) and relatively uncommon in emphysema (Pearson, 1957).

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Added respiratory load detection in normal subjects and patients with restrictive and obstructive ventilatory defects

N K BURKI The sensation generated by added inspiratory loads has been examined in several studies in healthy subjects and in patients with increased airways resistance. It has been shown, both in normal subjects (Wiley and Zechman, 1966), and in asthmatics (Burki *et al*, 1978) that the difference threshold for added resistive loads is a function of the initial, intrinsic load (Weber-Fechner relationship). Similar studies have not been performed in patients with increased pulmonary elastance (that is, with restrictive lung disease), nor has the correlation between elastic (E) and resistive (R) load detection in the same subject been studied.

Six patients with chronic airways obstruction (CAO), six patients with restrictive lung disease (RLD), and 15 normal subjects were studied. Spirometry, body plethysmography, pulmonary resistance by the interrupter method (R_{int}) and total thoracic elastance (E_{tot}) were measured in all patients and subjects. The difference thresholds for detection of resistive and elastic loads (expressed as the load detected 50% of the time, $\triangle$R50 and $\triangle$E50, respectively) were measured on at least two separate occasions. Mean $\triangle$R50 was higher in both the CAO and the RLD groups than in the normal subjects; the Weber fraction $\triangle R50/R_0$ (where $R_0 = R_{int}$ + minimal resistance of apparatus) was very similar in the normal and CAO groups (0·19 and 0·18 respectively) but was higher (0·26) in the RLD group. Mean $\triangle$E50 was significantly greater in both patient groups compared with the normal group, as was the Weber fraction for elastic loads, $\triangle E50/E_0$, where E_0 is equal to E_{tot}. The correlation of difference thresholds in the individual subjects and patients, that is, the correlation coefficient between $\triangle$R50 and $\triangle$E50 was good in the normal subjects ($r = +0{\cdot}71$, $P < 0{\cdot}005$), but not significant in the CAO group ($r = +0{\cdot}52$, $P > 0{\cdot}1$) and poor in the RLD group ($r = -0{\cdot}07$).

These results indicate that the increased intrinsic elastic load in RLD patients alters the difference threshold value for externally applied resistance loads and similarly the increase in lung elastance alters the elastic load difference threshold. The significant difference in the Weber fraction for elastic load difference thresholds for both CAO and RLD patients compared with the normal group may reflect the possibility that the change in thoracic elastance does not reflect the magnitude of change in lung elastance, hence underestimating the denominator in the Weber fraction. The poor correlation between $\triangle$R50 and $\triangle$E50 in the patient groups probably reflects differences in the relative intrinsic resistive and elastic loads in these patients.

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Dynamic collapse of large airways in chronic obstructive lung disease

K PROWSE and S BRADBURY A study of maximal flow-volume loops was carried out in 124 patients with chronic obstructive lung disease. All patients had spirometric evidence of airflow obstruction, as shown by an FEV_1 less than 70% predicted normal and an FEV_1/vital capacity ratio less than 60%.

The shape of the flow-volume loop was indicative of dynamic airway collapse (DAC) during expiration in 46 patients (37%). The expiratory curve showed a rapid fall from peak expiratory flow to a much reduced rate of flow over a small part of the vital capacity (VC), and the flow rate then remained fairly constant for the remainder of expiration. The shape of the flow-volume loop was abnormal in a further 48 patients (39%) but did not show evidence of DAC.

In the patients with DAC the ratio of forced expiratory to forced inspiratory flow at the midpoint of VC (FMEF/FMIF) was $0{\cdot}31 \pm 0{\cdot}15$, significantly lower than in those without DAC ($0{\cdot}53 \pm 0{\cdot}32$; $P < 0{\cdot}001$).

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The subjects with DAC also showed significantly lower values for FEV_1, VC, and transfer factor (TL) and significantly higher values for TLC and RV. Twenty-six patients with DAC (57%) had radiological evidence of emphysema compared to 16 (20%) of those without DAC.

In 19 patients with DAC fibreoptic bronchoscopy confirmed the presence of pronounced tracheal narrowing during expiration, and tracheal tomography showed variable tracheal narrowing in a further 10 patients.

The development of the low-flow plateau occurred after expiration of $22{\cdot}5 \pm 7\%$ VC and probably indicates that the tracheal lumen has reached minimal size.

Although loss of airway distending forces may account for airflow obstruction under static conditions in subjects with emphysema, dynamic factors may be important during forced expiration (Leaver *et al*, 1974). Regrouping of our patients into "emphysema," "bronchial," and "indeterminate" subgroups according to the criteria of Burrows *et al* (1966) showed that 33 out of 49 patients in the emphysema subgroup had evidence of DAC, whereas only seven out of 40 in the bronchial and six out of 35 in the indeterminate subgroups showed DAC.

We conclude that dynamic collapse of large airways is relatively common in emphysema and suggest that it may be a more important cause of disability than has hitherto been accepted.

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Relationships between radiographic progression, lung function decline, and asbestos exposure level

H WEILL, J E DIEM, R N JONES, J C GILSON, and H GLINDMEYER Previous studies from this unit have shown that radiographic and physiological evidence of asbestosis and excess lung cancer mortality are dose related in asbestos cement manufacturing workers (Weill *et al*, 1975; Hughes *et al*, 1978). In a cohort ($n=204$) of this population followed longitudinally (six years) average length of exposure was 22 years, and individual exposure dose was reconstructed using duration and average levels of dust exposure. Two readers (JCG and RNJ) independently assessed progression on a four-point scale using paired films of known sequence. Progression was assumed in 17 individuals where one or both readers classified the film pair in one of the two upper categories (probable or definite progression).

Average and cumulative exposure at time of study entry correlated significantly with progression of small irregular opacities (logistic regression analysis, $P<0{\cdot}001$), but not with small rounded opacities or pleural thickening. Progression of pleural thickening and calcification depend only on length of exposure. Smoking did not correlate with progression of small irregular opacities. Annual decline of forced vital capacity and forced expiratory volume in one second correlated significantly with level of past dust exposure ($P<0{\cdot}04$) beyond a significant smoking effect ($P=0{\cdot}01$). Radiographic progression was strongly associated with larger annual decline in FEV_1 and FVC ($P<0{\cdot}001$). Progression of small irregular opacities appears to be more specifically related to asbestos dust effect than is decline in lung function.

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A proposed diagnostic classification for asbestosis

G R EPLER, J M SAMET, B ROSNER, and E A GAENSLER Guidelines for diagnosis of asbestosis are essential for clinicians, compensation boards, and industrial environmental control officers. We undertook this study to determine if a classification based on clinical and radiographic criteria could be developed to define asbestosis. Altogether 852 employees of asbestos and shipbuilding industries were studied. Data included MRC questionnaire, forced vital capacity (FVC), forced expired volume in one second (FEV_1), and single breath diffusing capacity (Dsb). Chest radiographs were coded by the ILO U/C international classification for the pneumoconioses.

We classified workers into three groups. The first was "definite asbestosis," which comprised all workers with (a) radiographic profusion (severity) of at least 2/1 or (b) a film of 1/0–1/2 plus two of three criteria: bilateral fine crackles, FVC or Dsb of less than 80% of the predicted value. The second group was designated as "possible asbestosis" and included all workers with (a) film of at least 1/0 or (b) two of three criteria, if the film was normal. All remaining workers were classified as "unlikely."

The 852 workers were further divided into those exposed or not exposed to asbestos. Among 433 with exposure, 61 or 14% were classified as "definite" and 91 or 21% as "possible," while among the 419 non-exposed, less than 1% were classified as "definite" and 11% were in the "possible" group. In the "definite" group 51% had bilateral crackles, the mean FVC was 74%, and the mean Dsb was 70%, while in the "possible" group, 14% had crackles, the mean FVC was 91%, and the mean Dsb was 95%.

There were 567 employees with sufficient follow-up studies to determine yearly change of FVC, FEV_1, and Dsb values. The yearly decrease of the FVC was 110 ml, 70 ml, and 49 ml for the exposed workers in the "definite," "possible," and "unlikely" group respectively. Several exposed workers in the "possible" group progressed to "definite" on subsequent tests.

Finally, lung biopsy results were available from several of the workers and other asbestos exposed patients. Using our diagnostic classification for these 46 confirmed cases of asbestosis, 74% were classified

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as "definite" and the histological grade of severity was significantly higher than the 15% who were classified as "possible."

Spectral and wave-form analysis of crackles

M MORI, K KINOSHITA, H MORINARI, T SHIRAISHI, S KOIKE, and S MURAO We performed waveform and spectral analysis of crackles recorded from six patients, four with tuberculosis and two with chronic bronchitis. Lung sounds were recorded by placing an air-coupled dynamic-type microphone firmly on the chest wall where crackles were heard by auscultation. We used a memory (TDK 8810), which has a capacity of 1 kilowords, for the sampling and time expansion. We expanded the time scale 1600 times for the waveform analysis, and for the spectral analysis we set the sampling frequency at 64 KHz and the time window at 31·25 msec.

By waveform analysis we could separate a waveform of a single crackle into two portions, initial high pitched portion (HP) and the subsequent low pitched portion (LP). We measured amplitudes and half-periods of the wave components in the low pitched portion out of 286 crackles recorded from six patients and found that the attenuation of the amplitude was almost exponential and that in 92% the half-periods became longer with the development of the waveforms. In crackles with high amplitudes we noticed as in shock waves triangular distortions at the top of the waveforms. The spectrum of a single crackle had a peak near 200 Hz and a notching between 250 and 350 Hz. Since this notching is caused by an interaction of the two waveforms, initial high pitched portion and subsequent low pitched portion, we can calculate using basic characteristics of Fourier transform the time interval between the two (HP and LP) from the inverse of the notch frequency. We found this time interval about 3 msec (2·84–3·91 msec). On the bases of these observations we speculate crackles are shock waves similar to a sonic boom.

Pulmonary hypertension accompanying combined ventricular septal defect and patent ductus arteriosus. Management in infancy and early childhood

J M REID, E N COLEMAN, and J G STEVENSON The combination of patent ductus arteriosus (PDA) and ventricular septal defect (VSD) is relatively uncommon, Keith *et al* (1978) recording a VSD in only 5% of PDA patients. During 1959–78 41 children were encountered with this combination. The age at presentation ranged from 1 month to 11 years (mean 19·7 months), and 24 were under the age of 1 year. These 24 presented within the first three months of life. After treatment of the failure, cardiac catheterisation was performed. Haemodynamic data obtained included presence or otherwise of pulmonary hypertension (present in 32 of the 41), the pulmonary : systemic blood flow ratio (Qp : Qs), pulmonary vascular resistance (PVR), the pulmonary to systemic pressure (Pp : Ps), and the pulmonary to systemic resistance (Rp : Rs).

Four patients had no surgical treatment, but 37 underwent various surgical procedures that will be discussed fully. Thirteen patients had pulmonary vascular disease (Rp : Rs>0·24) (Kirklin, 1965). Of the 41 patients, six died, two of whom had pulmonary vascular disease.

From an analysis of the data obtained in our patients, a policy of management is advocated. All who have cardiac failure require treatment of this followed quickly by catheterisation. The finding of serious pulmonary hypertension or failure to thrive are indications for early surgical treatment. Ligation of the PDA is performed first; only if the pulmonary artery pressure does not fall significantly is repair of the VSD considered necessary. In all patients in whom either surgery is deferred or PDA ligation alone is performed, repeat catheterisation is mandatory at 1 year to assess whether pulmonary vascular disease is developing; if so early operation is necessary.

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Total and differential counts in smokers and some pulmonary disorders

P L HASLAM One significant smoking-related feature has been identified from total and differential lung wash cell counting in 86 Brompton Hospital patients. Heavy "pigmentation" of variable numbers of macrophages was observed in 43 smokers ($P<0·001$) and 20 ex-smokers ($P<0·01$) contrasting with their extreme rarity in non-smokers.

Trends distinct from any influence of smoking were identified in differential lung wash cell counts from smokers with cryptoegnic fibrosing alveolitis (CFA). Macrophage percentages tended to be lower in smokers with "lone" CFA ($P<0·01$) and in smokers with CFA associated with other connective tissue disorders ($P=0·01$) than in 13 smoking control patients without peripheral lung disease. These decreases reflected increases in percentages of eosinophils ($P<0·001$ for lone CFA; $P<0·025$ for CFA with associated disorders), neutrophils ($P<0·05$ for CFA with associated disorders) and lymphocytes ($P<0·025$ for lone CFA). Total cell yields in smokers with CFA did not, however, differ from those in the smoker controls. These observations generally confirm findings for patients with CFA reported by Reynolds *et al*, 1977, and Weinberger *et al*, 1978. We also confirmed their findings of striking increases in percentages of lymphocytes—predominantly T-lymphocytes—in patients with hypersensitivity pneumonitis in one of our own patients with symptomatic budgerigar fancier's lung. We were unable, however, to confirm lymphocyte increases in four of our patients with clinically "active" sarcoidosis. (Statistical comparisons were made using the Mann-Whitney U test.)

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Clinical correlations with bronchoalveolar lavage in cryptogenic fibrosing alveolitis

C W G TURTON, P HASLAM, B HEARD, and M TURNER-WARWICK The inflammatory cell exudate in patients with cryptogenic fibrosing alveolitis (CFA) has been investigated by differential cell counts in bronchoalveolar lavage fluid. Twenty-four patients were lavaged, and 17 had open lung biopsy. Lavage differential cell counts were compared with histology assessed semiquantitatively and with differential cell counts of cells extracted from lung tissue in vitro. Correlations were made with response to treatment with corticosteroids, and with "disease progression" assessed retrospectively. Histology always showed a mixed picture with intra-alveolar cell exudate and alveolar wall fibrosis, and did not predict response to treatment. Correlations between lavage and histology were weakly positive and not significant statistically, but lavage may be more representative because of wider sampling. Correlations between lavage and cell extraction were more positive, and significant for neutrophils ($r_s=0{\cdot}63$, $P=0{\cdot}02$) suggesting that lavage is sampling much more than airways. There was a trend for the percentage of lavaged lymphocytes to be greater in treatment responders and this was significant for cells extracted from tissue ($P<0{\cdot}01$). Macrophages were increased in "rapid progressors" ($P<0{\cdot}05$), but the parallel decreases in other cells were not significant. Bronchoalveolar lavage is relatively non-invasive and may sometimes help in managing CFA.

Alveolar macrophage enzymes and C_3b receptors in CFA

R DU BOIS The alveolar macrophage has been shown to contain and secrete a wide variety of biochemically and immunologically active substances. Animal models of chronic inflammation suggest that the secretion of lysosomal acid hydrolases may be important in pathogenesis, and we present evidence that this may be true in cryptogenic fibrosing alveolitis (CFA).

Alveolar macrophages were obtained by lavage from 13 patients with CFA and 12 with no interstitial lung disease. Enzyme levels of the acid hydrolase N-acetyl-β-D-glucosaminidase were found to be lower in the CFA macrophages and higher levels were found in the lavage *fluid* from these patients, suggesting in-vivo release. Using a rosetting technique, it was shown that CFA macrophages possess fewer C_3b receptors than the control group. This could be explained if C_3b, generated in vivo, had already occupied macrophage receptor sites, thereby stimulating acid hydrolase secretion.

A further functional difference between the groups was illustrated by the increased spreading on glass of CFA monolayer cultures of macrophages.

In conclusion, alveolar macrophages from patients with CFA appear to be functionally different from those from patients with no interstitial lung disease, and may play an active role in the perpetuation of the chronic inflammatory response.

Technique of bronchoalveolar lavage at fibreoptic bronchoscopy

J V COLLINS Routine fibreoptic bronchoscopy was performed via the nose with the patient semi-recumbent. Biopsy specimens were obtained where indicated, and lavage was carried out in the other lung. The tip of the bronchoscope was normally impacted in inspiration in a segmental or more peripheral bronchus in the lateral or posterior segment of the lower lobe and held in place by an assistant. Using a hand-held syringe, 60 ml of sterile 0·9% sodium chloride solution (corrected to pH 7·0) at 37°C was injected while the patient inhaled very slowly to total lung capacity and then quietly exhaled to functional residual capacity. Further quantities of the solution were injected until 120–180 ml had been inserted. The tip of the bronchoscope was withdrawn by 1–2 cm, and the fluid was aspirated as the patient breathed quietly within the tidal range. The procedure was repeated until about 100–150 ml of fluid had been recovered, this usually entailed the injection of 300–500 ml of solution.

Contraindications to the procedure include severe ventilatory defect ($FEV_1<1$ litre), hypoxaemia at rest ($Pao_2<9$ kPa) and cardiac disease. Because significant hypoxaemia developed with lavage in six patients' studies (mean Pao_2 fell from 11·2 to 8·2 kPa) it is recommended that oxygen be given during and after the procedure. The other common sequelae of slight fever and radiographic shadowing occurred most often in patients with a history of recurrent chest infections but did not require specific treatment.

Alveolar washings in recurrent respiratory infections including cystic fibrosis: detecting defects in macrophage function

PETER COLE Phagocytosis and killing of *Staphylococcus pyogenes* by alveolar macrophages (AM) from 73 patients with frequent acute respiratory infections, 14 patients with bronchiectasis, and seven patients with cystic fibrosis have been tested using glass-adherent cells harvested from bronchoalveolar washings and characterised as AMs by electron microscopy. Normal ranges for these assays was established using seven healthy and 14 non-infective respiratory disease control subjects.

Phagocytic function was assessed after a 30-minute infection period using a multiplicity of infection of 50 bacteria to one phagocyte and was found to be normal in all 14 bronchietatic patients. In all seven cystic fibrosis patients, however, and in 11 of the 73

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patients with recurrent-acute infections phagocytosis was subnormal ($P<0.01$), and this defect was serum-dependent. Five patients in the latter group were IgA deficient.

Bacterial killing was measured over a 60-minute period and bronchiectatic patients' AMs killed more than 70% of the phagocytosed inoculum that composed the lower limit of the normal range. All seven cystic fibrosis patients were subnormal in bacterial killing, and this appeared to be serum-dependent. The bacterial killing of AMs from 15 out of 73 patients with frequent acute infections was subnormal ($P<0.01$), not improved by incubation in normal serum but improved by incubation in levamisole 5 μg/ml.

Although the results could be interpreted as being secondary to infection, patients with recurrent-acute infections were studied between episodes. It is concluded that there is a serum opsonin defect for AM function in some patients with cystic fibrosis and with frequent acute infections, and that the AMs themselves appear to be defective in killing Staphylococcus in a small number of the latter group.

Serum lysozyme in farmer's lung

C W G TURTON, G FIRTH, B G RIDGEN, and M TURNER-WARWICK Serum lysozyme (LYS) may be raised in some granulomatous inflammatory disorders including tuberculosis and sarcoidosis. LYS has been measured in 60 asymptomatic Devon farmers previously diagnosed as having farmer's lung (FL) and in 51 healthy farming controls. Criteria for the diagnosis of FL were a typical history, chest radiographic abnormality, and circulating precipitins to *Micropolyspora aeni.* LYS was assayed by spectrophotometric measurement of the rate of lysis of *Micrococcus lysodeiktious* using a standard human lysozyme from urine of patients with monocytic leukaemia. LYS in 31 FL subjects assessed in the water was higher than 36 winter control farmers ($P<0.01$), and higher than 18 FL subjects assessed in summer ($P<0.01$). In summer there was no difference between FL and controls. LYS tended to be lower in FL in those working on large farms, those with full time assistance, and those using silage, but not significantly so. The results suggest that there may be active inflammation in FL in the absence of acute symptoms.

Monitoring provocation tests in the investigation of allergic alveolitis

D J HENDRICK, R MARSHALL, and JENNIFER FAUX Inhalation provocation tests were carried out on 31 subjects using four- and five-fold sequential increments in antigenic exposure (interspersed with indistinguishable control challenges) until either characteristic "alveolar" reactions were obtained or the arbitrarily chosen maximum dose had produced no response. Subjects and observers alike were convinced of the positive or negative nature of the result from the ensuing symptoms and signs in all but 15 of the 144 tests. To assess the potential diagnostic usefulness of several monitoring parameters, the distributions of the changes noted in association with the 23 positive tests were compared with those associated with the 82 obligatory negative tests (all control tests plus all active tests in the 13 non-reactors). Diagnostic end-points were chosen to produce specificities of about 95%. The subjective parameters—symptoms of a "flu"-like illness, undue breathlessness on exertion, signs of an unwell appearance, increased respiratory effort on exercise—were the most discriminatory, but these largely determined the initial result category. The objective parameters monitoring the systemic responses —body temperatures exceeding 37·2°C, circulating neutrophil increases of at least $2{\cdot}5\times10^9$/l, circulating lymphocyte decreases of at least $0{\cdot}5\times10^9$/l to levels of absolute lymphopenia—had sensitivities of 78%, 68%, and 50% respectively. Those monitoring the pulmonary responses—increases in minute ventilation and respiratory frequency during exercise of at least 15% and 25%, decreases in vital capacity of at least 15% —had sensitivities of 85%, 64%, and 48% respectively. These ten parameters allowed eight of the 15 "equivocal" tests to be reclassified retrospectively as "positive." Auscultation, chest radiography, and measurement of diffusing capacity or lung volume subdivisions apart from the vital capacity, proved to be so insensitive as to be worthless, though changes did occur in association with the stronger reactions. It is concluded that responses that do provoke significant changes in these less sensitive monitoring parameters are unnecessarily distressing and, presumably, hazardous.

Abrogation of bronchial, cardiovascular, and cutaneous sensitivity in a canine model of IgE mediated hypersensitivity

W KEPRON, A H SEHON, and K S TSE We have induced specific IgE antibody to dinitrophenol (DNP) and ovalbumen (OA) by administering a conjugate of DNP and OA (DNP_2-OA). Inhalation challenge of sensitised dogs with either 5 mg of aerosolised OA or a polyvalent conjugate of DNP with bovine IgG (DNP_{15}-BGG) produced a five-fold increase in airway resistance as measured by the forced oscillation technique (Kepron *et al*, 1977). Abrogation of specific IgE anti-DNP antibody in sensitised dogs was produced by administering the tolerogenic conjugates of DNP with either canine IgG (DNP_9-CGG) or the copolymer of D-glutamic acid-d-lysine (DNP_{16}-DGL) (Tse *et al*, 1978). Inhalation challenge of dogs after IgE anti-DNP antibody had been abrogated failed to show airway resistance changes to DNP_9-BGG aerosolisation. Profound falls in systemic blood pressure in sensitised dogs were recorded after intravenous administration of 25 mg of either DNP_{15}-BGG or OA. After abrogation of IgE anti-DNP antibody, intravenous challenge with DNP_{15}-BGG did not produce any change in blood pressure. Similarly, sensitised animals were recorded as having direct skin test reactivity to intracutaneous injection of 1 ηg of DNP_{15}-BGG. This

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skin reactivity was completely abolished after abrogation of IgE anti-DNP antibody, and skin testing with up to a 10^6 increasel concentration of DNP_{15}-BGG was entirely negative. Sensitivity to OA after abrogation of IgE anti-DNP antibody remained unaffected, and IgE anti-OA antibody production and bronchial, cardiovascular, and skin reactivity to appropriate challenge with OA remained unaltered from pretolerogen administration levels. These results indicate that specific abrogation of the serum IgE antibody response of sensitised dogs by appropriate tolerogenic conjugates was associated with a corresponding loss of systemic allergic sensitivity.

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Epithelial cell adherence as a determinant of respiratory tract colonisation

J H HIGUCHI and W G JOHANSON, jun Nosocomial pneumonia due to Gram-negative bacilli (GNB) is a serious threat among ill patients. Colonisation of the upper respiratory tract with GNB usually precedes the development of pneumonia. In the present study we investigated the adherence of *Pseudomonas aeruginosa* (PA) to respiratory epithelial cells (buccal cells) in vitro to determine whether changes in the cell-binding characteristics could explain the occurrence of colonisation with GNB. In groups of rats subjected to 0%, 50%, 75%, and 100% nephrectomies (N) buccal cell adherence was studied in vitro using washed buccal cells that were incubated with PA for two hours; attachment results were assayed by both quantitative cultures and visual counting and expressed as number of PA per cell. To correlate buccal cell adherence in vitro with susceptibility to colonisation in vivo, each animal was inoculated once (day 1) intraorally with a gentamicin-resistant strain of PA; colonisation was defined as the persistence of this organism in the oropharynx, using gentamicin-containing selective media. Results are shown in the table.

Attachment of PA was similar for all groups preoperatively and was unchanged subsequently in shams; 1 of 18 became colonised. Fifty per cent N was followed by a transiently increased attachment in vitro and colonisation tended to persist. Among 75% N, attachment in vitro postoperatively increased and colonisation in vivo persisted. One hundred per cent N caused death in 36–56 hours; attachment in vitro was greatly increased and all were colonised.

Buccal cell adherence of *Ps aeruginosa* in vitro and colonisation by *Ps aeruginosa* in vivo

Group	*No*	*Preop*	*Day 1*	*Day 2*	*Day 4*
Sham	(18)	4·9±1·7*	5·6±1·3	5·3±1·3	—
Colonised		—	1/18†	1/18	1/18
50% N	(6)	4·1±0·8	17·2±1·7	5·9±0·6	—
Colonised		—	6/6	4/6	0/6
75% N	(6)	5·8±2·6	17·2±2·0	25·8±6·7	—
Colonised		—	6/6	6/6	6/6
100% N	(6)	4·2±1·2	28·0±3·4	46·2±10·1	—
Colonised		—	6·6	2·2	—

**Ps aeruginosa*/cell (mean±SD).
†No animals colonised/No animals inoculated.

These data show a significant relation between epithelial cell binding of PA in vitro and susceptibility to colonisation by GNB in vivo. The nature of the change in cell properties is not known.

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Role of digitalis treatment in cor pulmonale

MILENA L LEWIS and LYNN C CHRISTIANSON Digitalis apparently enhances the inotropic state of the right ventricle, when administered acutely (Ferrer *et al*, 1950; Jezek and Schrijen, 1973), but its role in the management of chronic cor pulmonale remains ambiguous (Green and Smith, 1977). This ambiguity is partly due to lack of adequate definition of the type and severity of respiratory illness in many case studies. Therefore, we have matched two groups of patients with chronic pulmonary disease, in stable clinical condition, for severity of lung disease, as indicated by ventilatory parameters and compared their haemodynamic function. Group 1 had been on chronic digitalis, whereas group 2 had not. Average values for the parameters of respiratory disease were:

	N	*Age*	*Pa_{O_2}*	*Pa_{CO_2}*	*FVC, % pred*	*FEV_1/FVC, %*	*MVV, % pred*
Group 1	15	56	53	49	55	51	41
Group 2	15	54	54	49	51	53	41

None of the differences between the two groups are statistically significant.

Values of cardiac index (CI), stroke index (SI), right ventricular ejection fraction (Ef_R), right ventricular diastolic volume (VDV_R), as determined from pre-

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cordially detected isotope dilution curves (Lewis *et al*, 1970) and lesser circulation pressures were compared in the two groups.

	CI	*HR*	*SI*	Ef_R	VDV_R, ml/M^2	*PRA*	*PPA*	*PLA*
Group 1	3·3	89	37	0·40	101	4	37	8
Group 2	3·6	85	43	0·44	105	6	30	8

Differences of mean values of haemodynamic parameters between the two groups were not statistically significant, although pulmonary artery pressure tended to be higher in the group on digitalis.

Differences between mean values of haemodynamic parameters were not statistically significant. Obvious abnormalities include raised pulmonary artery pressure and reduction of ventricular ejection fraction. The ventricular ejection fraction is an indicator of myocardial contractility. In the presence of increased afterload, however, a reduced Ef_R does not necessarily imply right ventricular dysfunction. In fact, from normal ventricular pressure-volume loops, the heart in these patients may be shown to exhibit increased contractility.

In the normal heart, the role of digitalis is problematical. An analogy can be drawn between present observations and those published regarding the negligible effects of digitalisation on cardiac performance in patients with mitral stenosis, without heart failure (Beiser *et al*, 1968). The trend to greater pulmonary hypertension in patients with cor pulmonale on digitalis may represent a direct vasoconstrictor effect of the drug on the pulmonary vasculature, and would be detrimental. The data presented cast doubt on the value of maintenance digitalis treatment in cor pulmonale in the absence of a low cardiac output.

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Oat cell carcinoma of the bronchus—is there a place for surgery?

M J DRAKELEY, H R MATTHEWS, and DEIDRE WATSON

Uncertainty exists regarding the proper treatment of oat cell carcinoma of the bronchus. Chemotherapy is effective only in the short term and, particularly after the Medical Research Council's study comparing surgical treatment with radiotherapy, many clinicians now consider that surgery is no longer indicated in treating this tumour. We have reviewed 494 patients with oat cell carcinoma of the bronchus who were treated by surgery alone during the 20 years from January 1951 to December 1970 at the Liverpool Regional Cardiothoracic Surgical Unit. Altogether 366 tumours proved suitable for resection, and 52 patients survived for more than five years, of whom 19 patients lived for more than 15 years, three of them still being alive more than 23 years after surgery. After a review of the histological slides, two patients were excluded. Seventeen patients had positive preoperative bronchoscopic biopsies, the other 33 having peripheral tumours. Fifteen of the 50 survivors had lymph nodes affected by tumour, and tumour cells were found in the resection line in three others. Twenty patients have since died, and of the 19 for whom information is available, only 7 died with recurrent disease.

Similar five-year survival figures can be extracted from other published surgical series which, although not high, are better than those for patients treated with cytotoxic drugs or radiotherapy. Our concern is that with the advent of the fibreoptic bronchoscope more peripheral tumours will be diagnosed before surgery, and the patient denied a potentially curable operation. As the results of immunotherapy will be enhanced by the removal of the tumour, we are certain that surgery still has a place in the treatment of oat cell carcinoma of the bronchus.

Regional lung function in patients with inoperable bronchogenic carcinoma studied before and after palliative radiotherapy

F FAZIO, T A PRATT, C G MCKENZIE, and R E STEINER

Ventilation/perfusion ($\dot{V}/\dot{Q}$) scans, a clinical assessment of breathlessness, routine chest radiographs and (in most cases) tests of overall lung function were obtained in 45 patients with inoperable carcinoma of the bronchus. Thirty-five patients were then reinvestigated after palliative radiotherapy. Seventeen of them had one or more further follow-up studies up to 490 days from the end of radiotherapy.

Semiquantitative assessment of regional $\dot{V}$ and $\dot{Q}$ showed that both were, at the initial evaluation, always reduced to the lung affected by the tumour, $\dot{Q}$ being generally more impaired than $\dot{V}$. These abnormalities were either undetected or underestimated by an evaluation of regional perfusion derived from the standard chest radiograph. After radiotherapy, a significant improvement of regional $\dot{V}$ and $\dot{Q}$ (probably due to shrinkage of the tumour) was observed, which was associated to a corresponding amelioration of breathlessness. Slow but progressive deterioration of both regional lung function and breathlessness was subsequently observed in the follow-up. This was often associated to the development of radiation fibrosis. On the contrary, tests of overall lung function (VC, FEV_1), which were moderately impaired at the initial assessment, did not show significant changes after radiotherapy or in the follow-up, thus confirming previous independent findings (Saunders *et al*, 1978).

We conclude that (a) impairment of overall pulmonary function tests in patients with carcinoma of the bronchus is likely to be due to coexisting mild or moderate chronic airways obstruction, rather than to a direct effect of the tumour on the airways; and (b) isotope studies of regional lung function ($\dot{V}/\dot{Q}$) being more sensitive and more specific than tests of overall lung function, can be a valuable adjunct to chest

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radiographs for the assessment, guidance to effectiveness of treatment, and follow-up of patients with inoperable carcinoma of the bronchus.

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Transthoracic needle lung biopsy after denitrogenation with 100% oxygen

Y CORMIER, M LAVIOLETTE, and A TARDIF Transthoracic needle lung biopsy is an effective and widespread diagnostic procedure. One drawback of this useful technique is its frequently resulting pneumothorax (Sinner, 1975; Herman and Hessel, 1976; Lalli *et al*, 1977). The objective of this study was to evaluate the effect of breathing 100% oxygen during the procedure. Since oxygen, in a closed collapsible cavity, reabsorbs faster than nitrogen (Dale and Rahn, 1952), it was expected that this substitution would enhance pneumothorax's reabsorption and thus decrease the associated morbidity. Fifty consecutive biopsies on 46 hospital patients were randomised and performed on subjects breathing either 100% oxygen or compressed air. The selected gas was given for five minutes before the biopsy and continued until 30 minutes after. Twenty-six procedures were done on air (group 1) and 24 on 100% O_2 (group 2). Four subjects in group 2 were eliminated because they were unable to sustain the required oxygen breathing. Results showed fewer pneumothorax with subjects breathing 100% O_2 (four out of 20) than with those breathing air (11 out of 26). Three patients in group 1 but none in group 2 required chest tube drainage for symptoms of dyspnoea. The peak area of gas accumulation for each pneumothorax, calculated by the method described by Northfield (1971), was smaller in group 2, with a mean surface area of 27·1 cm^2 (range 9·6–63·8), than in group 1 (mean of 68·1 cm^2 (range 6·4–172·4)). These results were statistically significant ($P<0.05$). Neither the patients' characteristics nor the biopsy procedure could account for these observed differences. We conclude that 100% O_2 breathing during transthoracic needle biopsy decreases the number and size of pneumothorax and therefore may help avoid the need for chest tube drainage. We propose this simple technique to decrease the morbidity of transthoracic needle lung biopsy.

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Comparison of techniques for diagnosis of cor pulmonale in cystic fibrosis

C J L NEWTH, I MITCHELL, K BLOOM, R FOWLER, and D GILDAY Cor pulmonale is a major cause of death in cystic fibrosis (CF). The diagnosis is often difficult to make in CF because classic clinical signs are often absent or misleading (Goldring *et al*, 1964), radiological signs occur late, and the electrocardiogram is insensitive (Lamarre *et al*, 1972).

Because of these difficulties, we performed thallium 201 myocardial perfusion scan, a vectorcardiograph, and M-mode echocardiograph assessments of the right ventricle in 36 patients with CF, on the same day. We used the echocardiogram as the standard test for cor pulmonale arbitrarily, on the basis of published data showing good correlation between angiographic (Liebman *et al*, 1976) and necropsy (Gewitz *et al*, 1977) measurements of right ventricular anterior wall thickness and those made by echocardiography. We also found good correlation between our echocardiographic and post-mortem assessments of cor pulmonale in the four patients in this study who died and had a necropsy performed.

Each of the echocardiograms, thallium scans, and vectorcardiograms were read by the same specialist in each field and the right ventricle graded as normal or hypertrophied (cor pulmonale). In two cases the echocardiograms were technically inadequate because of severe pulmonary hyperinflation between the heart and sternum, and in another case the vectorcardiogram could not be interpreted because of dextrocardia. The thallium scans in these cases were readily obtained and predicted right ventricular hypertrophy. Of the remaining 33 cases (19 boys, 14 girls), 21 (64%) had cor pulmonale by echocardiogram. Similarly, 16 (48%) patients had cor pulmonale by vectorcardiogram, whereas only 10 of 33 (30%) had positive thallium scans.

In nine of the patients all three tests were positive—in five patients, all three were negative. Thus in 14 of 33 patients we had complete agreement as to the state of the right ventricle by all three techniques. In a further five subjects there was agreement between echo- and vector-cardiograms.

In this study vectorcardiography was an unreliable index of cor pulmonale in agreement with previous reports (Siassi *et al*, 1971). Thallium myocardial perfusion scans were much less reliable in children with CF contrary to previously published data (Cohen *et al*, 1976) on adults with pulmonary disease.

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Mucosal droplet spread of Pseudomonas aeruginosa from cough of patients with cystic fibrosis

J BLESSING-MOORE, B MAYBURY, N LEWISTON, and A YEAGER

Pseudomonas aeruginosa is ubiquitous in the environment, colonises the GI tract and saliva of 6–24% of normal individuals (Young, 1977), and is a major pathogen in the immunologically compromised. The major portals of human entry include wounds, blood, respiratory tract, and urinary tract (Franklin and Franklin, 1971). In the mucous droplets it may survive for long periods and with evaporation the droplet nucleus becomes a potential airborne source of infection (Wistreich, 1976).

For hospital patients certain acquired serotypes may be more pathogenic (Moody, 1977), and the acquisition of an aminoglycoside resistant strain is a major threat. Family studies in which one or more children have cystic fibrosis (CF) have failed to show significant (nasal) carriage of the organism in non-CF members. Other CF members, however, may carry the same serotype (Lourdes *et al*, 1976).

We placed EMB culture plates at varying distances from 25 CF patients during an hour of chest physiotherapy (PVD) and within four feet of 15 patients during a four-hour period which included PVD. All plates were evaluated for growth of *Ps aeruginosa*. The data are presented as the percentage of plates which grew Pseudomonas.

In an attempt to find a reservoir for nosocomial infections we obtained throat, nasal, and rectal swabs from 25 professional personnel who had daily contact with CF patients. None of these cultures grew *Ps aeruginosa*.

Location	*No of plates*	*% with Pseudomonas/hour*
"Cough plates"—1 ft	42	19%
Bed during PVD—3–4 ft	11	9%
Room during PVD—1–9 ft	14	—
Breakfast tray after PVD 3–4 ft	5	—

Significant growth of *Ps aeruginosa* was noted on plates held at less than 1 ft from the mouth during the cough phases of the treatment. This may be important in determining hospital "isolation" policies for young CF patients. In the older patient with severe pulmonary disease the incidence of mucus bacterial spread was higher. Pseudomonas was not cultured from normal individuals caring for the patients. Nevertheless, cultures of the room showed organisms of the same sensitivities as the patient occupying the room—a potential reservoir for Pseudomonas.

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