

Proceedings of The Thoracic Society

The Summer Meeting of The Thoracic Society was held on 3–4 July 1975 at the University of Exeter. Summaries of the papers are given below:

Chest symptoms and farmer's lung: community surveys in Devon and Wales

D. C. MORGAN, J. T. SMYTH, R. W. LISTER, R. J. PETHYBRIDGE, J. C. GILSON, P. CALLAGHAN, and G. O. THOMAS During the winter 1970/71 and 1971/72, surveys were carried out on random samples of the farming population in Devon and Wales to estimate the prevalence of respiratory symptoms and of positive precipitin reactions to thermophilic fungi. Precipitins to *Micropolyspora faeni* were found in 29% of men in the first Devon survey and in 27% in the second Devon survey, and the corresponding proportions for men in Wales were 48% and 56%. There was no evidence that a positive precipitin test was more likely to be associated with past or present chest symptoms or disability. An unexpected finding was a significantly higher proportion of positive precipitin tests among non-smokers than smokers. Serological tests of 71 people examined on two occasions in Devon showed 55 (77%) readings were the same on both occasions, eight (11%) showed an increase in strength of a positive reaction, and eight showed a weaker reaction. Bronchitis, as defined, was found in 19% of men over the age of 45 years in Devon. One survey in Wales showed a similar proportion of men with bronchitis but the other survey, of hill farmers in Wales, showed a prevalence of 33%.

PHLS serological records as an index of exposure to farmer's lung antigens

C. A. MORRIS Although farmer's lung is an industrial disease, precise information on its regional prevalence or its variation from year to year in any one area is often lacking. Several laboratories in the Public Health Laboratory Service (PHLS) undertake routine serological tests for the detection of antibodies to farmer's lung antigens. The total number of positive serological tests obtained by PHLS laboratories is about 150–200 per annum. Since it can be assumed that subjects with demonstrable antibodies must have been exposed to farmer's lung antigens, data from PHLS records provide an objective means of assessing regional exposure. The information presented is based on an analysis of several hundred sera, originating principally from PHLS laboratories in England and Wales.

Precipitating antibody to *Micropolyspora faeni* in cattle herds—an index of exposure

CHRISTINE O. DAWSON, H. M. PIRIE, A. WISEMAN, and R. G. BREEZE Studies on precipitating antibody to *Micropolyspora faeni* in all adult housed cattle in selected herds (Pirie *et al.*, 1972) were continued and expanded to include titration of positive sera. This work has confirmed that the number of positives and the serum titres rise over the winters and fall over the summer. A reduced level of exposure to the allergen was noted during the second winter. Paired serum samples from individually identified cows have clarified the way in which the serological status of the herds changes and have shown that factors other than exposure affect these changes.

For individuals, serological tests could only confirm the clinical diagnosis of farmer's lung. However, from the herd serological results differences between normal or slightly affected herds and those with a farmer's lung problem became apparent.

Using these data it should be possible to predict the future serological status of a herd. Also, by serological examination of an adequate number of herds in autumn and in spring, one could estimate the amount of exposure and compare this from district to district and from year to year. Such comparative work would, however, depend on the availability of a suitable standard antigen.

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In vivo and *in vitro* activity of respirable mouldy hay dust

J. H. EDWARDS The inhalation of mouldy hay dust by susceptible individuals may result in an attack of farmer's lung. In the majority of such cases precipitating antibody is found in the serum, directed against mouldy hay dust and in particular against *Micropolyspora faeni*, a thermophilic actinomycete found in high concentration in the dust (Hapke *et al.*, 1968).

It is generally considered that the disease is mediated via immune complex activation of the complement system with a resulting tissue damaging (type III, Arthus type) reaction. However, some cases of farmer's lung have no detectable antibody, and for these, other mechanisms need to be considered (Edwards, Baker, and Davies, 1974).

Our studies on the interaction between respirable fractions of mouldy hay dust and normal human serum have shown complement to be activated by the alternative pathway of complement utilization and, at concentrations of mouldy hay dust of the order of 5 mg/ml and greater, significant quantities of complement are consumed.

In the experimental animal the introduction of zymozan, a well defined activator of the alternative pathway, induces histological features of acute phase farmer's lung. A similar response is seen when respirable mouldy hay dust fractions are introduced into unsensitized animals.

It is therefore considered that activation of the alternative pathway may produce disease in some farmers where exposure is sufficiently heavy, and in all exposures to mouldy hay dust biological activity of this nature may contribute towards the overall response observed.

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Measurement of antibody to *Micropolyspora faeni* using radioimmunoassay

G. BOYD and D. PARRATT Using radioimmunoassay, circulating antibody to the cell surface antigens of *Micropolyspora faeni* have been quantified (Nielson, Parratt, and White, 1973). This sensitive method for detecting antibody has been shown to be much superior to conventional precipitin tests in confirming the diagnosis of farmer's lung (Parratt *et al.*, 1975) and has afforded a means of observing the patterns of antibody response which occur during the course of the clinical disease.

A survey among 40 farmers in the west of Scotland showed that most individuals had evidence of sensitization to *M. faeni* and that the level of circulating IgG antibody to this organism correlated closely with the occurrence and intensity of symptoms, those most disabled having the highest levels. The likelihood of developing high levels of antibody appeared to depend more on the individual's own immunological responsiveness than on the length or intensity of exposure to antigen.

Extension of the radioimmunoassay technique to include the other main immunoglobulin classes confirmed that the antibody response following exposure and subsequent sensitization to *M. faeni* involved IgG, IgA, and IgM classes of antibody. Preliminary results indicated that the mean IgM antibody levels for those with acute farmer's lung were low compared with those with chronic symptoms and that they increased following recovery from an acute episode. IgG and IgA antibody levels varied more widely with no distinct pattern between symptomatic

and asymptomatic subjects although IgA antibody was higher in those with chronic symptoms.

The practice of recording the level of antibody at one arbitrarily selected time in the disease, even with this sensitive technique, is not a reliable basis on which to achieve a definitive diagnosis and prognosis. It is necessary to monitor antibody levels over a period of time in relation to challenge by antigen. In this way it should prove possible to relate the disease manifestations in time to the episodes of antigenic challenge and consequent antibody response.

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Hypertrophic pulmonary osteoarthropathy and its occurrence with pulmonary metastases from renal carcinoma

P. GOLDSTRAW and P. R. WALBAUM The literature of hypertrophic pulmonary osteoarthropathy (HPOA) has been reviewed with special reference to its occurrence with pulmonary metastases from extra-thoracic tumours. The conditions reported with HPOA are presented, the present theories on aetiology are discussed, and its relationship to finger clubbing and bronchogenic carcinoma reviewed.

A case is reported of HPOA as the presenting symptom of pulmonary metastases from renal carcinoma and its relief by pulmonary resection. This is the first such case in the English literature.

An ACTH-secreting malignant pulmonary chemodectoma

P. G. I. STOVIN and O. M. EDWARDS A 43-year-old woman with Cushing's syndrome was noted to have a small opacity in the right lower lobe. Following resection of the right lower and middle lobes her Cushing's syndrome regressed. Histological and electron microscopical studies showed that the tumour was a chemodectoma, and hormone estimations confirmed that this rare type of lung tumour was producing ACTH. This unique case adds another type of lung tumour to the list of those capable of ectopically producing one or more polypeptide hormones.

Seasonal asthma and the house-dust mite in tropical Africa

J. B. COOKSON The relationship between seasonal asthma and sensitivity to the house-dust mite has been investigated in a country with large seasonal variations in relative humidity.

Of 78 African asthmatic outpatients investigated in the asthma clinic at Harari Hospital, Salisbury, Rhodesia over a 12-month period, 64.1% gave a history probably suggestive of sensitivity to house dust and 55.1% a history strongly suggestive of such sensitivity. Only 10 patients thought they were sensitive to grass pollens and very few to other allergens.

On skin testing by the prick method, 35.9% had strong (weal diameter ≥ 5 mm after subtraction of control weal) reactions to the house-dust mite *Dermatophagoides pteronyssinus* compared with 1.9% of 51 matched controls without evidence of chest disease ($P < 0.0005$). Five patients had strong reactions to cat or dog dander but none had strong reactions to any of a variety of other allergens. Only the case of *D. pteronyssinus*, *Alternaria*, and snrub and flower pollens were weak reactions (< 5 mm diameter) significantly more common in the patients than the controls.

In 63 patients symptoms were seasonal, the great majority being worse during the months when the humidity averages between 70 and 80%. Hospital discharge rates for asthma show the same seasonal variations.

The growth of *D. pteronyssinus* is known to be mainly dependent on humidity levels, growing best at a humidity of between 70 and 80%. It stops growing and dies out when the humidity drops below 60%. It is suggested that the seasonal nature of our patients' symptoms is explained by their sensitivity to *D. pteronyssinus*.

Interpretation of provocation tests in asthma

S. P. HAYDU The use of provocation tests in asthma has been well described. It seems desirable in most situations to induce the smallest change which can be confidently ascribed to the provocative agent. One of the difficulties in the interpretation of small changes following provocation is the variability in tests of airways obstruction which may arise from spontaneous change or may be induced by performance of forced expiratory manoeuvres used to follow the changes in airways obstruction. An attempt has been made to establish the maximum degree of change in tests of forced expiration (FVC, FEV₁, and PEFR) which is likely to occur in asthmatic subjects without provocation, over the same periods of time and at the same intervals as were used to follow reactions to inhaled allergen. The results will be compared with the changes found in subjects following provocation with allergen, in both those who developed symptoms and those who did not.

It has been suggested that other tests of airways obstruction may be more sensitive indices of change. This may well be true, but it is essentially the variability of airways obstruction in asthma which can make the interpretation of small changes after provocation difficult. In subjects who show great

variation as a result of tests of forced expiration, measurement of airways resistance in the whole body plethysmograph may be better. Measurements made from flow volume curves did not appear to add greater sensitivity.

Mast cell saturation—a therapeutic approach to allergic asthma?

R. J. EARLAM Heartburn can be reproduced by pouring that allergic asthma is rare in communities where high IgE levels are found in association with widespread parasite infection. It is possible that parasite-induced IgE may protect against allergic disease by saturating IgE receptor sites on tissue mast cells and basophils, thus diminishing the chances of initiating immediate hypersensitivity reactions through antigen coupling of adjacent surface IgE molecules directed against environmental allergens.

This possibility has been tested *in vitro* by means of the chopped human lung technique. Normally, fragments of lung can be sensitized passively with serum from an allergic donor, so that histamine and other mediators are released following subsequent challenge with appropriate allergens. But when lung fragments were first exposed to sera from West African subjects having high total IgE levels, it proved impossible to release histamine from them by passive sensitization and allergen challenge. The inhibitory effect was shown to be quantitatively related to the IgE level of the 'blocking' serum. In contrast, when lung fragments were first sensitized passively and then exposed to IgE-rich serum, no inhibition of histamine release was found on subsequent allergen challenge.

On the nature of oesophageal pain

J. R. BENNETT Pain from several mediastinal structures may radiate, because of the phenomenon of referred pain, to the back, neck, shoulders, and arms. The viscera originating such pains include the oesophagus and the heart. The nervous connexions will be discussed.

The origin of oesophageal pain remains partly undetermined but in most instances arises either from direct irritation of its mucosal lining, or from strong contractions of its circular muscle—'spasm'.

In differentiating oesophageal pain from other causes of chest pain, the patient's description is of prime importance, but the nature of the pain, together with the common nerve supply of the mediastinal viscera, can make differentiation difficult. Reliance must then be placed either on demonstrating disease in the suspect organ by other means (for example, radiology and ECG) or by deliberately precipitating pain from an organ (for example, by exercise or oesophageal perfusion) which the patient can compare with his spontaneous symptoms. Both approaches have pitfalls, which will be discussed.

The pain of gastro-oesophageal reflux

M. ATKINSON Pain in gastro-oesophageal reflux does not show a close correlation with the degree of oesophagitis present because it may occur in patients with little endoscopic evidence of oesophagitis and be absent in patients presenting with bleeding from reflux oesophagitis.

Overnight recording of oesophageal acidity suggests that prolonged exposure of the oesophageal mucosa to high levels of acidity provokes pain but the acidity threshold for pain varies considerably from patient to patient and may be affected by other factors such as anxiety oesophagitis and disordered mobility.

Incoordinated motor activity can result from gastro-oesophageal reflux and, by interfering with oesophageal emptying, may increase the duration of mucosal exposure to high levels of acidity and so prolong pain and aggravate oesophagitis. Disordered motor activity can be abolished by anticholinergic drugs without relief of pain and hence is not an essential part of the pain mechanism in gastro-oesophageal reflux.

Rôle of pancreatic enzymes in the pathogenesis of hiatal hernia symptoms

G. SIMON BACHIR, J. LEIGH COLLIS, P. WILDING, and B. STARKIE Studies in this and other units have shown an increased quantity of bile salts in the gastric and oesophageal juices of hiatal hernia patients as compared with normal people (Crumplin *et al.*, 1974). The presence of bile salts indicates that pancreatic and biliary enzymes may also occur in the oesophagus.

To assess this, the alkaline phosphatase activity was measured in gastric juice, in five-hour oesophageal collections, and in the saliva. Alkaline phosphatase, which is inactivated in an acid medium, is secreted by the liver and is not secreted by the stomach or salivary glands. Tests were carried out on 54 patients divided into three groups—symptomatic hiatal hernia, peptic stricture, and controls.

Alkaline phosphatase could not be detected in either the gastric samples or in the saliva of any subject in the three groups. However, an activity of the enzymes was found in at least two oesophageal collections from all the subjects. Enzyme activity was greatest in the hiatal hernia group.

Since alkaline phosphatase and trypsin are active at alkaline pH, the possible reactivation of those enzymes after passage through the acid medium of the stomach was investigated. *In vitro* experiments have shown that alkaline phosphatase activity is reduced irreversibly by a decrease in pH. However, preliminary results suggest that although the activity of trypsin is severely curtailed by a pH decrease, some activity is regained when the pH is raised. It seems reasonable to assume that any upper alimentary collection which contains alkaline phosphatase will also contain pancreatic enzymes.

In conclusion therefore, the possible rôle of pancreatic enzymes in the pathogenesis of hiatal hernia symptoms cannot be completely excluded.

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Other types of oesophageal pain

R. J. EARLAM Heartburn can be reproduced by pouring 0.1 N HCl down a nasogastric tube and this retrosternal feeling is usually accepted as the commonest type of oesophageal pain. Using modern manometric techniques and accurate quantitation of the acid perfusion, it has been shown that pain in the upper abdomen can also arise from the lower oesophagus (Earlam, 1970, 1972a). This is localized to the epigastric region and can be relieved immediately by perfusing a sodium bicarbonate solution. If nocturnal waking is used as an index of severity, then every patient having such pain at night can have this upper abdominal pain reproduced by acid in the lower oesophagus. There is evidence that patients with free reflux and heartburn have an incompetent gastro-oesophageal sphincter and that patients with epigastric pain have a weaker sphincter and less reflux (Earlam, 1975).

It has also been shown that pain in the back, whether it is in the interscapular region, lower thoracic or lumbar region, can frequently arise from the oesophagus and be relieved by antacids. In addition, the vague feelings of distention, bursting, heaviness, spasm, and dysphagia found in oesophageal motility disturbances such as achalasia, diffuse oesophageal spasm, and scleroderma will be discussed and compared with the pathophysiology of Chagas' disease (Earlam, 1972b). This leads to two general principles: (1) oesophageal dilatation usually results from an abnormal gastro-oesophageal sphincteric response to swallowing, and the subsequent dilatation is frequently asymptomatic; (2) abnormal peristalsis in the body of the oesophagus does not usually cause dilatation, but it is likely to produce symptoms.

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Why measure regional lung function?

J. M. B. HUGHES Inhalation and intravenous injection of radioisotopes detected by external counting over the chest has replaced bronchspirometry as a measure of the relative perfusion and ventilation of different lung regions. While too expensive ever to be used routinely or in epidemiological surveys, measurement of regional lung function may be useful in the following circumstances: (a) diagnosis and follow-up

in pulmonary embolism; (b) preoperative assessment and postoperative follow-up in bullous emphysema, bronchiectasis, and lung neoplasms; (c) early detection of disease in groups at risk; (d) diagnostic help in unexplained dyspnoea or hypoxaemia. In addition, major contributions towards the better understanding of lung physiology have been made.

The lung perfusion scan, following intravenous injection of albumin macroaggregates or microspheres, has gained widespread acceptance as a screening test in cases of suspected pulmonary embolism, but good techniques for ventilation scanning have been lacking. Breathing radioactive aerosols or single breath inhalations of radioactive gases (for example ^{133}Xe) are conventionally used but have certain disadvantages. We are presenting two methods, both relatively simple for the patient who continues to breathe normally throughout the test: (1) clearance of ^{15}N after intravenous injection or rebreathing, and (2) continuous inhalation of $^{81\text{m}}\text{Kr}$. The first gives a quantitative assessment of the efficiency of regional ventilation, and the second a functional image of ventilation with a resolution comparable to the lung perfusion scan and well suited for routine examinations.

Sources of error in regional measurements using external scintillation detectors

D. M. ACKERY Measurement of radioactivity within the chest by external detectors is simple for both the patient and the operator, and many techniques have been designed to express the results in terms of an index of regional lung function. Errors which arise from these measurements can be broadly classified into those due to the physical problems of radiation detection, and those arising from physiological variables affecting ventilation and pulmonary blood flow.

Physical factors which influence the accuracy of a particular measurement include the sensitivity, spatial resolution, and uniformity of response of the detector. Also of importance are the characteristics of the radioisotope which is used: in this respect ^{133}Xe is not ideal, since it has a low energy gamma emission and is slightly soluble in blood and other tissues.

Physiological problems can arise with the position of the patient, the change in distribution of inspired gas at different lung volumes and different inspiratory flow rates, and the mechanisms which control the interrelationship between ventilation and perfusion.

When choosing a particular technique for regional lung function it is necessary to examine these and other factors in order to perform the routine clinical test with a minimum of error.

Unevenness of ventilation and ventilation-perfusion ratios in lung fibrosis

PAMELA W. EWAN In interstitial lung disease, multi-breath nitrogen washout curves are normal, and a

diffusion defect was previously thought to play a more important rôle in the efficiency of gas exchange than ventilation-perfusion inequality. In addition, studies with radioactive gases showed a loss of the normal gradient of ventilation and perfusion in different zones of the lung in pulmonary fibrosis, implying less mismatching than in normal subjects. The x-ray changes in this condition are most marked in the lower zones, and this study was undertaken to measure ventilation-perfusion ratios in different regions of the lung using radioactive tracers, so that functional abnormalities could be correlated with structural changes.

Nitrogen-13 was given by inhalation and by intravenous injection. The clearance of the isotope from the lung field was monitored continuously with a gamma camera. The efficiency of ventilation was calculated by comparing the results with those expected in an 'ideal' lung. The normal range for efficiency of ventilation in the upper zones is 45–60%, and in the lower zones 55–70%. The efficiency of ventilation was normal in some patients with pulmonary fibrosis but reduced in the majority. Where the x-ray changes were most marked, ventilation and ventilation-perfusion ratios were most impaired and the distribution of perfusion was most abnormal. On the other hand, the single-breath diffusing capacity did not correlate with the disturbance of ventilation-perfusion ratios, suggesting that \dot{V}_A/\dot{Q} mismatching and diffusion defects can contribute separately to the hypoxaemia.

Local perfusion and ventilation in chronic bronchitis and emphysema

NOEMI M. EISER It is well known that mismatching of ventilation and perfusion occurs in both chronic bronchitis and emphysema; ^{133}Xe clearance has shown the existence of perfused lung units with very low ventilation. In chronic airways obstruction associated with a raised arterial PCO_2 , raising the inspired oxygen concentration may cause the Pa, CO_2 to increase further. Previously the major cause was thought to be 'underventilation' due to a reduction in central respiratory drive following relief of hypoxaemia. Another possibility is that abolition of alveolar hypoxia overcomes local vasoconstriction in the more poorly ventilated units.

Nitrogen-13 was inhaled or injected intravenously in patients with chronic airways obstruction, and its clearance followed in lung regions with a gamma camera linked to a computer. Following inhalation of ^{15}N , regional clearance rates reflect the distribution and efficiency of ventilation; following injection clearance rates reflect the ventilation of perfused units, that is, regional ventilation-perfusion ratios. Measurements were made breathing air and then 30% oxygen.

All patients showed greatly prolonged clearance times in all lung regions with an uneven distribution of ventilation and \dot{V}_A/\dot{Q} ratios. In some patients the

total ventilation needed to clear 90% of the ^{15}N in each region increased by up to 175% when the inspired oxygen tension was raised. Since the increase was greater following the intravenous injection of ^{15}N the effect of oxygen breathing was principally to cause vasodilatation in hypoxic units with poor ventilation.

Assessment of regional lung ventilation with $^{81\text{m}}\text{Kr}$

F. FAZIQ and T. JONES The 190 KeV gamma emitter $^{81\text{m}}\text{Kr}$, 13 seconds half-life, can be continuously produced in the gas phase from its 47 hours half-life parent ^{81}Rb . If continuously added to inspired air during normal breathing, equilibrium of the isotope with alveolar gas is never reached because of the short half-life: thus the distribution becomes representative of ventilation rather than volume, unlike other radioactive gases for the same manoeuvre. Functional images of ventilation can be obtained in multiple views from a gamma camera on Polaroid photographs or 35 mm films. These images can be compared directly with the functional images of lung perfusion obtained after administration of macro-aggregates labelled with $^{99\text{m}}\text{Tc}$, owing to the close energy of the two isotopes. Using these isotopes, ventilation and perfusion scans have been of value in the diagnosis of pulmonary embolisms and in the assessment of the distribution of regional ventilation in asthma and chronic bronchitis before and after treatment.

The advantages of this technique over previous methods are: simplicity and short time required for the procedure for patient and operator; good resolution and statistics of the functional image; direct comparison with the perfusion scan; immediate repeatability; no need of a cyclotron on site; and a small radiation dose for the patient.

Functional lung capillary changes in the shock lung syndrome

W. A. CROSBIE and V. PARSONS Those concerned in the management of patients in the intensive care unit are now challenged by the condition called 'the shock lung syndrome'. Following a period of hypotension/resuscitation the lungs become oedematous and stiff and show a progressive impairment in their ability to transfer gas. There appear to be several pathological processes involved, but the common factor seems to be a change in lung capillary function. Excess fluid gathers in the interstitial tissue of the lung and progresses to overt pulmonary oedema.

We have been investigating changes in lung capillary permeability in this syndrome using the multiple indicator-dilution technique where four isotopes (^{125}I human serum albumin, ^{24}Na , ^{14}C urea, tritiated water) were injected simultaneously. We studied 10 patients in stage 3 of the syndrome and in two of these subjects again when they were recovering. We confirmed that a high cardiac output (mean 8.4 l/min SD 2.2) and increased venous admixture (Q_s/Q_t greater than 10%) was present in all the sub-

jects. The lungs contained excess water (pulmonary extravascular water space 520 ml SD 188). The relative recovery of labelled sodium was less than 90% of the labelled albumin in five of the patients but the labelled urea showed a different pattern. In the two subjects who were restudied the shape of the sodium and urea curves was almost back to normal. Hence changes in the permeability of lung capillaries occur in the shock lung syndrome, and new techniques can be used to follow these changes.

Respiratory disturbances associated with rabies encephalitis

D. A. WARRELL, N. MCD. DAVIDSON, HELEN M. POPE, and P. LEWIS Classical hydrophobia was seen in 13 patients with rabies in the north of Nigeria. Violent spasms of inspiratory muscles associated with a sensation of terror were triggered by attempts to drink water or by the sight, sound or mention of water and by other stimuli applied to the skin and upper respiratory tract. Terror was not explained by gross airways obstruction, pain or a conditional reflex. Hydrophobia could be overcome by tracheostomy and reassurance in some cases. As the encephalitis progressed, other types of periodic and ataxic breathing were observed, suggesting lesions at the mid-pontine level or pontomedullary junction. These disturbances are compared with respiratory myoclonus, van Leeuwenhoek's disease (Phillips and Eldridge, 1973).

Postmortem examination of three patients showed diffuse brainstem encephalitis. In two cases changes were particularly severe in the region of the nucleus ambiguus, thought to be the location of the inspiratory motor neurones (Merrill, 1970).

A mechanism for hydrophobia is suggested. Several basically protective reflexes, including coughing, sneezing, and aspiration and immersion reflexes, involve contraction of inspiratory muscles after mechanical stimulation of receptors in the upper respiratory tract (Widdicombe and Sterling, 1970). In the early stages of rabies encephalitis neurones inhibiting the inspiratory centre may be eliminated, thereby potentiating those reflexes causing inspiration. Exaggeration of the arousal associated with these reflexes might explain the terror of hydrophobia. The reason why hydrophobia is peculiar to rabies may be that in this encephalitis there is severe brainstem involvement at a time when full consciousness is retained.

Intensive care, which offers the only hope of survival in human rabies, was attempted in three patients, but all died with evidence of respiratory failure. The importance of respiratory disturbances as a cause of death in human rabies is discussed.

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Growth of the pulmonary circulation in congenital heart disease

SHEILA G. HAWORTH and LYNNE REID Different types of congenital heart disease can be regarded as vicarious experiments from which it is possible to derive information about the relation between structure and function in the lung of the newborn and child. In the pulmonary circulation abnormal haemodynamic conditions modify structure even *in utero* and after birth rapidly influence development of the acinar region. In ventricular septal defect, arterial medial hypertrophy has been correlated with the degree of elevation of pulmonary vascular resistance during life. Two patterns of response have been identified that are relevant to an understanding of the development and natural history of pulmonary vascular disease in this condition during infancy and early childhood.

Elongation of the costal cartilages

L. D. ABRAMS The mechanism which produces pectus excavatum is obscure. The deformity is not simply depression of the sternum which varies in extent. The level of angulation differs, and sometimes the whole sternum is tilted backwards. Moreover many patients have marked infraclavicular bulges and considerable flare of the costal margin. Even when the spine is straight the condition may be asymmetrical.

Pectus carinatum also varies markedly in both extent and degree. The keel is always formed by a row of 'knuckles' in the costal cartilages, the sternum being rotated and pushed forward. Occasionally the condition is so slight that it is limited to a few knuckles on one side of the sternum, and sometimes patients present with a solitary projection of one costal cartilage in adolescence and develop more later.

Occasionally isolated bumps and hollows are seen in the lower costal cartilages, producing quite ugly deformity.

It is suggested that all these deformities can be caused by elongation of the appropriate costal cartilages with consequent changes in position and shape of the sternum and ribs.

Correction can be carried out through a transverse incision by subperichondrial resection of cartilages and sometimes of incurved rib ends. The sternum is supported by a malleable stainless steel bar (Abrams, 1961) so shaped that it holds the sternum in proper relation to the rib ends and also corrects its rotation. The sternum should not be transected. Short segments of cartilage are replaced in their beds to hasten repair of the chest wall. The bar is removed more than six months later. Follow-up shows that correction of the deformity persists for periods of more than 10 years.

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Immune response to neoplasms

G. T. STEVENSON Any tumour is an antigenically complex mass in a host capable of a vast array of

immune responses. Animal work indicates that immune responses can sometimes be mounted against a variety of antigens on a single tumour, and that any single response might retard, promote or have no significant effect on the tumour growth.

In man it is useful to consider separately the immune responses against subclinical and overt tumours. The hypothesis of immunological surveillance states that most tumours are ablated immunologically at an incipient stage. Two types of evidence now support this idea: (a) the much higher subclinical than clinical incidence of certain tumours (for example neuroblastoma, and thyroid carcinoma), with the possibility that the immune response is one factor blocking the neoplastic progression; (b) the strikingly high incidence of certain tumours in the presence of immune deficiency.

The emergence of a tumour clinically would suggest that any surveillance mechanism has been overwhelmed. Nevertheless evidence of an immune response can often be found in one or more directions: the histology of the tumour and its regional nodes, the presence of antibodies and cutaneous delayed hypersensitivity to tumour constituents, and a range of responses given *in vitro* by the patient's lymphocytes on exposure to tumour cells or cell extracts. The last group of reactions has recently received much attention. It includes cytostatic and cytotoxic effects exerted on the tumour cells, blastic transformation by the lymphocytes, and the release of lymphocytic mediators. Reproducibility is a problem for a variety of technical reasons.

The responses thus revealed are frequently of dubious efficacy in retarding the tumours. Nevertheless there are hopes of marshalling the responses in a useful manner, or of mounting a new immunological attack on tumour-specific antigens. With all its difficulties and limitations the immunological approach has a considerable attraction in its promise of being able to hunt down and destroy the very last neoplastic cell.

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Immunological mechanisms in host resistance to tumours: therapeutic implications

G. A. CURRIE The use of immunotherapy for the treatment of cancer has been a promising idea for over 80 years and yet there is still little or no evidence that any form of such therapy is of clinical benefit. The demonstration of tumour-directed immunological reactions in cancer patients has in recent years given rise to yet another burst of enthusiasm for clinical immunotherapy. Recent studies will be reviewed and their lack of success emphasized.

An examination of the effector mechanisms operating either to kill or to inhibit the growth of tumour cells *in vivo* may allow a more rational application of immunotherapy. Two modes of tumour directed attack are discussed:

- (a) specific cell-mediated immunity;
- (b) immunologically non-specific but tumour-discriminating cellular mechanisms.

Studies of lymphocyte cytotoxicity and its inhibition by serum factors in patients with malignant melanoma indicate that specific cellular mechanisms do appear to correlate with clinical progress. Using such assay systems, various forms of immunological manipulation have been employed and a pilot study of immunotherapy for disseminated malignant melanoma is described.

However, there is considerable evidence that non-immunological mechanisms are operating in host resistance, and one such possible mechanism is provided by the activated macrophage. Studies of the mode of action of activated macrophages will be described and their possible implications for therapy will be discussed.

Fibrinogen metabolism and diffuse intravascular coagulation in chronic obstructive airways disease

JANE BRADLEY and J. A. HICKMAN Radioactive ^{125}I -labelled fibrinogen was used to study fibrinogen metabolism (Hickman, 1971) in 16 patients with respiratory failure due to chronic airways obstruction. Patients who were in a steady state were found to catabolize their fibrinogen normally. Those who were acutely ill had a rapid fibrinogen turnover which was controlled by heparin. It is suggested that these patients were depositing their fibrinogen as fibrin clot due to activation of the intrinsic pathway of coagulation. It would appear that long-term treatment of such patients with oral anticoagulants is not indicated but treatment with heparin may prove to be of benefit in the acute episode.

REFERENCE

Hickman, J. A. (1971). A study of the metabolism of fibrinogen after surgical operations. *Clinical Science*, 41, 141-152.

Effects of a molecular defect in collagen on lung structure and function

N. N. STANLEY, R. ALPER, E. L. CUNNINGHAM, N. S. CHERNIACK, and N. A. KEFALIDES Growing rats were given a diet containing semicarbazide (0.1% g/g). This is one of several lathyritic agents which impair the maturation of fibrous proteins by inhibiting the formation of intermolecular and intramolecular cross-linkages. After six weeks the animals were sacrificed and the mechanical, histological, and biochemical properties of their excised lungs were compared with those of control rats reared on a normal diet.

Static pressure-volume measurements during inflation and deflation with saline showed normal recoil pressures and compliance within the physiological range for lung volume. However, when inflated beyond normal limits the experimental lungs ruptured at a recoil pressure of only 2.58 (± 0.17) kPa compared with 3.36 (± 0.14) kPa in the controls ($P < 0.001$). Histological appearances were identical in

lungs of both groups when fixed at an inflation pressure of 2 kPa, but when fixed at 3 kPa there was widespread dilatation of terminal air spaces and rupture of alveolar walls in experimental lungs which was not apparent in the controls. At the lower fixation pressure the mean linear intercepts (Lm) in the experimentals ($56.2 \pm 2.5 \mu\text{m}$) and controls ($55.5 \pm 2.2 \mu\text{m}$) were virtually equal, but after fixation at 3 kPa the Lm in the experimentals ($71.4 \pm 4.4 \mu\text{m}$) was significantly higher than in the controls ($58.7 \pm 2.4 \mu\text{m}$) ($P < 0.05$). Biochemical analyses revealed a deficiency of collagen cross-linkages in experimental lungs, but no change in their total collagen content. There were no detectable changes in the quantity or quality of lung elastin.

It is concluded that a selective defect in collagen cross-linking reduces the tensile strength of lung tissue without altering its elasticity within physiological volume limits. Although compatible with normal lung structure and function, such a defect might provide a pathway to emphysema by predisposing the lung to rupture under conditions of physical stress.

Acute effects of inhaling tobacco and tobacco substitutes on pulmonary function

J. F. COSTELLO, N. J. DOUGLAS, D. C. FLENLEY, and M. F. SUDLOW New materials have been developed for use as substitute tobacco in the manufacture of cigarettes. We have studied the acute effects of inhaling smoke from one cigarette containing one of these materials—New Smoking Material—produced by ICI Ltd. This substance, NSM, produces a smoke with less tar than tobacco, no nicotine but similar concentrations of carbon monoxide. Condensates of NSM are less carcinogenic when painted on mouse skin than those from tobacco.

We have studied six normal subjects (five non-smokers, one pipe-smoker). Various tests of pulmonary function were used, some supposedly sensitive to narrowing of small airways in the lung. We compared the results of smoking one cigarette containing 70% tobacco and 30% NSM, 100% NSM and 100% tobacco yielding medium tar and nicotine.

Airways resistance increased in five out of six subjects after smoking 70% and 100% tobacco. Changes were maximal at 5-10 minutes and returned towards normal at 20 minutes. 100% NSM was without effect and this was also the case for smokers.

Measurements of closing volume were unaffected by either tobacco. The frequency dependence of compliance showed only small and variable changes within the accepted normal range.

Analysis of forced expiration using maximum expiratory flow volume curves and partial flow-volume curves (a forced expiration from 50% of the vital capacity) did not show any consistent changes, but in some subjects there was a fall in the maximum flow at 50% VC after smoking 100% tobacco not seen after NSM.

These results suggest that cigarette smoking has no acute effects on the small airways in normal subjects and we are finding similar results in a group of heavy smokers.

30% NSM with 70% tobacco has effects similar to 100% tobacco in these acute studies, whereas 100% NSM is apparently innocuous. However, more extensive, long-term studies are required before any complete assessment of its effects on pulmonary function can be made.

Bird-fancier's lung and coeliac disease—a clinical association

W. T. BERRILL Following the chance discovery of jejunal villous atrophy in a patient with allergic alveolitis due to contact with budgerigars, the possible association between these two conditions has been studied in two ways. First, in 16 patients with bird fancier's lung, evidence of small bowel pathology has been sought, including barium follow-through and jejunal biopsy where the history and/or initial screen-

ing tests suggested the possibility. To date villous atrophy has been found in five patients of whom without further exposure, two have had a second episode of apparent bird fancier's lung. Secondly, the sera from 38 patients with coeliac disease and 40 apparently normal control subjects were examined for avian precipitins. These were found in five of the patients with coeliac disease but in none of the controls. Three of the five had not been exposed to birds; none had evidence of bird fancier's lung.

An association between these two uncommon and apparently unrelated conditions may be due to:

- (1) both conditions being associated with an increased tendency to form immune complexes;
- (2) cross reactivity between gluten and avian antigen;
- (3) the intestinal lesion in some cases of coeliac disease being due to ingested avian antigen rather than gluten;
- (4) a damaged jejunal mucosa allowing increased absorption of avian antigen.

These alternatives are being explored.