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# Proceedings of The Thoracic Society

The Spring Meeting of The Thoracic Society was held on 7 February 1974 at the Royal College of Physicians, London. There were 10 short papers, one symposium, and one workshop. Summaries follow:

## Asthma in workers manufacturing ampicillin

R. J. DAVIES and D. J. HENDRICK Three men employed in the manufacture of the semisynthetic penicillin antibiotics developed attacks of shortness of breath and wheezing 21 to 24 months after their first exposure to the fine dusts of ampicillin, benzyl penicillin, 6 amino-penicillanic acid, and related compounds. Of the three workers, one was atopic, the other two non-atopic. Skin prick testing with the compounds they encountered at work was negative.

Occupational type provocation challenge testing (Pepys *et al.*, 1972) by inhalation of the fine dusts of ampicillin mixed with lactose produced late asthmatic reactions in all three workers. However, this was not the case on similar challenge with the fine dusts of benzyl penicillin and 6 amino-penicillanic acid in both commercial and specially purified forms and ampicillin manufactured by a different process. While each of these products gave rise to late asthmatic reactions in some of the workers, the substances to which each man responded varied widely.

Oral challenge by ingestion of one capsule of 500 mg benzyl penicillin or 500 mg ampicillin produced late asthmatic reactions similar to those produced by inhalation challenge.

Inhalation of 200 $\mu$g beclomethasone dipropionate before and in some cases three-hourly after provocation challenge blocked these late asthmatic reactions, but similar inhalation of 40 mg sodium cromoglycate had no such inhibitory effect.

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## Lung absorption and metabolism of inhaled drugs

J. W. PATERSON, MARION E. EVANS, and GILLIAN M. SHENFIELD Anti-asthmatic drugs are commonly given by inhalation. In recent years this has tended to be either from pressurized aerosols or, in the case of disodium cromoglycate (DSCG), a dry powder delivered from a Spinhaler. A large part of an 'inhaled' dose is swallowed (Blackwell *et al.*, 1970; Evans *et al.*, 1971), and therefore blood and urinary levels of drug following inhalation show the same pattern as is seen after oral administration. It is not possible, therefore, from analysis of blood and urine levels following inhalation to assess the effect of the lung on the small portion of drug which reaches it. To overcome this problem doses of drugs equivalent to those given by inhalation have been introduced directly into the lung at diagnostic bronchoscopy. Following the diagnostic procedure, a thin catheter was threaded down the bronchoscope to the level of a basal bronchus, and a solution of the labelled drug was injected. Studies have been performed using DSCG, salbutamol, and a new selective sympathomimetic bronchodilator drug, rimiterol.

The plasma picture following bronchoscopic administration showed that all drugs were very rapidly absorbed from the lung. With DSCG, 33% and 46% of the dose was recovered from the urine in 24 hours in two studies. In contrast, only 0·2% was recovered in the urine after an oral dose (Walker *et al.*, 1971). All the recovered radioactivity was unchanged compound. DSCG is rapidly and well absorbed from the lung as compared with the gastrointestinal tract, and the small percentage recovered from the urine after the use of a Spinhaler confirms that the majority of this dose is swallowed.

In two studies, 80% and 88% of a bronchoscopic dose of salbutamol were recovered in the urine in 24 hours. Metabolite accounted for only 27% and 40% of recovered radioactivity. In comparison, after oral administration as much as 60% of recovered radioactivity was metabolite (Evans *et al.*, 1973). Thus salbutamol is rapidly absorbed from both the lung and the gastrointestinal tract. Salbutamol is metabolized on passage through the gastrointestinal tract and/or in the liver, but not in the lung.

In contrast, rimiterol is absorbed and metabolized by the lung. Rimiterol, a catecholamine, is a substrate for catechol-O-methyltransferase. After direct introduction into the lung a much larger proportion of the drug is 3-O-methylated than after oral administration.

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### Muscle hypertrophy in the pulmonary circulation in cystic fibrosis

D. RYLAND and LYNNE REID In some cases of cystic fibrosis hypertrophy of muscle in small arteries is present without any increase in right ventricular weight although the duration and severity of lung involvement are similar to those in patients with right ventricular hypertrophy. Such 'dissociation' has not been seen in obstructive airway disease in the adult.

The degree of right ventricular hypertrophy correlates significantly with the degree of hypertrophy of small arteries and, somewhat surprisingly, even more significantly with increase in vein wall thickness. The relationship to muscle hypertrophy of the numbers of alveoli and small arteries and of the clinical and radiological features has also been investigated.

### Areas of ignorance in pulmonary pharmacology

G. R. BARER, P. HOWARD, B. THOMPSON, and P. M. WARREN Crucial questions about the action of drugs on the pulmonary circulation remain unanswered. We rarely know if the action is on arterial or on venous vessels, but the consequences for alveolar capillary blood volume, gas exchange, and fluid filtration will differ in the two cases. For some substances, including acetyl choline, histamine, and carbon dioxide, the action is in some circumstances vasoconstriction and in others vasodilatation; this dual action is unexplained. The relative effects of drugs on bronchial and on vascular smooth muscle and hence on pulmonary ventilation-perfusion relationships are also poorly documented. For example, we need to know more about bronchodilator drugs which contribute to hypoxaemia by increasing blood flow through unventilated lung.

Drugs and natural substances were studied in animals by methods designed to answer these questions. The methods included simultaneous measurements of airway and pulmonary vascular resistances, the use of atelectasis to induce active vasoconstriction by local hypoxia (Barer, Howard, and Shaw, 1970), and perfusion in a way which enabled us to determine whether the action of drugs was on arterial or on venous vessels. The results are discussed in relation to normal and abnormal lung function.

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Barer, G. R., Howard, P., and Shaw, J. W. (1970). *Journal of Physiology*, **211**, 139–155.

### Dietary pulmonary hypertension

D. A. HEATH There are many well-known causes of pulmonary arterial hypertension which include congenital cardiac septal defects, an elevated left atrial pressure, and recurrent pulmonary thromboembolism. It is not so widely appreciated that pulmonary hypertension may be dietary in origin. A group of plants which contain pyrrolizidine alkaloids may give rise to elevated pulmonary arterial pressure with associated pulmonary vascular disease characterized by medial hypertrophy and necrotizing arteritis. An example is *Crotalaria spectabilis* grown as a cover crop in the United States. Another is *Crotalaria fulva* which is used to prepare bush tea in Jamaica and which is also an aetiological agent of veno-occlusive disease of the liver. In Great Britain the common ragwort, *Senecio jacobaea*, is a familiar weed of hedgerows which is sold in some health stores for treatment of a variety of ailments; it gives rise to pulmonary hypertension in rats. Another plant now suspect is *Crotalaria laburnoides* which grows in Tanzania and may find its way into the brews of witch doctors. This group of plants, while admittedly exotic, establishes the important concept of dietary pulmonary hypertension.

### Effects of fulvine on pulmonary veins in rats

C. A. WAGENVOORT Female Wistar albino rats were given a single intraperitoneal or oral dose of fulvine. As with other pyrrolizidine alkaloids, the pulmonary arteries developed medial hypertrophy and fibrinoid necrotizing arteritis. In addition, narrowing and obliteration of pulmonary veins and venules began three to four weeks after administration of fulvine. In some cases the altered veins simulated arteries and required serial sections for identification.

Electron microscopic study of the intimal reactions in the veins showed that proliferation of both endothelial and smooth muscle cells had contributed to obstruction of the lumen. Signs of metabolic activity in both types of cell preceded the deposition of fibrin and necrosis of the venous wall. Such fibrinoid necrosis of small veins, however, is less common than the corresponding alteration in pulmonary arteries. The appearances suggest that fulvine affects both pulmonary arteries and veins. The involvement of both may detract from its usefulness as an animal model for pulmonary arterial hypertension.

### The aminorex controversy

J. M. KAY Aminorex (2-amino-5-phenyl-2-oxazoline) is an appetite suppressing drug which was available in Switzerland from November 1965 to October 1968. In 1967 a sudden 20-fold increase in the incidence of primary pulmonary hypertension was observed in a Swiss medical clinic. It was noticed that a considerable number of these patients had taken aminorex to

reduce weight. An increase in the incidence of primary pulmonary hypertension was observed in other clinics in Switzerland, and also in Austria and Germany where aminorex was available. An increased incidence of the disease was not apparent in countries where this drug was not available. A decline in the incidence of primary pulmonary hypertension occurred in Switzerland following the withdrawal of aminorex from the market. Microscopic examination of lung tissue from patients with pulmonary hypertension following aminorex ingestion has revealed the histological features of classical primary pulmonary hypertension with dilatation lesions. Acute and chronic experiments using rats, dogs, cows, and monkeys have failed to demonstrate that aminorex will produce hypertensive pulmonary vascular disease in animals. Despite the statistical evidence, there is no proof that aminorex causes pulmonary hypertension in man. Nevertheless it is worthwhile seeking a history of drug ingestion in patients presenting with unexplained pulmonary hypertension.

### Effects of chlorphentermine on the lung parenchyma

P. S. HASLETON There is now a suspicion that certain anorexigen drugs produce pulmonary arterial disease and give rise to a clinical picture of primary pulmonary hypertension. Chlorphentermine hydrochloride is an anorexigen which is marketed in Great Britain as Lucofen SA but which has been banned in both Sweden and West Germany. When administered intraperitoneally to rats, it does not produce disease of the pulmonary arteries.

However, it produces striking changes in the lung parenchyma. Prominent granular pneumocytes line the alveolar wall. Numerous large cells with a foamy cytoplasm appear in the alveoli and in places they are necrotic and break down to form intra-alveolar debris. On electron microscopy these foam cells are found to be macrophages which have ingested osmiophilic lamellar inclusions. Osmiophilic lamellar inclusions were also present in the endothelial cells of the pulmonary capillaries, in type 1 membranous pneumocytes, and in the Clara cells of the respiratory bronchioles.

These changes represent a toxic alveolitis due to the administration of chlorphentermine. Chronic administration of the drug may conceivably lead to either a fibrosing alveolitis or pulmonary arterial disease.

### The pulmonary response to Iprindole

B. CORRIN and G. S. VIJEYARATNAM Iprindole BP is a tricyclic antidepressant which has not been associated with untoward pulmonary effects in man but which in large doses causes changes in the rat lung relevant to certain human lung diseases. Large oral doses lead to the accumulation of free cells in the pulmonary alveoli simulating the appearances of desquamative interstitial pneumonia (DIP) while with chronic dosing these appearances gradually change to those of pulmonary alveolar proteinosis (PAP). Electron microscopy shows interstitial oedema and degenerative changes in the alveolar epithelium and capillary endothelium. Lipidic bodies extruded from the epithelium stimulate an initial alveolar macrophage reaction responsible for the DIP-like picture while in the long term, breakdown of these cells, release of their ingested epithelial bodies, and compaction of this granular lipidic material results in PAP. These changes will be compared with human cases of DIP and PAP studied with the electron microscope. The Iprindole model lends support to the idea that DIP and PAP represent characteristic but non-specific pulmonary responses rather than specific disease entities. Transmutation of DIP to PAP is uncommon in man but has been observed by Bhagwat *et al.* (1970).

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### Clinical aspects of drug-induced lung diseases

C. M. OGILVIE Drug-induced disorders of the respiratory system include central effects on ventilation, airways obstuction, inflammatory lesions in the lung itself, and disturbances of the pulmonary circulation. Some causes, clinical features, and methods used for the early detection of drug-induced lung disease will be discussed, with particular reference to fibrosing alveolitis.

### Paraquat lung

P. H. SMITH Following accidental ingestion of the herbicide, paraquat, there is often early clinical evidence of pulmonary oedema which is sometimes associated with dyspnoea. Administration of paraquat to experimental rats is also associated with the early development of pulmonary oedema and dyspnoea. The primary lesion responsible for this is hydropic degeneration followed by disintegration of the alveolar epithelium causing denuded capillaries to be brought into direct contact with alveolar air. In some rats this stage regresses as in some non-fatal human cases of paraquat poisoning. In the majority of rats the lungs become infiltrated by numerous primitive pro-fibroblasts which differentiate into a dense, cellular, intra-alveolar fibrosis. The development of this fibrosis is inexorable and leads to dyspnoea of increasing severity culminating in death from respiratory failure. The pulmonary fibrosis of paraquat poisoning in man is frequently described as a diffuse interstitial fibrosis of the lungs. However, there is evidence to suggest that, in fact, it has an intra-alveolar origin similar to its pathogenesis in the rat. This might explain the lack of success of steroid therapy as applied to human cases of paraquat poisoning.

### Contribution of aortic valves to coronary blood flow

J. F. CORNHILL, J. TEIJEIRA, A. J. GUNNING and J. A. ABBOTT

The haemodynamics of the main left coronary artery (MLCA) were examined in 12 anaesthetized goats with normal and experimentally created incompetent aortic valves. The flow patterns in the MLCA were measured by means of an electromagnetic flow probe.

In animals with normal aortic valves, the flow curves were biphasic with 10% to 20% of the total MLCA flow occurring in systole. The systolic component is probably stored in the capacitor-like epicardial vessels and perhaps the outer myocardium. Only very slight retrograde flow was observed at the onset of systole.

When the aortic valve was made incompetent by tearing the non-coronary sinus leaflet, the systolic contribution of MLCA flow increased to a maximum of 90% of the total flow in the severely incompetent case. A very large retrograde flow occurred at the beginning of diastole. The large systolic flow into the epicardial capacitor is due to the rapid increase in blood pressure from the lowered diastolic pressures to systolic levels. At the onset of diastole, the epicardial vessels discharge the blood not only into the myocardium, as in the case with a normal aortic valve, but also into the aorta due to the low diastolic pressure associated with aortic incompetence. The total MLCA flow is thus greatly reduced with aortic incompetence.

### The lung capillary bed during exercise in right and left heart failure

W. A. CROSBIE The structure and function of the lung capillary bed change when the heart is failing. In left heart failure the lung capillaries become congested when the pulmonary venous pressure rises, and in right heart failure the basic disease process may damage the alveolar tissue itself.

We have investigated the response to exercise of the lung capillary bed in a group of 5 subjects with cor pulmonale and in a group of 6 uraemic patients with congested lungs. We measured the blood/gas parameters, cardiac output, and distribution volumes of labelled water and sodium in the lungs of these patients at rest and then again while exercising on a bicycle ergometer.

Our results show that the gas exchange deteriorated on exercise in the right heart failure group even though the cardiac output increased but the sodium exchange in the lungs remained normal. This was in contrast to the subjects with congested lungs in whom the gas exchange continued normally when the cardiac output increased but deteriorated when the cardiac response was poor. In addition, the sodium exchange in the lung increased when left ventricular failure was present.

These findings suggest that the ability of the lung capillary bed to respond to the demands of excercise is different in the two states. In cor pulmonale there is minimal flexibility of the lung vascular bed to respond to increased perfusion, while in lung congestion the vascular bed can still respond to increased perfusion. This basic difference is important when planning treatment of the two clinical states.

### Lung mechanics during extracorporeal circulation

M. GREEN, G. KELMAN, L. HANSEN and P. DRINKER There have been conflicting reports as to the effects of extracorporeal circulation on the mechanics of normal lungs (Weedn *et al.*, 1970; Ellis *et al.*, 1969). We therefore measured the pulmonary resistance and compliance in sheep during extracorporeal circulation.

Experiments were performed on five supine sheep, anticoagulated and anaesthetized with chloralose and succinyl choline. The animals were tracheostomized and ventilated with positive end expiratory pressure of 2 cm of water. We used a venoarterial extracorporeal circulation. Blood passed from the right atrium through three parallel Lande-Edwards oxygenators and was pumped through a heat exchanger and a blood filter via the right femoral artery into the aorta.

Intrapleural pressure was measured with an oesophageal ballon. Air-flow rate was recorded from a pneumotachograph and integrated to give volume. Breath to breath dynamic lung compliance and airways resistance were measured by subtraction techniques (Mead and Whittenberger, 1953).

Measurements were made continuously before, during, and after extracorporeal bypass. Bypass was started at a low extracorporeal flow rate and increased in steps to 3 l/min or more so that five to seven different extracorporeal flow rates with 30-minute measurement periods were established for each sheep. Extracorporeal circulation caused no significant changes in airway resistance or pulmonary compliance, and there was no correlation between bypass flow rate and either resistance or compliance.

Experiments were performed on four of the sheep to study the effect of reduction in systemic blood volume while pulmonary blood flow was maintained constant. The sheep were stabilized on an intermediate extracorporeal flow rate. They were then bled about 500 ml, and simultaneously the extracorporeal flow rate was reduced to prevent reduction in pulmonary blood flow. Following systemic haemorrhage there was a marked increase in airway resistance (mean +52%) and a decrease in compliance (mean −22%). Compliance and resistance returned to pre-haemorrhage levels following re-transfusion of the shed blood. These changes were unaltered by vagotomy.

It is concluded that pulmonary mechanics are relatively insensitive to pulmonary blood flow but sensitive to systemic vascular volume.

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### Vascular complications of cervical rib

G. W. TAYLOR Vascular complications are usually seen in association with the complete variety of cervical rib which articulates anteriorly with the first rib. These complications are embolic in nature, and the emboli arise from the area of post-stenotic dilatation in the subclavian artery immediately distal to the cervical rib. The clinical presentation may be sudden severe digital ischaemia unheralded by previous warning signs or symptoms. In these circumstances the patient should be given heparin immediately and the subclavian artery should be explored as a matter of urgency. If embolectomy is unsuccessful, upper thoracic sympathectomy should be done. Prophylactic excision of cervical ribs should be considered in patients with complete ribs and high riding subclavian arteries.

### Acquired conditions of the chest wall

M. BATES The thoracic surgeon incises the chest wall on numerous occasions in order to deal with diseases of the heart, lung, and mediastinum but infrequently finds anything wrong with the structures of the chest wall.

When reading a chest radiograph it is easy to miss gross pathology in the ribs and sternum if too much attention is focused on the intrathoracic structures.

I thought the chest wall diseases which I have seen over the last 20 years while working in three hospitals would be of interest, and I have studied them under the following headings: *(a)* Primary tumours of ribs and sternum; *(b)* Secondary tumours of ribs and sternum; *(c)* Cysts; *(d)* Secondary pressure effects on ribs; *(e)* Infections; *(f)* Miscellaneous.

*(a)* 1. Man of 30 with bilateral rib chondromata
2. Girl of 13 with a right 10th rib chondroma, missed at first X-ray and becoming chondrosarcoma 3 years later
3. Man of 50. Chondrosarcoma right 10th rib treated with preoperative DXR and operation
4. Man of 56. Chondrosarcoma right 2nd rib presented as a primary tumour
5. Woman of 81. Chrondrosarcoma of sternum treated by total excision
6. Woman of 65 with fibrosarcoma of rib

*(b)* 1. Man of 60. Rib secondaries from carcinoma of the prostate
2. Woman of 50. Rib secondaries from carcinoma of the thyroid
3. Man of 55. Direct secondary involvement of rib from primary lung tumour

*(c)* 1. Boy of 14 with aneurysmal bone cyst
2. Man of 50 with multiple cysts from parathyroid tumour

*(d)* Case of: 1. Neurofibroma; 2. Ganglioneuroma; 3. Neurosarcoma; 4. Coarctation of the aorta

*(e)* Case of: 1. Tuberculous rib; 2. Boy of 14 with actinomycosis of ribs

*(f)* Case of: 1. Multiple myelomatosis; 2. Paget's disease of rib; 3. Eosinophilic granuloma.

### SI units in clinical respiratory physiology

J. E. COTES The units in which the lung function results are reported are now in process of modification to bring them into line with the new internationally agreed version of the metric system, the so-called SI system of units. The latter are based on three primary units, the metre, the kilogram, and the second. From these is derived the new unit of pressure, the pascal or newton per square metre which is the pressure exerted over an area of 1 square metre by a mass of 1 kilogram acting under an acceleration of 1 m $s^{-2}$. The system can be applied with varying degrees of sophistication, but in practice it mainly affects two quantities, the pressure, which in the context of lung physiology is now measured in kilopascal (kPa) where 1 kPa is 10·2 $cmH_2O$ or 7·5 mmHg, and the quantity of chemical substance, for example oxygen, which is now reported in millimoles (mmol) where 1 mmol in the case of an ideal gas is 22·4 ml STPD. The minute may continue to be used where it is appropriate to do so. The changes affect in particular the units for peak expiratory flow rate (1 $s^{-1}$), lung compliance (1 $kPa^{-1}$), airways resistance (kPa $1^{-1}$ s), ventilatory response to breathing $CO_2$ (1 $min^{-1}$ $kPa^{-1}$), transfer factor for the lung (mmol $min^{-1}$ $kPa^{-1}$), and gas exchange (mmol $min^{-1}$). In the latter instances the time may alternatively be reported in seconds.

The new units for gas exchange render obsolete the use of the symbol $V$ to represent the amount of gas absorbed or excreted in the lung. This is now symbolized by $n$ for number of moles; thus the uptake of oxygen is represented as $nO_2$ instead of $VO_2$. It is suggested that the new units should in future be used by contributors to the Society's meetings.

### Chest injuries: Introduction: review of five years' experience

B. J. BICKFORD During 1968–72, 88 patients with chest injuries were treated in the Regional Thoracic Surgical Centre, Liverpool; 74 (84%) were males, and 61 (69%) followed road accidents. The peak age incidence was in the 5th to 7th decades, and mortality was much higher in the 38 patients over 50 (26%) than in 50 patients younger than this (2%). The overall death rate was 12·5%.

Cases were classified as:

Group I Chest injury alone: 40 cases, 27 needing some form of surgery; 2 deaths (5%).

Group II Injury to chest and one other body region: 25 cases, 23 needing surgery; 4 deaths (17%).

Group III Multiple injuries: 24 patients, 22 needing surgery; 6 deaths (25%).

In groups II and III the upper part of the body (head, face, arms, and upper abdomen) was predominantly injured.

Of the whole series 25% (22) required tracheostomy, and 19 needed to be ventilated mechanically. Of the latter, 7 (37%) died, and again the mortality over the age of 50 was very much greater (75%) than in younger patients (9%).

Mortality is related to the severity of the injury, especially if this is initial 'contusion' of the lungs. Infection by Gram-negative organisms following IPPV is frequently fatal, especially in older patients.

It is concluded that IPPV should be avoided whenever possible, perhaps by wider use of surgical stabilization of the chest. It is, however, very difficult to suggest an adequate alternative for many of these severely injured patients.