the risk of pregnancy. On the other hand, a woman with mild focal glomerular disease may have two or three successful pregnancies under supervision without apparent ill-effect. One cannot be dogmatic about the outcome of any particular pregnancy. At this stage, we have only broad general principles to guide us. Diffuse glomerular disease is more serious for mother and foetus than focal glomerular disease. Hypertension complicating renal disease may be a serious development and if severe, may require immediate termination of pregnancy. A pregnancy may be successful in spite of serious impairment of renal function but further impairment usually occurs during pregnancy and this may be sudden and of very serious significance for the mother.

Acknowledgments

This work was largely carried out at the Royal Women's Hospital, Melbourne, and at the Queen Victoria Hospital, Melbourne.

We gratefully acknowledge help which we have had from the Honorary Obstetric staff, resident staff and Departments of Bacteriology, Biochemistry and Radiology at these hospitals.

We are particularly indebted to Dr Margaret Bullen, Research Assistant at the Queen Victoria Hospital, and Dr John Laver, the Medical Superintendent of the Royal Women's Hospital, for their help.

This work was supported by a grant from the N.H. and M.R.C. of Australia and from the Wellcome Foundation.

References

- BROWNE, F.J. & BROWNE, J.C.Mc. (1960) *Antenatal and Postnatal Care*, p. 27. Churchill, London.
- FAIRLEY, K.F., BOND, A.G. & ADEY, F.D. (1966) The site of infection in pregnancy bacteriuria. *Lancet*, i, 939.
- KASS, E.H. (1960) In: *Biology of Pyelonephritis* (Ed. by E. H. Kass and E. L. Quinn). Little Brown, Boston.
- KINCAID-SMITH, P. (1965) In: *Progress in Pyelonephritis* (Ed. by E. H. Kass), p. 11. Davis, Philadelphia.
- KINCAID-SMITH, P. & BULLEN, M. (1965) Bacteriuria in pregnancy. *Lancet*, i, 395.
- LEBLANC, A. & MCGANITY, W.J. (1965) *Progress in Pyelonephritis* (Ed. by E. H. Kass), p. 58. Davis, Philadelphia.
- LITTLE, P. J. (1967) The incidence of urinary infection in 5000 pregnant women. *Lancet*, ii, 925.
- MACKAY, E.V. (1963) Pregnancy and renal disease. *Aust. N.Z. J. Obstet. Gynaec.* 3, 21.
- STUART, K.L., CUMMINS, M.B. & CHIN, M.A. (1965) In: *Progress in Pyelonephritis* (Ed. by E. H. Kass), p. 45. Davis, Philadelphia.
- WILSON, C. (1958) *A Symposium on Non-Toxaemic Hypertension in Pregnancy* (Ed. by N. E. Morris and J. C. M. Brown). Churchill, London.

Research into bronchitis and emphysema

C. M. FLETCHER

N. L. JONES

E. J. M. CAMPBELL

Royal Postgraduate Medical School, London

DURING the first half of this century the chest illness usually termed 'chronic bronchitis and emphysema' did not receive the attention merited by its high morbidity and mortality. When the Postgraduate Medical School was set up in a Municipal Hospital at Hammersmith it soon became apparent that chronic airways obstruction was responsible for a form of heart failure which was not the rarity which it had appeared to be to those whose view of medicine was confined to cases admitted to undergraduate teaching hospitals. The first British study of the haemodynamics of this condition was published from Hammersmith (Mounsey *et al.*, 1952) and a clinico-pathological conference held there of a case of respiratory and cardiac failure in which emphysema was not found at necropsy was reported at the same time (*Postgraduate Medical Journal*, 1951). Physiological techniques for the study of disordered pulmonary function and techniques for post-mortem examination of the lungs

in the inflated state were later developed (Heard, 1958) and laid the foundation of more recent investigations into the relationship between function and structure, which have enabled definitions to be clarified. A spate of epidemiological studies of early disease were stimulated by the smog of the late 1950s and early 1960s and have been carried on in parallel with these clinical and pathological studies of the later stages.

Epidemiologists, interested in comparative studies, cannot use the clinician's unstandardized methods of diagnosis (Cochrane, Chapman & Oldham, 1951). To overcome this difficulty a questionnaire on respiratory symptoms was designed, and later tested by duplicate studies on a group of Post Office workers. The errors encountered (Fairbairn, Wood & Fletcher, 1959) enabled improvements to be made and led to the production and publication of a standardized questionnaire (M.R.C., 1960) which, during the past 10 years, has had world-wide use and has

been translated into at least twelve languages (M.R.C., 1966a). The first survey in which the questionnaire was used (Fletcher, Elmes & Fairbairn, 1959) showed that productive cough was much more prevalent in men than in women, chiefly due to differences in smoking habits. There was a significant relationship between productive cough (simple bronchitis), frequency of chest illnesses (infective bronchitis) and impairment of ventilatory capacity (obstructive bronchitis; M.R.C., 1965), and later surveys have confirmed this finding. Some men were found to have a severe degree of ventilatory impairment without any symptoms. This late development of symptoms makes it difficult for clinicians to study early stages in the natural history of bronchitis and emphysema.

The association between hypersecretion of mucus, recurrent infection, and airways obstruction, observed both by epidemiologists and clinicians, led to the hypothesis that the three were causally related. Hypersecretion was thought to encourage infection which damaged the bronchi and lungs, thus causing obstructive bronchitis and emphysema (Fletcher, 1959). This hypothesis is being tested by a prospective study of some 900 working men. This has shown that the rate of development of airways obstruction is in fact unrelated either to sputum volume or to frequency of chest infection (Fletcher *et al.*, 1967). It has also been found that the more severe the airways obstruction, the faster it increases. Thus, smokers who already have significant obstruction appear to be at special risk of disabling bronchitis. More detailed study of those men who are developing airways obstruction but are still symptomless may help to elucidate the nature of this early disease. Another observation made in this study was a steady decline in the severity and prevalence of simple bronchitis, which may possibly be due to the simultaneous decline in pollution of London air which has followed the Clean Air Act.

Among clinicians it has always been thought that while bronchitis, 'the English disease', was the commonest clinical form of airways obstruction in England, emphysema was more prevalent in the U.S.A. where bronchitis was rarely diagnosed. Comparative studies in the United Kingdom and the United States using standardized techniques showed that while simple bronchitis in smokers is only slightly more prevalent in England, there is much more mucopurulent and obstructive bronchitis, particularly in urban areas (Reid *et al.*, 1964; Holland *et al.*, 1965). This finding is compatible with the thirty-to-one difference in bronchitis mortality between the

two countries. It is likely that air pollution may combine with cigarette smoking in the causation of chronic airways obstruction.

An opportunity to compare the apparently different incidence of the clinical forms of disease was afforded by Dr Benjamin Burrows of the University of Chicago who, in 1960, suggested a co-operative study of patients attending his 'Emphysema' clinic and the Hammersmith Hospital 'Bronchitis' clinic, in order to find the extent to which such differences depended on differing terminology, rather than on true differences between the type of patient usually seen. Standardized techniques were used to study fifty patients in each clinic; a similar incidence of cough and dyspnoea was found and the range of pulmonary function abnormalities was also similar (Fletcher *et al.*, 1964). Serial studies of the same patients during the years following the initial study have also shown a similar mortality and progression of symptoms and functional abnormality (Jones *et al.*, 1967a). The morbid anatomical changes in patients who died were also similar (Burrows *et al.*, 1966).

The relative incidence of bronchitis and of emphysema among patients with chronic airways obstruction has been the subject of considerable argument, which has been complicated by confused terminology. A rational approach to standardized terminology was initiated by the CIBA Symposium (1959) and there is now general agreement that chronic bronchitis should be defined in terms of bronchial hypersecretion (M.R.C., 1965) and that the diagnosis of emphysema should be based on morbid anatomical criteria (W.H.O., 1961). Laws & Heard (1962), by comparing inflated lung specimens with radiographs of the same lungs during life, were able to show that a reduction in the number and the calibre of the peripheral pulmonary vessels in the chest radiograph was associated with severe emphysema. These findings were applied in a detailed study of sixteen patients (Fletcher *et al.*, 1963). The total lung capacity and its subdivisions were measured by a helium dilution technique first described by McMichael (1939), gas exchange properties were measured by carbon monoxide uptake, by analysis of arterial blood gases and by rapid analysis of expired gases using a mass spectrometer (West *et al.*, 1957). The patients were grouped according to the history of bronchitis and radiographic changes into three groups—severe emphysema without bronchitis, chronic bronchitis with emphysema and chronic bronchitis without emphysema. In the first group alveolar distension and destruction were reflected in an increased total lung capacity

and impaired transfer of carbon monoxide, but arterial blood gases were relatively normal and right heart failure was not seen. These findings contrasted with those in the third group; although the total lung capacity and carbon monoxide uptake were normal, hypercapnia and hypoxaemia were common, ventilation-perfusion abnormalities severe, and right heart failure frequent. The second group, with bronchitis and emphysema, were intermediate between the other two groups. This study suggested clinical and physiological criteria for the diagnosis of emphysema which were applied to the larger series of patients at Hammersmith and Chicago (Burrows *et al.*, 1964). X-ray changes of a sparse attenuated peripheral vascular pattern, low carbon monoxide uptake and increased total lung capacity were used as signs of emphysema (Type A patients) and large sputum volumes, normal CO uptake and total lung capacity, hypercapnia and cor pulmonale to indicate chronic bronchitis without significant emphysema (Type B patients). Of the 100 patients in the co-operative London/Chicago studies forty fulfilled Type A criteria and twenty-five the criteria for Type B; the remainder showed mixed or intermediate features (Type X) (Jones *et al.*, 1967a). Since the proportion of these three types of patient was similar in London and Chicago the Anglo-American disparity of diagnosis was shown to be largely semantic, but it remains probable that the total amount of chronic respiratory disease of all kinds is greater in the U.K. Necropsy examination of the lungs of patients studied fully in life have enabled the diagnostic criteria for emphysema to be refined (Burrows *et al.*, 1966). It is now well recognized that most patients with severe emphysema maintain normal resting P_{CO_2} and do not develop cor pulmonale until late in their disease, and that many patients with chronic hypercapnia and cor pulmonale are found to have relatively little emphysema at necropsy. The paradoxical finding of more severe blood gas disturbances in the patients with the less emphysematous lungs has been investigated by two studies of gas exchange during exercise. Blood gas measurements showed that an improvement in the distribution of ventilation-blood flow ratios in the lung often occurred when Type B patients exercised, whereas little improvement was seen in Type A patients (Jones, 1966). It has also been shown that gas exchange assessed by CO transfer improves on exercise in Type B but not in Type A patients (Bedell & Ostiguy, 1967). This improvement is presumably brought about by an increase in the ventilation of areas which are poorly ventilated

at rest. The ventilatory response to carbon dioxide may be studied using a simple rebreathing procedure (Clark, Clarke & Hughes, 1966) and Clark (1967) has found that the response is usually less in Type B than in Type A patients. Although mechanical factors undoubtedly play a part in the development of CO_2 unresponsiveness, it is likely that other factors, such as the relative absence of a hypoxic stimulus during exercise, may also be important. Many studies have emphasized the importance of studying patients during exercise; Campbell (1967a), in a recent review, has described an approach to the investigation of effort intolerance, and emphasized the increased information which is obtained from cardiovascular and pulmonary measurements if they are made during exercise instead of only in the resting state. A technique for studying the integrated responses to exercise of ventilation, gas exchange and cardiac output has now been developed (Jones *et al.*, 1967b), which can be simply applied in patients to assess functional abnormality, progress and the effect of treatment. One important measure which is obtained is the maximal ventilation in exercise, which is often much higher in patients with chronic airways obstruction than would be predicted from the simple tests of ventilatory capacity (Clark, Freedman & Campbell, 1967).

Once chronic airways obstruction is established most patients show a gradual progression which is, however, variable in its rapidity. Some patients deteriorate very slowly indeed and this should be remembered in assessing progress. The greater rate of decline in the forced expiratory volume in those most severely affected, as observed in the early stages of the disease, has also been found in patients with more severe obstruction (Jones *et al.*, 1967a). The fall in ventilatory capacity was found to be correlated with the progression of dyspnoea and the development of CO_2 retention. The same study showed that mortality was mainly related to CO_2 retention and was higher in Type B patients than in Type A. Type B patients are more prone to develop fluid retention and cor pulmonale. McMichael (1948) was among the first to point out that severe cor pulmonale may often occur in patients who are later found to have little or no emphysema.

When patients are referred to hospital on account of recurrent infections or progressive dyspnoea, airways obstruction is usually already established. Stopping smoking may on rare occasions lead to a dramatic improvement in airways obstruction. Several studies have demonstrated the beneficial effect of tetracycline

(M.R.C., 1966b) and ampicillin (Ayliffe & Pride, 1962) in the treatment of bronchial infection. Long-term tetracycline in a dose of 250 mg four times daily does not prevent chest colds, but reduces their duration (*British Medical Journal*, 1964); thus antibiotics are best used intermittently rather than for prophylaxis. Bronchodilators either by aerosol or oral administration are helpful. Treatment with steroids is occasionally unexpectedly effective; as their value in asthma is well known and as early studies suggested that they are mainly useful in chronic bronchitis with variable airways obstruction, we hoped that it might be possible to predict which patients would respond by measuring the bronchial reaction to inhaled histamine aerosol, using a body plethysmograph. The bronchial reactivity of bronchitics was found to be intermediate between the marked reactivity of typical asthmatic patients and normal subjects. No relation was found between the histamine response and the effect of a 2-week course of prednisolone in the majority of bronchitic subjects, but the most reactive subjects did show a response to steroids (Fletcher, 1967).

An acute respiratory infection will often lead to an increase in airways obstruction and ventilatory failure, particularly in Type B patients. On admission to hospital they are usually found to be severely hypoxaemic (arterial P_{O_2} 25–50 mmHg), hypercapnia being less severe (arterial P_{CO_2} 60–80 mmHg) (McNicol & Campbell, 1965). Treatment should aim at improving hypoxaemia at least to a level of arterial oxygenation which ensures an adequate tissue oxygen supply (arterial O_2 saturation of 70%), without leading to a progressively increasing P_{CO_2} (Campbell, 1967b). High levels of oxygenation will occasionally lead to severe hypercapnia with rises of 30 mmHg or more in as many minutes. More modest increases in the inspired oxygen concentration, to 24% or 28%, increase the inspired oxygen tension by 25–50 mmHg: although not all this increase is passed on to the arterial blood, arterial P_{O_2} increases by at least 10–30 mmHg usually without leading to progressive hypercapnia. If CO_2 tension does increase, a limit is set on the extent of the rise, for the oxygen tension will fall back to its original level before CO_2 has risen by more than 10–30 mmHg. Convenient methods for administering controlled oxygen at high flows have been developed by incorporating a venturi in a disposable mask and in a small head-tent (Campbell & Gebbie, 1966). Patients require intensive nursing care, physiotherapy, and frequent assessment in the early stages of treatment. Signs

of carbon dioxide retention are unreliable (Gross & Hamilton, 1963) and it is best to depend only on the patient's mental state and ability to cough and raise sputum, together with frequent measurement of mixed venous CO_2 pressure (Campbell & Howell, 1962). If, in spite of careful controlled oxygen administration and intensive attention, the CO_2 pressure increases and the mental state deteriorates stimulants, such as nikethamide, are tried (McNicol *et al.*, 1963); these will often lead to an improvement in consciousness which will allow the other measures to be used more effectively. Assisted ventilation is required probably in less than 10% of patients (Campbell, 1967b) and is now usually performed using an endotracheal tube rather than via a tracheostomy.

Rehabilitation of these patients is improved if they are fully assessed after recovery from episodes of acute respiratory failure and are seen two or three times a year in a special clinic where facilities for the study of lung function exist. The management of a patient whose lung function is not as bad as his symptoms suggest is different from that of a patient who, despite severe respiratory failure, minimizes his symptoms.

Conclusion

Two or three decades ago the problem of chronic airways obstruction was largely ignored. A patient with chronic cough, sputum or wheezing who became persistently breathless was said to have emphysema and this was thought to carry a grave prognosis. It has now been shown that it is the patient with severe obstruction without emphysema who has the worst outlook, though with modern management he may survive several episodes of oedematous cor pulmonale. The fundamental principles underlying the application of physiological techniques to clinical problems which were pioneered by John McMichael have been central to the role of the Royal Postgraduate Medical School in its contribution to these changing concepts.

References

- AYLIFFE, G.A.J. & PRIDE, N.B. (1962) Treatment of exacerbations of chronic bronchitis with ampicillin. *Brit. med. J.* ii, 1641.
- BEDELL, G.N. & OSTIGUY, G.L. (1967) Transfer factor for carbon monoxide in patients with airways obstruction. *Clin. Sci.* 32, 239.
- BRITISH MEDICAL JOURNAL (1964) Attacks of bronchitis. *Brit. med. J.* i, 718.
- BURROWS, B., FLETCHER, C.M., HEARD, B.E., JONES, N.L. & WOOLIFF, J.S. (1966) The emphysematous and bronchial type of chronic airway obstruction. *Lancet*, i, 830.

- BURROWS, B., NIDEN, A.H., FLETCHER, C.M. & JONES, N.L. (1964) Clinical types of chronic obstructive lung disease in London and Chicago: a study of 100 patients. *Amer. Rev. resp. Dis.* **90**, 14.
- CAMPBELL, E.J.M. (1967a) Exercise tolerance. *Sci. Basis Med. ann. Rev.* **8**, 129.
- CAMPBELL, E.J.M. (1967b) The management of acute respiratory failure in chronic bronchitis and emphysema. *Amer. Rev. resp. Dis.* **96**, 626.
- CAMPBELL, E.J.M. & GEBBIE, T. (1966) Masks and tent for providing controlled oxygen concentrations. *Lancet*, **i**, 468.
- CAMPBELL, E.J.M. & HOWELL, J.B.L. (1962) Rebreathing method for measurement of mixed venous PCO_2 . *Brit. med. J.* **ii**, 630.
- CIBA FOUNDATION GUEST SYMPOSIUM (1959) Terminology, definitions and classification of chronic pulmonary emphysema and related conditions. *Thorax*, **14**, 286.
- CLARK, T.J.H. (1967) Thesis presented for the degree of M.D., London University.
- CLARK, T.J.H., CLARKE, B.G. & HUGHES, J.M.B. (1966) A simple technique for measuring changes in ventilatory response to carbon dioxide. *Lancet*, **ii**, 368.
- CLARK, T.J.H., FREEDMAN, S. & CAMPBELL, E.J.M. (1967) Ventilatory capacity in chronic airway obstruction. (In preparation.)
- COCHRANE, A.L., CHAPMAN, P.J. & OLDHAM, P.D. (1951) Observers errors in taking medical histories. *Lancet*, **i**, 1007.
- FAIRBAIRN, A.S., WOOD, C.H. & FLETCHER, C.M. (1959) Variability in answers to a questionnaire on respiratory symptoms. *Brit. J. prev. soc. Med.* **13**, 175.
- FLETCHER, C.M. (1959) Chronic bronchitis. Its prevalence, nature and pathogenesis. *Amer. Rev. resp. Dis.* **80**, 483.
- FLETCHER, C.M. (1967) Bronchial infection and reactivity in chronic bronchitis. *J. roy. Coll. Physns Lond.* (In press).
- FLETCHER, C.M., ELMES, P.C. & FAIRBAIRN, A.S. (1959) The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *Brit. med. J.* **ii**, 257.
- FLETCHER, C.M., HILL, I.D., SPEIZER, F.S. & TINKER, C.M. (1967) Report to the Medical Research Council's committee on bronchitis. Unpublished.
- FLETCHER, C.M., HUGH-JONES, P., McNICOL, M.W. & PRIDE, N.B. (1963) The diagnosis of pulmonary emphysema in the presence of chronic bronchitis. *Quart. J. Med.* **32**, 33.
- FLETCHER, C.M., JONES, N.L., BURROWS, B. & NIDEN, A.H. (1964) American emphysema and British bronchitis: a standardized comparative study. *Amer. Rev. resp. Dis.* **90**, 1.
- GROSS, N.J. & HAMILTON, J.D. (1963) Correlation between the physical signs of hypercapnia and the mixed venous PCO_2 . *Brit. med. J.* **ii**, 1096.
- HEARD, B.E. (1958) A pathological study of emphysema of the lungs with chronic bronchitis. *Thorax*, **13**, 136.
- HOLLAND, W.W., REID, D.D., SELSTER, R. & STONE, R.W. (1965) Respiratory disease in England and the United States. *Arch. environm. Hlth*, **10**, 338.
- JONES, N.L. (1966) Pulmonary gas exchange during exercise in patients with chronic airway obstruction. *Clin. Sci.* **31**, 39.
- JONES, N.L., BURROWS, B. & FLETCHER, C.M. (1967a) Serial studies of 100 patients with chronic airway obstruction in London and Chicago. *Thorax*, **22**, 327.
- JONES, N.L., CAMPBELL, E.J.M., MCHARDY, G.J.R., HIGGS, B.E. & CLODE, M. (1967b) The estimation of carbon-dioxide pressure of mixed venous blood during exercise. *Clin. Sci.* **32**, 311.
- LAWS, J.W. & HEARD, B.E. (1962) Emphysema and the chest film: a retrospective radiological and pathological study. *Brit. J. Radiol.* **35**, 750.
- McMICHAEL, J. (1939) A rapid method of determining lung capacity. *Clin. Sci.* **4**, 167.
- McMICHAEL, J. (1948) Heart failure of pulmonary origin. *Edinb. med. J.* **55**, 65.
- McNICOL, M.W. & CAMPBELL, E.J.M. (1965) Severity of respiratory failure. Arterial blood-gases in untreated patients. *Lancet*, **i**, 336.
- McNICOL, M.W., PRIDE, N.B., REYNOLDS, E.O.R. & SEMPLE, S.J.G. (1963) Nikethamide for severe CO_2 retention in exacerbations of chronic bronchitis. *Brit. med. J.* **i**, 646.
- MEDICAL RESEARCH COUNCIL (1960) Standardized questionnaire on respiratory symptoms. *Brit. med. J.* **ii**, 1665.
- MEDICAL RESEARCH COUNCIL (1965) Definition and classification of chronic bronchitis for clinical and epidemiological purposes. *Lancet*, **i**, 775.
- MEDICAL RESEARCH COUNCIL (1966a) Instructions for the use of the questionnaire on respiratory symptoms. Distributed by W. J. Holman Ltd, Dawlish.
- MEDICAL RESEARCH COUNCIL (1966b) Value of chemoprophylaxis and chemotherapy in early chronic bronchitis. *Brit. med. J.* **i**, 1317.
- MOUNSEY, J.P.D., RITZMAN, L.W., SELVERSTONE, M.J., BRISCOE, W.A. & McLEMORE, G.A. (1952) Circulatory changes in severe pulmonary emphysema. *Brit. Heart J.* **14**, 153.
- POSTGRADUATE MEDICAL JOURNAL (1951) Clinico-pathological conference No. 10: 'Emphysema'. *Postgrad. med. J.* **27**, 25.
- REID, D.D., ANDERSON, D.O., FERRIS, B.G. & FLETCHER, C.M. (1964) An Anglo-American comparison of the prevalence of bronchitis. *Brit. med. J.* **ii**, 1487.
- WEST, J.B., FOWLER, K.T., HUGH-JONES, P. & O'DONNELL, T.V. (1957) Measurement of the ventilation-perfusion ratio in the lung by the analysis of a single expirate. *Clin. Sci.* **16**, 530.
- WORLD HEALTH ORGANIZATION (1961) Chronic cor pulmonale. Report of an expert committee. *Wld Hlth Org. Techn. Rep. Ser.* No. 213, Geneva.