Sinclair-Smith, who all helped to create the Institute, and who have done so much for cardiology in Australia.

The Lungs and Circulation in Chronic Pulmonary Disease

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The investigational programme of the respiratory laboratory in the Department of Medicine of the University of Sydney covers a wide spectrum of normal and disordered pulmonary function in health and disease. The central theme is the definition of mechanisms causing disability and determining prognosis. There are obviously many points of overlap, but for convenience of description the programme can be broadly divided into five aspects.
PULMONARY VASCULAR RESPONSIVENESS

Fowler and Read (1961, 1963a) developed a new technique for determining the proportion of blood flow passing through the upper and lower zones of the lung in normal subjects. This technique depended upon analysis of the cardiogenic oscillations on gas tension plateaus when these were recorded continuously with a respiratory mass spectrometer during expiration. The technique was developed shortly after the earliest isotopic techniques for examining regional pulmonary blood flow; it was in no way competitive with them, but rather complementary. Since it involved no radiation hazard, measurements could be repeated every few minutes in order to follow the pattern of redistribution of pulmonary blood flow in response to various physiological stimuli.

The technique was used to study the effect of alveolar hypoxia (Fowler and Read, 1963b) and of exercise (Read and Fowler, 1964) in normal subjects. A curious and reproducible pattern of behaviour emerged. In approximately two-thirds of subjects, breathing a low-oxygen mixture led to a redistribution of pulmonary blood flow towards the upper zones of the erect lung; in the remaining one-third there was no such redistribution. A similar pattern emerged in the same subjects in response to exercise.

It was postulated that normal subjects were showing a spectrum of response to alveolar hypoxia ranging from no response at all up to a classical brisk pulmonary vasoconstriction, with consequent rise of pulmonary artery pressure and increased perfusion of upper lung zones. Segal, Bishop, and Fowler (unpublished) working in Birmingham subsequently confirmed this interpretation by combining the Sydney technique with cardiac catheterisation observations during alveolar hypoxia.

Thus, it seemed that normal subjects showed a wide spectrum of innate pulmonary vascular responsiveness to stimuli such as hypoxia. Without inferring that there were two clear-cut categories, the descriptive phrases ‘responders’ and ‘non-responders’ were introduced to indicate the extremes of this spectrum of responsiveness. At that time certain predictions were made, for subsequent exploration, of the possible influence of this innate characteristic on the progression of chronic lung disease in individual patients (Pain et al., 1962; Read and Fowler, 1962; Read, 1964).

When a subject develops obstructive lung disease, part of his lungs becomes hypoventilated and hypoxic due to regional airways obstruction. If he were a non-responder, no great regional vasoconstriction in the hypoventilated regions would be expected. The low ventilation-perfusion ratio in such regions would lead to arterial hypoxaemia and hypercapnia. If he were a responder, one might expect some local regional vasoconstriction in poorly
ventilated regions, with movement of local ventilation-perfusion ratios towards normal. Arterial blood gas tensions would thus be preserved at a better level than otherwise but only at the cost of an increase of pulmonary vascular resistance. In essence, it was postulated that, for a given variety and degree of chronic lung disease, a subject's innate pulmonary vascular responsiveness might play a large part in determining both maintenance of blood gas tensions and the development of right heart changes. These opposing actions would obscure any simple relationship between blood gas tensions and the development of cor pulmonale.

It was not possible to predict the likely effect of these interactions on overall prognosis. During subsequent years we have undertaken a series of studies directed to exploration of these hypotheses, and these studies are continuing.

Pain et al. (1965) reported studies in 54 patients with chronic obstructive lung disease (OLD) in whom the effects of breathing oxygen were examined in some detail. It had been well documented that some patients with OLD who breathed oxygen developed an increase of arterial $P_{CO_2}$ and that subjects with OLD breathing oxygen sometimes hypoventilated. Remarkably, it was largely a matter of assumption that these two changes ran in parallel in the same patients. There were, in fact, very few reported studies in which both ventilation and arterial $P_{CO_2}$ had been measured while breathing oxygen. In the Pain et al. group of patients, increase of arterial $P_{CO_2}$ was common but was not always associated with a fall of minute ventilation, or, if hypoventilation occurred, it was often quite insufficient to account for the rise in arterial $P_{CO_2}$. There was indirect evidence to support the postulation that oxygen was acting as a pulmonary vasodilator and that, in those patients (responders) in whom regional airways obstruction had led to regional compensatory vasoconstriction, oxygen breathing produced vasodilatation with a worsening of overall ventilation-perfusion distribution. This study was extended by Lee and Read (1967) who demonstrated, by serial measurements of $V_D/V_T$ ratio during oxygen breathing in patients with OLD, that oxygen produced a worsening of ventilation-perfusion distribution, wholly attributable to more even distribution of pulmonary blood flow. In both series of patients the proportion of apparent responders to non-responders was 2 to 1, the same proportions as had been demonstrated previously among normal subjects.

The other pulmonary vasodilator used to test for the presence of responders and non-responders among abnormal subjects was aminophylline. Pain et al. (1967) showed that when patients with OLD were given 250 mg of aminophylline intravenously, arterial oxygen tension fell significantly in about two-thirds of them. This was again interpreted as indicating that these subjects
(but not the remaining one-third) had pre-existing regional compensatory vasoconstriction in some parts of their lungs, reversed by the action of the injected drug.

Read and Lee (1967) examined the influence of pulmonary vascular responder status on the incidence of right-sided electrocardiographic changes and a previous history of heart failure. When ventilatory capacity was very considerably reduced (to less than 0.75 litre), there was no difference in the incidence of cardiovascular complications between responders and non-responders. At higher levels of \( \text{FEV}_1 \) right-sided ECG changes and a previous history of heart failure were confined to pulmonary vascular responders. Read and Lee (1967) and Pain et al. (1965) also found that blood gas tensions were better preserved among responders than among non-responders for a given level of airways obstruction. It was thus shown that being a pulmonary vascular responder did lead to preservation of blood gas tensions, but that it was associated with a higher incidence of cor pulmonale at an earlier stage of the lung disease (Read et al., 1967).

The most recent study in this series (Lindsay and Read, 1969; Lindsay, 1970) was an examination of prognosis in 247 patients with OLD, whose status as pulmonary vascular responders or non-responders had been established earlier in the laboratory. Follow-up extended from one to ten years. Using a life table analysis, they showed that three-year survival in patients with an initial \( \text{FEV}_1 \) of less than 0.5 litre was poor (about 30 per cent) for both responders and non-responders. As survival was traced through groups with increasing initial \( \text{FEV}_1 \), responders fared less well than non-responders. In the group with an initial \( \text{FEV}_1 \) greater than 1 litre, mortality from cardio-respiratory causes was confined to responders, and this mortality rate (45 per cent at 3 years) was about the same as in responders with an initial \( \text{FEV}_1 \) between 0.5 and 1 litre. The situation thus arises that pulmonary vascular status as a responder seems more important than the absolute level of \( \text{FEV}_1 \) (provided this is greater than 0.5 litre), in determining death from cardio-respiratory causes among patients with obstructive lung disease. This phenomenon represents an interesting example of the natural history of a single disorder being significantly modified as between individuals by an innate biological characteristic. The characteristic in this case confers a short-term advantage (better blood gas tensions) at a major long-term cost in prognosis.

**STRATIFIED PULMONARY BLOOD FLOW**

Uneven distribution of pulmonary blood flow in the normal subject has been considered mainly at lobar or zonal level; in abnormal subjects the effects of...
pulmonary vascular occlusion, distortion or destruction have been the main
effects considered. Over the past five years attention has been directed in our
laboratory to the possibility of uneven distribution of pulmonary blood flow
at the lobular level in normal and abnormal states.

The secondary lobule represents the essential functional unit of the lung
and contains all those structures concerned with gas exchange. It is a conical
structure, about 1 cm long in man, arising from a terminal bronchiole. It
consists of a repeatedly branching system of small airways (respiratory bron-
chioles and alveolar ducts) with their accompanying blood vessels. These re-
branching airways are largely lacking in walls, which are replaced by the
outpouchings of alveoli. Essentially then, the alveoli are arranged in a series
fashion from proximal to distal parts of the lobule. It follows that the alveoli
closest to the feeding terminal bronchiole will receive a larger proportion
of fresh inspired air (i.e. be better ventilated) than those most distally placed. If
blood were evenly distributed to all parts of the lobule, there would be very
considerable disparities of ventilation-perfusion ratios throughout every
lobule.

Studies based on detailed analysis of expired gas tension plateaus (Read,
1966a,b) suggested that, as well as a gradient of ventilation, there was also a
gradient of pulmonary blood flow between the central and peripheral parts
of the lobule. The evidence suggested that the blood flow per unit of lung
volume was up to four times greater in the central than in the peripheral
portion.

Studies of the distribution of blood flow in the secondary lobule of the rat
lung provided more direct evidence on the matter (Wagner et al., 1967) and
confirmed the indirect human data. Radio-iodinated macro-aggregated
albumin was injected intravenously in the rat, as a marker of pulmonary blood
flow distribution. Its lobular distribution was examined by preparing counter-
stained radioautographs of frozen sections of the inflated rat lungs. These
studies indicated a gradient of blood flow per unit of lung volume of about 4
to 1 from apex to base of the secondary lobule.

This gradient of stratified blood flow distribution is in the same direction
as the ventilation gradient imposed by the arrangement of alveolar spaces in
series. The blood flow gradient will reduce the disparity of ventilation-blood
flow ratios that would otherwise exist along the gas exchange axis, though
it is not of sufficient magnitude to ablate them completely.

Exercise commonly produced a redistribution of blood flow within the
secondary lobule of normal subjects (Read, 1969a). In most normal subjects
there was, during exercise, an increased blood flow to the distal part of the
secondary lobule; in some subjects such redistribution was minimal or absent.
It is of interest that those who altered the proportions of blood flow going through different parts of the lobule during exercise were also those who had been defined as responders by the techniques described earlier in this paper. The significance of the interrelationship is at the moment far from clear.

Based on likely distribution of ventilation and blood flow within the secondary lobule, it is possible to calculate the extent to which different parts of the lobule will participate in normal gas exchange. The proximal portion of the lobule, with its higher ventilation-perfusion ratio and its very much higher blood flow, will account for a disproportionately large part of total oxygen and CO₂ exchange. It thus represents a particularly vulnerable region: small areas of damage there might lead to disproportionately great changes in function. Read (1969b) has suggested that this may account for a significant part of the functional defect in patients with centrilobular emphysema. Apart from the considerable interference with gas exchange that would result if the central part of the lobule were destroyed, the consequences for the pulmonary circulation might be disproportionately great. For example, a loss of about 20 per cent of the lung parenchyma, if this were confined to the central part of lobules, would produce a 60 per cent increase in calculated pulmonary vascular resistance; and loss of the central half of the lobule would lead to more than a trebling of pulmonary vascular resistance. Such considerations as these may account for the failure of good correlation between the anatomical amount of lung destruction and the changes in the right ventricle encountered in patients with emphysema. Equally, if pulmonary micro-emboli are preferentially swept to vessels in the central part of the lobule, and obstruct them, this could help account for disproportionate increases in pulmonary artery pressure produced by relatively small amounts of embolic material.

CONTROL OF VENTILATION
D. J. C. Read (1967) developed a novel and simple method for assessing ventilatory response to CO₂. He used the well-known procedure in which a subject rebreathes from a closed bag. He showed that if the PₐCO₂ at which the procedure begins is appropriately adjusted, there is a linear relationship between rising PₐCO₂ and ventilation over the subsequent four minutes of rebreathing. If, for each half minute interval of the rebreathing period, minute ventilation was plotted against PₚCO₂, a ventilation-PₚCO₂ response line was produced. He showed (D. J. C. Read, 1967; D. J. C. Read and Leigh, 1967) that the slope of this ventilation-PₚCO₂ relationship was the same as that which resulted from prolonged steady-state studies. Since a steady-state study takes several hours if one is to obtain three or four points on the line, and since the new rebreathing method takes only four minutes for a
determination of ventilatory response to CO₂, it clearly represents a significant advance in methodology, particularly for use in sick patients at the bedside or in the laboratory.

This technique has subsequently been used to explore a number of situations: the range of normality in healthy subjects (D. J. C. Read, 1967), and in athletes (Rebuck, 1969); the effect of imposed chest restriction (Thompson and D. J. C. Read, 1968); differences between Europeans and natives of Papua-New Guinea (D. J. C. Read, 1970); the situation in exercise-induced asthma (Rebuck and Read, 1968); and serial changes occurring in patients with asthma as they recover from acute episodes (Rebuck and Read, 1970).

**Bronchial Asthma**

An active programme of investigation into various aspects of the functional disturbances of bronchial asthma has been going on since 1963. The earliest studies examined lung volumes during episodes of severe asthma. Woolcock and Read (1965, 1966) showed that functional residual capacity (FRC) was elevated in many patients with asthma sufficiently severe to require admission to hospital, and that total lung capacity (TLC) was elevated in about half of these patients. Compared with the levels after recovery, the elevation of FRC and TLC often amounted to several litres.

There were two important implications of these findings. First, the elevation of FRC meant that resting ventilation was taking place at a higher point in lung volume than normal and that in some patients the elastic work of inspiration might well be considerably increased. The second implication has an important bearing on the interpretation of serial FEV₁ values in patients recovering from asthma or being subjected to a trial of anti-asthmatic therapy. Some patients showed only a minimal change in FEV₁ or a change that would be judged insufficient to account for a major change in clinical state between an episode of severe asthma and clinical recovery. In a number of such patients Woolcock and Read (1966) showed that the clinical improvement was associated with a very considerable deflation of lung volumes, even though the change in FEV₁ might be small. In a situation where the demonstration of objective improvement is important (such as in a trial of elective corticosteroid therapy for a patient with apparent chronic asthma), measurements of lung volumes should therefore be combined with simple measurements of FEV₁ if effective therapy is not to be denied to some patients who would derive real benefit from it.

In their 1966 paper, Woolcock and Read postulated that increase of FRC and probably of TLC should be invariable accompaniments of severe asthma, although they were not able to demonstrate these changes in all patients when
using a helium dilution method. They predicted that a foreign gas dilution method might fail to show the full extent of lung volume changes in severe asthma because of development of non-ventilated but non-collapsed regions in the lung. More recent comparison of helium dilution lung volumes with those obtained by body plethysmography in patients with severe asthma has confirmed this prediction (Woolcock et al., 1970). Other studies (Woolcock and Read, 1968) have also shown reversible loss of elastic lung recoil during episodes of asthma.

It is perhaps a reflection of attitudes to asthma that prior to 1967 there were virtually no published data available on blood gas tensions in episodes of asthma. Tai and Read (1967a) produced data in 76 patients, 12 in status asthmaticus and 64 with clinically less severe asthma. Patients in status asthmaticus commonly showed profound reduction of arterial oxygen tension combined with an arterial $P_{O_2}$ ranging from low to grossly elevated (in one case as high as 200 mm Hg, with a blood pH of 6.8). Perhaps more surprisingly, arterial $P_{O_2}$ was reduced in almost all patients with less severe asthma, and 14 of the 64 less-ill patients showed $P_{O_2}$ values of less than 60 mm Hg. In the less severe episodes elevation of arterial $CO_2$ tension was far less common. These findings have been confirmed and extended in a subsequent large series of patients admitted to hospital with severe asthma. Hypoxaemia is universal; arterial carbon dioxide tensions are totally unpredictable, ranging from low to greatly elevated.

Tai and Pain (1965) first drew attention to the fall in arterial oxygen tension that might follow the administration of intravenous aminophylline to patients with asthma. This phenomenon was systematically investigated by Tai and Read (1967b), in relation to both aminophylline and isoprenaline. The latter authors demonstrated that in some patients with asthma the administration of either of these agents was followed by a fall in arterial $P_{O_2}$, a finding confirmed by others. Interpretations of the data have varied, but we would explain it in terms similar to those outlined in our paragraphs on pulmonary vascular responders and non-responders. Both aminophylline and isoprenaline are powerful pulmonary vasodilators, and it is postulated that they produce the fall of arterial oxygen tension only in those patients who, as result of their asthma, have regions of compensatory vasoconstriction in hypoxic regions of their lungs.

Direct evidence that pulmonary blood flow may be very considerably maldistributed in patients with asthma was provided by an early study from this laboratory of the pattern of perfusion lung scans in asthma. Woolcock et al. (1966) showed that there was often major maldistribution of pulmonary blood flow in patients with episodes of asthma, with reversion towards a more
normal pattern on clinical recovery. Despas et al. (1970) correlated the inhalation and perfusion patterns on lung scans of patients with asthma and showed that there was often a remarkable correspondence between areas of diminished isotope inhalation and diminished blood perfusion.

CHRONIC OBSTRUCTIVE LUNG DISEASE

Obviously a number of aspects of the investigational programme described in previous sections have a considerable bearing on chronic obstructive lung disease. Two of them particularly relate to disturbances of pulmonary blood flow in that disorder: the distinction between responders and non-responders, and the anatomical distribution of any lung destruction in relation to the anatomy of the secondary lobule. Both these factors may play a significant role in determining the onset or setting the background for a situation of pulmonary hypertensive cor pulmonale.

A further factor may be relevant in the genesis of heart failure in acute-on-chronic respiratory failure (Dintenfass and Read, 1968). Blood viscosity depends in large measure on the viscosity of the red cells contained within it. Polycythaemia alone causes a marginal increase in blood viscosity, but this increase is multiplied by the presence of hypoxia or acidosis. A further factor increasing blood viscosity is increased aggregability of red cells (which is reflected by an elevation of ESR). Hypoxia, acidosis, and an elevated ESR are precisely the factors that accompany episodes of severe respiratory tract infection; it is suggested that in a patient with secondary polycythaemia due to chronic lung disease, and in the presence of a pulmonary vascular bed already restricted by that disease, they may precipitate pulmonary hypertensive right ventricular failure due to a very marked increase in blood viscosity.

In the process of studying disturbances of blood flow in chronic obstructive lung disease, the influence of ventilation-perfusion ratio maldistribution on some other parameters of pulmonary function has been investigated. The effect of non-uniformity of the lungs on measurement of pulmonary diffusion capacity was clarified (Read et al., 1965). It was possible to define which disturbances of distribution were likely to lead to falsely low or falsely high values for pulmonary diffusing capacity, unrelated to the true diffusing characteristics of the lung. The same study predicted (and confirmed) that falsely high or even negative values for pulmonary diffusion capacity might be obtained by the steady-state technique in patients with occlusive pulmonary vascular disorders.

The insensitivity of $V_D/V_T$ ratio (as an index of ventilation-perfusion maldistribution) to changes of tidal volume was demonstrated in a large series of patients with obstructive lung disease. Read and Lee (1969) showed that
V_D/V_T ratio changed very little despite large changes in tidal volume. This has important consequences for examining the effect of drugs and other agents on the pulmonary circulation in such patients. Changes of V_D/V_T ratio (but not in the absolute value of physiological dead space) beyond certain narrow limits may be taken as indicating changes in the distribution of pulmonary blood flow, rather than any change in the distribution of pulmonary ventilation.

**SUMMARY**

The themes running through investigations in this laboratory over the past ten years have been the definition of certain functional abnormalities and their underlying mechanisms, and the examination of the way in which these mechanisms may modify disease states in man. Particular attention has been directed to differences between individuals (innate or acquired) that may determine different patterns of clinical progression of disease.

**Acknowledgements**

The work reported in this paper has clearly depended on the efforts of many colleagues. At various stages grant support has been received from the National Heart Foundation of Australia, the Asthma Foundation of New South Wales, the Australian Research Grants Committee, and the Consolidated Medical Research Fund of the University of Sydney.

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The Rheology of Blood in Vascular Disease

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Our knowledge and understanding of the mechanisms of hypertensive and ischaemic diseases are still limited, notwithstanding recent contributions, for example, in the fields of neural and endocrine control. Furthermore, the role of the vascular content itself, the blood and the factors determining its flow, has been neglected. Blood cannot be regarded as an inert fluid in blood vessels, nor can it be viewed as a Newtonian, that is a water-like, fluid. Factors contributing only to blood viscosity play a distinctive role in the flow of blood and the formation of thrombi. Furthermore, the pressure and flow functions of blood may be altered in certain segments of the microcirculation and the products of tissue damage may further modify the circulation.

The study of blood rheology can shed new light on fundamental aspects of the circulation in health and disease, particularly in terms of dynamic and flow affected blood coagulation and thrombus formation.

Instruments Used

New instruments have been developed in order to study blood viscosity and blood coagulation.

(a) Rotational Viscometers

These include the cone-in-cone viscometer (Dintenfass, 1962a,b, 1963b,