

## Lung Function



# Lung Function

## Physiology, Measurement and Application in Medicine

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# Contents

Foreword, vii

Preface, ix

Acknowledgements, xi

## **Part 1 Foundations, 1**

- 1 Early Developments and Future Prospects, 3
- 2 Getting Started, 13
- 3 Development and Functional Anatomy of the Respiratory System, 23
- 4 Body size and Anthropometric Measurements, 31
- 5 Numerical Interpretation of Physiological Variables, 42
- 6 Basic Terminology and Gas Laws, 52
- 7 Basic Equipment and Measurement Techniques, 59
- 8 Respiratory Surveys, 82

## **Part 2 Physiology and Measurement of Lung Function, 97**

- 9 Thoracic Cage and Respiratory Muscles, 99
- 10 Lung Volumes, 111
- 11 Lung and Chest Wall Elasticity, 118
- 12 Forced Ventilatory Volumes and Flows (Ventilatory Capacity), 130
- 13 Determinants of Maximal Flows (Flow Limitation), 143
- 14 Theory and Measurement of Respiratory Resistance (Including Whole Body Plethysmography), 150
- 15 Control of Airway Calibre and Assessment of Changes, 164
- 16 Distribution of Ventilation, 181

17 Distribution and Measurement of Pulmonary Blood Flow, 196

18 Inter-Relations between Lung Ventilation and Perfusion ( $\dot{V}_a / \dot{Q}$ ), 209

19 Transfer of Gases into Blood in Alveolar Capillaries, 224

20 Transfer Factor (Diffusing Capacity) for Carbon Monoxide and Nitric Oxide ( $Tl_{co}$ ,  $Tl_{no}$ ,  $Dm$  and  $V_c$ ), 234

21 The Oxygenation of Blood, 258

22 Gas Exchange for Carbon Dioxide and Acid–Base Balance, 275

23 Control of Respiration, 285

24 Newborn Babies, Infants and Young Children (Ages 0–6 Years), 304

## **Part 3 Normal Variation in Lung Function, 315**

- 25 Normal Lung Function from Childhood to Old Age, 317
- 26 Reference Values for Lung Function in White (Caucasian) Children and Adults, 333
- 27 Genetic Diversity: Reference Values in Non-Caucasians, 366

## **Part 4 Exercise, 383**

- 28 Physiology of Exercise and Changes Resulting from Lung Disease, 385
- 29 Exercise Testing and Interpretation, including Reference Values, 416
- 30 Assessment of Exercise Limitation, Disability and Residual Ability, 437
- 31 Exercise in Children, 446

**Part 5 Breathing During Sleep, 453**

- 32 Investigation and Physiology of Breathing During Sleep, 455
- 33 Assessment and Treatment of Sleep Related Breathing Disorders, 464

**Part 6 Potentially Adverse Environments, 471**

- 34 Hypobaric: High Altitude and Aviation Physiology and Medicine, 473
- 35 Immersion in Water, Hyperbaria and Hyperoxia Including O<sub>2</sub> Therapy, 487
- 36 Cold, Heat and the Lungs, 499
- 37 Airborne Respiratory Hazards: Features, Protective Mechanisms and Consequences, 504

**Part 7 Lung Function in Clinical Practice, 529**

- 38 Patterns of Abnormal Function in Lung Disease, 531
- 39 Strategies for Assessment, 539
- 40 Lung Function in Asthma, COPD, Emphysema and Diffuse Lung Fibrosis, 545
- 41 How Individual Diseases Affect Lung Function (Compendium), 560
- 42 Lung Function in Relation to General Anaesthesia and Artificial Ventilation, 593
- 43 Lung Function in Relation to Surgery, 604
- 44 Pulmonary Rehabilitation, 610

Index, 617

# Foreword

It is not every day one of my icons asks for my opinion. This is that day and I am deeply honored to have been asked to write the Foreword to this edition of John Cotes' Lung Function. I have admired this book in its earlier incarnations and am happy to report this is perhaps the best of all.

For this 6th edition, Dr Cotes has been ably assisted by two other authorities in pulmonary medicine and lung physiology (Dr David Chinn and Dr Martin Miller) and obtained critiques by other experts for individual chapters. It is the most comprehensive and up-to-date book on lung function testing and pulmonary physiology available and has elements that will be of importance for everyone who works in the field. Moreover, it is a pleasure to read. The style is crisp, clean, and precise.

Early chapters cover the evolution of the earth's atmosphere, the early history of lung physiology and the developmental aspects of the respiratory system. They are followed by a chapter summarizing what you need to know to assess lung function including the equipment you need and measurement techniques. The discussion of numerical interpretation of lung function presents impressive illustrations showing how using numbers improperly can result in errors in interpreting physiologic variables. It was good to be reminded that errors can occur with as simple a process as how and when numbers are rounded and the discussion of why errors occur at the boundaries of the normal distributions was particularly insightful. Chapters on flow limitation and the forced volumes and flows provide clear information for both the expert and the novice.

There are sections on lung function physiology for the complete spectrum of human life (from birth to old age). Since I work mostly with adults, I was intrigued with the information on infant lung function. For older people, the mechanisms for the normal aging changes were particularly enlightening.

Reference values were covered in some detail, with emphasis on the issues that must be addressed to optimize the value of reference comparisons. The issues involved in choosing a set of

reference values are addressed and there is an entire chapter on reference values in non-Caucasians.

There are chapters dedicated to special circumstances including high altitude, aviation physiology, exercise, near drowning, diving and hyperbaric oxygen therapy. Another chapter looks at respiratory hazards in home and occupational environments.

I found chapter 39 on Strategies for Assessment (of lung function) to be particularly informative. The reason airways resistance has not claimed a spot in routine pulmonary function testing is clarified. The chapter goes far beyond the primary tests offered in most laboratories and includes testing strategies for diseases. The comprehensive interpretative flow diagram is somewhat different from that included in the recently published American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations but is a good adjunct to it. The differences in the diagrams enhanced my understanding of the strategies in both.

Chapter 40 focuses on lung function in several lung disease categories that constitute the majority of all pulmonary patients, i.e. asthma, COPD, emphysema and lung fibrosis. This chapter in particular deepened my understanding of the physiology in each category. The descriptions of how other diseases affect the lungs was particularly illuminating. A large number of diseases are catalogued and the descriptions of lung effects are concise and helpful.

This is a book to read straight through and also to keep at the ready to address questions as they arise. Pulmonary technicians, laboratory directors, pulmonary physicians and pulmonary physiologists will all gain something here.

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# Preface

## About the authors

*John Cotes* became interested in breathlessness as a result of taking part in athletics as a schoolboy. His subsequent career has spanned the development of modern lung function testing from its emergence out of aviation physiology at the end of World War II through to the present. The first edition of *Lung Function* in 1965 arose from this interest. It was a theoretical text and practical handbook, written to complement *The Lung* by Julius Comroe and colleagues [1], and the formula that he adopted worked well for five editions. The book has underpinned the subject for nearly half a century! For the present sixth edition new authors have been brought in and the text has been remodelled.

*David Chinn* is a clinical lung physiologist, teacher and research worker whose accuracy in clinical and longitudinal epidemiological studies of lung function has exceeded what many have thought possible. His authorship ensures that the new text is grounded on recent practical experience.

*Martin Miller* is a respiratory physician and clinical teacher who contributed materially to the Guidelines for the Measurement of Respiratory Function of the British Thoracic Society and Association for Respiratory Technology and Physiology [2]. He was a member of the European Respiratory Society Task Force on Peak Flow and the joint American Thoracic Society and European Respiratory Society Task Force on standardisation of lung function testing [3]. His authorship ensures that this book embraces current world thinking on symbols, methods and other aspects of standardisation and that it is clinically relevant.

*Other significant contributors.* The preparation of the manuscript entailed extensive consultations with other knowledgeable persons. Their contributions are indicated in the Acknowledgements section.

## Aims and contents

The book gives a comprehensive account of lung function and its assessment in healthy persons and those with all types of

respiratory disorder, against a background of respiratory, exercise and environmental physiology. It is a theoretical textbook and practical manual for respiratory physicians and surgeons, staff of lung function laboratories and others who have a professional interest in the function of the lungs at rest or on exercise and how it may be assessed. Physiologists, anthropologists, paediatricians, anaesthetists, occupational physicians, explorers, epidemiologists and respiratory nurses should also find the book useful.

The text incorporates the technical and methodological recommendations for lung function testing of the American Thoracic Society and European Respiratory Society up to the time of publication. The approach to measurement is through human anatomy, physiology and pathology, the basic sciences of maths, physics, chemistry and biology and applied clinical science (pathophysiology). Mathematical treatments are kept to a minimum and most can be skipped by readers not concerned with making measurements. However, the bottom-up approach has inevitably identified instances where current practice is at odds with basic theory. Such difficulties are discussed constructively and, where appropriate, alternative practices are suggested.

## Comparison with previous editions

The text is based on that of the previous editions but is more clearly laid out with 44 chapters instead of 18, numbered sections and more concise writing. Amongst the new chapters are ones on respiratory surveys, respiratory muscles, neonatal assessment, exercise, sleep, high altitude, hyperbaria, the effects of cold and heat, respirable dusts, fumes and vapours, anaesthesia, surgery and respiratory rehabilitation. There is a compendium of lung function in selected individual diseases. The numbers of diagrams and illustrative cases have been increased materially. Unlike in previous editions most statements are attributed to original sources; these are given as numbered references at the end of chapters and the classification of references by topics has been abandoned. At the same time in the interests of brevity

the number of authors for each citation has been reduced to the first three or four. Compared with the fifth edition the quantity of information in the book is greatly increased and is more accessible.

## Using the book

This is a textbook of pure and applied respiratory physiology and the lung function component of respiratory medicine, including breathlessness. It is also a practical manual for assessing the function of the lungs and reporting on and interpreting the findings. Thus entry into the book can be at any of several levels.

The text progresses from basic science through lung mechanics, distribution of gas and blood in the lungs, gas exchange and respiratory control to more applied aspects, including exercise, sleep, unusual environments, breathing polluted air and changes in lung function in disease. Each topic is presented in a simple manner and can be explored separately. However, in life the topics interact, so what starts as a single structural or functional abnormality comes to embrace most aspects of function, including exercise. A common outcome is incapacitating breathlessness. In the book the primary features and methods of investigating each topic are described in appropriate detail, the implications are spelt out and cross-references are given to other sections in the book where there is additional information and/or practical examples. Inevitably, tracking the

interactions through to their origins initially requires diligence, but this is likely to be rewarded by a clearer understanding of end results.

## Feedback

As authors we have done our best to eliminate errors, but inevitably some will have evaded us. We invite readers to draw these lapses to our attention and also make other suggestions for improving any subsequent edition. Such material should be sent to [LungFunction@Coterie.globalnet.co.uk](mailto:LungFunction@Coterie.globalnet.co.uk)

JE Cotes  
DJ Chinn  
MR Miller

## References

1. Comroe JH, Forster RE, DuBois AB, Briscoe AW, Carlsen E. *The lung, clinical physiology and pulmonary function tests*. 2nd ed. Chicago, Year Book Medical Publishers, 1962.
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In the preparation of the new text Martin Miller wrote the first drafts of the chapters in Parts 5 and 7. David Chinn drafted Chapter 8 and John Cotes supported by David Chinn drafted the remainder. David Chinn also prepared many new charts. All chapters were then revised and, where appropriate, the material was passed to independent referees. Considerable help in drafting the respective chapters was received from Professor Ole Pedersen (Chapter 13), Dr James (Jim) Reed (Chapter 23) and Professor Janet Stocks (Chapter 24). Dr Reed reviewed many of the physiological chapters and Dr Sarah Pearce the mainly clinical ones. Mr Kevin Hogben responded to many technical queries. Dr R.A.L. Brewis and Mr M.F. Clay kindly prepared the cartoons.

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## **PART 1**

# Foundations



## CHAPTER 1

# Early Developments and Future Prospects

*This chapter describes how the theory and practice of lung function testing have reached their present state of development and gives pointers to the future.*

- |                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                               |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"><li>1.1 The gaseous environment</li><li>1.2 Functional evolution of the lung</li><li>1.3 Early studies of lung function</li><li>1.4 The past 350 years<ul style="list-style-type: none"><li>1.4.1 Lung volumes</li><li>1.4.2 Lung mechanics</li><li>1.4.3 Ventilatory capacity</li></ul></li></ul> | <ul style="list-style-type: none"><li>1.4.4 Blood chemistry and gas exchange in the lung</li><li>1.4.5 Control of respiration</li><li>1.4.6 Energy expenditure during exercise</li><li>1.5 Practical assessment of lung function</li><li>1.6 The position today</li><li>1.7 Future prospects</li><li>1.8 References</li></ul> |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

### 1.1 The gaseous environment

The basis of respiratory physiology is Claude Bernard's concept of a 'milieu interieur' that remains constant and stable despite changes in the environment. However, the two are not independent since life on earth has evolved symbiotically with changes in earth's atmosphere and this process is continuing. At first, the composition of the atmosphere was determined by physical processes, and then by the biological ones. Now changes in the composition of air are being driven by man's own actions. It remains to be seen how and to what extent the system will adapt.

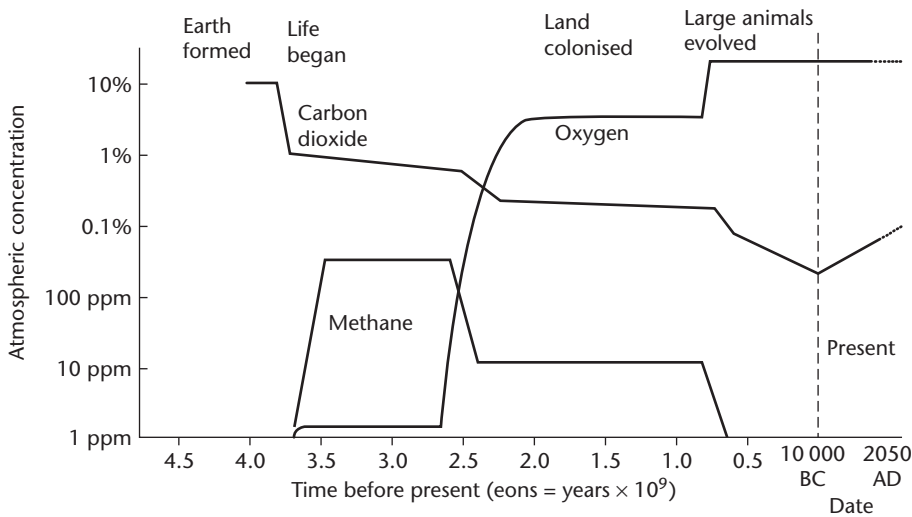
Initially the atmosphere was mainly nitrogen. Then as the earth cooled, carbon dioxide was formed by chemical reactions beneath the earth's crust and released by volcanic activity. Some of the gas was taken up by combination with minerals and deposited as sediment at the bottom of the oceans. Oxygen was released, but immediately combined with iron and other elements, and so the atmospheric concentration was very low [1, 2]. Subsequently, the concentration of oxygen increased as a result of biological activity [3]. A hypothesis as to how this happened was proposed by Lovelock [4] whose concept of the living earth (Gaia) is on a par with evolution as one of the formative influences of our time.

Free oxygen first appeared some  $3.5 \times 10^9$  years ago coincidentally with the development of organisms capable of photosynthesis. The organisms multiplied and their growth reduced significantly the atmospheric concentration of carbon dioxide. Some organisms (methanogens) developed an ability to form free methane gas. The methane was liberated into the atmosphere where it shielded the earth's surface from ultraviolet light. The

shielding allowed ammonia gas to accumulate and this provided a substrate for the growth of photosynthesising organisms; as a result, at the beginning of the Proterozoic era some  $2.3 \times 10^9$  years ago, the atmospheric concentration of oxygen began to rise. By geological standards the increase was rapid, from 0.1 to 1% over about one million years (Fig. 1.1).

When the ambient oxygen concentration reached 0.2%, aerobic organisms became abundant in the surface layers of lakes and oceans and at 2% life began to move onto the land. A concentration of 3% may have been attained some  $1.99 \times 10^9$  years ago. At 10% photosynthesis was at its peak; this further raised the concentration of oxygen and lowered that of carbon dioxide. The changes reduced the available substrate ( $\text{CO}_2$ ) and increased the formation of hydrogen peroxide, superoxide ions and atomic oxygen that were potentially lethal to cells. Photosynthesis was reduced in consequence. With other factors, the balance between promotion and inhibition of photosynthesis formed a feedback loop that stabilised the atmospheric concentration of oxygen at its present level (21.93%,  $F_{\text{I},\text{O}_2} = 0.2193$ ).

The concentration of oxygen stabilised at the start of the Phanerozoic era some  $6 \times 10^8$  years ago. It led to the evolution of animals with skeletons. Thereafter, the concentrations of carbon dioxide, and to some extent oxygen, appear to have oscillated in response to secondary factors. These included fluctuations in the balance between the relative dominance of plants and animals. Some  $5 \times 10^8$  years ago the species that were net consumers of oxygen (e.g. bacteria, fungi and insects) were in the ascendancy and  $\text{CO}_2$  levels were relatively high. Then, plants that fix  $\text{CO}_2$  as lignin appeared and the levels fell. The plants



**Fig. 1.1** Approximate timescale for the evolution of the gaseous environment. Source: After [4].

led to the evolution of dinosaurs and other animals that could feed off and digest the cellulose. The species flourished and the cycle was reversed. From time to time the sequence was unsettled by dust clouds from meteors and volcanic eruptions. The dust interfered with photosynthesis by obscuring the sun, but up to the present the equilibrium has always been restored.

Currently, the atmosphere is under threat from human activity. Clearance of forests and the replacement of grassland by buildings and roads are reducing the earth's capacity for photosynthesis. Hence, the amount of carbon dioxide removed from air is falling. Concurrently, the quantity released is increasing because of massive combustion of fossil fuels. As a result, the earth's temperature is rising and this is increasing the formation of methane gas that could raise the temperature further. However it also has other effects, and so the long-term outcome is unpredictable. In the short term any change in gaseous equilibrium is likely to occur slowly.

*In summary*, living organisms first appeared in an anaerobic environment that they helped to convert to an aerobic one. Hence they were adapting to the new conditions as they were creating them. On this account, the capacity to tolerate conditions of hypoxia and hypercapnia are part of man's heritage. How this is achieved is described in subsequent chapters. The evolutionary history also indicates the importance of natural protection against oxygen radicals. However, there is only limited evidence for Berken and Marshall's suggestion [1] that the relevant mechanisms emerged during periods of what we would now regard as hyperoxia.

## 1.2 Functional evolution of the lung

Aerobic organisms developed in an aqueous medium where the amount of oxygen is determined by its partial pressure and by the solubility; this is such that the concentration in water is only about one fortieth of that in air (Table 1.1). By contrast carbon dioxide is highly soluble, so at physiological partial pressures the

**Table 1.1** Atmospheric concentrations and solubility in water of oxygen and carbon dioxide.

|                               | Units                                                   | Oxygen | Carbon dioxide |
|-------------------------------|---------------------------------------------------------|--------|----------------|
| Atmospheric concentration     | vol./vol.                                               | 0.2093 | 0.003          |
| Solubility in water at 1 atm: |                                                         |        |                |
| Temperature 20°C*             | $\frac{\text{vol. of gas(STPD)}}{\text{vol. of water}}$ | 0.031  | 0.88           |
| Temperature 37°C*             | $\frac{\text{vol. of gas(STPD)}}{\text{vol. of water}}$ | 0.024  | 0.55           |

\*Solubility in blood plasma is approximately 10% less.

concentration in water is nearly as great as in air. The differences in solubility have consequences for gas exchange [5].

For the fish the problem of obtaining sufficient oxygen was solved by the evolution of the gill system. This organ is perfused by a large volume of water from which almost all the oxygen is extracted; the blood leaving the bronchial clefts contains oxygen in a concentration equal to that in blood leaving the lung in man. However, the water perfusing the gill takes with it the carbon dioxide in solution and this lowers the CO<sub>2</sub> tension in the blood to less than 0.7 kPa (5 mm Hg). Mainly on this account the blood pH is relatively high (approximately 8.0 pH units at a temperature of 20°C). At higher water temperatures the pH falls to approach that in the blood of man. Concurrently, the solubility of oxygen in water delivered to the gill clefts is reduced.

In hot climates a high ambient temperature might cause streams to dry up, leaving any fish stranded. To meet this hazard some fish developed lung-like pouches in the back of the pharynx; they also developed primitive limbs with which to crawl along streambeds in search of water. For this type of existence a gill for the exchange of carbon dioxide and a primitive lung for exchanging oxygen formed a life-saving combination. The lung was further developed in the reptiles. In birds the pouches

were adapted as reservoirs from which air was pumped through parabronchi; these supplied air to the diffusive zones where the whole of the surface was lined with capillaries. This arrangement resulted in a very compact lung with a high capacity to transfer gas. The amphibians developed in a different way by shedding their scales to leave a soft vascular skin; this replaced the gill as a means of exchanging carbon dioxide with the surrounding water. Somewhere between these diverging species emerged the primitive mammals and eventually man.

### 1.3 Early studies of lung function

Erasistratus (c. 280 BC) and Galen (129–201) demonstrated the role of the diaphragm as a muscle of respiration, the origin and function of the phrenic nerve and the function of the intercostal and accessory muscles. The function of the diaphragm was further explored by da Vinci (1452–1519) who observed that during inspiration the lung expanded in all directions following the movement of the thoracic cage. The lung collapse that followed puncture of the pleura was described by Vesalius (1514–1564).

The need for fresh air was recognised by Galen who believed it reacted with the blood in the left heart and arteries to produce the ‘vital spirit’. The absence of a visible communication between the pulmonary artery and the pulmonary vein led him to suggest that blood passed through invisible pores between the two sides of the heart; thus, he failed to comprehend the function of the lung. This was surmised by Ibn-al-Nafis (c. 1210–1289) and by Servetus (1511–1553) who separately recognised the impermeability of the interventricular septum and proposed that blood passed from the pulmonary artery through the lung to the pulmonary vein. Harvey (1578–1657) demonstrated that blood circulated through the lung and Malpighi (1628–1694) showed that the blood capillaries were in close proximity to the smallest air spaces. These observations prepared the way for a correct understanding of lung function.

The role of ventilation in maintaining life was demonstrated by Vesalius who was able to restore the activity of the heart in an apnoeic dog by insufflating air into the trachea through a reed. Hooke (1635–1703) subsequently showed that the essential factor was a supply of fresh air. Boyle (1627–1691) and, to a lesser extent Mayow (1643–1679), demonstrated that the constituent of air that supported combustion also supported life. Lower (1631–1691) further showed that the uptake of air in the lung caused the blood to change colour. These discoveries laid the foundations for subsequent studies of gas exchange but their importance was not immediately apparent. The confusion was such that on 22 January 1666, after a meeting of the Royal Society on the subject of respiration, Samuel Pepys wrote in his diary: ‘it is not to this day known, or concluded on among physicians how the action is managed by nature, or for what use it is’.

### 1.4 The past 350 years

The information about the lung that was necessary for the birth of respiratory physiology was available by about the year 1667.

Thereafter aspects of the subject developed at different rates, reflecting their immediate interest and the techniques that were available for their investigation.

#### 1.4.1 Lung volumes

The volume of air that a man can inhale during a single deep breath was first measured by Borelli (1679). Subsequent work established that this quantity in an average adult is about 200–300 in<sup>3</sup> (3.3–4.9 l) at ambient temperature. The need for a temperature correction was pointed out by Goodwyn (1788). In 1831 Thackrah showed the volume of air to be less in women than in men and to be reduced amongst workers in flax and other occupations due to the inhalation of dust [6]. The measurement of vital capacity was put on a quantitative basis by Hutchinson in 1846 [7]. Hutchinson defined it as ‘the greatest voluntary expiration following the deepest inspiration’ and designed a spirometer for its estimation. He showed that the vital capacity is related to the height such that ‘for every inch of height (from 5 to 6 ft) eight additional cu. inches of air at 60°F are given out by forced expiration’. The equivalent parameter in metric units is 5.8 l m<sup>-1</sup>, which is similar to values used today (Section 26.5). He further showed that the vital capacity decreased with age and was reduced by excess weight and by disease of the lung. The measurement of residual volume by a gas dilution method was first performed by Davy (1800). The method using whole body plethysmography was developed by DuBois and colleagues (1956).

#### 1.4.2 Lung mechanics

The role of the elastic recoil of the lung in causing expiration was demonstrated by Donders (1853) who was the first to measure the retractive force. This work was extended by Dixon and Brodie (1903) and by Cloetta (1913). Concurrently, Rohrer (1915) was applying the concepts of Newtonian mechanics to explain the relationship between the force exerted by the respiratory muscles and the rate of airflow. This approach was extended by his successors Neergaard and Wirz (1927) who used the pneumotachograph of Fleisch (1925). Neergaard also demonstrated the role of surface forces in the lung by comparing the relationship of the lung volume to the retractive force when the air in the lung was replaced by water. This work was repeated independently by Radford (1954) who, with Pattle (1955) Clements (1956) and Avery and Mead (1959), established the physiological and chemical significance of lung surfactant. Knowledge of the viscoelastic properties of the lung was extended by Bayliss and Robertson (1939), Dean and Visscher (1941), Rahn, Otis, Chadwick and Fenn (1946), Mead and Whittenberger (1953), and their many collaborators; a seminal review was prepared by Mead [8]. The role of antitrypsin in protecting the lung from proteolytic enzymes was discovered by Eriksson [9].

### 1.4.3 Ventilatory capacity

The relationship of breathlessness on exertion to vital capacity was considered by Peabody (1915). He also compared the ventilation during exercise with that during breathing carbon dioxide. The use of the forced vital capacity was introduced by Strohl (1919). The role of changes in lung distensibility in causing breathlessness was explored by Christie (1934). The maximal breathing capacity was introduced as a dynamic test of lung function by Jansen, Knipping and Stromberger (1932) who calculated it from the forced vital capacity. The maximal voluntary ventilation was first measured by Hermannsen (1933). The use of the proportion of the vital capacity that could be expired in one second as a guide to airways obstruction was introduced by Tiffeneau (1948). The measurement was facilitated through the addition of a timing device to the spirometer by Gaensler (1951) and subsequently by McDermott and colleagues (1960). A convenient and reasonably accurate peak flowmeter was developed by Wright (1959) and other instruments followed.

### 1.4.4 Blood chemistry and gas exchange in the lung

During the eighteenth century, the lung's role as an organ of gas exchange was obscured by the belief of Lavoisier (1777) and others that it was the site of combustion. This was disproved by Magnus (1837) who used an extraction technique to analyse the gases in arterial and venous bloods. The use of such data for the calculation of cardiac output was proposed by Fick (1870), whilst the true site of oxidation was demonstrated by Pflüger (1872). The techniques for analysing gases were improved by Haldane and described in *Methods of Air Analysis* (1899); an improved method for determining the concentrations in the blood was described by Haldane and Barcroft (1902). The tonometer methods for measuring the blood gas tensions were developed by Bohr (1890) and Krogh (1910); other technical advances were reported by Peters and Van Slyke in *Quantitative Clinical Chemistry* (1932). The application of these and other techniques to human arterial blood was made possible through the introduction by Hurter (1912) of the procedure of arterial puncture.

The relationship of the pressure to the content of oxygen in the blood was explored by Paul Bert and described in *La Pression Barometrique* (1878); in this he showed that the pressure and not the concentration of gases in the atmosphere is of physiological significance. The oxygen dissociation curve was described by Bohr (1904). With Hasselbalch and Krogh (1904), Bohr showed that its shape is greatly influenced by the coexisting tension of carbon dioxide. Further advances were made by Barcroft and summarised in *The Respiratory Function of the Blood* (1914). The dissociation curve for carbon dioxide was described by Christiansen, Douglas and Haldane (1914) and the chemical reactions were further explored by Hasselbalch, Hastings, Roughton, Sendroy, Stadie and others. Some of this work is described by L.J. Henderson in *Blood: A Study in General Physiology* (1928).

The exchange of gas across the alveolar capillary membrane was considered by Bohr (1891). He found that the tension of oxygen was sometimes higher in the arterial blood than in the alveolar gas and concluded that oxygen was secreted by the alveolar cells. The measurements were in error, but the hypothesis was supported by Haldane and Smith (1896–1898); these workers inhaled gas containing carbon monoxide (CO), and observed differences between the observed and expected CO tensions in blood. This could best be explained by secretion of oxygen. Their view was opposed by the Kroghs (1910) and by Barcroft, who believed correctly that the transfer of oxygen took place solely by diffusion. The controversy led Bohr (1909) to develop his integration method for determining the mean tension of oxygen in the pulmonary capillaries and to calculate the diffusing capacity of the lung for carbon monoxide. It also stimulated physiological expeditions to high altitudes, including to Pikes Peak, described by Douglas, Haldane, Y. Henderson and Schneider (1913), and to Cerro de Pasco, described by Barcroft in the second edition of *The Respiratory Function of the Blood*. Studies of conditions at high altitude were also undertaken by Dill, Christensen and Edwards (1936), and by Houston and Riley (1947). Subsequently, interest shifted to the Himalayas where the physiological adaptations necessary for the ascent of Mount Everest were investigated by Pugh (1964) and West (1983), amongst others. Meanwhile, the transfer of oxygen from alveolar gas to pulmonary capillary blood was explored by Lilienthal and Riley (1946) and Piiper (1961). Understanding of the transfer of carbon monoxide was advanced by Roughton and Forster (1957). The single breath method for the measurement of transfer factor (diffusing capacity) for carbon monoxide was developed by Marie Krogh (1915) and improved under Comroe's guidance by Forster, Fowler and colleagues (1954). The anatomical basis of gas exchange was described in quantitative terms by Weibel (1963).

The distribution of gas in the lung was considered by Zuntz (1882) who introduced the concept of dead space; this was first measured at post-mortem by Loewy (1894). The dead space for carbon dioxide was measured during life by Bohr (1891) as well as by Haldane and others who used the method of sampling the alveolar gas devised by Haldane and Priestley (1905). By this method Douglas and Haldane (1912) showed that the dead space increased with the depth of inspiration, but the magnitude of the increase was disputed by Krogh and Lindhard (1913–1914) who sampled the end tidal gas. Part of the increase was believed by Haldane to represent ventilation of the alveolar ducts and atria where the ventilation per unit of perfusion (i.e. the ventilation–perfusion ratio) was higher than in the alveoli. Haldane, Meakins and Priestley (1918–1919) explored the effects of uneven lung function upon the composition of alveolar gas and arterial blood. The application of these concepts to patients with lung disease was described by Meakins and Davies in *Respiratory Function in Disease* (1925).

The role of the pulmonary circulation was clarified through the application of the newly discovered technique of cardiac catheterisation by Cournand (1942) and by McMichael and

Sharpey-Schafer (1944). However, there was disagreement as to whether or not it was ethical to apply the technique to healthy people. The mechanisms underlying uneven lung function were further illuminated by the development of bronchspirometry by Jacobaeus (1932), the concept of regional inhomogeneity by Rauwerda (1945), the respiratory mass spectrometer by Fowler (1957), the oxygen electrode by Clark (1953) and radioisotope assay methods by Knipping (1955). These techniques were used to good effect by Rahn and Fenn (1955), Gilson and colleagues (1955) and West (1969) who, with Wagner (1974), developed the multiple inert gas elimination technique for describing ventilation–perfusion inequality.

### 1.4.5 Control of respiration

Knowledge of the central nervous regulation of respiration stems from the observations of Legallois (1812) and Flourens (1824) that a lesion in a small area of the medulla oblongata caused breathing to cease. The location of the respiratory region was defined with increasing precision by many workers, including Lumsden (1923) and Pitts, Magoun and Ranson (1939). At an early stage, Hering and Breuer (1868) separately showed that the region received, via the vagi, sensory information on the distension of the lung. This provided the basis for a mechanism of self-regulation whereby the inflation of the lung tended to terminate inspiration and to initiate expiration whilst deflation of the lung had the opposite effect.

Activity in single vagal fibres was recorded by Adrian (1933) and others. Their work paved the way for dramatic advances in understanding the role of pulmonary receptors. Subsequent contributors included Whitteridge (1950) and his pupils Paintal, Widdicombe and Guz. Sears (1963) showed that the muscle spindles in the respiratory muscles played a part in regulation, whilst Campbell and Howell (1963) explored the role they might play in the sensation of dyspnoea. The Hering–Breuer centenary symposium provided a seminal review [10]; it also introduced respiratory physiologists to some psychological techniques for the quantification of breathlessness.

The stimulant effects upon respiration of both a relative deficiency of oxygen and a moderate excess of carbon dioxide were known to Pflüger (1868) who believed the former to be the more important factor. In this he was in agreement with Rosenthal (1862). Evidence for the role of carbon dioxide was provided by Miescher-Rusch (1885), whilst Geppert and Zuntz (1888) demonstrated the stimulant action of other products of metabolism. The action of carbon dioxide in man was investigated quantitatively by Haldane and Priestley (1905) who, over a wide range of barometric pressures, demonstrated that the ventilation was adjusted to maintain the alveolar carbon dioxide tension at a constant level.

J.S. Haldane's great contribution is summarised in *Respiration* (1922). It was republished jointly with Priestley in 1935. The role of the blood hydrogen ion concentration in controlling breathing was suggested by Winterstein (1911) and elabo-

rated, amongst others, by Yandell Henderson in *Adventures in Respiration* (1938). Gesell (1923) believed the response of the respiratory region of the brain to be affected by the metabolism of chemosensitive cells. The role of hypoxaemia was advanced through the identification by Heymans (1926) and De Castro (1930) of the chemoreceptors in the carotid and aortic bodies; their function was further studied by Comroe and Schmidt (1938). The interdependence of the responses of ventilation to hypercapnia and hypoxaemia was demonstrated by Nielsen and Smith (1951), whilst the effects of inhalation of oxygen were studied by Leonard Hill and Flack (1910), A.V. Hill, Long and Lupton (1924), Asmussen and Nielsen (1946), Comroe and Dripps (1950), Dejours (1966) and others. The combined effects on respiration of these and other factors were synthesised into a multiple theory of respiratory regulation by Gray in *Pulmonary Ventilation and its Physiological Regulation* (1950).

### 1.4.6 Energy expenditure during exercise

The rates of exchange of oxygen and carbon dioxide in the lung were measured by Lavoisier (1784) who showed that they varied with the level of activity. The relationship of resting metabolism to body surface area was demonstrated by Robiquet and Thillaye (1839). The underlying biochemical processes were investigated by Liebig (1842), Voit (1857), Rubner (1883) and others. One important landmark was the demonstration by Fletcher and Hopkins (1907) that lactic acid was produced in muscles during anaerobic contractions.

The measurement of human metabolism by indirect calorimetry was facilitated by Zuntz (1891) when he developed a portable apparatus. The method was validated by Atwater and Rosa (1897) using a human calorimeter. Other equipment was introduced by Tissot (1904), Douglas (1911), Benedict and Roth (1922), Kofranyi and Michaelis (1940), Müller and Franz (1952) and Wolff (1958). The need to relate the results to the body mass of the subjects was recognised by Frenzel and Reach (1901). The energy expenditure during activity was measured by many workers, including Benedict (1915), whilst the relationship to the speed of locomotion was analysed in detail by Magne (1920), A.V. Hill and his colleagues, including Lupton (1922), Atzler and Herbst (1927), Fenn (1930), Margaria (1939) and others.

## 1.5 Practical assessment of lung function

Most of the physiological concepts described in this chapter were applied to the assessment of patients with respiratory disease, starting with the vital capacity in the early nineteenth century [7]. In the 1930s, Knipping's laboratory in Hamburg was setting the trend, using a wide range of tests, all of which have their counterparts today (Table 1.2).

In 1950, when Comroe reviewed the subject, the scope of the tests had broadened to include aspects of lung mechanics. However, the forced expiratory volume was scarcely known outside France and no test had reached its current form. This mainly

**Table 1.2** Tests of respiratory efficiency in Knipping's laboratory.

| Aspect          | Test                                      | Normal level    |
|-----------------|-------------------------------------------|-----------------|
| Anatomical      | Vital capacity                            | >70% pred.      |
| Physiological   | Ventilation equivalent for O <sub>2</sub> | <3 l/100 ml     |
|                 | Ventilating power                         | Not defined     |
|                 | Respiratory style ( $t_{exp}/t_{insp}$ )  | <1.4            |
|                 | Composition of arterial blood             |                 |
| Epiratory force | Mercury U-tube (Flak) test                | 40 mm Hg > 40 s |
| Symptoms        | Dyspnoea ratio                            |                 |
|                 | (VE recovery/VE rest)                     | Average 1.64    |

Source: [11].

happened during the next 12 years (Table 1.3); the developments were aided by a transfer of technical expertise from wartime aviation medicine [35]. Photographs of some of those who contributed are given in Fig. 1.2.

Since the 1960s, the means for calibration have been improved, the convenience of the tests increased and the subtlety of interpretation extended. New tests have mainly emerged in the related

fields of medical physics and anthropometry. Some of them are included in the present account.

The changes have led to the loss of many procedures from the days when laboratory equipment comprised beautiful glassware and 'bits and pieces' held together by 'string and sealing wax'. The methods were often very practical (Fig. 1.3 and Table 1.4) and the routine analysis of expired gas was usually performed with greater accuracy than is the case today (Table 1.3, [34]).

## 1.6 The position today

Modern lung function testing is based on detailed understanding of the underlying physiology. This has been reviewed extensively in many publications. The most comprehensive is *The Lung, Scientific Foundations*, edited by Crystal and colleagues [38]. Other reviews are listed in the appropriate chapters of the present account.

## 1.7 Future prospects

The mechanisms that underlie the respiratory function of the lung are now quite well understood. The practical assessment

| Aspect                             | Authors                 | Year | Reference |
|------------------------------------|-------------------------|------|-----------|
| Obstruction index                  | Tiffeneau               | 1948 | [12]      |
| Closed circuit spirometry          | Gilson and Hugh-Jones   | 1949 | [13]      |
| Symbols                            | Pappenheimer et al.     | 1950 | [14]      |
| Dynamic spirometry                 | Gaensler                | 1951 | [15]      |
| Bronchial provocation              | Tiffeneau and Drutel    | 1951 | [16]      |
| Exchange of inert gases            | Kety                    | 1951 | [17]      |
| Gas exchange                       |                         |      |           |
| O <sub>2</sub>                     | Riley and Cournand      | 1951 | [18]      |
| CO <sub>2</sub>                    | Roughton                | 1954 | [19]      |
| O <sub>2</sub> and CO <sub>2</sub> | Rahn and Fenn           | 1955 | [5]       |
| Blood PO <sub>2</sub> electrode    | Clark et al.            | 1953 | [20]      |
| Lung mechanics                     | Mead and Whittenberger  | 1953 | [21]      |
| First Entretiens de Nancy*         | Sadoul                  | 1954 | [22]      |
| Body plethysmography               | DuBois et al.           | 1956 | [23]      |
| Distribution of gas                | Otis et al.             | 1956 | [24]      |
| The Lung                           | Comroe et al.           | 1955 | [25]      |
| Single breath DLco                 | Forster et al.          | 1954 | [26]      |
|                                    | Jones and Mead          | 1961 | [27]      |
| Terminology                        |                         |      |           |
| FEV <sub>1</sub>                   | Gandevia and Hugh-Jones | 1957 | [28]      |
| TI                                 | Cotes                   | 1963 | [29]      |
| Respir. Mass spectrometry          | Fowler and Hugh-Jones   | 1957 | [30]      |
| Peak flow meter                    | Wright and McKerrow     | 1959 | [31]      |
| Flow-volume curve                  | Fry and Hyatt           | 1960 | [32]      |
| Progressive cycling test           | Borg and Dahlstrom      | 1962 | [33]      |
| Quality control – gas analysis     | Cotes and Woolmer       | 1962 | [34]      |

**Table 1.3** Some developments in the post-war period 1945–1965.

\*Led to formation of Societas Europea Physiologiae Clinicae Respiratoriae (SEPCR), forerunner of European Respiratory Society.

**Fig. 1.2** Some contributors to applied lung physiology. Collage including some participants in the Haldane Centenary Symposium, Oxford, 1961. The figure does not indicate the relative heights of subjects in the middle rows. Source: Adapted from [36]; see also [37].

Row 1 (back). AB DuBois, DV Bates, P Hugh-Jones, DJC Cunningham, JE Cotes, EJM Campbell, ED Robin, JB West, P Dejours.  
 Row 2. WO Fenn, JH Comroe Jr, AB Otis.  
 Row 3. JC Gilson, A Cournand, H Rahn, RL Riley, BB Lloyd, JBS Haldane, P Sadoul, FJW Roughton.  
 Row 4 (front). A Asmussen, EH Christensen, M Nielsen, G Liljestrand, CG Douglas, C Heymans.



of lung function is an accepted part of clinical medicine, occupational medicine and epidemiology. The techniques for assessment have been standardised between workers in different countries and computerised equipment has become available in bewildering variety; thus the subject has matured.

Forthcoming challenges are to hold onto what we now know in the face of competition from other disciplines, exploit emerging technologies and discover how to benefit from

recent developments in pharmacology and molecular and cell biology, including the mapping of the human genome (Table 1.5).

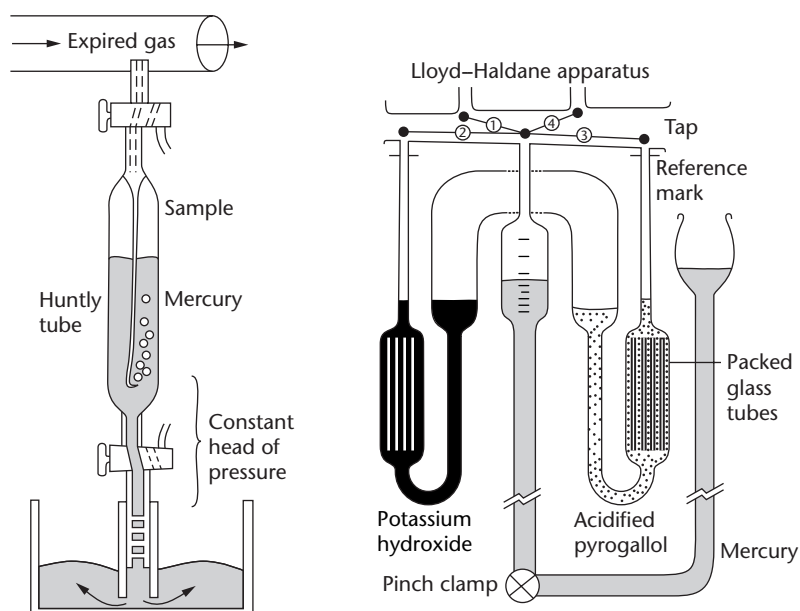
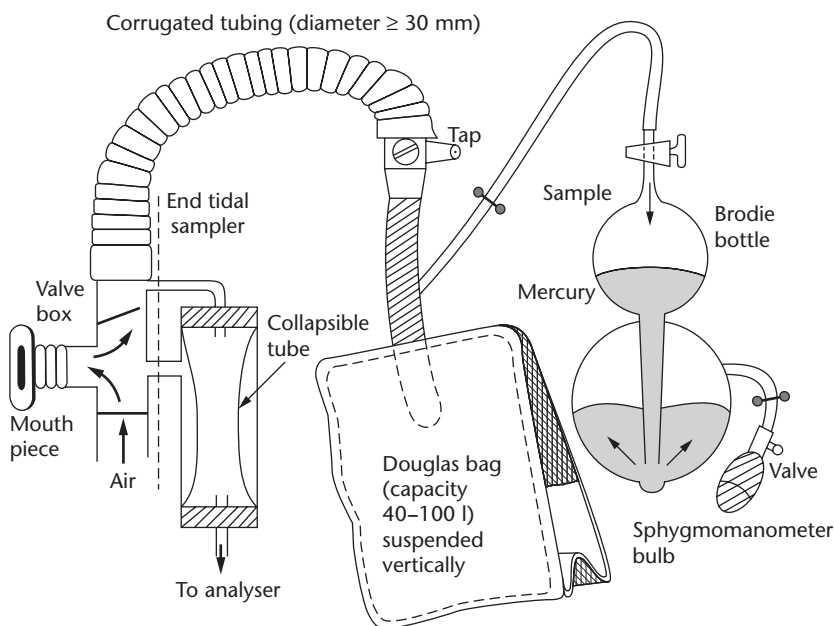
The immediate benefits are likely to be considerable and in the longer term they could be immense. But they will only be realised if high standards are maintained; this might be done by building on the techniques and underlying physiology that are described in this book.

**Table 1.4** Reagents for use with the chemical absorption methods of gas analysis at or above 20°C.

|                                                                                                                                                                |   |                                                     |        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|---|-----------------------------------------------------|--------|
| Acid rinse                                                                                                                                                     |   | Glycerol                                            | 21 ml  |
|                                                                                                                                                                |   | H <sub>2</sub> SO <sub>4</sub> (concentrated)       | 1 ml   |
|                                                                                                                                                                |   | Na <sub>2</sub> SO <sub>4</sub> (anhydrous)         | 66.4 g |
|                                                                                                                                                                |   | H <sub>2</sub> O                                    | 400 ml |
| 40 mg of pulverised K <sub>2</sub> Cr <sub>2</sub> O <sub>7</sub> is added to 50 ml of this solution immediately before use.                                   |   |                                                     |        |
| Absorber for CO <sub>2</sub>                                                                                                                                   |   | KOH                                                 | 8.86 g |
|                                                                                                                                                                |   | K <sub>2</sub> Cr <sub>2</sub> O <sub>7</sub>       | 40 mg  |
|                                                                                                                                                                |   | H <sub>2</sub> O                                    | 100 ml |
| Absorber for O <sub>2</sub>                                                                                                                                    | A | KOH                                                 | 5 g    |
|                                                                                                                                                                |   | H <sub>2</sub> O                                    | 100 ml |
|                                                                                                                                                                | B | Na <sub>2</sub> SO <sub>4</sub> · 2H <sub>2</sub> O | 24 g   |
|                                                                                                                                                                |   | Anthraquinone                                       | 0.1 g  |
| The oxygen reagent is made up by dissolving 1.3 g of B in 10 ml of A. In this form it will only keep for a few days but the components will keep indefinitely. |   |                                                     |        |

**Table 1.5** Future directions of research.

| Topic                                | Aspect                                                                 | Location           |
|--------------------------------------|------------------------------------------------------------------------|--------------------|
| Emerging technologies [39]           | Exercise flow–volume loops                                             | Section 28.8.1     |
|                                      | Negative pressure assisted flows                                       | Section 12.5.1     |
|                                      | Forced oscillations for measuring resistance                           | Section 14.4.4     |
| Understanding human respiration [40] | All                                                                    | This book          |
| Environmental contaminants           | Determinants of chronic respiratory disorders                          | Chapters 38 and 39 |
| Molecular biology [41–43]            | Genetic basis for normal respiratory function                          | Chapter 27         |
|                                      | Diagnosing and evaluating treatments for genetic respiratory disorders | Chapter 39         |
| Lung function                        | Better use of exercise tests                                           | Part 4             |



**Fig. 1.3** Traditional equipment for collecting and sampling expired gas. The Douglas bag is suspended vertically. Prior to use, its dead space is flushed with expired gas. After collection, the gas is mixed by pummelling the bag and a small amount is passed through the side arm. A sample is then transferred to a Brodie bottle (capacity 50 ml) or direct into a chemical analyser (e.g. Lloyd-Haldane, lower right; also Table 1.4). Gas volume is measured by using a wet gas meter and constant flow pump that cuts out at a predetermined negative pressure. Alternatively a Tissot spirometer (capacity 100 l) is used. The sampler for end tidal gas (top left) is operated by the pressure changes in the valve box. The sample collects in the collapsible tube and is sucked off at a flow of  $50\text{--}200\text{ ml min}^{-1}$  into a Huntly tube or other apparatus. The Huntly tube (capacity 50 ml, lower left) provides a means of collecting a representative sample of mixed gas over a period of 1 or 2 min.

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## CHAPTER 2

# Getting Started

*The chapter summarises the basic information needed to enter the subject of lung function testing, discover what is entailed in setting up a laboratory and start using this book.*

**2.1** Brief description of the lungs and their function  
**2.2** Deviations from average normal lung function  
**2.3** Uses of lung function tests  
**2.4** Assessment of lung function

**2.5** Setting up a laboratory  
**2.6** Conduct of assessments  
**2.7** References

### 2.1 Brief description of the lungs and their function

*The gas exchanger.* The lung is a sophisticated conglomerate of alveolar air sacs that has several functions. The principal one is as the body's organ of gas exchange. It also provides air for phonation and buoyancy during immersion in water. The latter function was important during man's evolution. The lung is at risk of being traumatised if the barometric pressure changes abruptly.

*Connection to atmosphere.* The alveoli are connected with the atmospheric air via branching tubes (bronchioles, bronchi and trachea). The atmosphere is a source of oxygen for metabolism and a dump for carbon dioxide, which is the principal waste product. The airways are also a portal of entry for potentially noxious gases, particles, respirable fibres and micro-organisms. Much of this material is removed in the nose and airways. The remainder is either exhaled or ingested and to some extent inactivated by phagocytic cells.

*Respiratory muscles.* The lungs are ventilated through the actions of respiratory muscles. The principal muscle is the diaphragm; this functions as a piston within the thoracic cage formed by the ribs and vertebral column. The ribs are stabilised and moved by intercostal muscles. Their functions can be supplemented by the actions of skeletal muscles that are attached to the thoracic cage; some of the muscles form the anterior abdominal wall.

*Lung volumes and ventilatory capacity.* The lung volume at the equilibrium position of the thoracic cage is functional residual capacity (FRC). Inspiration to total lung capacity (TLC) is

effected by the respiratory muscles stretching the elastic tissue of the lungs. Expiration to residual volume (RV) is effected by the elastic tissue squeezing air from the lungs. The exhalation is accompanied by inward movement of the thoracic cage.

Vital capacity (VC) is the maximal tidal excursion from TLC to RV, or vice versa. When the full expiratory manoeuvre is performed with maximal effort the volume of air expired in the first second reflects the maximal ventilatory capacity of the lung. This forced expiratory volume in 1 s (FEV<sub>1</sub>) is a widely used index of lung function.

The lungs grow during childhood; subsequently they deteriorate as a result of ageing and intercurrent illnesses. Smoking causes additional damage.

The normal levels of lung volume and other indices of function (reference values) are defined in terms of age and stature (height) for the two sexes separately. For optimal accuracy, allowance should also be made for ethnic group and body composition.

*Blood supply.* The output of the right ventricle of the heart flows into the pulmonary artery and thence into capillaries present in the walls of alveoli. Here the blood is conditioned by exchange of oxygen and carbon dioxide with alveolar gas.

*Control of respiration.* Ventilation of the lungs is controlled by respiratory centres in the brain. These have an intrinsic rhythmicity. Their function is modulated by information from other parts of the brain including its contained blood, the carotid bodies (which monitor the oxygen and carbon dioxide in arterial blood), the lungs via the vagus nerves and the skeletal muscles. Drive to ventilation is increased in many circumstances, including exercise and when the partial pressure of oxygen in inspired

air is reduced by ascent to high altitude. The drive is reduced when the function of the respiratory centres is depressed.

*Matching of lung ventilation and perfusion.* Ventilation and perfusion of individual lung units are influenced by anatomical factors and gravitational force. In the absence of control mechanisms these factors would lead to imperfect gas exchange from imbalance between ventilation ( $\dot{V}$ ) and perfusion ( $\dot{Q}$ ). The difficulty is overcome by adjustments to the calibres of individual small airways and blood vessels.

*Gas exchange.* Ventilation of the lungs renews the contained gas down to the level of the respiratory bronchioles. From there to the surface of the alveoli – a distance of approximately 1 mm – the movement of gases is by diffusion. The subsequent stages for oxygen uptake include solution in the fluid of the alveolar lining, diffusion from that point across the alveolar wall into plasma in the alveolar capillary and chemical combination with haemoglobin present in red blood cells. The capacity of these processes can be represented by the transfer factor ( $TL$ ); this is the amount of gas that transfers from alveolar gas to capillary blood per minute per unit partial pressure gradient across the alveolar capillary membrane. The transfer factor is usually measured using carbon monoxide as the indicator gas.

## 2.2 Deviations from average normal lung function

*Overall function.* Lung function and capacity for exercise are correlated. However, the scope for improving the function by training is rather limited. The size of the lungs is reduced by obesity.

*Airways.* The commonest abnormality in lung function arises from narrowing of airways. This can be episodic or persistent and may or may not be ameliorated by therapy. Causes include recurrent episodes of bronchitis, smoking and bronchial hyper-responsiveness, which can be associated with asthma. The presenting symptom is often wheeze or breathlessness on exertion. The FRC is usually increased and the FEV<sub>1</sub> reduced but the latter can often be restored towards normal by inhalation of a bronchodilator drug.

*Parenchyma.* The parenchymal tissue of the lung is attenuated in patients with emphysema. The elasticity of the tissue that remains is then reduced and the TLC is often increased. Conversely, in alveolitis and interstitial fibrosis the amount of tissue and the elasticity are increased, whilst the TLC is reduced. Both types of disease of the lung parenchyma are associated with a reduced transfer factor and a fall in the blood oxygen level during exercise (hypoxaemia). Restriction to lung expansion is also a feature of abnormalities of the pleura, chest wall and respiratory muscles.

*Cardiac overload.* Overload of the right ventricle can result from pulmonary vasoconstriction secondary to persistent narrowing

of airways or from obliteration of blood vessels by fibrous tissue or other cause. These changes can lead on to congestive cardiac failure.

A rise in left atrial pressure from any cause (for example, mitral stenosis or failure of the left ventricle) leads to pulmonary congestion; this may progress to oedema. The consequences include rapid, shallow breathing from stimulation of pulmonary J-receptors and changes in gas exchange.

*Respiratory control.* Excessive ventilation (hyperventilation) occurs during pregnancy, in some disorders that affect the lung parenchyma, diabetic acidosis, anxiety, malingering and other conditions. Hypoventilation can result from depression of the respiratory centres in the brain (for example by drugs or by severe hypoxaemia, or hypercapnia), and some abnormalities of the chest wall or respiratory muscles. The condition may lead on to stopping of breathing (apnoea), either intermittently or altogether. Apnoea during sleep can occur as a result of obstruction of the upper airways.

## 2.3 Uses of lung function tests

*Respiratory medicine and surgery.* Measurements of FEV<sub>1</sub> and VC before and often after inhalation of a bronchodilator aerosol are necessary for diagnosis and day-to-day management of many respiratory patients, both adults and children. Information on lung volumes, transfer factor and the physiological responses to progressive exercise contribute to diagnosis and assessment of patients with abnormalities of the lung parenchyma, including patients who may go on to lung surgery and transplantation of the lungs or heart. Exercise tests are an essential adjunct to programmes of respiratory rehabilitation, including portable oxygen therapy. Dedicated procedures are used for diagnosis of sleep apnoea and for monitoring treatment.

*General surgery.* Lung function is one consideration in determining suitability for general anaesthesia.

*Occupational medicine.* Knowledge of lung function is necessary for the diagnosis and management of most occupational disorders of the lung, including the pneumoconioses, extrinsic allergic alveolitis and occupational asthma. Diagnosis of the latter condition can depend on the response to inhalation challenge undertaken in the lung function laboratory.

Lung function and the response to exercise are essential components of assessment of disability and fitness for work. They also contribute to the pre-employment assessment, to routine surveillance throughout employment, and to appraisals for medico-legal purposes.

*Screening at work and in epidemiology.* The FEV<sub>1</sub>, VC and peak expiratory flow have been used in community surveys to provide evidence on overall respiratory health and life expectancy. In occupational surveys the mean levels in a work force can identify

respiratory hazards at an early stage. Individual results can identify persons in need of medical treatment. Screening of targeted groups within a general population can sometimes be helpful but non-selective screening for evidence of respiratory disease is seldom cost-effective.

*Human biology.* The size of the lungs relative to the size of the person varies depending on ethnic group and a host of environmental factors. These are still being documented.

*Physically active pursuits.* Lung function and capacity for exercise contribute to performance in athletics, mountaineering, competitive sports, fire fighting and rescue work and other high-level activities. The tests can identify the need for and response to physical training.

*Abnormal environments.* Exposure to high or low barometric pressures exerts both acute and long-term effects upon the lungs. Inappropriately rapid changes in pressure also have significant effects. Hence, most codes of practice for aircrew and for professional underwater divers require the long-term monitoring of personnel. Patients and members of the general public may need individual, specialist assessment prior to exposure.

## 2.4 Assessment of lung function

*Guidelines.* These have been prepared by respiratory learned societies and are comprehensive ([1–6], also references in individual chapters). However, the recommendations are not always

concordant, some are compromises and some have not been fully validated. Thus, there is need for an independent viewpoint.

*Criteria for tests.* Over the past 50 years many lung function tests have been introduced and many have been abandoned. The choice has been mainly empirical. However, a set of criteria for selecting tests was proposed early in the evolution of the subject [7] and the current version has a wide measure of support (Table 2.1). The criteria are relevant for evaluating any new test that may emerge in future.

*Which measurements?* Four domains where lung function tests are undertaken are shown in Table 2.2, together with tests that are appropriate for each location and purpose. All assessments should include accurate measurement of stature and a record of age, smoking status, gender, ethnic group and respiratory symptoms. Body mass or composition is usually also necessary. A fuller list of procedures is in Table 2.3.

## 2.5 Setting up a laboratory

*Location.* Some patients will be disabled, and so the laboratory should be accessible to the car park, chest clinic, ward and toilets. However, observing the patient take a short walk can assist in diagnosis and be of therapeutic value, and so close proximity is not essential. Laboratories may also conduct cardiac evaluations for which similar considerations apply. Proximity to the radiographic and physiotherapy departments can be advantageous.

**Table 2.1** Criteria for tests.

| Aspect                   | Criterion                                                                                                                                                                                        | Presentation                         |
|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| Acceptability            | Safe, simple and not unpleasant for subject                                                                                                                                                      | Arbitrary                            |
| Objectivity              | Result not too much under subject's control                                                                                                                                                      |                                      |
| Repeatability            | Closeness of agreement over a short space of time with same method, observer, instrument, location and conditions of use                                                                         | Differences between replicates       |
| Reproducibility          | As above but with a change in one or more of the conditions                                                                                                                                      |                                      |
| Accuracy                 | Results do not deviate systematically from the correct values                                                                                                                                    | Amount or percentage                 |
| Validity                 | Test should be relevant and discriminatory in the relevant circumstances                                                                                                                         |                                      |
| Sensitivity              | A high proportion of affected persons should be identified as abnormal                                                                                                                           | Percentage                           |
| Specificity              | A high proportion of unaffected persons should be identified as normal                                                                                                                           | Percentage                           |
| False positives          | Relatively few normal persons should be wrongly identified as having the condition                                                                                                               | Percentage or likelihood ratio (LR)* |
| False negatives          | Relatively few persons with the condition should escape detection                                                                                                                                | Percentage or likelihood ratio (LR)† |
| Technical considerations | Test should be of short duration, require compact equipment that is convenient to use, calibrate and service and for which intermediate results can be displayed for purposes of quality control | Arbitrary                            |

\* LR of a positive test =  $\frac{\text{probability of obtaining an abnormal test result in diseased subjects}}{\text{probability of obtaining an abnormal test result in disease-free subjects}}$

This can be represented as Sensitivity/(100 – Specificity).

† LR of a negative test =  $\frac{\text{probability of obtaining a normal test result in diseased subjects}}{\text{probability of obtaining a normal test result in disease-free subjects}}$

This can be represented as (100 – Sensitivity)/Specificity.

**Table 2.2** Tests for use in different circumstances.

|                                                                                                                                      | Time (min)*        |
|--------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| <i>Basic screening.</i>                                                                                                              |                    |
| Stature. Questionnaire                                                                                                               | 10                 |
| Forced expiration test for measurement of FEV <sub>1</sub> , FVC and/or peak expiratory flow. Other tests have also been recommended | 15                 |
| <i>Primary care/Consulting room</i>                                                                                                  |                    |
| Stature. Measurement of VC, FEV <sub>1</sub> and related indices before and after inhalation of bronchodilator aerosol               | 20–70 <sup>†</sup> |
| <i>Secondary care/District hospital</i>                                                                                              |                    |
| Essential measurements                                                                                                               |                    |
| Stature and body mass                                                                                                                | 5                  |
| VC and FEV <sub>1</sub> before and after inhalation of bronchodilator aerosol                                                        | 20–70 <sup>†</sup> |
| Transfer factor for carbon monoxide                                                                                                  | 20                 |
| Arterial blood gas tensions (unless measured elsewhere)                                                                              | 10–20              |
| Chest radiology                                                                                                                      |                    |
| Recommended measurements                                                                                                             |                    |
| Total lung capacity and subdivisions                                                                                                 | 20                 |
| Physiological response to exercise (preferably on a treadmill, Section 29.4.1)                                                       | 20–40              |
| Body fat and fat-free body mass                                                                                                      | 10                 |
| Simple monitoring of respiratory muscle strength                                                                                     | 10                 |
| Simple monitoring for sleep apnoea                                                                                                   | 12h                |
| <i>Specialist centre.</i> All the above with appropriate additions, e.g.                                                             |                    |
| Airway resistance by whole body plethysmography                                                                                      | 15                 |
| Compliance of the lung by oesophageal intubation                                                                                     | 20                 |
| Assessment of function of respiratory muscles                                                                                        | 10–20              |
| Full assessment for sleep apnoea (polysomnography)                                                                                   | 12h                |
| Challenge tests for bronchial hyperresponsiveness and extrinsic asthma                                                               | 30–60              |
| Skin allergy tests if not done previously                                                                                            | 20                 |
| CT and other scans                                                                                                                   |                    |

\* Timings are a rough guide and will depend on the patient's condition, cooperation and safety.

<sup>†</sup> The time depends on which drug is being used (Section 15.7.2).

*Staff qualifications and training.* The presence of two clinical respiratory physiologists is a working minimum (see Footnote 2.1). Both should have received four years of basic training leading to a diploma in physiological measurement or hold an appropriate higher qualification. One member should be trained in health and safety issues and all staff should be competent in cardiopulmonary resuscitation. Medical cover should be available in the building. Staff should be capable of adopting an unassuming and friendly but firm approach (e.g. see Section 30.4.3) and not mind performing the tests on themselves. This can be necessary both to supplement verbal instructions to new patients and to check on instrument calibrations.

Footnote 2.1. 'Clinical respiratory physiologist' is used here to describe any person judged competent under his or her national accreditation arrangements to conduct lung function assessments in a clinical setting. The term covers, for example, clinical scientist, medical technical officer, respiratory therapist, respiratory technologist, lung function technician and respiratory nurse.

The formal training of staff is a responsibility of the head of department [8]. It should include regular attendance at departmental meetings where lung function is integrated with other aspects of individual cases. Participation in continual professional development courses and scientific meetings along with clinical respiratory physiologists from other centres is also necessary. Such gatherings are arranged by national and international respiratory societies (Table 2.4). Clinical respiratory physiologists should be members of whichever of their national, professional societies hold meetings for those working in lung function laboratories.

*Equipment.* The equipment should preferably be compact, robust and easy to calibrate, clean and service adequately. Arrangements should be made for long-term servicing and details of it recorded in an equipment logbook. The measurements should be in a form that meets the specification of the user. This includes both physical characteristics (e.g. Table 2.5) and conventions for selecting and processing the measurements. The technical specification provided by the manufacturer should be scrutinised,

**Table 2.3** Checklist of respiratory laboratory procedures.

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><i>Lung mechanics</i></p> <ul style="list-style-type: none"> <li>• Peak expiratory flow</li> <li>• Spirometry</li> <li>• Flow–volume curves (maximal and partial)</li> <li>• Lung volumes (gas dilution, body plethysmography, radiography)</li> <li>• Chest wall mechanics • Lung compliance</li> <li>• Respiratory muscle function</li> <li>• Resistance (oscillometry, plethysmography, oesophageal manometry, airflow interruption)</li> </ul> <p><i>Gas exchange (rest and exercise)</i></p> <ul style="list-style-type: none"> <li>• Blood sampling (ear lobe and arterial)</li> <li>• Blood analysis (gases, pH, haemoglobin, pulse oximetry, transcutaneous measurements)</li> <li>• Gas analysis (O<sub>2</sub> uptake, CO<sub>2</sub> output)</li> <li>• Transfer factor and components</li> <li>• Distributions of blood flow and ventilation (<math>\dot{V}_A/\dot{Q}</math>)</li> <li>• Physiological and anatomical shunts</li> </ul> <p><i>Ventilatory control at rest</i></p> <ul style="list-style-type: none"> <li>• Tidal breathing, pattern and minute ventilation</li> <li>• Hyperventilation responses, hypoxic and hypercapnic challenge, pressure output</li> <li>• Response to mechanical loading</li> <li>• Flight (altitude) simulation</li> <li>• Diving simulation</li> </ul> <p><i>Sleep studies</i></p> <ul style="list-style-type: none"> <li>• Simple screening (oximetry, actigraphy, snore detection)</li> <li>• Limited multichannel studies (oxygen saturation, cardiac frequency, airflow, chest wall movement)</li> <li>• Full polysomnography, incorporating electrophysiology</li> <li>• Assessment of interventions (mechanical, pharmacological, etc.)</li> </ul> | <p><i>Physique</i></p> <ul style="list-style-type: none"> <li>• Body mass and composition, stature</li> </ul> <p><i>Physiological responses to exercise</i></p> <ul style="list-style-type: none"> <li>• 6/12 min walk tests, shuttle walk tests, step tests, exercise-induced asthma Cardiorespiratory exercise testing</li> <li>• Gas exchange, ventilation and work rate</li> <li>• Blood gases</li> <li>• Respiratory and other symptoms</li> <li>• Cardiac responses (cardiac frequency, 12 lead ECG, blood pressure, cardiac output)</li> <li>• Maximal exercise, disability assessment</li> </ul> <p><i>Responses to therapeutic interventions</i></p> <p>Pharmacological interventions</p> <ul style="list-style-type: none"> <li>• Supplemental oxygen (rest and exercise), bronchodilators, corticosteroids, antibiotics, etc.</li> </ul> <p>Non-pharmacological interventions</p> <ul style="list-style-type: none"> <li>• Non-invasive ventilatory support</li> <li>• Pulmonary rehabilitation including exercise retraining, inspiratory muscle training</li> </ul> <p><i>Impact of respiratory disease</i></p> <ul style="list-style-type: none"> <li>• Symptoms (indirect and direct methods)</li> <li>• Health status (generic and disease-specific questionnaires)</li> </ul> <p><i>Systemic and airway responsiveness</i></p> <ul style="list-style-type: none"> <li>• Bronchodilator response</li> <li>• Skin allergen testing</li> <li>• Bronchial challenge testing</li> <li>• Exercise-induced asthma</li> <li>• Cough reflex</li> </ul> <p><i>Acute and domiciliary services and support</i></p> <ul style="list-style-type: none"> <li>• Planning assessments, interpreting results, surveying patients</li> </ul> |
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Source: S Hill, personal communication, 2004.

**Table 2.4** Websites for some respiratory societies.

| Country/continent | Society                                                         | Address*                                                               |
|-------------------|-----------------------------------------------------------------|------------------------------------------------------------------------|
| United Kingdom    | Association for Respiratory Technology and Physiology(ARTP)     | <a href="http://www.artp.org.uk">www.artp.org.uk</a>                   |
| United Kingdom    | British Thoracic Society                                        | <a href="http://www.brit-thoracic.org.uk">www.brit-thoracic.org.uk</a> |
| Europe            | European Respiratory Society (ERS)                              | <a href="http://www.ersnet.org">www.ersnet.org</a>                     |
| Europe            | International Union Against Tuberculosis and Lung Diseases      | <a href="http://www.ariatd.org">www.ariatd.org</a>                     |
| North America     | American Thoracic Society (ATS)                                 | <a href="http://www.thoracic.org">www.thoracic.org</a>                 |
| Canada            | Canadian Thoracic Society                                       | <a href="http://www.lung.ca/cts">www.lung.ca/cts</a>                   |
| Latin America     | Latin American Thoracic Association                             | <a href="http://www.alat.brz.net">www.alat.brz.net</a>                 |
| Australasia       | Australia & New Zealand Society of Respiratory Science (ANZSRS) | <a href="http://www.anzsrs.org.au">www.anzsrs.org.au</a>               |
| Australasia       | Thoracic Society of Australia & New Zealand                     | <a href="http://www.thoracic.org.au">www.thoracic.org.au</a>           |
| Middle East       | Arab Respiratory Society                                        | <a href="http://www.imhotep.net/ars.html">www.imhotep.net/ars.html</a> |
| Japan             | Japanese Respiratory Society                                    | <a href="http://www.jrs.or.jp">www.jrs.or.jp</a>                       |
| South Africa      | South African Thoracic Society                                  | <a href="http://www.pulmonology.co.za">www.pulmonology.co.za</a>       |

\* Sites include hyperlinks to other web addresses.

**Table 2.5** Qualitative appraisal of assessment procedures for the study of lung mechanics.

| Aspects of lung function and method or apparatus | Technical aspects* |                 |                     |             |              |              |                   | Location (Chapter or Section) |
|--------------------------------------------------|--------------------|-----------------|---------------------|-------------|--------------|--------------|-------------------|-------------------------------|
|                                                  | Simplicity         | Reproducibility | Ease of calibration | Portability | Capital cost | Cheap to run | Use               |                               |
| Lung volumes                                     |                    |                 |                     |             |              |              |                   | 10.3                          |
| Closed circuit spirometry                        | B                  | A–B             | A–B                 | C           | C            | C            | Routine           |                               |
| Forced rebreathing                               | B                  | B               | B                   | A           | B            | A            | Surveys           |                               |
| Plethysmography                                  | C                  | A–B             | B                   | D           | D            | B            | Specialist centre |                               |
| Radiography                                      | C                  | A–B             | C                   | D           | D            | C            | Research          |                               |
| Ventilatory capacity                             |                    |                 |                     |             |              |              |                   | 12.3 to 12.6                  |
| Peak flowmeter                                   | A                  | A               | B                   | A           | A            | A            | Clinic            |                               |
| Bellows spirometer                               | A                  | A               | A–C                 | A           | A            | A            | Clinic            |                               |
| Rolling seal spirometer                          | B                  | A               | B                   | B–C         | C            | B            | L.F. Lab          |                               |
| Pneumotachography                                | B                  | A               | B                   | B           | D            | A            | L.F. Lab          |                               |
| Resistance to flow                               |                    |                 |                     |             |              |              |                   | Ch 14                         |
| Airway interruptor                               | B                  | B               | C                   | A           | B            | A            | Surveys           |                               |
| Forced oscillation                               | C                  | C               | C                   | C           | B            | B            | L.F. Lab          |                               |
| Plethysmography                                  | C                  | A–B             | B                   | D           | D            | B            | Specialist centre |                               |
| Oesophageal balloon, etc.                        | C                  | C               | C                   | C           | C            | C            | Research          |                               |
| Lung elasticity                                  |                    |                 |                     |             |              |              |                   | 11.8                          |
| Oesophageal balloon, etc.                        | C                  | C               | C                   | C           | C            | C            | Specialist centre |                               |

\* Scale A–D: A indicates simple test, yielding reproducible results from equipment that is easily calibrated, cheap to buy and run. D indicates complex test, yielding non-reproducible results from equipment that is not easily calibrated, not portable, expensive to buy and run.

including the algorithms in any software for calculating intermediate results. Alternative non-standard procedures are usually best avoided. If in doubt, expert advice should be sought from experienced colleagues; these are sometimes only to be found in other institutions.

The need for advice is greatest with multi-purpose equipment. Such equipment is often economical and can be satisfactory, but may not meet the technical specifications for all the intended applications. The stepwise acquisition of dedicated quality instruments can be a better policy.

*Bringing a test into use.* Before applying a new test the clinical respiratory physiologist should receive appropriate training. The manufacturer sometimes provides this. The equipment should be calibrated under the conditions in which it is to be used (Section 7.15) and the result recorded in a book kept for this purpose. The clinical respiratory physiologists should then try out the test on themselves and on volunteer visitors and patients.

The reproducibility and accuracy of the equipment and operator together should next be determined (Section 7.15). The accuracy should not be in doubt if the calibration is satisfactory and the correct procedure followed. Despite this, systematic errors can occur. They are usually due to neglect of some apparently trivial aspect of the procedure or a defect in the equipment that is not readily amenable to calibration. The operator performing a biological calibration can detect such errors. This entails applying the test to a group of subjects with apparently normal lungs.

The results should be comparable with those published in the literature (Chapter 26). To ensure that this level of performance is maintained, a routine should be established for the regular repetition of the calibration. Only at this stage is the equipment ready for use.

## 2.6 Conduct of assessments

*The appointment, arrangements and underlying considerations.* Arrangements for the appointment should lead to the appropriate measurements being made including those needed for interpretation. This is best achieved by including in the form completed by the referring doctor both a clear statement as to why the patient has been referred and the option that the choice of tests be delegated to the laboratory (Fig. 2.1).

For the patient the notification should usually include an indication of the likely duration of the procedures. Patients should be asked to bring their reading glasses and wear loose clothing. It is advisable that they do not smoke or consume alcohol on the day of the test or attend soon after undertaking heavy exercise or eating a big meal. Any medication should be taken at the normal times; the clinical respiratory physiologist should record the times. However, where the response to bronchodilator is of interest, the patient may be asked not to use any bronchodilator drug or inhaler during the four hours prior to the appointment. Exposure to cold air should be avoided.