Respiratory Physiology

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General preface to series

Student textbooks of medicine seek to present the subject of human diseases and their treatment in a manner that is not only informative, but interesting and readily assimilable. It is also important, in a field where knowledge advances rapidly, that the principles are emphasized rather than details, so that information remains valid for as long as possible.

These factors all favour an approach which concentrates on each disease as a disturbance of normal structure and function. Therapy, in principle, follows logically from a knowledge of the disturbance, though it is in this field that the most rapid changes in information occur.

A disturbance of normal structure without any disturbance of function is not important to the patient except for cosmetic or psychological considerations. Therefore, it is the disturbance in function which should be stressed. Preclinical students must get a firm grasp of physiology in a way that shows them how it is related to disease, while clinical students must be presented with descriptions of disease which stress the basic disturbance of function that is responsible for symptoms and signs. This approach should increase interest, reduce the burden on the student's memory and remain valid despite alterations in the details of treatment, so long as the fundamental physiological concepts remain unchallenged.

In the present Series, the major physiological systems are each covered by a pair of books, one preclinical and one clinical, in which the authors have attempted to meet the requirements discussed above. A particular feature is the provision of cross-references between the two members of a pair of books to facilitate the blending of basic science and clinical expertise that is the goal of this Series.

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Preface

This book is intended to help students understand the basic aspects of respiratory physiology. For the medical student it should provide a preparation for the 2nd MB Examination or its equivalent, although the passages in smaller print give information in greater detail than required by most medical courses. The companion volume (Cameron and Bateman *Respiratory Disorders* 1983) will be of special value in illustrating the clinical relevance of basic physiology to medicine, and should prove particularly appropriate for students at medical schools where there is a degree of integration of the curriculum. For science students the text should give a basic understanding of respiratory physiology, but supplementary reading will be needed for those taking honours courses in respiration. The book will undoubtedly be used to prepare for that bane of student life—examinations. Readers may take solace in the fact that using this book provides them with an opportunity to examine the authors and possibly their own examiners. However, no two examiners have ever agreed on the exact scope and depth of an examination syllabus.

Many colleagues have assisted with the production of this book but we would especially like to thank Dr Paul Richardson and Professor Ian Cameron for reading and commenting on some of the chapters. We are also extremely grateful to Dr Rodger Pack for the micrographs, Dr Mary Davies for the learning objectives and Carolyn Hollins for her help with the manuscript.

Finally, we greatly appreciate the help of Mrs Rita Perry for typing and manipulating the many versions and revisions of the manuscript, and the publishing staff for their efficiency and patience in dealing with the unreliable authors.

London, 1983

JGW
ASD

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Two notes on the chapters

At the end of each chapter is a list of 'learning objectives'. They are not inclusive, and in particular they omit throughout a major objective for medical students, to be able to relate basic studies to clinical applications. However if the reader can confidently and honestly deal with each objective then this is an indication that the material in the chapter has been well digested. If the objective appears meaningless or unattainable then further study is required. The learning objectives may also, as a by-product, suggest the kind of questions that may be set in examinations.

Also at the ends of the chapters are suggestions for further reading. These references relate in particular to the content of each preceding chapter. More general references to texts on respiratory physiology, either for supplementary reading or for greater detail, are:

Comroe, J. H. Jr. (1974). *Physiology of Respiration*, 2nd Edn. Yearbook Medical Publishers, Chicago.

Bouhuys, A. (1974). *Breathing, physiology, environment and lung disease*. Grune & Stratton, New York.

Widdicombe, J. G. (Editor) (1974, 1977, 1981). *Respiratory Physiology I, II and III,* International Review of Physiology, volumes 2, 14 and 23, University Park Press, Baltimore.

Lenfant, C. (Executive Editor). *Lung Biology in Health and Disease*, 18 volumes published to date. Marcel Dekker, New York.

Progress in Respiration Research.

Review Articles in *Physiological Reviews, Annual Review of Physiology* and *American Review of Respiratory Diseases.*

Contents

1

Lung structure and function

The need for air by higher forms of life must have been obvious to the ancients. Anaximenes of Miletus (born *c.* 570 BC) stated that air, or 'pneuma' (literally 'breath', *Greek*), was essential to life. The function of air was open to speculation. Plato (428–345 BC) stated 'as the heart might easily be raised to too high a temperature by hurtful irritation, the genii placed the lungs in its neighbourhood, which adhere to it and fill the cavity of the thorax, in order that air vessels might moderate the great heat of that organ, and reduce the vessels to an exact obedience'.

Galen (AD 130–199) was probably the first person to have insight into the true nature of respiration, for he compares it to a lamp burning in a gourd: 'When an animal inspires it is, I think, similar to a perforated gourd, but when respiration is prevented at the appropriate place on the trachea, you may compare it to a gourd unperforated and everywhere closed'. With the benefit of modern gas-analysing equipment, Galen would have discovered that the respiration of animals is in fact very similar to the action of a burning lamp, consuming O_2 and giving off CO_2. It is the function of the respiratory system to facilitate this exchange of gases between the cells of the organism and its surroundings.

What is respiration?

The word respiration has come to have several applications. Physiologists use it as the equivalent of 'breathing' (spiro, *Latin*, 'I breathe'). Biochemists use it to refer to the oxygen-requiring chemical processes in tissues, cells and cell fragments; the vast subject of 'tissue respiration' will not be discussed here. Rather, this book is concerned with breathing and the transport of gases to and from the lungs and tissues via the bloodstream. 'Respiration' integrates nervous control of breathing, the function of the lungs, the circulation of the blood and the metabolism of the tissues. It is therefore not surprising that the full study of respiration includes the traditional core-subjects of basic medical science—anatomy, physiology, biochemistry, pharmacology and psychology; even sociology could be incorporated since patterns of breathing, quite apart from speech and singing, can be a form of communication!

The basis of respiration

Microscopic organisms can rely on *diffusion* to carry O_2 to their cells and to remove CO_2. Most multicellular organisms are too large to allow diffusion alone to be effective—the distances gases would have to diffuse are too great to maintain life. Although in man the same passive force of diffusion alone supplies and removes these gases (there is no active chemical transport of O_2 and CO_2), it is aided by complicated respiratory and cardiovascular systems which accomplish what the surrounding pond water does for amoebae. These systems are susceptible to breakdowns, which are considered in the companion volume (Cameron and Bateman, 1983); here we will concentrate on the normal functioning of a system which, with a lung volume of less than 10 litres, provides a respiratory surface of over 90 m^2 and can accommodate metabolic changes from rest to extreme exercise in a wide variety of environmental conditions.

The constant environment

To operate efficiently, the cells of our bodies must be provided with a stable environment, relatively independent of external changes and the activity of the whole organism. This is especially true of the cells in the central nervous system.

Neophytes in physiology often lay great stress on the role of the respiratory system in supplying O_2 to the tissues. This role is important, but of greater immediate urgency is the removal of CO_2, one of the products of oxidative metabolism. The importance the body places on eliminating this substance can be judged by re-breathing from a plastic bag for a few minutes. Most of the drive to breathe and the unpleasant sensation which forces you to stop this rather dangerous manoeuvre are due to hypercapnia (high concentrations of CO_2). Carbon dioxide is an 'acid' gas. It dissolves in body fluids to form carbonic acid which dissociates into bicarbonate and hydrogen ions.

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO^-_3 + H^+ \qquad 1.1$$

It is to keep its acidity (often measured as pH, which is $-\log_{10}[H^+]$ in $mol \cdot l^{-1}$) within tolerable limits that the body responds so strongly to any build-up of CO_2. Blood is normally maintained close to pH 7.40, in part by adjustments in respiration. Those who are overly impressed by the narrowness of the normal pH range (7.35–7.45) should remember that pH is on a $\log_{10}$ scale and so a change of one unit of pH means a tenfold change in $[H^+]$. If pH were to change by 10 per cent from 7.00 to 7.70, about the extreme possible range, $[H^+]$ would change 500 per cent from 0.0001 to 0.00002 $mmol \cdot l^{-1}$.

Circulation and respiration

The circulation of the blood is intimately related to respiration. It forms the transport link between the lungs and the tissues, the two sites of gas exchange. We shall see in Chapter 7 that the matching of blood flow and ventilation in the lungs is of prime importance to their efficient functioning, just as the

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balance of blood flow and metabolism in the tissues is crucial to their normal function.

The time courses of events in the respiratory and circulatory systems are rather different. At rest your heart may beat sixty times per minute while you only take fifteen breaths. The gas in the lungs changes in composition during inspiration as fresh air is added to the reservoir of gas in the chest, and during expiration as gas exchange with the blood continues. Blood pulsing through the lungs absorbs these respiratory oscillations in gas tensions. In conditions such as exercise, not only will the size and timing of the cardiac and respiratory cycles be different, but both should match metabolism. For breathing, this matching is brought about by a control system in the brain which receives information from many sources, including sensors which monitor O_2 and CO_2 tensions in the blood and the extracellular fluid of the brain, and others that respond to mechanical changes in the lungs and chest wall. This information is used to determine a pattern of breathing which maintains appropriate blood O_2 and CO_2 tensions with the minimum expenditure of energy.

The lungs also have passive roles as an elastic liquid reservoir supplying the left ventricle of the heart with blood, and as a filter with millions of capillaries which trap clots, detached cells, air bubbles and particles, thereby protecting the more vulnerable coronary and cerebral circulations from blockage.

Structure

Before we begin to discuss in detail the functioning of the respiratory system, we must know something about its structure. The respiratory system can be divided into extra- and intrathoracic parts. The nose, mouth, pharynx, larynx and upper part of the trachea are extrathoracic and are therefore not subjected to the changes in pressure in the thorax brought about by contractions of the diaphragm and chest muscles in breathing. Inside the chest the lower trachea divides at the carina into the right and left main bronchi. These continue to divide by an irregular dichotomous (each airway dividing into two 'daughters' of different sizes) system into smaller and smaller tubes until the respiratory surface of the alveoli is reached. The dimensions of some of the tubes that make up this *tracheobronchial tree* are given in Table 1.1.

It is interesting, and important, to note that while the airways are getting narrower they are getting far more numerous, so the total cross-sectional area is increasing enormously. Computer models show us that the angles between the airways and the dimensions of the airways are exactly right to cram the maximum alveolar surface area into the minimum volume. Each lung is anatomically divided into lobes made up of segments which are subdivided into lobules (Fig. 1.1).

The lungs lie on both sides of the mediastinum which contains the trachea, heart, major blood vessels, nerves and oesophagus. The lungs are covered by a thin layer of tissue called the *visceral pleura* and the mediastinum and chest wall are lined by *parietal pleura*. The pleurae are lubricated by a small amount of slimy solution and slip over each other during breathing.

The blood vessels of the pulmonary circulation follow the same pattern as

Table 1.1 Dimensions of some of the airways that make up the human tracheobronchial tree. Note the increase in cross-section and percentage total volume in the last few generations

Generation	Name	Diameter (cm)	Total cross-section (cm^2)	Cumulative volume (%)	Number
0	Trachea	1.80	2.5	1.7	1
10	Small bronchi	0.13	13.0	4.0	10^3
14	Bronchioles	0.08	45.0	7.0	10^4
18	Respiratory bronchioles	0.05	540.0	31.0	3×10^5
24	Alveoli	0.01	8×10^5	100.0	3×10^8

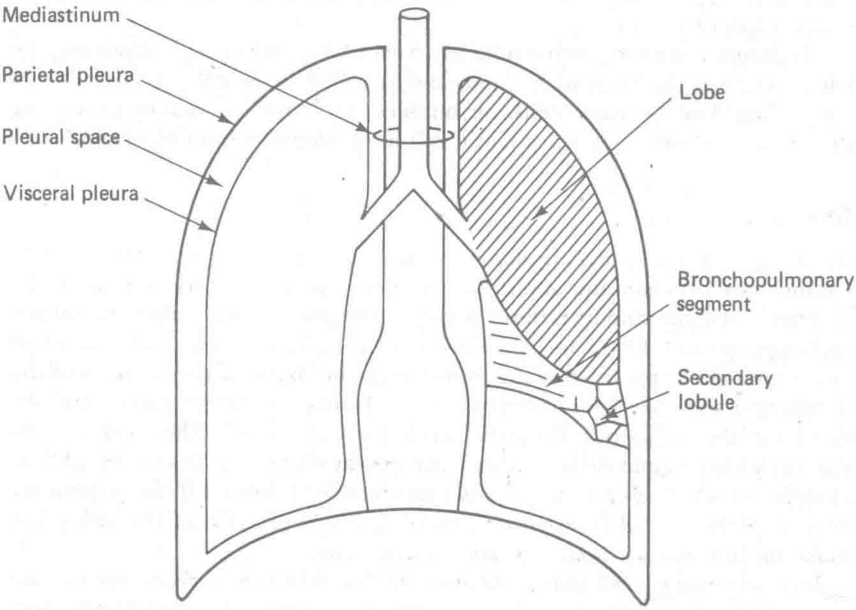

Fig. 1.1 Diagram of the lungs and their subunits and their relationship to the pleura.

the airways, dividing again and again until they are at the respiratory surface. Here the blood and air are in intimate contact, separated only by two very thin layers of cells (Fig. 1.2).

Nerves running with the blood vessels and bronchi control smooth muscle fibres in the walls of the airways and blood vessels and the mucus-secreting glands. Nerves also conduct sensation and sensory reflex information in the opposite direction, from lungs to brain. The main nerves involved are the vagi (Xth cranial nerves) which travel from the brain through the base of the skull down the neck, through the chest to the abdomen (vagus means 'wanderer').

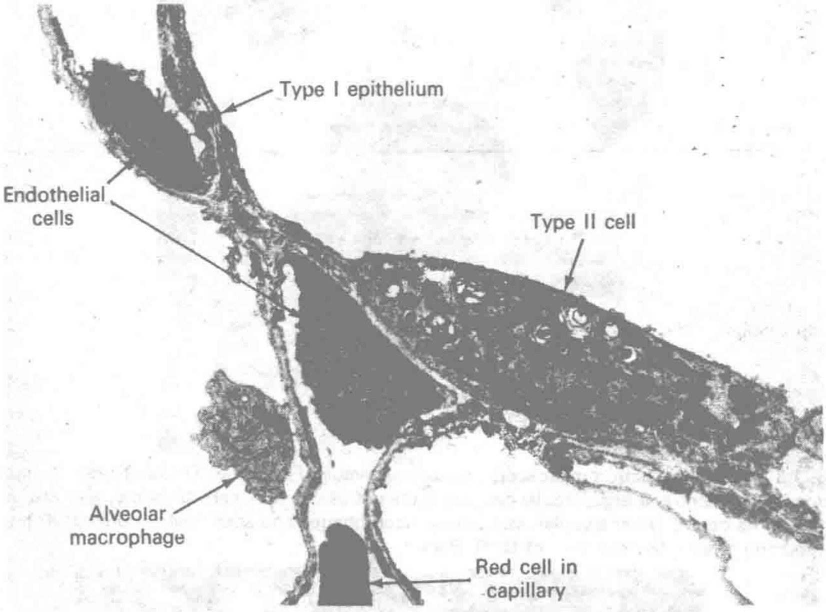

Fig. 1.2 Transmission electron microscopic picture of the alveolar wall. A Type II cell with osmiophilic inclusions is shown, and the epithelial extensions of Type I cells. The nuclei of two capillary endothelial cells are shown, with a red cell in one capillary. Within an alveolus, an extension of an alveolar macrophage is visible. (By courtesy of Dr R. Pack.)

Sympathetic system nerves from the thoracic spinal cord also supply the lungs.

Lymphatic vessels drain the tissues of the bronchi and bronchioles, but not the alveoli where lymph capillaries might obstruct the passage of respiratory gases.

Ultrastructure

At the *alveolar level,* there are capillary endothelial and alveolar epithelial cell layers (Fig. 1.2); the epithelium consists of flat Type I cells, and also Type II cells that secrete *surfactant*, a detergent-like substance that helps prevent collapse of the alveoli. The scanning electron microscope allows us to look into the alveoli (Fig. 1.3). Alveoli do not look like the regular balloons or bunches of grapes that are stylistically represented in some textbooks, but are pock-marked cavities with holes joining adjacent alveoli (pores of Kohn) and with macrophages wandering about ready to engorge and digest debris and foreign particles.

A scanning electron micrograph of the *bronchial* wall (Fig. 1.4) reveals a sheet mainly of ciliated cells which transport mucus up the airways to the

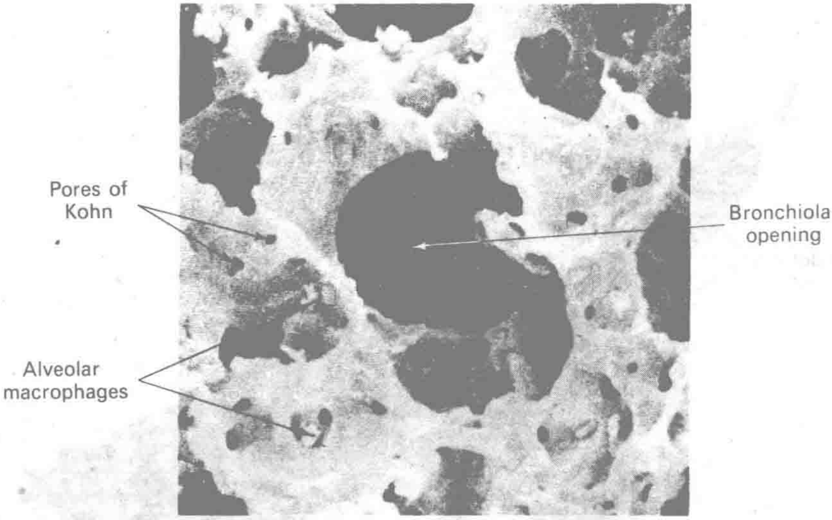

Fig. 1.3 Scanning electron microscopic picture of alveoli of a mouse. The lung has been cut across. In the centre, a large circular opening is the orifice of a terminal bronchiole, with alveoli visible in its depth. Other alveolar walls show macrophages and small holes (pores of Kohn) connecting alveoli. (By courtesy of Dr R. Pack.)

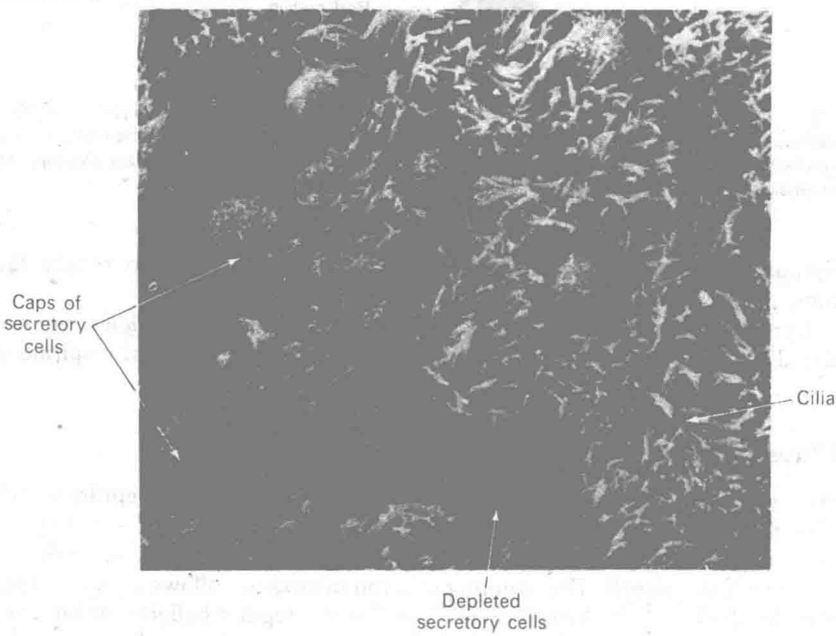

Fig. 1.4 Scanning electron microscopic picture of a bronchial wall. The cells are mainly ciliated, but secretory cells with prominent protruding caps are also visible. These may be mucus-secreting goblet cells. Their surfaces have microvilli rather than cilia. Denuded areas of the epithelium may result from cells having secreted their contents. In normal conditions, the mucociliary epithelium would have mucus on its surface, but this has been removed. (By courtesy of Dr R. Pack.)

larynx and pharynx, where it would be swallowed down or coughed up (Fig. 1.4 omits this layer of mucus). Interspersed between these ciliated cells are cells that secrete mucus. Deep to the epithelium is the submucosa, a spongy tissue containing blood vessels, lymphatics, nerve bundles, submucosal mucus-secreting glands and various other cells. Even deeper, we come to cartilage and smooth muscle. Figure 1.5 is a diagram of these tissues.

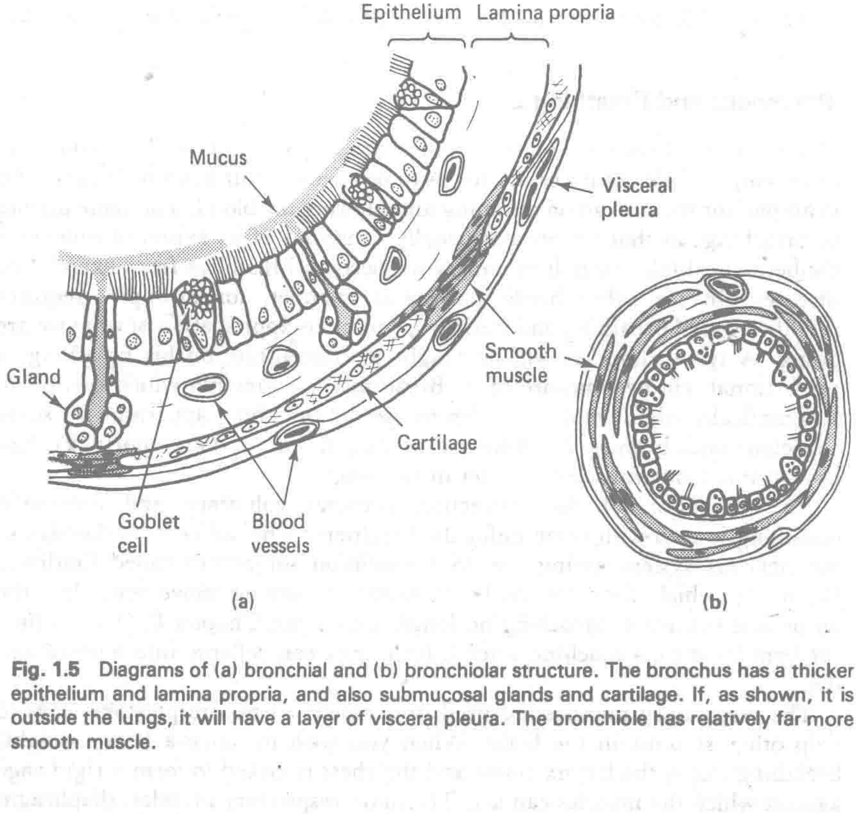

Fig. 1.5 Diagrams of (a) bronchial and (b) bronchiolar structure. The bronchus has a thicker epithelium and lamina propria, and also submucosal glands and cartilage. If, as shown, it is outside the lungs, it will have a layer of visceral pleura. The bronchiole has relatively far more smooth muscle.

How we breathe

Separating the thorax from the abdomen is a sheet of muscle, the diaphragm. At rest, this bulges up into the thorax. The phrenic nerve supplies the diaphragm, and its motor activity causes the diaphragm to flatten and, acting like a plunger in a syringe, to draw air into the chest. The external intercostal muscles between the ribs also contract and increase the diameter of the chest to supplement the action of the diaphragm. Thus inspiration is an active muscular process. Expiration, on the other hand, is largely passive when you are at rest; it relies on the elasticity of the lungs and chest to return all structures to their original positions, although the internal intercostals exert a small active expiratory effect. In exercise or during a cough or sneeze, the powerful muscles of the abdomen contract to make expiration more forceful.

This will be apparent if you press your fingers into your abdominal wall and cough.

In expiration and inspiration there must be differences in pressure between the gas in the alveoli and the outside air: no difference in pressure—no airflow. Because the lungs are flexible, any *change* in pressure within the chest, due to movement of the diaphragm, is rapidly transmitted to the air within the alveoli. This does not mean that the *actual* pressure between the two layers of pleura is the same as that in the alveoli, as will be explained in Chapter 2.

Behaviour and breathing

Many of the functions of our bodies are carried out without conscious intervention. It is not necessary for us to be aware of our heart or kidneys, for example, for them to go on pumping and filtering the blood. The same applies to breathing, in that we are not usually conscious of its existence unless we deliberately think about it or unless we become breathless from exercise or disease. On the other hand, playing a trumpet, for example, requires modification of breathing and initially a conscious appreciation of what we are doing. A tyro-trumpeter will be taught to concentrate on his breathing; a professional will be unaware of it. Breathing is a function which carries on automatically when we do not wish to use the breathing apparatus for some conscious task; exercise is a similar example, in that we do not normally *think* how to make our muscles contract in running.

An illustration of the distinction between voluntary and automatic breathing is seen with some unfortunate patients who suffer from damage to the nervous system giving rise to a condition sometimes called Ondine's Curse, in which they can make conscious breathing movements but the automatic control of breathing no longer exists (see Chapter 8). Unless they are ventilated by a machine when asleep, they can collapse into a coma and die.

The respiratory muscles are used in a variety of non-respiratory ways to help other systems in the body. When you wish to move a heavy weight, breathing stops, the larynx closes and the chest is locked to form a rigid cage against which the muscles can act. The main respiratory muscles, diaphragm and abdominals, contract simultaneously to raise abdominal pressure in vomiting, defaecation and childbirth. Conversely, the respiratory muscles are switched off when we swallow food or drink, which might otherwise be inhaled. The respiratory system can help to cool you when you develop a fever. Changes in pattern of breathing can signal emotion, amicable or otherwise. Above all, we use the respiratory system to communicate by speech and vocalization.

Metabolic activity of the lungs

The lungs are more than a passive respiratory surface for the exchange of gases, powered by the activity of the muscles of the heart and thoracic wall. Because of their vast vascular bed, the lungs have a large surface area of

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