Chapter Ten

Pulmonary Drug Delivery

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STRUCTURE AND FUNCTION OF THE PULMONARY SYSTEM

The major function of the pulmonary system is the oxygenation of blood and the removal of carbon dioxide from the body. Breathing ventilates the respiratory tissue leading to gaseous exchange in the lungs. The tissue is therefore specialized to present the largest available surface area within the protection of the thoracic cavity. The large oxygen requirement is necessary to support the high metabolic rate of mammals.

The respiratory system in man is divided into the upper and lower respiratory tracts. The upper respiratory tract consists of the nose, nasal passages, paranasal passages, mouth, Eustachian tubes, the pharynx, the oesophagus and the larynx. The trachea and bronchi are sometimes included as part of the upper respiratory tract. The lower respiratory tract consists of the true respiratory tissue, i.e. the air passages and alveoli.

The lung

The organ lung comprises of a left and right lung, divided in slightly unequal proportions that occupy most of the intrathoracic space. The right lung represents 56 percent of the total lung volume and is composed of three lobes, a superior, middle, and inferior lobe, separated from each other by a deep horizontal and an oblique fissure. The left lung, smaller in volume because of the asymmetrical position of the heart, has only two lobes separated by an oblique fissure. The space between the lungs is filled by a connective tissue space containing the heart, major blood vessels, trachea with the stem bronchi, oesophagus and thymus gland. In the thorax, the two lungs rest with their bases on the diaphragm, while their apices extend above the first rib.

Upper airway

As discussed in Chapter 9, the function of the nose is to provide humidification, filtration and warming of the inspired air. Although the nose is designed as the primary route of entry for gases, most people also breathe through the mouth, particularly during stress. In this case many of the nasal defensive pathways are lost. Hence the lung also has to have mechanisms to condition the air and remove foreign particles.

The nasopharynx is primarily a passageway from the nose to the oral pharynx for air and secretions. It is also connected to the tympanic cavity of the middle ear through the auditory tubes that open on both lateral walls. The act of swallowing briefly opens the normally collapsed auditory tubes and allows the middle ears to be aerated and pressure differences to be equalized. In the posterior wall of the nasopharynx is located a lymphatic organ, the pharyngeal tonsil.

The larynx is an organ of complex structure that serves a dual function: as a controlling air canal to the lungs and as the organ of phonation. Below the larynx lies the trachea, a tube about 10 to 12 centimetres long and two centimetres wide. Its wall is stiffened by 16 to 20 characteristic horseshoe-shaped, incomplete cartilage rings that open

toward the back and are embedded in a dense connective tissue. The dorsal wall contains a strong layer of transverse smooth muscle fibres that span the gap of the cartilage. In an adult, the trachea is 11 to 13 cm in length and 1.5 to 2.5 cm in diameter, and bifurcates to form the right and left main bronchi (Figure 10.1). The right bronchus divides into the upper, middle and lower branches whilst the left bronchus divides only into an upper and a lower branch. These lobar bronchi give rise to branches called 'segmental bronchi'. The branching angle of 37° appears to be optimal to ensure smooth airflow.

Structure of the tracheo-bronchial tree

The hierarchy of the dividing airways, and partly the blood vessels, in the lung largely determines the internal lung structure. Functionally the system can be subdivided into three zones, a proximal, purely conducting zone, a peripheral, purely gas-exchanging zone, and a transitional zone in between. Morphologically the relatively thick-walled, purely air-conducting tubes can be distinguished from those branches of the airway tree structurally designed to permit gas exchange.

Every branching of the tracheo-bronchial tree produces a new 'generation' of tubes, the total cross-sectional area increasing with each generation (Figure 10.2). The main bronchi are known as the first generation, the second and third generations are the lobar and segmental bronchi respectively. The fourth to ninth generations are the small bronchi and in these segmental bronchi the diameters decrease from approximately 4 to 1 mm. At a diameter of less than 1 mm they lie inside the lobules and are then correctly termed bronchioles. Here the function of the tissue changes from conducting airway to gas

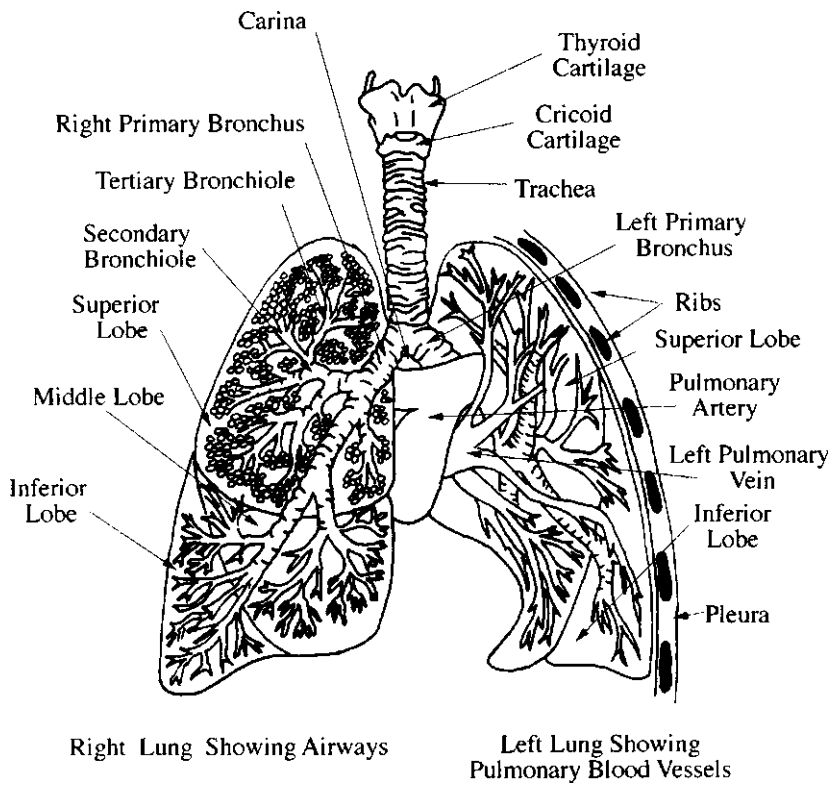

Figure 10.1 Structure of the lungs

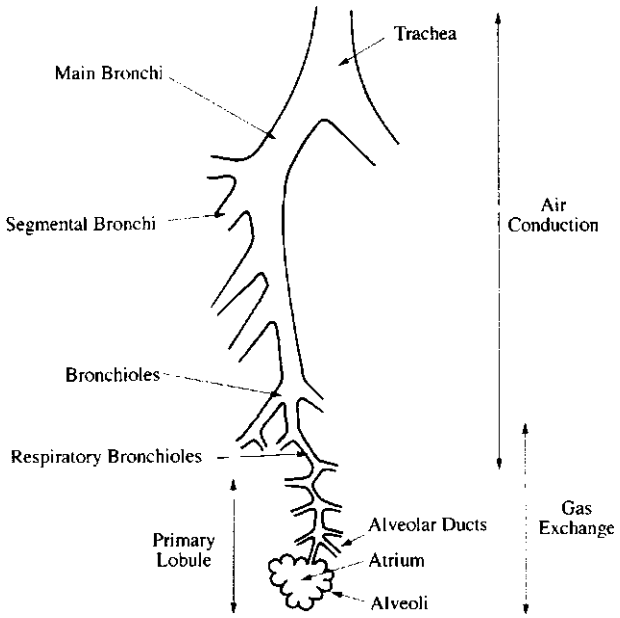

Figure 10.2 The tree structure of the lung

exchange. Although the decrease in diameter minimizes the deadspace, it is associated with a large increase in resistance to flow. For example, a 10% reduction in diameter is associated with an increase in airway resistance of more than 50%. Thus the airways should be as wide as possible to minimize resistance, but this will of course increase deadspace. In the body these opposing factors are balanced by finely tuned physiological control which is easily disturbed by lung pathologies such as asthma and bronchitis.

The respiratory gases diffuse from air to blood, and vice versa, through the 140 square metres of internal surface area of the tissue compartment. The gas-exchange tissue proper is called the pulmonary parenchyma, while the supplying structures, conductive airways, lymphatics, and non-capillary blood vessels belong to the non-parenchyma. The parenchyma of the lung consists of approximately 130,000 lobules, each with a diameter of about 3.5 mm and containing around 2,200 alveoli. It is believed that each lobule is supplied by a single pulmonary arteriole. The terminal bronchioles branch into approximately 14 respiratory bronchioles, each of which branches further into the alveolar ducts. The ducts carry 3 or 4 spherical atria that lead to the alveolar sacs supplying 15–20 alveoli (Figure 10.3). Additional alveoli arise directly from the walls of the alveolar ducts, and these are responsible for approximately 35% of the total gas exchange. It has been estimated that there are 300 million alveoli in an adult human lung. The volume of an alveolus changes with the degree of inflation, but assuming 75% lung inflation, the diameter of an alveolus is thought to be between 250 and 290 μm. It is estimated that each alveolus has a volume of 1.05×10^{-5}ml, with an air-tissue interface of 27×10^{-4}cm^2. For these calculations, it was assumed that the lung had a total air volume of 4.8 L, a total respiratory zone volume of 3.15 L and a total alveolar air-tissue interface of 81 m^2.

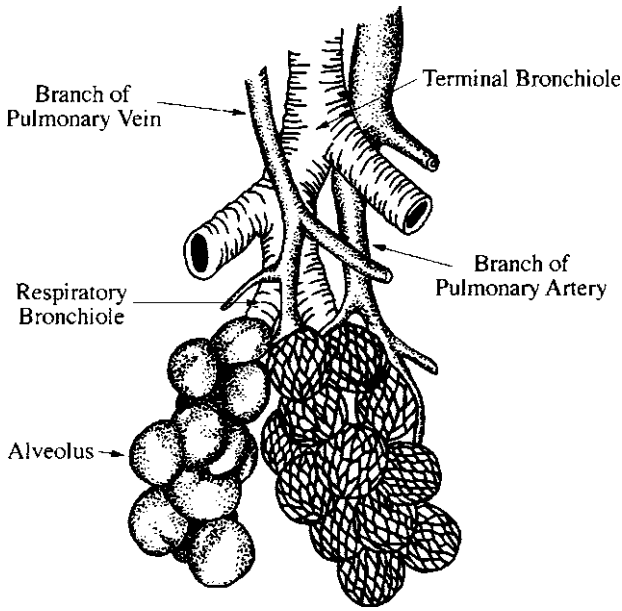

Figure 10.3 Structure and perfusion of the alveoli

Epithelium

Upper airways

The nasal cavity, the nasopharynx, larynx, trachea and bronchi are lined with pseudostratified, ciliated, columnar epithelium with many goblet cells. There are also coarse hairs in the nasal region of the respiratory tract.

Bronchi and bronchioles

The bronchi, but not the bronchioles, have mucous and serous glands present. The bronchioles, however, possess goblet cells and the wall contains a well-developed layer of smooth muscle cells, capable of narrowing the airway. The epithelium in the terminal and respiratory bronchioles consists largely of ciliated, cuboidal cells and smaller numbers of Clara cells. The ciliated epithelial cells each have about 20 cilia with an average length of 6 μm and a diameter of 0.3 μm Each cilium is composed of a central doublet and 9 peripheral filaments which function as a structural support. Contractions result in successive beats of the cilia creating a wave which consists of a fast propulsion stroke followed by a slow recovery stroke. Clara cells become the most predominant type in the most distal part of the respiratory bronchioles. They have ultrastructural features of secretory cells but the nature and function of the secretory product is poorly understood.

Alveoli

In the alveolar ducts and alveoli the epithelium is flatter and becomes the simple, squamous type, 0.1 to 0.5 μm thick. The alveoli are packed tightly and do not have separate walls, adjacent alveoli being separated by a common alveolar septum with communication between alveoli via alveolar pores (Figure 10.4). The alveoli form a honeycomb of cells around the spiral, cylindrical surface of the alveolar duct. The exposed alveolar surface is normally covered with a surface film of lipoprotein material.

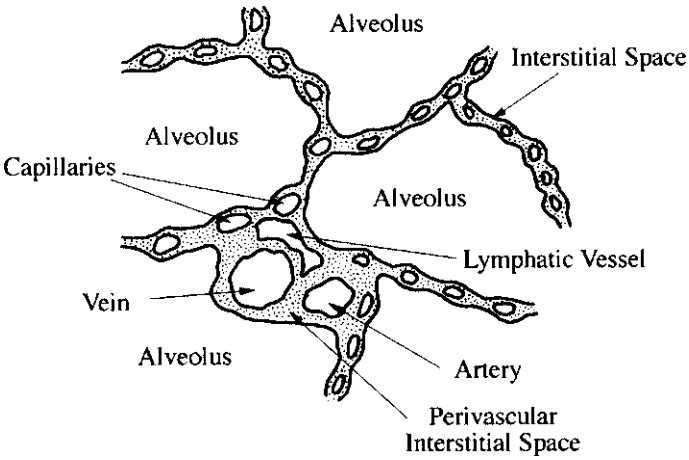

Figure 10.4 Cross-section of the alveoli

There are several types of pulmonary alveolar cells. Type I (or small type A), are non-phagocytic, membranous pneumocytes. These surface-lining epithelial cells are approximately 5 μm in thickness and possess thin squamous cytoplasmic extensions that originate from a central nucleated portion. These portions do not have any organelles and hence they are metabolically dependent on the central portion of the cell. This reduces their ability to repair themselves if damaged.

Attached to the basement membrane are the larger alveolar cells (Type II, type B or septal cells). These rounded, granular, epithelial pneumocytes are approximately 10 to 15 μm thick. There are 6 to 7 cells per alveolus and these cells possess great metabolic activity. They are believed to produce the surfactant material that lines the lung and to be essential for alveolar repair after damage from viruses or chemical agents.

Alveolar-capillary membrane

The blood and alveolar gases are separated by the alveolar capillary membrane (Figure 10.4) which is composed of a continuous epithelium of 0.1 to 0.5 μm thickness, a collagen fibre network, a ground substance, a basement membrane and the capillary endothelium. The interstitium is composed of the basement membrane of the endothelium, a ground substance, and epithelium. It forms a three dimensional skeleton to which the alveoli and capillaries are attached. Maximum absorption probably occurs in the areas where the interstitium is the thinnest (80 nm) since the surfactant is also thin in these areas (15 nm). Drainage of the interstitial fluid occurs by passage into the lymphatics, which often happens long after passage along the alveolar wall.

The thickness of the air-blood barrier varies from 0.2 μm to 10 μm. The barrier is minimal when the thickness is less than 0.5 μm since the epithelium and endothelium are present only as thin cytoplasmic extensions and the interstitium exists as a narrow gap between mostly fused membranes. When the diameter exceeds 0.5 μm additional structural elements are present. The minimal barrier thickness is nearly identical in structure and dimensions in all mammalian species that have been investigated. This is in contrast to the alveolar surface areas which increase proportionally with body weight.

Lung permeability

The alveolar epithelium and the capillary endothelium have a very high permeability to water, most gases and lipophilic substances. There is an effective barrier however for many hydrophilic substances of large molecular size and for ionic species. The alveolar type 1 cells have tight junctions, effectively limiting the penetration of molecules to those with a radius of less than 0.6 nm. Endothelial junctions are much larger, with gaps of the order of 4 to 6 nm. Clearance from the alveoli by passage across the epithelium bears an approximate inverse relationship to the molecular weight. The normal alveolar epithelium is almost totally impermeable to proteins and small solutes, for example the half-time for turnover of albumin between plasma and the alveolar compartment is of the order of 36 hours[1]. The microvascular endothelium, with its larger intercellular gaps, is far more permeable for all molecular sizes and there is normally an appreciable leak of protein into the systemic circulation.

Lung mucus

A thin fluid layer called the mucous blanket, 5 μm in depth, covers the walls of the entire respiratory tract (Figure 10.5). This barrier serves to trap foreign particles for subsequent removal and prevents dehydration of the surface epithelium by unsaturated air taken in during inspiration.

There are about 6000 tracheo-bronchial glands in man, with an average of one cell per square millimetre of surface area. The ratio of goblet cells to ciliated cells is 1 to 5 in the large airways and 1 to several hundred in the bronchioles. The mucus largely originates from the vagally innervated, submucosal glands, with a smaller contribution from goblet cells. Within the gland, distal serous cells secrete a watery fluid, whereas the mucus cells near the neck secrete a gel. It is speculated that the secretions of the serous cells help in the movement of the swollen gel to the surface. Although the mucus producing cells are under vagal control and can be regulated by cholinergically mediated drugs, goblet cells discharge mucus without physiological stimulation.

The main component of nasal mucus appears to be a mucopolysaccharide complexed with sialic acid. Mucus contains 2–3% mucin, 1–2% electrolytes, and the remainder water. Tracheo-bronchial mucus has viscoelastic properties and it averages 5% solids, including

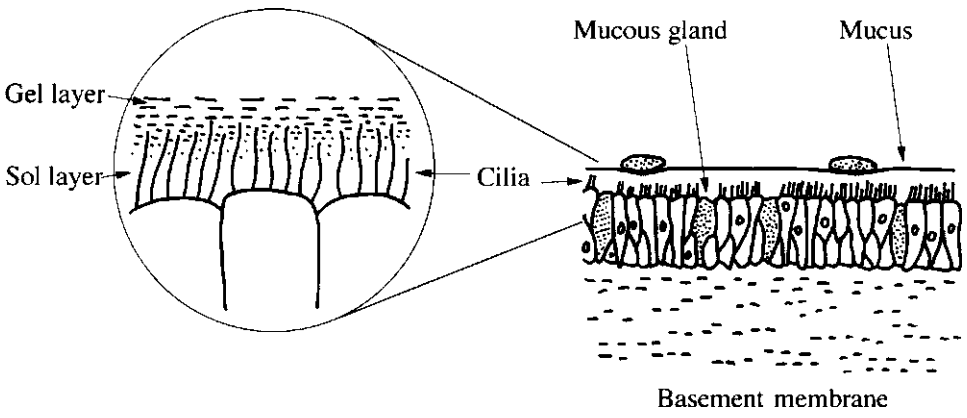

Figure 10.5 The mucociliaiy escalator

2% mucin, 1% carbohydrate, less than 1% lipid and 0.03% DNA. Pulmonary secretions are slightly hyperosmotic, but that secreted from the smaller bronchi and bronchioles are thought to be isosmotic, being in equilibrium with tissue and vascular fluids. The pH of rat tracheal secretions has been reported to be between 6.0 and 7.6.

Increased mucus secretion is brought about by cholinergic and a-adrenergic agonists which act directly on the mucus secreting cells of the submucosal gland. Serous secretions are stimulated by b-agonists or cholinergic stimulation, whereas the goblet cells do not appear to be innervated. The peripheral granules, in which the mucus is stored, are discharged continuously and form a reservoir which is secreted after exposure to an irritant stimulus. Disease states can drastically change the distribution of goblet cells and composition of respiratory tract fluids. Conditions such as chronic bronchitis are characterized by increased sputum and chronic irritation, leading to an increased number of glandular and goblet cells which result in a crowding of ciliated cells. Mucus transport is thus slowed and the increased viscosity of the mucus exacerbates the problem.

Lung defenses

The respiratory tract possesses a complicated but comprehensive series of defenses against inhaled material due to its continual exposure to the outside environment. The lung has an efficient self-cleansing mechanism referred to as the muco-ciliary escalator (Figure 10.5). The mucus gel layer floats above the sol layer which has been calculated to be approximately 7 μm thick. The cilia extend through this layer so that the tip of the villus protrudes into the gel. The co-ordinated movement of the cilia propels the mucous blanket and deposited foreign materials at the rate of 2–5 cm min^{-1} towards the pharynx where they are swallowed. It has been estimated that 1 litre of mucus is cleared every 24 hours. Cigarette smokers demonstrate a considerable slowing in the clearance mechanisms of the large airways, resulting in an accumulation at the hilius, the junction between the lymph node and efferent lymphatic vessel.

The alveolar phagocytes or "dust cells" remove inhaled particles which reach the alveoli since this region is not ciliated. These cells can ingest and destroy bacteria and viruses and engulf inhaled particulates, migrating to the ciliated areas of the bronchial tree, where they are transported up the muco-ciliary escalator. Some macrophages with engulfed particles slowly penetrate the alveolar wall, especially in the region of the alveolar duct, pass into the tissue fluid and lymphatics. They also secrete chemicals that attract white blood cells to the site, and hence they can initiate an inflammatory response in the lung. Particles picked up by macrophages are removed by them into the lymphatic system of the lung and stored in adjacent lymph glands. Soluble particles are removed into the bloodstream, to be finally excreted by the kidney.

The composition of expectorated liquid and sputum varies, but consists of tracheobronchial, salivary, nasal and lacrimal gland secretions plus entrapped foreign material, dead tissue cells, phagocytes, leucocytes, alveolar lining and products of microbial infections.

Lung surfactant

The elastic fibres of the lung and the wall tension of the alveoli would cause the lung to collapse if this were not counterbalanced by the presence of the lung surfactant system. This covers the alveolar surface to the thickness of 10 to 20 nm. The surfactant has a liquid crystalline or gel structure which consists of phospholipids (74%), mucopolysaccharides and possibly proteins. It forms a continuous covering over the alveoli and is constantly renewed from below. Fifty percent of the surfactant comprises of dipalmitoyl lecithin, replacement of which is rapid with a half-life of 14 hours. Enzymes, lipids and detergents

can destroy the surfactant. If the surfactant is removed by irrigation of the lung with saline, no harm appears to result since it is rapidly replaced. Generation of surfactant in neonates does not occur until the time of birth, so preterm infants often suffer from respiratory problems. Replacement surfactants, such as Exosurf® (GlaxoWellcome) can be administered to alleviate this problem.

Blood supply

The pulmonary artery arises from the right ventricle of the heart and thus supplies the lung with de-oxygenated blood. The lung tissue itself receives a supply of oxygenated blood from the bronchial arteries. Smaller capillaries branch from the main arteries to supply the terminal bronchioles, respiratory bronchioles, alveolar ducts, air sacs and alveoli. The average internal diameter of the alveolar capillary is only 8 μm with an estimated total surface area of 60 to 80 square metres and a capillary blood volume of 100 to 200 ml. The large surface area allows rapid absorption and removal of any substance which may penetrate the alveoli-capillary membrane thereby producing good sink conditions for drug absorption. Blood takes only a few seconds to pass through the lungs and it has been estimated that the time for passage through the alveolar capillaries of males at rest to be about 0.7 s, falling to 0.3 s on exercise.

Lymphatic system

In the adult lung, the lymphatic channels surround the bronchi, pulmonary arteries and veins. A deep system of lymphatics has been identified which lie adjacent to the alveoli. Movement of fluid from the alveolar lumen to the lymphatics has been described as a two-stage process. The first step is the passage across the epithelial lining through the intercellular clefts and/or through the cytoplasmic layer by diffusion or pinocytosis. The second step is the movement of fluid along the alveolar wall into the lymphatic area.

Nervous control

Both sympathetic and parasympathetic nerves supply the tracheo-bronchial tree. The primary role of these nerves is the control of ventilation of the lungs under varying physiological demand and the protection of the lung by the cough reflex, bronchoconstriction and the secretion of mucus. The lung is heavily innervated, as are the smooth muscle sheets that surround the airways, the intercostal muscles and the diaphragm.

Stimulation of the sympathetic nerves via the $ß_2$ adrenergic receptors primarily results in active relaxation of bronchial smooth muscle. Stimulation of parasympathetic nerves via the nicotinic and muscarinic receptors results in increased glandular activity and constriction of bronchial smooth muscle.

Cough reflex

Cough is accomplished by suddenly opening the larynx during a brief Valsalva manoeuvre which is a forceful contraction of the chest and abdominal muscles against a closed glottis. The resultant high-speed jet of air is an effective means of clearing the airways of excessive secretions or foreign particles. Cough receptors are found at the carina (the point at which the trachea divides into the bronchi) and bifurcations of the larger bronchi. They are much more sensitive to mechanical stimulation, and inhalation of dust produces bronchoconstriction at low concentration and elicits the cough reflex with larger amounts. Lung irritant receptors, located in the epithelial layers of the trachea and larger airways, are much more sensitive to chemical stimulation and produce a reflex bronchoconstriction and hyperpnoea (over respiration) on stimulation by irritant gases or histamine. The constriction

is relieved by isoprenaline or atropine which suggests that the effect is due to contraction of smooth muscle, mediated through post-ganglionic cholinergic pathways.

Biochemical processes which occur in the lung

Almost all of the drug-metabolizing enzymes found in the liver are also present in the lung, although in much smaller amounts. The lung has been observed to be responsible for the release of 5-hydroxytryptamine, synthesis of prostaglandins, conversion of angiotensin I to angiotensin II, histamine release, and inactivation of bradykinin. The mast cells located around the small blood vessels and in the alveolar walls are rich in histamine, heparin, 5-hydroxytryptamine and hyaluronic acid. Histamine release accounts for many of the symptoms of bronchial asthma and allergies. It causes capillary dilatation, increased capillary permeability, contraction and spasm of smooth muscle, skin swelling, hypotension and increased secretion of saliva, mucus, tears and nasal fluids.

The mammalian lung can actively synthesize fatty acids, particularly palmitic and linoleic, and incorporate these into phospholipids which are predominantly saturated lecithins. The active synthesis of proteins by the alveolar cells has also been reported.

Breathing

Breathing is an automatic and rhythmic act produced by networks of neurons in the hindbrain (the pons and medulla). The respiratory rhythm and the length of each phase of respiration are set by reciprocal stimulatory and inhibitory interconnection of these brainstem neurons.

The forces that normally cause changes in volume of the chest and lungs stem not only from muscle contraction but also from the elastic properties of both the lung and the chest. A lung is similar to a balloon, it resists stretch, tending to collapse almost totally unless held inflated by a pressure difference between its inside and outside. Air moves in and out of the lungs in response to differences in pressure. When the air pressure within the alveolar spaces falls below atmospheric pressure, air enters the lungs (inspiration), provided the larynx is open; when the air pressure within the alveoli exceeds atmospheric pressure, air is blown from the lungs (expiration). The flow of air is rapid or slow in proportion to the magnitude of the pressure difference. Atmospheric pressure remains relatively constant, hence flow is determined by how much above or below atmospheric pressure the pressure within the lungs rises or falls.

The respiratory pump is versatile, capable of increasing its output 25 times, from a normal resting level of about 6 L min^{-1} to 150 L min^{-1} in adults.

Respiratory disease

The respiratory tract is the site of an exceptionally large range of disorders since it is exposed to the environment and therefore dust or gases in the air may cause damage to the lung tissue or produce hypersensitivity reactions. Secondly, the entire output of the heart has to pass through its large network of capillaries, hence diseases that affect the small blood vessels are likely to reach the remainder of the lung. Cough is a particularly important sign of all diseases that affect any part of the bronchial tree. The presence of blood in the sputum is an important indication of disease. It may result simply from an exacerbation of an existing infection, it may also indicate the presence of inflammation, capillary damage, tumour or tuberculosis.

Asthma

Particles of foreign protein may be deposited directly in the lung and hence it is not surprising that allergic reactions are very common. The most common and most important

of these is asthma. The most common triggers are pollens, mold spores, animal proteins of different kinds, and proteins from a variety of insects, particularly cockroaches and mites that occur in house dust. Spasmodic asthma is characterized by contraction of the smooth muscle of the airways and, in severe attacks, by airway obstruction from mucus that has accumulated in the bronchial tree resulting in difficulty in breathing.

Extrinsic asthma is caused by an identifiable allergen, in which antigens affect tissue cells sensitized by a specific antibody. Intrinsic asthma occurs without an identifiable antigen or specific antibody. Extrinsic asthma commonly manifests in childhood because of a genetic predisposition or "atopic" characteristic. Hayfever and asthma are common atopic conditions. Exacerbation of extrinsic asthma is precipitated by contact with any of the proteins to which sensitization has occurred; airway obstruction is often worse in the early hours of the morning, for reasons not yet entirely elucidated. Intrinsic asthma may develop at any age, and there may be no evidence of specific antigens. Persons with intrinsic asthma experience attacks of airway obstruction unrelated to seasonal changes, although it seems likely that the airway obstruction may be triggered by infections, which are assumed to be viral in many cases.

Acute bronchitis

Acute bronchitis most commonly occurs as a consequence of viral infection. It may also be precipitated by acute exposure to irritant gases, such as chlorine, sulphur dioxide and ammonia. The bronchial tree in acute bronchitis is reddened and congested and minor blood streaking of the sputum may occur. Most cases of acute bronchitis resolve over a few days and the mucosa repairs itself.

Chronic bronchitis

This is a common condition and is generally produced by cigarette smoking and characterized by chronic cough and excess sputum production. The mortality rate from chronic bronchitis and emphysema soared after World War II in all western countries. The number and size of mucous glands lining the large airways increase after a number of years of smoking. The speed at which this occurs may be enhanced by breathing polluted air and by a damp climate. The changes are not confined to large airways, though these produce the dominant symptom of chronic sputum production. Changes in smaller bronchioles lead to obliteration and inflammation around their walls. All of these changes together, if severe enough, can lead to disturbances in the distribution of ventilation and perfusion in the lung, causing a fall in arterial oxygen tension and a rise in carbon dioxide tension. By the time this occurs, the ventilatory ability of the patient, as measured by the velocity of a single forced expiration, is severely compromised. It is not clear what determines the severity of these changes, since many people can smoke for decades without evidence of significant airway changes, while others may experience severe respiratory compromise after 15 years or less of exposure.

Pulmonary emphysema

This irreversible disease consists of destruction of alveolar walls and the consequent increase in size of the air spaces distal to the terminal bronchiole. It occurs in two forms, centrilobular emphysema, in which the destruction begins at the centre of the lobule, and panlobular (or panacinar) emphysema, in which alveolar destruction occurs in all alveoli within the lobule simultaneously. In advanced cases, the destruction is so great, that the two forms cannot be distinguished. Centrilobular emphysema is the form most commonly seen in cigarette smokers, and some observers believe it is confined to smokers. It is more common in the upper lobes of the lung (for unknown reasons) and probably causes

abnormalities in blood gases out of proportion to the area of the lung involved by it. By the time the disease has developed, some impairment of ventilatory ability has occurred. Panacinar emphysema may also occur in smokers, but it is the type of emphysema characteristically found in the lower lobes of patients with a deficiency in the antiproteolytic enzyme known as alpha 1-antitrypsin. Like centrilobular emphysema, panacinar emphysema causes ventilatory limitation and eventually blood gas changes. Other types of emphysema, of less importance than the two major varieties, may develop along the dividing walls of the lung (septal emphysema) or in association with scars from other lesions.

Bronchiectasis

Bronchiectasis consists of a dilatation of major bronchi. It is believed usually to begin in childhood, possibly after a severe attack of whooping cough or pneumonia. The bronchi become chronically infected, and excess sputum production and episodes of chest infection are common. The disease may develop as a consequence of airway obstruction or of undetected (and therefore untreated) aspiration into the airway of small foreign bodies such as plastic toys.

DOSAGE FORMS FOR PULMONARY DRUG DELIVERY

Direct delivery of a drug to the lung has a number of advantages over oral administration, including the use of less drug to achieve the same therapeutic benefit, a reduction in the likelihood of systemic side effects, and a more rapid onset of action. There are two possible mechanisms for delivery of drugs to the lung, either via an aerosol or direct instillation. The most commonly used is the aerosol, which consists of finely divided liquid droplets or solid particles in a gaseous suspension. An atomizer is the general term for a device which generates an aerosol and may be electrically, pneumatically or mechanically powered. Unfortunately today, the term aerosol, in general usage, has become synonymous with a pressurized package.

Pharmaceutical aerosols may be divided into two types. Space sprays disperse the drug as a finely divided spray with particles not exceeding 50 μm Surface-coating aerosols produce a coarse or wet spray and are used to coat surfaces with a residual film. Only space sprays are used for pulmonary drug delivery. The main types of device used at present to produce aerosols are nebulizers, metered dose inhalers (MDI) and dry powder inhalers (DPI), although development of the technology is causing the distinctions between these devices to become blurred.

Pressurized inhalation aerosols

Pressurized metered-dose inhalers for delivery of medications have been available since the mid 1950s. In these systems, the drug is usually a polar solid which has been dissolved or suspended in a non-polar liquefied propellant. If the preparation is a suspension, as is most commonly the case, the powder is normally micronised by fluid energy milling and the suspension is stabilized by the addition of a surfactant. Lecithin, oleic acid, and the Span and Tween series surfactants have been widely used for this type of formulation. Oleic acid is particularly favoured and is added in some excess over the amount required for suspension stabilization, since it also functions as a lubricant for the metering valve.

Metered dose inhalers (MDIs) are the most commonly used drug delivery system for inhalation (Figure 10.6). The propellants have a high vapour pressure of around 400 kPa at room temperature, but since the device is sealed, only a small fraction of the propellant exists as a gas. The canister consists of a metering valve crimped on to an aluminum can. Individual doses are measured volumetrically by a metering chamber within the valve. Each

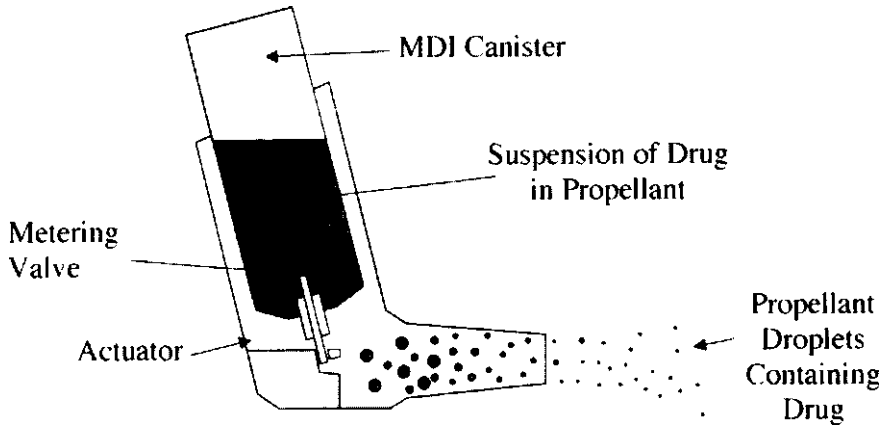

Figure 10.6 The metered dose inhaler

MDI canister can hold between 100 and 200 doses of between 20 μg and 5 mg of drug, which is released within the first 0.1 s after actuation.

The valve stem is fitted into an actuator incorporating a mouthpiece. The aerosol, consisting of propellant droplets containing drug, is delivered from the actuator mouthpiece at very high velocity, probably about 30 ms^{-1}. There is partial (15–20%) evaporation of propellant prior to exit from the atomizing nozzle ("flashing"), and further break up of droplets beyond this point caused by the violent evaporation of the propellant. This results in a wide droplet size distribution from 1 to 5 μm. Only 10% of the particulates delivered in a single dose released by a metered-dose inhaler actually reach the lungs, since the bulk of it impacts in the oropharynx and the mouthpiece. Reduction of the plume velocity, for example in the Gentlehaler® device[2] causes a significant reduction in oropharyngeal deposition.

A flurry of activity in aerosol formulation and technique of administration occurred following the adoption of the Montreal Protocol in 1987. This banned the manufacture of certain chlorofluorocarbon (CFC) propellants[3] by developed countries for environmental reasons. The temporary exception was for those used in the treatment of asthma and chronic obstructive lung disease. In many inhalers CFC propellants have now been replaced with hydrofluoroalkanes (HFAs). These compounds do not deplete the atmospheric ozone layer, but unfortunately are still considered "greenhouse gases," and may contribute to global warming[4].

With drugs which can be dissolved in the propellant, delivery to lungs can be increased to 40% of the ejected dose[5] since the particle size of the drug remaining after propellant vaporization can be very small. Altering the vapour pressure of these systems can also improve deposition. Lung depositions of 51 and 65% were reported with low and high vapour pressures respectively[6]. The changeover of propellant from CFCs to HFAs has had a notable effect on the delivery of some drugs, notably beclomethasone dipropionate. This has a 51% delivery to the lungs in HFA, in which it is soluble, compared to 4% in CFC, in which it is a suspension[7]. Unfortunately both HFAs and CFCs are relatively poor solvents and so it not often possible to take advantage of this type of formulation, even with the addition of cosolvents such as ethanol.

In order to be effective, metered dose aerosols must be triggered as the patient is inhaling. Some patients have difficulty with this feat of coordination, and breath actuated

inhalers such as the Autohaler® have been designed to overcome this by triggering the valve as the patient breathes in[8]. The Mist-Assist® inspiratory flow control device (IFCD, Ballard Medical, Draper, UT) is a compact device (similar in size to a spacer) through which both an MDI or medication from a nebulizer can be administered. By use of a floating ball within the inspiratory chamber, it provides visual and auditory (clicking sound) feedback to optimize timing of medication delivery and rate of inspiratory flow. Most important, the inspiratory flow rate (and therefore inspiratory resistance) can be adjusted on the device. This inspiratory flow control enhances laminar flow of particles and gas and increases the lung deposition.

Dry powder inhalers

The environmental concerns surrounding the use of chlorofluorocarbons have led to a resurgence of interest in dry powder inhaler devices. Early dry powder inhalers such as the Rotahaler® used individual capsules of micronized drug which were difficult to handle. Modern devices use blister packs (e.g. Diskus®) or reservoirs (e.g. Turbuhaler®) (Figure 10.7). The dry powder inhalers rely on inspiration to withdraw drug from the inhaler to the lung and hence the effect of inhalation flow rate through various devices has been extensively studied. The major problem to be overcome with these devices is to ensure that the finely micronized drug is thoroughly dispersed in the airstream. It has been recommended that patients inhale as rapidly as possible from these devices in order to provide the maximum force to disperse the powder[9]. The quantity of drug and deposition pattern varies enormously depending on the device[10], for example the Turbuhaler® produces significantly greater lung delivery of salbutamol than the Diskus®. Vidgren and coworkers[11] demonstrated by gamma scintigraphy that a typical dry powder formulation of sodium cromoglycate suffers losses of 44% in the mouth and 40% in the actuator nozzle itself.

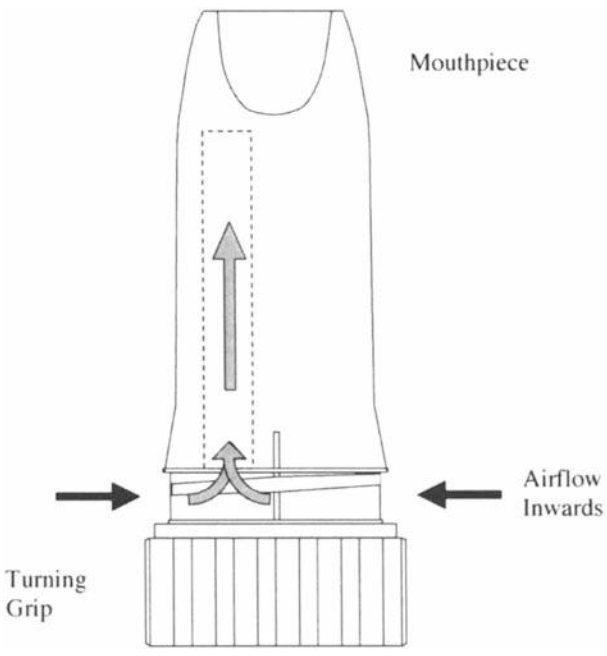

Figure 10.7 A simplified view of the Turbuhaler, a typical dry powder device

Nebulizers

Medical nebulizers can be divided into two main groups, pneumatic and electric. A pneumatic generator operates from a pressurized gas source, while an electric generator derives its power from an electric source. There are two types of pneumatic nebulizers (jet and hydrodynamic) and one electric generator (ultrasonic) presently used for medical purposes.

The jet nebulizer is a system in which a high-velocity gas flow is directed over a tube that is immersed in a water reservoir (Figure 10.8). The expansion of the driver gas decreases the pressure over the tube, which draws the formulation into the gas stream. The high shear rate in the jet stream then nebulizes it. The hydrodynamic nebulizer uses a system that prepares a film of water for aerosol formation by flowing it over a hollow sphere. A small orifice in the sphere expels gas at supersonic velocity. This high-velocity gas ruptures the thin film of water and produces a continuous dispersion of fine, liquid particles. A gas cylinder or compressor supplies the gas pressure. The ultrasonic nebulizer consists of a piezo-electric crystal which produces high frequency sound waves in the liquid in the nebulizing unit. The surface waves produce small droplets (Faraday crispations) which are conducted away by an airstream for inhalation. All these devices produce relatively broad droplet size distributions in which a large fraction of coarse droplets are present. Consequently most use some sort of baffle system in the airstream; coarse droplets impact on this and are returned to the reservoir for re-nebulization, while the smaller particles avoid the baffle and are passed to the patient.

The properties of nebulizers vary widely; while all produce droplets with sizes in the range 1–10 μm, they vary significantly in droplet size distribution and pulmonary deposition[12 13]. Despite this they have a number of advantages that is causing a renewal of interest in their use. Because MDIs and DPIs have a relatively high gas flow rate, they show high oropharyngeal impaction. This problem is reduced in nebulizers since the airflow can be adjusted to suit the patient's inhalation rate. Continuous nebulization can deliver very large quantities of drugs if necessary, from aqueous solutions without major formulation

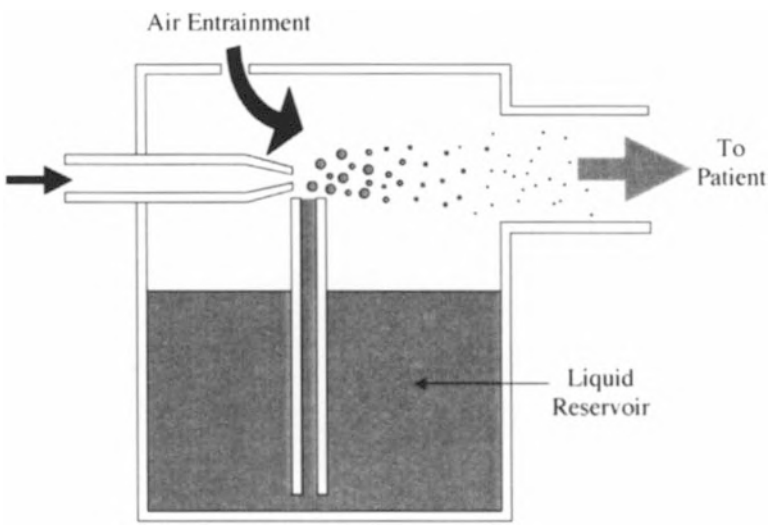

Figure 10.8 An air-driven nebulizer

problems. Unfortunately most nebulizers are bulky and require a fixed power source, which limits their use severely.

In order to combine these advantages of nebulizers with the portability of MDIs, Boehringer Ingelheim have developed the Respimat®, a spring-driven spray with a similar outward appearance to a conventional MDI. Unlike an MDI, the Respimat® delivers its spray in a slow low-velocity cloud. This leads to increased central pulmonary deposition[14], which is probably due to the increased time available for droplet evaporation before inhalation, and the reduced plume velocity, which reduces oropharyngeal impaction. Since these two factors are the main reasons for the success of spacer devices (see below), the addition of a spacer to a Respimat® caused no significant improvement in deposition.

Spacer devices and ancillary equipment

A number of techniques have been used in an attempt to improve the deposition of inhaled drug particles. The best known of these are the various kinds of spacers, chambers which are placed between the inhaler device and the patient's mouth (Figure 10.9). These devices cause considerable improvements in the fraction of dose deposited in the lungs and operate through a number of mechanisms. Firstly they provide a delay time before inhalation to allow full evaporation of propellant, so that the particles have reached their minimum size. Secondly they slow down the particle cloud so that the impaction velocity on the oropharynx is reduced, thus reducing impaction in this region. Finally they have a reservoir function which makes the timing of inhalation by the patient less critical. A typical example of such a device is the Nebuhaler®, which was studied by Thorsson et al for the delivery of budenoside. The Nebuhaler® caused a significant increase (from 12% to 38%) in pulmonary deposition, and an improvement in peripheral deposition. When assessing studies of such devices, it is important to realize that the spacer itself acts as an impaction filter and a proportion of the larger droplets are removed by it. In addition plastic devices accumulate wall charges and act as electrostatic precipitators, causing significant drug losses which vary with handling, humidity and cleaning or priming history[15].

Several methods have been developed to fire the aerosol device when the patient's breathing is correctly timed. We have already mentioned the Autohaler® which is fired by a pressure switch. More recent devices such as the SmartMist® and AERx® add the sophistication of microprocessor control so that usage can be logged and the device can be controlled with a degree of sophistication[16 17].

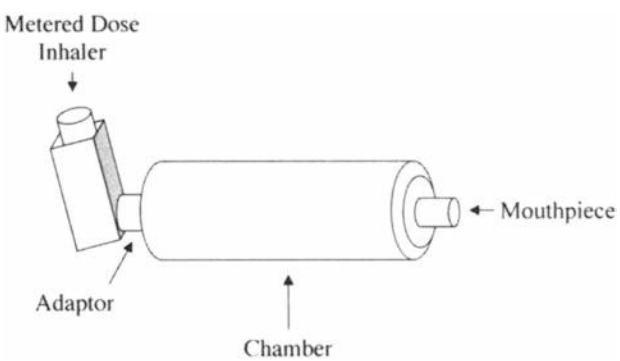

Figure 10.9 A typical spacer device

ASSESSMENT OF DEPOSITION BY GAMMA SCINTIGRAPHY

One of the most convenient methods to assess the pattern of distribution of therapeutic aerosols in the lung is by the use of gamma scintigraphy[18]. This can measure deposition in the lung, oropharynx and stomach. A critical feature for the success of gamma scintigraphy is a meticulously validated radiolabelling process to give confidence that the radiolabel is behaving in a manner which is representative of the system under study. Conventional planar gamma scintigraphy does not allow clear distinction between central and peripheral deposition since there is an overlay of structures e.g. alveoli, small and large airways, which is most marked centrally. Single photon emission computed tomography (SPECT)[19] and positron emission tomography, (PET) have the potential to give more detailed data on regional lung deposition as the image they provide is three-dimensional. Currently these techniques are more expensive and employ higher radiation doses, so are less widely used than planar imaging.

The procedures used for planar scintigraphic assessment of deposition are straightforward. The patient is given the appropriate number of doses of labelled formulation containing 1–2 MBq of activity, usually with a specified inhalation technique, and is then imaged with anterior and posterior views for 30 seconds to 1 minute. There is little point in performing kinetic studies of activity decay over longer periods since it is extremely difficult to ensure that the movement of the label *in vivo* represents a measurement of any useful physiological or formulation behaviour. If simultaneous pharmacokinetic studies are to be performed, the 'charcoal block' technique can be used, in which the subject is given a charcoal suspension drink prior to administration of the formulation. The object of this is to absorb any drug which may be swallowed and absorbed by the normal gastrointestinal route.

In order to facilitate the construction of regions of interest in the images, krypton 81m gas is commonly used to show the total ventilated area of the lungs. This radioactive gas has a half-life of 13 seconds and therefore the subject is imaged while breathing in the gas from a generator. This area can then be compared to the deposition of radiolabel from a test system. The region of interest can be drawn around the whole lung volume, but it is more common to divide the lung into central and peripheral areas, despite the fact that some peripheral areas must overlie the central area due to the viewing projection. The ratio of peripheral to central deposition is usually termed a 'penetration index'.

Studies based on 3-dimensional acquisition such as SPECT are performed in a similar manner but using a much higher (>100 MBq) activity level. Perring and coworkers[19] combined this technique with CT imaging of the lungs and used computer-based methods to transform the data to a concentric-shell lung model, and were thus able to provide a much more rigorous analysis of lung penetration. At present however the technique is considerably more specialized than planar imaging, which is used for the majority of routine studies.

Choice of radiolabel

Aqueous phases can be followed using technetium-99m labelled diethylenetriaminepentaacetic acid (DTPA). It is absorbed from the lungs with a half time of about 1 h and rapidly cleared from the body via the kidneys. If prolonged imaging is needed, then a label that clears more slowly from the lung such as ^{99m}Tc-labelled albumin should be used. Materials such as ^{99m}Tc stannous phytate show better alveolar deposition than pertechnetate or ^{111}In-DTPA with a slow clearance[20]. It has been hypothesized that phytate bears a strong structural resemblance to triphosphoinositide, a component of the lung surfactant material, and that it binds to alveolar wall receptors competing for inositol receptors. ^{99m}Tc Hexakis (t-butyl isonitrile) TBIN has been used to label the lipid phase of an aerosol[21].

Some attempts have been made to label the drug itself. A bronchodilator, the anticholinergic compound ipratropium bromide, has been labelled using a cyclotron-produced radionuclide ^{77}Br. This radionuclide has a half-life of 58 hours with peak gamma-ray energies, 239 and 521 KeV which are not ideal but are usable for scintigraphic studies. The powder produced was incorporated into pressurized canisters and it was shown that upon actuation, radioactivity was lost from the canisters at a rate equal to that of the drug[22].

Labeling inhalation formulations

Significant effort has been expended in attempts to radiolabel particles in aerosol formulations. All have significant problems and require validation prior to use, since it is possible that the label may not become associated with the drug particle.

1. In many early studies, the label in solution was added to the dry canister, and the solvent evaporated prior to adding the MDI propellants and solids. Some workers extract the ^{99m}Tc into butanone prior to adding it to the canister[23]. The whole is then sonicated in an attempt to redistribute the label. This is one of the least satisfactory methods, since it normally uses a water-soluble label such as ^{99m}Tc-DTPA. This forms a dry film on evaporation, which is later broken up into an ill-defined population of particles in the water-immiscible propellant. It has been suggested that the label associates with the surfactant layer around the particles, but since some of the surfactant will be present in solution, the validity of this ill-characterized technique seems unclear.

2. The drug is labelled by co-crystallizing or co-precipitating with added label prior to micronizing and formulation. This is extremely difficult since the levels of activity required to label a micronizable batch of drug (1–10 g minimum) are extremely high if a useful activity (e.g. 1 MBq in 100 μg) is to be obtained in the final doses. Extensive radiation protection is required and the apparatus requires a significant decay time. In addition there may be no guarantee of success since the label may crystallize or precipitate separately from the drug and form its own population of particles.

3. Addition of labelled particles (e.g. Teflon) to the formulation. These can be made to specific sizes, e.g. by spinning disc generator. The main problem here is that is difficult to ensure that the size distribution of the test particles is representative of that of the drug, and thus it becomes extremely difficult to ensure that the labelled particles behave *in vivo* in the same way as the drug particles. In addition the preparation of very small labeled model particles is problematic.

4. Addition of a propellant-soluble label such as ^{99m}Tc hexamethylpropyleneamine oxidase (HMPAO) to the pMDI. This label then evaporates down on to the surface of the drug particle when the pMDI is actuated. This is probably the most interesting technique but makes a number of assumptions; firstly that propellant evaporation is complete by the time the plume enters the upper airways (which is widely contested), and secondly that each propellant droplet contains at least one drug particle. Droplets which contain no drug particles will evaporate down to a very small size which is determined by the concentration of label and soluble components (surfactants and lubricants) and may thus suggest a deposition pattern which does not match that of the drug.

5. Spray-drying of the label on to the particle surface prior to formulation[24]. This method can be used for powders intended for both MDI and DPI administration. It has the advantage that the label is specifically associated with the particle, but validation is required in the case of MDI formulations to ensure that the label does not redissolve into the propellant.

Labeling dry powder inhalers

Dry powder inhalers contain usually pure drug and a carrier. Usually the diameter of the carrier substance particles is greater that the pure drug. In order to ensure that only the drug is labelled, it has to be labelled prior to mixing with the carrier. To achieve this the drug has to be suspended in a solvent which dissolves the label but not the drug. The radiolabel is added to the drug suspension, which is then evaporated. The drug particles are disaggregated, blended with carrier and loaded into the inhaler.

Validation

Whichever of these techniques is chosen, it is necessary to ensure that the label behaves in an aerodynamic manner in the same way as the drug particles. The most rigorous way to do this is to fire the device into a multistage classifier (normally an Andersen sampler with 8–10 stages) and verify that the distribution of radiolabel activity in the various stages is the same as the distribution of drug measured by direct chemical assay. If the label distributes similarly to the drug in the classifier, it is a reasonable assumption that it will do so *in vivo*, although it is not impossible that differences may still exist. For example, while the classifier operates in normal air, the air in the lung has nearly 100% humidity. This can lead to differences in particle growth rates that are not seen *in vivo*.

Generally, it is not necessary to perform a measure of label binding, as is the case in oral formulations, since it must be assumed that the micronized drug particle will dissolve instantaneously on contact with the pulmonary mucosa, and absorption of the drug and label will be rapid. Thus in most cases anything other than an immediate measure of drug/label distribution is of little value. The exception is for formulations such as liposomes and microparticles, in which the delivery agent is postulated to remain intact in the lung for a period of time and hence clearance can be measured[17].

FACTORS AFFECTING PARTICLE DEPOSITION IN THE LUNG

Aerosols used by patients should reach the desired location in sufficient quantity to be effective, and hence it is important to consider the factors which influence the amount and distribution of retained aerosols. The physical characteristics of the aerosol cloud such as particle size, velocity, charge, density and hygroscopicity will affect its penetration and deposition. Deposition is also affected by physiological variables, including respiration rate, airway diameter, presence of excessive mucus and respiratory volume.

Physicochemical properties

The three main mechanisms of deposition are inertial impaction, sedimentation and Brownian diffusion, the particle diameter determining the relative importance of these mechanisms.

Inertial impaction is the most important mechanism of deposition for particles greater than 5 μm in diameter[25]. If particles are large or are travelling at high velocities they may be unable to follow a change in direction in the airstream, for example in the upper airways at bifurcations, and hence they will impact on the airway walls. Impacted deposition is also enhanced where airways are partially obstructed at high flow rates, and by a turbulent airflow in the trachea and major bronchi. Sedimentation occurs when particles settle under gravity. The rate of settling is proportional to the square of the particle diameter (Stokes' law) and so becomes less important for small particles. Brownian diffusion is an important mechanism of deposition only for particles less than about 0.5 μm in diameter. The particles are displaced by random bombardment of gas molecules and collide with airway walls.

As a consequence of these diameter-sensitive processes, the deposition of particulates in the lung is highly dependent on their size (Figure 10.10). Droplets larger than 10 μm

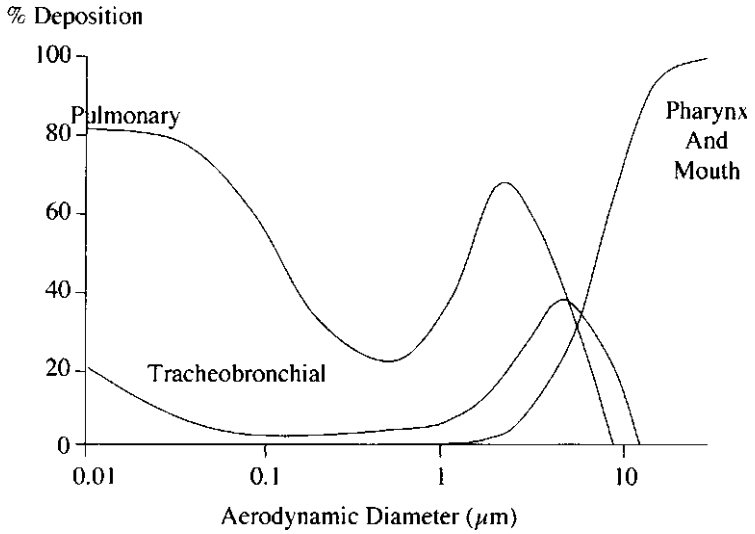

Figure 10.10 Dependence of deposition of particulates on particle size

impact in the upper airways and are rapidly removed by mucociliary clearance. Smaller droplets which escape impaction in the upper airways, in the range 0.5 to 5 μm, are sufficiently large to deposit by sedimentation, while those below 0.5 μ m are too small to sediment efficiently and migrate to the vessel walls by Brownian motion. The optimum diameter for pulmonary penetration has been determined by studies of the deposition of monodisperse aerosols to be 2 to 3 μm[26]. Smaller particles are exhaled before sedimentation can occur, although breath-holding can improve deposition in these cases. Extremely small aerosols, below 0.1 μm, appear to deposit very efficiently through Brownian diffusion to the vessel walls, but such fine aerosols are extremely difficult to produce.

Often the particle size does not remain constant as an aerosol moves from the delivery system into the respiratory tract. Volatile aerosols may become smaller through evaporation whereas hygroscopic aerosols may grow dramatically. The exact relative humidity within airways is not known, but particles produced from dry atmospheric aerosols have been found to double in diameter when the relative humidity is increased to 98%. Particle growth due to absorption of moisture does not appear to affect total drug deposition in the respiratory tract[27].

Air in the deep branches of the lung has been estimated to contain around 40 g water per cubic metre. Most aerosol particles will absorb moisture to a degree that depends on temperature, relative humidity and the nature of the aerosol particle. The degree of saturation is also device dependent since aerosols formed by jet nebulizers may have a very low humidity, while ultrasonic nebulizers produce an aerosol with a much higher humidity.

Thermophoresis of particles has been reported to occur in the lung. This is a movement of droplets towards the cooler areas due to the more rapid Brownian motion in the warm areas. It is thought that this effect is small and short-lived in the lung, since the air in the deeper airways is rapidly brought to thermal equilibrium. Finally, electrostatic effects, in which the droplets are attracted to the vessel walls by virtue of a surface charge interaction, are thought to be unimportant in pulmonary delivery, due to the high humidity.

Deposition patterns from different dose forms

The delivery device largely influences the deposition of drug via the emitted particle size and velocity of the aerosol, as described above. Consequently it is important that the device emits a plume of particles in the 2–5 μm size band. A number of formulation factors may conspire to prevent this; for example the particles suspended in MDI propellants are generally aggregated, and it is assumed that they are disaggregated efficiently by the shear forces in the actuator. Poor formulation, for example a poor choice of surfactant in the suspension, may cause the particles to be irreversibly aggregated. A similar problem occurs in dry powder devices, in which the fine drug powder is often cohesive and may not readily disperse. In the Turbuhaler® (AstraZeneca) the particles are broken up by a spiral in the mouthpiece producing a high resistance to the patient's inspiratory flow[28]. The Turbuhaler® produces twice as many particles with diameters less than 4.7 micrometers than does the MDI with spacer. The Diskus® (GlaxoWellcome) is also a dry powder inhaler, but this device has a low resistance to inspiratory flow. Thus, it is a less efficient producer of respirable particles under 4.7 micrometers than an MDI plus a metal spacer device, or the Turbuhaler®. As a consequence, the Turbuhaler® DPI delivers 20% to 30% of drug to the lung, approximately twice as much drug as the equivalent dose in the corresponding MDI.

Physiological variables

The average respiratory rate is approximately 15 breaths per minute with a tidal volume of about 500 ml and a residence time for tidal air of 3 seconds. A slowing of the respiratory rate increases the dwell time and retention of aerosol particles in the lung. Increasing the respiratory rate decreases dwell time, increases the turbulent flow and particle velocity. Severe turbulence retards the flow of gases into and out of the lung and results in premature deposition of the aerosol particles high into the respiratory tract since the collision rate with the walls is increased. Slowing inspiration and expiration minimizes turbulent flow. As a result deposition to the deep lung can be improved if the breath is held after actuation[17].

The resting pressure within the trachea is equal to atmospheric pressure, but during inspiration the pressure may drop to 60 to 100 mm Hg below atmospheric pressure, creating the gradient responsible for the inward flow of the aerosol cloud. The flow into each segment of the lung may vary considerably according to the pressure differential across each passageway and its resistance. Increasing the pressure differential increases the flow and penetration by aerosols. Aerosol delivery with children is problematic due to compliance issues and smaller airways and lung volumes.

Inhaler technique

Inhaler technique is a common problem, particularly in the elderly. Pressurized metered-dose inhalers in particular can be difficult to administer properly. There are significant variables of inhaler technique, such as timing of actuation and inspiratory flow rate. In a study which assessed the use of seven common inhaler devices in 20 patients with chronic obstructive pulmonary disease, fourteen patients had a fault that would result in no drug delivery at some time during the study. The fault occurred at some point for each inhaler device[29]. These faults were most common with the Diskhaler®. Patients ranked the metered dose inhaler and Accuhaler highest for ease of use and preference. Even when the correct method of using an inhaler is taught to the patients, their technique declines within 1 hour after instruction.

Although a large volume of inhalation is desirable, a fast inspiratory flow rate is not. Marked differences in bronchodilator response occur in patients with known airway reactivity following inhalation of beta-adrenergic bronchodilators at a slow rate[30]. Bronchodilation was significantly reduced when the inhaled flow rate was increased to 80

$L.min^{-1}$ from 25 $L.min^{-1}$. The slow inhalation flow rate most likely allows the aerosol to penetrate more readily to the target receptor sites in the small, peripheral airways. Most asthmatic patients, however, tend to inhale too rapidly and pressurized inhalers in this group were used at peak inspiratory flow rates ranging from 50 $L.min^{-1}$ to 400 $L.min^{-1}$ [31]. A period of breath-holding increases the number of particles deposited in the lungs at their furthest point of penetration by the process of sedimentation. A new strategy to improve aerosol delivery to the lung involves devices that limit the inspiratory flow rate and increase inspiratory resistance. Examples of these devices are the Turbuhaler® or an inspiratory flow control device (IFCD) plus a metered-dose inhaler. Each is superior to drug delivery via a metered-dose inhaler plus the more common spacer device.

Effects of disease

The inhalation of aerosols, their penetration and deposition into the lungs, their absorption and activity is affected by the severity of pulmonary disease. Bronchoconstriction or obstruction of airways will lead to diversion of flow to non-obstructed airways. In advanced disease the remaining airways and alveoli may be increasingly exposed to inspired particles. Disease-induced structural changes, such as the increased resistance to airflow seen in patients with obstructive airway disease, leads to a more central deposition of aerosol. Asymptomatic smokers also tend to deposit aerosol particles centrally, possibly due to airway goblet cell hypertrophy.

Narrowing of airways by mucus, inflammation or bronchial constriction can increase linear velocities of airflow, enhance inertial deposition and cause more deposition in the central airways. In adult respiratory distress syndrome, characterized by acute inflammatory oedema, the lung permeability to proteins increases and accumulation of fluid occurs. Lung deposition from MDI's was not found to be significantly different in asthmatics when compared to normals[7 32], however a greater proportion of the dose was located more centrally in asthmatic subjects. This resulted in faster clearance of the drug as penetration into the lung is lessened[33].

A large number of other diseases and conditions can lead to altered respiratory flow. These include microbial infections, pneumoconiosis, carcinoma and obstructive pulmonary disease. In the majority of cases these lead to increasing lung rigidity, a decrease in tidal volume and an increase in respiratory rate, together with mechanical obstruction of parts of the airway. It is unfortunate that all these factors reduce deposition in exactly the region in which treatment is needed, so that the dose may target only the healthy regions of the lung.

DRUG ABSORPTION

Inhaled drugs can be absorbed from their deposition site in various parts of the respiratory tract, including the upper airways, mouth, pharynx and lower airways. Due to the large surface area and blood supply, there is considerable interest in delivering drugs systemically via the lung, particularly for drugs such as peptides which are degraded in the gastrointestinal tract. Since the blood from the pulmonary circulation is returns to the heart and is pumped to the tissues, no first-pass metabolism occurs in the liver. The rate-limiting portion of the barrier is thought to be the alveolar membrane itself[34]. It is believed that this barrier exhibits passive transport characteristics similar to other organs lined with epithelial cells. Lipid soluble drugs are usually absorbed by passive diffusion at rates that correlate with their lipid/water partition coefficients. Anaesthetics and respiratory gases cross the alveolar-capillary membrane quite readily, water crosses easily and in large quantities, but isotonic sodium chloride is only slowly absorbed. The membrane is only slightly permeable to aqueous solutes. Hydrophilic compounds are absorbed by diffusion through aqueous membrane pores, their absorption rate being inversely related to their molecular size.

Compounds such as disodium cromoglycate are at least partly absorbed by a saturable, carrier-type transport mechanism[35]. Interestingly, high molecular weight amides and alkyl amines pass more readily than their low molecular weight homologues, suggesting that a number of specific transport systems may be present.

PHARMACOKINETICS

Pharmacokinetic studies of drug absorption have been hindered by the need to separate pulmonary absorption from that occurring in the gastrointestinal tract. Drug will be swallowed following oropharyngeal deposition when the aerosol is fired, and the dose administered by this route may be greater than that entering the lungs. In addition drug impacting on the upper airways may be cleared by the mucociliary escalator and swallowed at a later time. Pulmonary absorption is expected to be fast since the drug arrives rapidly at the target site, compared to the delay involved in transit through the gastrointestinal tract. Studies involving salbutamol administered from a pressurized aerosol showed that peak plasma levels were reached 3–5 hours after dosing, but in this case the peak plasma level was probably related to the gastrointestinal absorption of the swallowed part of the dose[36]. Another study involving terbutaline indicated that after inhalation, the peak plasma level was reached within 30 to 60 minutes[37]. In this experiment ingested charcoal was used to prevent absorption from the gastrointestinal tract; without charcoal the peak plasma level was reached at 1–6 hours. This confirms that absorption from the airways is more rapid than from the gut. However, it may be possible that the peak plasma concentration results from absorption from the oral and pharyngeal mucosa for some drugs.

DRUGS ADMINISTERED VIA THE PULMONARY ROUTE

Anti-allergy agents

When the asthmatic response is triggered by an external allergen such as pollen, a major part of the primary immune response consists of the release of histamine from mast cells, a process termed 'degranulation'. Histamine has a wide range of actions in tissues, but in the bronchial tissues it causes constriction of smooth muscle via the H, receptors. This action can be prevented by sodium cromoglycate, which inhibits mast cell degranulation. As a result it has a powerful prophylactic action in asthma, but is of little use for relief of an acute attack. It is valuable for the management of extrinsic asthma and exercise-induced asthma. Cromoglycate is now thought to have an additional actions such as inhibition of pulmonary sensory C-fibre discharge[38 39]. Anew drug in the category of anti-allergies is nedocromil sodium, which is equipotent with sodium cromoglycate[40].

Beta receptor agonists

When an asthmatic attack has been triggered by histamine at H_1 receptors, the objective is to redilate the bronchi with a $ß_2$ receptor agonist in the upper and mid airways. These cause relaxation of bronchial smooth muscle and thus allows the airway to dilate. These materials are mainstays of the treatment of asthma, as well as a variety of other pulmonary diseases in which it is desired to decrease airway resistance. They provide rapid symptomatic relief where the predominant cause of reduced airway calibre is bronchial smooth muscle contraction, or they may be used as regular maintenance therapy to avert symptoms. Their preventative effect is particularly seen in the suppression of exercise-induced asthma[41]. Beta receptor agonists also increase the rate of mucociliary clearance, known to be abnormally slow in patients with obstructive airways disease. Inhaled $ß_2$ receptor agonists are less effective if airway inflammation is a major factor in the disease. The oldest member of the class is salbutamol (called albuterol in the U.S.), and a range of other materials are available, including metaproterenol, fenoterol and terbutaline.

Adrenocorticosteroids

Adrenocorticosteroids (generally simply termed 'steroids') inhibit the inflammatory process by mechanisms which are poorly understood. It is possible that they may include interference with prostanoid formation and the inhibition of the cellular signaling between cells involved in the immune response. They prevent not only the early inflammatory phenomena such as oedema and increased blood flow, but also later effects such as phagocyte activity and capillary proliferation. The drugs used, e.g. beclomethasone dipropionate, betamethasone and budesonide, exert a topical effect in the lungs but are generally inactivated when swallowed. The doses required are low (400–800 μg daily), resulting in low plasma concentrations thereby minimizing systemic side effects. Modern treatment of asthma in childhood favours the use of small doses of steroid to keep inflammatory processes suppressed.

Leukotriene inhibitors

The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) are products of arachidonic acid metabolism and are released from various cells, including mast cells and eosinophils. These eicosanoids bind to cysteinyl leukotriene receptors (CysLT) found in the human airway. Cysteinyl leukotrienes and leukotriene receptor occupation have been correlated with the pathophysiology of asthma, including airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process, which contribute to the signs and symptoms of asthma. Singulair (Montelukast sodium) is an orally active compound that binds with high affinity and selectivity to the $CysLT_1$ receptor (in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or ß-adrenergic receptor). Montelukast sodium inhibits physiologic actions of LTD_4 at the $CysLT_1$ receptor without any agonist activity.

Other bronchodilating agents

Other bronchodilators include anticholinergic drugs which act by blocking the muscarinic action of acetylcholine, and thus preventing bronchial muscles from being constricted via innervation. Since reflex bronchoconstriction may be mediated through the stimulation of pulmonary sensory fibres, there is much interest in inhibition of this pathway as a method of controlling asthma. A quaternary derivative of atropine, ipratropium bromide, is commonly delivered by nebulizer and has been successful in the control of acute asthma. Methyl-xanthines (for example theophylline and aminophylline) have been used for many years in the USA as a first line treatment for asthma, but theophylline cannot be inhaled and must be injected, as it is an irritant to the lung. Methyl-xanthines are however less effective than $ß_2$-receptor agonists administered by aerosol[41].

Mucolytics

Various pharmacological agents alter the rheological function of mucus, which has been exploited particularly to thin mucus to aid in its clearance from the bronchi. Water, saline and mucolytic aerosols are important as aids in the removal of the bronchial secretions which accumulate in chronic bronchitis, bronchiectasis, cystic fibrosis and asthma. Inorganic and organic iodides act directly on mucus and are used therapeutically. Addition of potassium iodide reduces the apparent viscosity, presumably due to an effect of the halide on the configuration of the glycoprotein[42].

Traditionally aerosols have been used in an attempt to liquefy secretions and induce sputum clearance, either by mucociliary action or coughing. Inhalation of aerosolized water does liquefy and clear secretions[43]. It can however be an irritant and cause broncho-constriction in asthmatics[44]. Saline aerosol is bland and may well improve mucociliary

clearance, particularly in a hypertonic concentration where it facilitates expectoration[41]. It may liquefy sputum by enhancing chloride (and water) flux across the bronchial mucosa[45]. Mucolytic aerosols are also widely used; N-acetyl-cysteine (Airbron) being best known in Britain, and 2 mercapto-ethane ethane sulphonate (Mistabron) in Europe. Mistabron appears to enhance mucociliary clearance in patients with chronic bronchitis[46]. Other molecules such as DL-penicillamine and dithiothreitol act on the sulphhydryl bonds in mucus causing thinning, though nebulization of dithiothreitol causes intense irritation and is therefore unsuitable for clinical exploitation[47].

On rare occasions antihistamines and antibiotics may by given as aerosols. Antibiotics are given because in asthmatics the mucus thickens and "plugs" the bronchiole. This plug may then become a focus for infection. Some antibiotics, notably the tetracyclines[48], interact with mucus glycoprotein causing thickening. The exudates formed during inflammation and disease probably cause a mucus thickening by physical entrapment of mucus with biopolymers such as albumin, IgG, or IgA leading to changes in mucus viscoelasticity.

Systemically-absorbed drugs

As has been mentioned, the pulmonary route has been used to achieve systemic delivery. A product containing ergotamine tartrate is available as an aerosolized dosage inhaler (360 µg per dose) and has the advantage of avoiding the delay in drug absorption due to gastric stasis associated with migraine. In vaccine delivery, aerosol administration of para-influenza Type 2 vaccine has been found to be more effective than subcutaneous injection[49]). Penicillin reaches the bloodstream in therapeutic quantities after pulmonary delivery, but kanamycin is poorly absorbed from the lung so can only be used for local drug delivery.

The deep lung has been investigated as a site for delivering large molecule proteins and peptides as it is believed that the morphology of the alveolar epithelium predisposes it to absorb large molecule compounds. The pulmonary route has been explored for the delivery of insulin and human growth hormone, and absorption was found to be greatest in those subjects with the highest penetration index, implying that deep central deposition is a prerequisite for absorption[50 51]. The pharmacokinetics of these materials, which have extremely short intravenous half-lives of 3 and 40 minutes respectively, were dominated by the slower limiting pulmonary absorption rate.

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