ALVEOLAR NUMBER \( \times 10^6 \)

* = data from Dunnill; \( \times \) = data from Hogg et al.

Modified from Hogg et al.

FIG. 1. The numbers of alveoli at various ages. * = data from Dunnill; \( \times \) = data from Hogg et al. Modified from Hogg et al.

Neonatal Cardiorespiratory Physiology

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Although the major focus of the present review is on neonatal cardiorespiratory physiology, the intimate relationship between structure and function requires emphasis of certain aspects of growth and development of the lung that are important to our understanding of pulmonary physiology. More comprehensive reviews of pulmonary development and morphometry may be found elsewhere.¹-six

Growth and Development of the Lung

From a functional point of view, Weibel's has divided the lung into: 1) a conducting zone comprised of bronchi and bronchioles through which inspired air is distributed to terminal air units, and pulmonary arteries and veins that connect with the capillary networks; 2) a respiratory zone, usually conceived of as alveoli, in which blood-gas exchange occurs; 3) an intermediate zone, or zone of transition, linking the conducting and respiratory zones and consisting mostly of alveolar ducts. From an anatomic point of view, others have considered the zone of transition and the respiratory zone to consist of the respiratory bronchioles, alveolar ducts, atria, alveolar sacs, and alveoli, and have referred to this as the "acinus."

By the sixteenth week of human intrauterine life, all the conducting airways and preacinar vessels have developed.⁷-⁹ Subsequent intrauterine and postnatal growth of the conducting airways occurs only in the proportional increases in length and diameter and not in number of airways.⁴-⁷ The res-
passages to form new alveoli. Alveoli are also developed postnatally by means of segmentation and compounding of existing alveoli (fig. 2). As indicated above, the precise age at which alveolar growth stops is not clear. During the first few years of life, the increase in size (both weight and volume) of the lung results mainly from alveolar multiplication, with little change in alveolar diameter or size. During the next few years, until approximately 8 years of age, the size of each alveolus, as well as the total number, increases, after which only the size increases until the chest wall stops growing. Despite these changes in pulmonary architecture with growth, morphometric data in dogs indicate that pulmonary gas exchange capacity is linearly related to body weight during the period of growth of the lung. In addition, gas exchange capacity is increased by an increase in metabolic rate or by hypoxic environmental conditions, thus indicating that the gas-exchanging apparatus adjusts to the oxygen needs of the organism.

**STIMULI TO LUNG GROWTH**

There has been renewed interest recently in the growth responses of the lung to a variety of stimuli, including pneumonectomy and hypoxia. As might be expected, the growth potential of the younger animal is considerably greater than that of the adult. Following pneumonectomy equal enlargements of both alveoli and alveolar ducts deep within the lung have been found in young rats, while growth of alveolar ducts predominates in adult rats. In both young and adult rats growth of the lung results from hyperplasia rather than hypertrophy of cells. In addition, in young rats, there appears to be a proliferation of alveoli at the surface of the lung. In contrast to pneumonectomy, unilateral ligation of the pulmonary artery is said to result in contralateral hypertrophy only.

Hypoxia, both at sea level and at high altitude, remains a potent stimulus to growth. The effect is most marked in the younger animal, in which hypoxia induces...
increases in both numbers and sizes of alveoli and alveolar ducts; by contrast, hypoxia increases only the sizes of gas-exchanging units in mature animals. That the results of these studies are applicable to man is suggested by the observation that high-altitude native adults have greater lung volumes and diffusing capacities than would be predicted on the basis of body size.

CLINICAL IMPLICATIONS

The different rates of growth in length and in diameter (fig. 3) of the conducting airways obviously affect the change in airway resistance with age. Thus, Hogg has shown that the conductance of the peripheral airways is low in the child less than 5 years of age (fig. 4). Unlike the older child and adult, in whom peripheral resistance contributes a relatively small portion of the total airway resistance, in the small child the small airways contribute a relatively large proportion. It is believed that during the first few years, when alveolar multiplication is a prominent feature of growth of the lung, alveolar diameter is relatively constant. Presumably, the diameters of small airways do not increase markedly during this period. Subsequently, alveolar diameter does increase, and the physiologic data of Hogg et al. are consistent with the notion that airway diameter also increases. Since resistance varies as the fourth power of the radius, small increments in small-airway diameter should lead to disproportionate re-

![Image of Figure 3: Changes in airway diameter as a function of airway generation for various age groups. The data suggest that beyond the eighteenth generation, the airways are disproportionately narrow in children less than 5 years old. The vertical lines represent the range of airway diameter at each generation. From Hogg et al.]

![Image of Figure 4: Retrograde-catheter data showing the changes in conductance of central and peripheral airways per gram of lung tissue with age. Although there is relatively little change in central conductance with age, there is a marked increase in the peripheral airway conductance at about 5 years of age. From Hogg et al.]

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ductions in airway resistance. This no doubt explains why signs and symptoms of small-airway diseases that increase peripheral airway resistance (for example, bronchiolitis) are more severe in small children.

The morphologic changes during development have special clinical relevance to several types of congenital anomalies of the lung seen in early life. For example, following surgical correction of congenital diaphragmatic hernias, the respiratory status may depend upon how early in embryologic development the abdominal contents invaded the thorax, which in turn will determine whether an arrest of bronchial branching or alveolar proliferation is the primary disturbance. In at least two cases studied by quantitative morphometry, an incomplete complement of bronchial branches was present, equivalent in number to that of about 10 to 12 weeks of normal intrauterine development; the total number of alveoli was reduced, but the number per acinus was about normal.22 These studies have suggested that alveolar multiplication is regulated by acinar number.24

Congenital lobar emphysema is another anomaly that may result in severe cardiopulmonary embarrassment in early life. Although there is general agreement that there is a defect in deflation in this condition, there appear to be several possible causes, and in some cases the cause is not clear.25-28 There are intrinsic causes, e.g., mucous plugs or bronchial wall cartilage deficiency, as well as extrinsic causes, e.g., compression by cysts or blood vessels. As might be expected, variations in the disease may result not only from different causes but from differences in the periods of development in which the insult occurs. Thus, Reid and co-workers,24,29,30 using quantitative methods of pathologic examination, have identified three anatomic variations in the overinflated lobes: 1) a normal number of bronchial generations with an increased number of alveoli (polyalveolar lobe); 2) a normal number of bronchial generations with a normal number of alveoli; 3) a reduced number of bronchial generations with a reduced number of alveoli. It seems reasonable to assume that some of these variations in morphologic development may be reflected in major differences in pulmonary function. Indeed, some patients require surgical excision of the hyperinflated lobe as a surgical emergency, while other patients gradually become asymptomatic and have radiographic evidence of hyperlucency as the only residual abnormality.

One can only hope that as these morphometric techniques are applied we will develop a clearer picture of the growth potential of the neonatal lung and how it is altered by bronchiolitis, pneumonia, and other diseases in early life.

Stability of the Lung

The notion that the lining of the lung contained a substance that could reduce surface tension was important for at least two reasons. 1) It provided some insight as to how the alveoli could be kept open even when the distending pressure of the lung was low, thus insuring maintenance of a stable functional residual capacity (FRC); because of the prevention of alveolar collapse each breath does not require the large pressures necessary to open atelectatic lung. 2) Because surface tension is lowered as the alveolar surface lining is compressed, it provided a means by which surface tension could be altered with changing alveolar size. This is important because the Laplace relationship (P = 2T/r) suggests that if surface tension were unchanged, pressure would increase as the radius decreases. The smaller alveolus would empty progressively into the larger one and the lung would be unstable.

Biochemical Factors

Pulmonary surface-active material (surfactant) is a complex mixture of lipids and proteins. It contains a large amount of highly saturated lecithin and smaller amounts of cholesterol, neutral lipids, and other phospholipids.31,32 Studies of the biosynthesis of surfactant have been limited to the synthesis of lecithin, the physiologic importance of which is reflected in the direct correlation between pulmonary lecithin content and pulmonary stability during fetal life.32 Two major pathways for lecithin synthesis have
been recognized, 1) the choline incorporation pathway or phosphocholine transferase system \(^{31,27,24}\) and 2) the methylation pathway or methyltransferase system \(^{31,22,24}\). Several observations suggest that the phosphocholine pathway is by far the predominant route of lecithin synthesis starting in the latter part of gestation.\(^{24}\) During the last trimester there is an increase in the activity of the choline incorporation pathway, followed by an abrupt increase in total pulmonary lecithin.\(^{24}\) Methylation contributes a small proportion of the total lecithin in the lung (approximately 2–4 per cent of that contributed by the choline incorporation pathway) throughout prenatal and postnatal life.\(^{24}\)

Little is known about the mechanisms controlling the production of pulmonary surfactant. The administration of several drugs has been associated with enhanced stability of the lung:

**Corticosteroids:** The administration of several corticosteroids to the fetal animal just before normal maturation resulted in 1) accelerated maturation of alveolar type II epithelial cells, as indicated by the earlier appearance of osmiophilic inclusion bodies;\(^{25,26}\) 2) enhanced enzymatic activity in the choline incorporation pathway;\(^{27,28}\) 3) increased alveolar stability, as determined by in-situ pressure–volume characteristics;\(^{29,40}\) 4) increased survival of prematurely delivered lambs.\(^{41}\) A preliminary clinical trial of antepartum glucocorticoids suggested that respiratory distress syndrome (RDS) occurred less frequently in treated infants of less than 32 weeks’ gestation than in untreated controls of similar gestational age.\(^{42}\) That the post-natal administration of hydrocortisone to infants with RDS failed significantly to alter the course or outcome of the disease\(^{43}\) suggests that there is a critical period in development during which exogenous corticosteroids may be effective.

**Thyroxine:** The administration of thyroxine (T\(_4\)), an important regulator of lipid metabolism in vivo, also resulted in the accelerated appearance of osmiophilic inclusion bodies in alveolar type II cells in fetal rabbits.\(^{44}\) Administration of thyroxine to adult rats correlated with increases in size and number of inclusion bodies in the type II cells.\(^{45}\)

**Heroin:** The administration of heroin enhanced the stability of fetal rabbit lung, as demonstrated by in-situ pressure–volume measurements.\(^{46}\) This was consistent with the clinical observation that premature infants born of heroin-addicted mothers had a lower incidence of RDS than other infants of comparable gestational age.\(^{47}\)

It is postulated that corticosteroids enhance stability of the lung by increasing the synthesis of pulmonary lecithin through the induction of phosphocholine transferase.\(^{27,28}\) That thyroxine and heroin also appear to enhance pulmonary stability supports the hypothesis that they also may be responsible for the induction of activity of those enzymes involved in lecithin synthesis.

Pulmonary lecithin has a relatively short half-life of about 14 hours.\(^{48}\) This suggests that an effective, well controlled synthetic mechanism is necessary for stability of the lung. It also suggests that any process that leads to increased consumption of surfactant, e.g., going to the extremes of lung volume, will place an additional burden on the mechanism for synthesis. It seems reasonable to conclude that the early application of constant distending pressure to the lung not only improves gas exchange in neonatal RDS but also reduces the severity of the disease by reducing surfactant consumption.\(^{35}\)

One logical conclusion derived from the evidence that the fetal pulmonary fluid is actively formed from alveolar cells and flows into amniotic fluid (see below), is that sampling and analysis of such fluid during gestation might provide a means of assessing maturation of the lung with respect to surfactant production. Indeed, at least two such tests are now found to be useful clinically. One is based on the observation that the concentration of sphingomyelin (S) remains relatively constant throughout gestation while the concentration of lecithin (L), as already indicated, increases (fig. 5) as the lung reaches the stage where stable alveoli can be maintained; an L/S ratio of 2 or more in amniotic fluid gives reasonable assurance that the surfactant system is sufficiently mature to avoid RDS.\(^{49}\) The second test, com-
monly referred to as the "shake test" depends upon the ability to generate stable bubbles after shaking amniotic fluid diluted serially with ethanol. A positive test, i.e., stable bubbles, in dilution of \( \frac{1}{2} \) or higher also suggests that there is sufficient surfactant to prevent RDS.

MECHANICAL FACTORS

While most of the earlier work has focused on the presence of surfactant as a stabilizer of the lung, more recent work has emphasized the importance of mechanical factors operating through the interstitial network of fibers inter-connecting units of lung. Thus, mechanical behavior of adjacent units of lung is made interdependent by these fibers. The effect of a given force depends not only on the magnitude of the force but also on the surface area over which it operates. Hence, the pulls of the interconnecting fibers on adjacent units are the same only when the surface areas over which their force is exerted are the same. On the other hand, when a portion of lung inflates more slowly or remains smaller than an adjacent portion, the pull on the units in the smaller portion is increased or amplified.

Macklem has pointed out that this mechanism tends to maintain unstable alveoli in the inflated state in conditions associated with microatelectasis, such as the infantile RDS, and the amplification of pressures applied to the surface of microatelectatic areas by these mechanical factors may explain the beneficial effect of the use of only a few centimeters of end-expiratory pressure.

On the other hand, if such amplified pressures were applied to the surface of units of lung with complete airway closure and if there were diminished or absent collateral ventilation, as probably occurs in small infants, the absorption of gas would result in sufficiently low alveolar pressures to induce transudation of fluid and hemorrhagic atelectasis.

Oxygen Transport

Oxygen delivered to the tissues is equal to the product of blood flow and arterial oxygen content. Blood flow is dependent on blood pressure, vascular impedance (or hindrance) and blood viscosity, while oxygen content is dependent on oxygen saturation and hematocrit. Hence, the amount of oxygen delivered to the tissues is directly proportional to the arterial blood pressure, oxygen saturation, and hematocrit, and inversely proportional to the vascular impedance and blood viscosity. Although the increase in
hematocrit that occurs throughout gestation might be expected to increase oxygen transport to the tissues by increasing oxygen-carrying capacity, the greater viscosity of erythrocytes containing fetal hemoglobin, compared with adult erythrocytes, may decrease oxygen transport. Since blood viscosity is also increased by decreases in body temperature or arterial blood pressure, and since hematocrit may vary among large and small blood vessels because of plasma skimming, the interrelations are complex, and the ideal hematocrit for optimal oxygen delivery is not easy to predict.

The factors effecting the position of the oxyhemoglobin-dissociation curve are shown in figure 6. The affinity of human fetal blood for oxygen is greater than that of maternal blood. Thus, the oxygen tension at which fetal hemoglobin is half-saturated (P50) is approximately 6 torr lower than that of adult hemoglobin. Ordinarily, the greater oxygen affinity, recognized by a shift to the left of the oxyhemoglobin-dissociation curve, would be expected to oppose the unloading of oxygen in the tissues. Because the fetus can function at a lower P50, however, adequate amounts of oxygen can be unloaded despite the increased affinity. However, because of the range of alveolar P02 (PAA) usually encountered postnatally (100–110 torr), the high oxygen affinity of fetal blood offers little advantage to oxygen loading after birth. The P50 must decrease to lower levels in fetal compared with adult hemoglobin in order to meet the increased oxygen demand in periods of stress. For reasons as yet undefined, the low P50 is not as well tolerated postnatally as in fetal life. Hence, some, but not all, have advocated that the newborn infant with hypoxic stress might benefit from the replacement of its blood with fresh adult blood in order to enhance oxygen unloading. In respiratory acidosis, the benefits derived from an exchange blood transfusion are not easily predicted, and depend not only on the replacement of fetal hemoglobin with adult hemoglobin but also on the 2,3-diphosphoglycerate (2,3-DPG) concentration of the transfused blood, the hematocrit, and the effect of persisting acidosis on 2,3-DPG depletion. Since an increase in pH has a marked effect on 2,3-DPG repletion,
of 2,3-DPG.\textsuperscript{55} The more immature the infant, the greater the percentage of fetal hemoglobin, and hence the lower the $P_{O_2}$. The premature infant with RDS has a significantly lower $P_{O_2}$ than the healthy premature infant of comparable gestational age and weight. This is apparently related to a decrease in erythrocytic 2,3-DPG concentration.\textsuperscript{54,55}

Thyroid function may be related to the affinity of hemoglobin for oxygen. Studies in adults have shown that oxygen affinity increases in hypothyroidism and decreases in hyperthyroidism; these changes have been related to alterations in 2,3-DPG concentration.\textsuperscript{91} The premature infant with RDS is relatively hypothyroid and has a lower concentration of 2,3-DPG compared with the premature infant without RDS.\textsuperscript{58} Full-term infants after uncomplicated pregnancies and labors have $T_H$ levels that increase as their 2,3-DPG concentrations increase.\textsuperscript{57} The precise relationship of thyroid function and hemoglobin affinity for oxygen remains to be elucidated.

**Respiration**

**Breathing Movements in Utero**

Measurements of intratracheal intrapulmonary pressure and tracheal flow of fluid in experimental animals have shown progressive increases in breathing movements during gestation. These consist of occasional gasps and sighs and rapid, irregular movements that vary in depth and rate and are associated with rapid eye movement later in gestation.\textsuperscript{59-61} In all animal species studied, the weight of evidence suggests that the mature fetus normally does not have regular rhythmic respiratory movements in utero, provided there are no physical stimuli or asphyxial insults.\textsuperscript{56-63} Studies in which microelectrodes have been placed in the region of the fetal respiratory center have revealed that spontaneous discharges increase in association with any nonspecific neural input, \textit{e.g.}, thermal or sensory stimuli.\textsuperscript{64} Records of electrical activity in the phrenic nerve and diaphragmatic muscles of fetal sheep reveal that continuous intratracheal respiration probably occurs only with hypoxia, and that normally the fetal respiratory center is only minimally active \textit{in utero}.\textsuperscript{65} Thus, although irregular fetal breathing movements have been demonstrated, the mechanism responsible for initiating rhythmic respiration postnatally remains to be elucidated.

**The First Breath**

Although large changes in arterial blood gases, pH, and environmental temperatures\textsuperscript{64} are associated with the initiation of respiration, the observation that large changes in $P_{CO_2}$, $P_{O_2}$ or pH of arterial blood have not consistently stimulated respiration in experimental animals\textsuperscript{58} makes it difficult to assign priorities to the many chemical and physical stimuli that could initiate respiration at birth. In intact, anesthetized fetal sheep, severe hypoxemia ($P_{O_2}$, of the order of 10 torr) initiates respiration by stimulating central chemoreceptors. The ability of $P_{CO_2}$ (acting at the arterial chemoreceptors) to facilitate the response to hypoxia is of only limited magnitude, and is seen only at very high levels ($P_{CO_2} > 90$ torr).\textsuperscript{66} The results of these and other studies\textsuperscript{67} suggest that the first gasp, much like the last gasp, may be the response to a very stressful situation, \textit{i.e.}, severe hypoxia, and may involve mechanisms that differ from those of normal respiration.

When the vertex of the fetus is delivered, as much as 20 ml of fluid is passively expressed from the oropharynx and upper airway.\textsuperscript{68} Very large inflation pressures (fig. 7) are required to initiate the first breath, because a column of liquid must be moved ahead of air and because the viscosity of liquid is considerably greater than that of air. Also, additional pressure is needed to overcome surface forces, which become important as the alveoli fill with air and an alveolar air–liquid interface is established. The magnitude of the pressure required to overcome tissue resistance with the first breath remains unknown. Intrathoracic pressure changes of $-10$ to $-70$ cm have been measured with the first breath.\textsuperscript{69}

The respiratory tidal volumes of the first breath range from 12 to 67 ml.\textsuperscript{68} In all infants, the first breath is characterized by a distinct short inspiration, followed by a more prolonged and varied expiration. No end-expiratory pause is observed.\textsuperscript{69}
The bulk of fluid in the lungs is removed by one of three ways: 1) movement into blood, because the balance of forces across the fluid-exchanging vessels favors absorption; 2) drainage of liquid from terminal air spaces to lymphatics; 3) drainage out of the Airways. Approximately half the volume of alveolar fluid appears to be cleared by the lymphatic route.

Turning to the problems of the first expiration, it is obvious that if all the air entering the lungs on the first breath were to leave, lung collapse would occur, and every breath would require the same large pressures as the first (fig. 7). However, in normal pulmonary adaptation, a functional residual capacity is maintained because of the balance of lung and chest wall elastic recoil and because of the presence of the stabilizing effect of surfactant in the surface film lining those peripheral units of the lung that diastend with air. The volume of the FRC in the normal newborn infant has recently been shown to depend on airway resistance, and is larger during rapid breathing. Indeed, it has been suggested that the active Hering-Breuer reflex of the newborn increases respiratory rates and hence opposes collapse of the lung by increasing FRC.

**Respiratory Control**

Interest in pediatric respiratory control stems not only from a desire to understand the initiation of rhythmic breathing at birth but also from a desire to understand the basis for such abnormalities as apnea and periodic breathing, the latter is not only prevalent in prematurely born infants but has been observed in a third of normal full-term infants. Interest in the subject has been heightened recently by the growing consensus that the sudden infant death syndrome may represent some failure in respiratory control in which the nervous system is intimately involved.

Cunningham has provided a recent review integrating the many factors that are believed to be important in the regulation of respiration, and Avery has reviewed what is currently known about the responses of the newborn to both chemical and nonchemical stimuli to breathing. While there may be quantitative differences in the magnitudes of responses, in general one can say that the infant is able to respond to much the same stimuli as the adult. To be sure, there are important differences, for example, in thermal control, so that the ventilatory response to hypoxia is less in the first week of life when the infant is in a cool environment. Various studies have focused on the magnitudes of the ventilatory responses of infants, both full-term and premature, to increases in the level of CO₂ in the inspired air. There has been some controversy as to whether the young infant is more sensitive or less sensitive than the adult. Some of the differences depend upon whether rebreathing or steady-state responses to inhaled CO₂ are studied, as well as on the methods used to compare the responses of individuals of widely differing sizes. There is, however, convincing evidence from most of these studies that the infant's CO₂-response curve is shifted to the left (fig 8), i.e., for a given PaCO₂ the relative level of ventilation is greater in the infant, and that when comparison is made on the basis of body weight, the sensitivity to CO₂, as judged by the slope of the CO₂-response curve, does not vary with age.
Hypoxia is believed to stimulate arterial chemoreceptors and depress intracranial chemoreceptors in infants, as in the adult. The newborns of all species thus far studied, including man, have been demonstrated to have chemoreceptor (and baroreceptor) reflexes similar to those in adults.\textsuperscript{44,45} Like that of the adult, the ventilatory response of the newborn infant to hypoxia is augmented by hypercapnia; however, in contrast to the adult, the response is not sustained.\textsuperscript{46}

Normally the arterial chemoreceptors contribute a tenth to a third of the total CO\textsubscript{2} drive.\textsuperscript{42,46} Their response to hypoxia, while very important in the breath-to-breath regulation of respiration, is believed to be much less potent than the intracranial chemoreceptor response to CO\textsubscript{2} and H\textsuperscript{+}.\textsuperscript{46} This might lead one to conclude that the arterial chemoreceptors are not as important as the intracranial chemoreceptors, except perhaps under certain circumstances such as central nervous system depression. Recent studies have suggested that the arterial chemoreceptors have an important role regulating the activity of the intracranial CO\textsubscript{2} and H\textsuperscript{+} receptors.\textsuperscript{46}

The application of automatic control theory has been advocated as one way of increasing our insight into the several possible mechanisms by which the respiratory system may be made unstable, e.g., periodic breathing or apnea.\textsuperscript{49} In this type of analysis the

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**Fig. 8.** CO\textsubscript{2} response curves of infants and adults obtained by steady-state and rebreathing methods. From Avery et al.\textsuperscript{72}

**Fig. 9.** Left panel. Relation of ventilation to alveolar carbon dioxide tension (P\textsubscript{A\text{CO}_2}) at constant alveolar oxygen tensions (P\textsubscript{A\text{O}_2}) during wakefulness in adult man. The dashed lines represent the maintenance of ventilation at low P\textsubscript{A\text{CO}_2}, presumably by wakeful stimuli. Modified from Neilson M, Smith H: Studies on the regulation of respiration in acute hypoxia. Acta Physiol Scand 24:293–313, 1951.

system to be analyzed (respiratory system) consists of those elements that control the system (arterial and intracranial chemoreceptors, respiratory neurons, and the respiratory center) and those elements that are controlled (the respiratory muscles and the O₂ and CO₂ stores of the body). In general, any deviation from the desired levels of arterial blood gases or pH needs to be sensed, and corrective action (altered ventilation) set into motion as a result of feedback from some sensing element (e.g., chemoreceptors) detecting the deviation. When the system works well, the ventilation and circulation are so adjusted that there are minimal swings in blood-gas tension and pH despite wide swings in metabolic activity. An efficient feedback system is required, with sensitive sensors and a system that can respond rapidly and remain stable. If overdamped, the system will respond too slowly; if underdamped, it will respond too quickly, overshoot and oscillate. As in other feedback systems, instability of ventilation may result from several causes:

A) Delay in transmission of information within the system (e.g., prolonged circulation time). If the delays are sufficiently prolonged, the timing of the corrective action may be inappropriate, leading to large overshoots and prolonged cycling.

B) Alinearity of the controller. The ventilatory response to CO₂ is linear over a wide range of CO₂ tensions in the wakeful state (fig. 9). This is another way of saying that the CO₂ controller has a constant gain, and this in turn reduces the chances for instability. As Pₐₐ₈ decreases, wakeful stimuli become important in maintaining the linearity of the CO₂ response. However, when the sensorium is dulled, e.g., by anesthesia or pharmacologic agents, ventilation decreases markedly in the hypocapnic range, and apnea may result. The increase in ventilation with hypoxia is alinear (fig. 9), i.e., the increase in ventilation for a given decrease in P₀₂ is much larger in the hypoxic range than in the higher P₀₂ range. This alinearity tends to make the system more unstable. Since the effect of hypoxia is primarily at the arterial chemoreceptor, any factor that increases the proportion of drive coming from the arterial chemoreceptors is also likely to predispose to instability. Because of the interaction of CO₂ and O₂, i.e., CO₂ sensitivity is multiplied during hypoxia, the combined effect of CO₂ and O₂ on the controller during hypoxia is also alinear. Also because of the larger A-a gradient for oxygen in the infant compared with the adult, the infant functions at a lower Pₐ₈, and this may make him more prone to develop respiratory instability.

C) Underdamping of the controller. The oxygen stores in the body are relatively small compared with the CO₂ stores (fig. 10). Thus, equivalent changes in stored gas volumes are likely to be associated with a greater decrease in O₂ than in CO₂ tension. The infant may also be more prone to wide swings in O₂ because of his relatively higher metabolic rate compared with the adult on a weight basis. The CO₂ control system is stable not only because of the damping effect of the large CO₂ stores and the linearity of the response to CO₂ but also because of the increase in cerebral blood flow that accompanies hypercapnia. The latter has the effect of minimizing changes in the vicinity of the cerebral chemoreceptors when metabolic or environmental CO₂ changes.

Based on the above analysis, we might
predict that abnormal respiratory rhythm or apnea might be more likely to develop in infants in the presence of one or more of the following:

1) Altered state of alertness or central nervous system deficit. This may result from dulling of the sensorium by drugs or anesthesia. In old individuals this is also attributed to cerebrovascular disease. In the infant it may result from immaturity or brain damage as the result of perinatal asphyxia.

2) Very high or very low sensitivity to CO₂. An increased sensitivity to CO₂ has been found in adults with cortical disease, and leads to ventilatory instability. Whether hypoxic brain damage can increase CO₂ sensitivity in the infant is unknown; there is evidence to suggest that immaturity per se does not increase CO₂ sensitivity. At the other extreme, individuals with very little CO₂ drive are more dependent on oxygen at the arterial chemoreceptors, and the response of these is alinear.

An infant with failure of automatic control of ventilation during sleep (Ondine’s syndrome) demonstrated a reduced sensitivity to CO₂, and illustrates the interplay of factors 1) and 2) in producing instability of the respiratory control system.

3) Underdamping of the CO₂ or O₂ stores. The immature infant may have an ineffective cough, and may be more susceptible to atelectasis as a result of either mechanical instability of the lung or mucous plugging.

The reduced FRC and hence reduced O₂ stores coupled with a decreased Pao₂ will make his respiratory control system less stable. The infant with RDS is also prone to periodic breathing or apnea, again presumably as the result of reduced O₂ stores and hypoxemia. In both of these instances administration of oxygen usually restores more stable breathing.

4) Decreased Bohr or Haldane effect. Each of these has a damping effect on the change of blood gases. To what extent the magnitudes of these effects are altered by fetal or adult hemoglobin in vivo remains unclear.

5) Diminished response of the cerebral blood vessels (and hence cerebral blood flow) to CO₂. The proportion of the cardiac output to the head is greater with immaturity, and may be well above 50 per cent of the total cardiac output in very small infants. Also, it is known that the neonatal infant spends more time in active or REM sleep than the adult, and that, at least in the adult, cerebral blood flow is increased during this stage. Any impairment in the ability of the infant’s cerebral vasculature to respond to CO₂ would remove one stabilizing influence on the control of respiration. Existing studies suggest that 1) the increase in blood flow in fetal sheep and newborn lambs is at least as great as in the adult as Paco₂ increases over the range of 30 to 65 torr, and 2) the pattern of response and the magnitude of change in blood flow with alterations in Pao₂ in newborn lambs are similar to those in the adult baboon. However, the interaction between hypercarbia, hypoxia, blood pressure, and maturation in the control of the cerebral circulation has not been studied in great detail. Thus, the notion that alterations in cerebral blood flow may be a cause of periodic breathing in infants remains only a theoretic possibility.

6) Slowing of circulation time as a result of heart failure or shock. While the effect of each of these on the circulation could result in instability of ventilation in infants, it is unlikely that either is commonly the cause.

7) Oscillations in other systems. Cyclic changes in other systems, e.g., the cardiovascular system, are known to produce periodic
breathing; this appears to be rare in adult man, but has not been studied in infants.

Circulation

Several excellent reviews of the fetal and neonatal circulation and its controlling mechanisms have appeared recently. We focus here on some areas under current investigation.

FETAL CIRCULATION

With the development of techniques to assess cardiac output and the distribution of blood flow in utero, patterns of blood flow in the fetal animal have been described. Early studies using angiographic techniques revealed directions of blood flow in the fetus but could not quantitate the magnitude of flow. Subsequent studies using the Fick principle provided estimates of blood flow distribution. More recently, electromagnetic flowmeters have been used around major vessels to measure regional blood flow. Because most of these studies altered either the maternal or the fetal circulation as a result of exteriorization of the fetus and extensive surgical manipulation, it is difficult to draw conclusions regarding blood flow in the undisturbed fetus.

Most recently, the use of nuclide-labeled microspheres and the determination of umbilical blood flow by constant infusion of antipyrine have provided a means of studying distribution of blood flow to fetal organs during gestation. These studies confirmed that in the fetal lamb the placenta receives the largest proportion of the cardiac output, i.e., 40–45 per cent, the carcass receives 35 per cent, and all the organs combined receive 20–25 per cent of the cardiac output during the latter half of gestation (fig. 11). In absolute terms, perfusion of the lung increases from about 34 ml/kg/min at mid-gestation to 126 ml/kg/min at term. Since the latter represents only 7 per cent of the cardiac output, it is unlikely that pulmonary vasoconstriction from, for example, hypoxia can be responsible for much redistribution in utero. On the other hand, the peripheral blood vessels, which carry 35–40 per cent of the cardiac output, have been shown to be responsive to stimulation of sympathetic alpha-receptors during fetal asphyxia, and could be responsible for major redistributions of blood flow.

TRANSITIONAL CIRCULATION

Profound alterations in the cardiovascular system occur during the transition from fetal to neonatal life. Systemic vascular resistance increases rapidly as the cord is clamped and the large, low resistance of the placental circulation is removed. A decrease in pulmonary vascular resistance and an increase in pulmonary blood flow are associated with the onset of ventilation (fig. 12). Pulmonary blood flow increases with the gaseous expansion of the lungs secondary to dilatation of the pulmonary vessels regardless of the composition of the gas. Pulmonary vascular resistance decreases still further by increasing PaO2 as well as by decreasing PaCO2. Another important event in the transition
from the fetal to the adult circulation is the closure of the patent ductus arteriosus (PDA). Functional closure (mucosal constriction) is normally complete 10–15 hours after birth in the full-term infant. Anatomic closure usually occurs in 2–3 weeks. The major factor associated with the closure of the PDA is the postnatal increase in Fshp. This is supported, in part, by the higher incidence of the persistence of the PDA at high altitudes. Although there may be anatomic reasons to explain the increased persistence of patency of the ductus arteriosus in premature infants, e.g., decreased muscle in the media, the observation that those with lower Fshp's have persistent patency again emphasizes the importance of increased oxygen for ductal closure.

There is evidence suggesting that oxygen has a direct effect on the smooth muscle by interacting with the terminal oxidase of the cytochrome chain. However, since various vasoactive substances, i.e., bradykinin, catecholamines, and acetylcholine esterases, also produce constriction of the ductus, it is possible that an intermediary transmitter substance may also be involved. The precise mechanism by which oxygen produces ductal closure remains unknown.

Left-to-right shunts through the ductus arteriosus produce a) pulmonary engorgement and b) increased hemodynamic load on the left ventricle; when severe, a) and b) lead to pulmonary edema. The amount of the left-to-right shunt depends upon the magnitude of the pulmonary vascular resistance. Normally the thickness of the media of the pulmonary blood vessels thins during the neonatal period so that the adult level of pulmonary vascular resistance is reached by about two weeks of age. However, this thinning, or maturational process, may be delayed in the presence of a left-to-right shunt, and may not present a hemodynamically burdensome problem until after several weeks of life. The premature infant has less smooth muscle in the media of the pulmonary blood vessels than the full-term infant. This probably accounts for the earlier appearance of signs of pulmonary vascular engorgement in the immature infant, presumably because pulmonary vascular resistance falls more rapidly.

In early life a patent ductus arteriosus may produce clinical difficulties from shunts in either direction. When there is an increase in pulmonary vascular resistance, e.g., RDS, right-to-left shunting may occur through atelectatic alveoli, the foramen ovale, and the ductus arteriosus. Gerstony and co-workers have calculated that when hypoxemia is severe, the total right-to-left shunt can be 80 per cent of the cardiac output, with the flow through the ductus contributing more than half of this shunt. The right-to-left shunt through the ductus arteriosus may serve as a safety valve for the elevated pressure in the right ventricle. However, the hypoxemia that results from the right-to-left shunt may be a stimulus for a further increase in pulmonary vascular resistance, leading to a vicious circle. Clearly, the focus here must be to reverse the pulmonary disease and improve oxygenation.

While a left-to-right shunt through the ductus arteriosus may occur as an isolated abnormality, it may also complicate other congenital cardiovascular anomalies, as well as RDS. There are differences of opinion about the magnitude of the hemodynamic burden of the PDA in premature infants with RDS. This has been accompanied by some puzzling differences in the clinical experiences of managing these patients. Central to the issue is the question of the quantity of blood that flows left-to-right through the ductus in RDS and the effect of this shunt on hemodynamic alterations. These, in turn, affect fluid exchange in the lung, work of breathing, and alveolar gas exchange. Some have advocated the use of echocardiography to detect left atrial enlargement as a means of assessing the magnitude of left-to-right shunt. Even so, the controversy over the indications for early surgical closure may not be easily resolved. One can only hope that as our understanding of the chemical mediators involved in ducal closure improves, the ability to induce early non-surgical closure may be enhanced.

Although the transition from fetal to adult circulation usually occurs rapidly and smoothly, there is a group of infants who have what has been called "persistence of the fetal circulation," or more accurately, "persistence of the transitional circulation."
These infants maintain high pulmonary vascular resistance with right-to-left shunting through the foramen ovale and ductus arteriosus after the placental circulation has been eliminated and breathing has begun. The infants are full-term, generally cyanotic, and have no evidence of organic heart disease, central nervous system disturbances, methemoglobinemia, or pulmonary disease. Persistence of the transitional circulation has been reported to occur in infants with hyperviscosity of the blood and to be reversed following exchange blood transfusion. In another group, with neonatal hypoglycemia, cyanosis has also been attributed to increased pulmonary vascular resistance, and is reversed by administration of glucose. An atypical form of respiratory distress syndrome in full-term infants without marked acidosis or hypercarbia has also been attributed to a transient elevation of the pulmonary vascular resistance. Last, there is a group of infants with no obvious cause for the persistence of the transitional circulation. In addition to exploring the interaction of blood pressure, vascular impedance, blood viscosity, hematocrit, and oxygen saturation, it may be desirable to search for vasoactive chemical mediators in order to gain further insight into the pathophysiology of this group of patients with puzzling circulatory problems.

**NEURAL REGULATION**

Recent interest has centered on the autonomic nervous system because of its importance in the modulation of heart rate, contractility and distribution of blood flow. Although it is not known when the autonomic nervous innervation of the fetal myocardium and circulation first develops, "receptors" have been demonstrated to be present by the middle of the second trimester in fetal sheep. Histochemoanalytica, biochemical, and pharmacologic studies in animals suggest that parasympathetic and alpha-sympathetic innervation occurs earlier in gestation than beta-sympathetic innervation; the latter is incomplete at birth and continues to develop in early life. Although studies using pharmacologic agents with selective blockade of the parasympathetic and alpha- and beta-sympathetic receptors have demonstrated autonomic activity during the latter half of gestation and sympathetic nervous innervation of the pulmonary vasculature of the fetal lamb near term, the role of the autonomic nervous system in fetal cardiovascular control and homeostasis remains to be elucidated. While autonomic innervation of the fetal myocardium may be incomplete at birth, there is evidence indicating that the sensitivities of parasympathetic and sympathetic receptors that are present are similar to those of the adult. The apparent supersensitivity of the fetal myocardium to exogenous norepinephrine has been attributed to the incomplete sympathetic innervation.

Little information is available regarding the normal cardiovascular reflex function in the fetus. Current information suggests that aortic chemoreceptors of the fetal lamb are sensitive to modest changes in Po2. This sensitivity may be important for fetal survival during hypoxemia. Studies in the sheep fetus have demonstrated the presence of baroreceptor response, which increases with advancing gestation. The role of these reflexes in the control of the fetal circulation remains to be elucidated.

The extent to which the central nervous system controls the circulation in utero and the extent of development of the regulatory system have not been examined.

**MECHANICAL CONSIDERATIONS**

The age-dependent mechanical difference between the fetal and the adult cardiac muscle, e.g., the larger amount of active tension generated by the adult, has been attributed to a greater concentration of contractile myofilaments per unit muscle mass, and not to differences in the intrinsic strength of the individual contractile myofilaments.

Resting or passive tension of cardiac muscle is higher in the fetus and newborn than in the adult, suggesting that immature cardiac muscle has less compliance. In addition, the effect of filling one ventricle on the reduction in distensibility of the other ventricle is greatest in the fetus and newborn. Thus, the presence of lesions primarily increasing left ventricular volume or pressure
could have profound effects on the right ventricle, and may explain the ease with which left-sided lesions lead to systemic venous congestion in premature and newborn infants.

**VASOACTIVE SUBSTANCES**

It has been suggested that the cardiovascular changes throughout life, beginning with the fetus, are mediated by locally produced vasoactive substances. Since different tissues may produce different chemical mediators, this could be the explanation for the differences in responses of the pulmonary and umbilical vessels and ductus arteriosus to the same stimulus, e.g., oxygen. It is now recognized that the lung plays an important role in the handling of a large number of bioactive materials. Many of these are vasoactive (e.g., bradykinin, angiotensin, prostaglandins, histamine). To what extent they are responsible for the control of the fetal and neonatal circulation is unknown, although there is evidence suggesting their potential importance. For example, bradykinin has been shown to constrict the umbilical artery and ductus arteriosus and to dilate the pulmonary vasculature. The role of bioactive substances in the maturation of fetal lung and the adaptation of the fetus to extrauterine life remains an open subject and a fertile field for further investigation.

**Lung Fluid**

It has been assumed for many years that the fluid present in the fetal airways was inhaled amniotic fluid. However, the subsequent observation that its composition differs from that of amniotic fluid as well as plasma indicated that it must be derived from another source (table 1). It is now clear from a variety of studies in man and experimental animals that the fetal alveolar fluid is derived from the alveolar epithelium. That the fluid is formed by active rather than passive transport of ions is suggested by 1) the discovery of a small negative potential difference between the alveolar fluid and plasma, and 2) a large difference between the measured ionic flux ratio and that expected for a passive distribution. There are two additional pieces of evidence that would suggest that secretion of alveolar fluid is an active process: 1) an increased filtration of fluid into the pulmonary interstitium brought about by an infusion of fluids to raise vascular hydrostatic pressure did not increase the rate of alveolar fluid formation, and 2) when alveolar cells are poisoned by potassium cyanide, alveolar fluid disappears, presumably as the result of absorption (fig. 13). The actual rate of secretion is not known because the relative extent to which lung fluid is absorbed directly into the blood stream or

**Table 1. Mean Values (± SE) for Concentrations of Electrolytes, Protein, pH and P<sub>CO₂</sub> in Alveolar Liquid, Plasma, Lymph and Amniotic Liquid**

<table>
<thead>
<tr>
<th></th>
<th>Na⁺ (mM/kg H₂O)</th>
<th>K⁺ (mM/kg H₂O)</th>
<th>Ca⁺ (mM/kg H₂O)</th>
<th>Cl⁻ (mM/kg H₂O)</th>
<th>HCO₃⁻ (mM/kg H₂O)</th>
<th>P&lt;sub&gt;CO₂&lt;/sub&gt; (torr)</th>
<th>pH (Units)</th>
<th>Protein (g/100 ml)</th>
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<tr>
<td>Mean</td>
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<td>0.9</td>
<td>157</td>
<td>2.8</td>
<td>40</td>
<td>6.27</td>
<td>0.027</td>
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<td>SE</td>
<td>1.3</td>
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<td>0.08</td>
<td>4.1</td>
<td>0.3</td>
<td>3</td>
<td>0.05</td>
<td>0.002</td>
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<tr>
<td><strong>Plasma</strong></td>
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<td></td>
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<tr>
<td>Mean</td>
<td>150</td>
<td>4.8</td>
<td>3.3</td>
<td>107</td>
<td>24</td>
<td>43</td>
<td>7.34</td>
<td>4.09</td>
</tr>
<tr>
<td>SE</td>
<td>0.7</td>
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<td>1.2</td>
<td>4</td>
<td>0.04</td>
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<tr>
<td><strong>Lymph</strong></td>
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<tr>
<td>Mean</td>
<td>147</td>
<td>4.8</td>
<td>—</td>
<td>107</td>
<td>25</td>
<td>—</td>
<td>7.31</td>
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<tr>
<td>SE</td>
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<td>0.3</td>
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<td>—</td>
<td>0.02</td>
<td>0.41</td>
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<tr>
<td><strong>Amniotic liquid</strong></td>
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<td>Mean</td>
<td>113</td>
<td>7.6</td>
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<td>5.0</td>
<td>3</td>
<td>7</td>
<td>0.09</td>
<td>0.01</td>
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* Adapted from Adamson, et al.
cleared by the pulmonary lymphatics in utero is not known. However, alveolar fluid secretion must exceed fluid removal, since measurements of tracheal flow, both directly and by dilution techniques, indicate the net secretion to be 2 ml/kg/hr. The functional importance of this fluid is not known. It has been suggested that it may be important in determining the formation, size and shape of the developing air spaces. It has been assumed that pulmonary fluid secretion stops at birth because the air-filled lung collapses distal to a bronchial obstruction, in contrast to the fluid-filled fetal lung, which becomes distended distal to an obstruction. Additional evidence that suggests but does not prove that alveolar secretion ceases after birth is that the slower pulmonary lymph flow rate in the newborn lamb compared with the mature fetus. It is conceivable that prior to birth secretion exceeds absorption, whereas following birth the converse may be true. Although the dynamics of the interstitial space have not been studied in utero, it seems likely that the negative interstitial pressure described for the normal lung is established after an alveolar air-liquid interface is developed. Presumably, surface tension lowers pericapillary pressure. A lower pulmonary interstitial fluid pressure favors movement of fluid to the interstitium and then to the lymphatics. Movement through the lymphatics is enhanced by the milking action of ventilation and lymphatic peristalsis. During the first 5 to 6 hours after the onset of ventilation the interstitial spaces and the lymphatic spaces become distended, suggesting that these are important routes for the clearance of alveolar fluid. In addition, as the lung expands the number of capillaries that are perfused increases. Fluid absorption directly into the blood stream is induced by a fall in pulmonary vascular pressure. The magnitude of fluid movement is increased by an increase in capillary surface area. The slower lymphatic flow in the newborn lamb than in the mature fetus may simply reflect a lower net filtration pressure in the fluid-exchanging vessels. When there is a delay in fluid removal by the pulmonary lymphatics, impaired gas exchange results. This has been suggested as the cause of the transient tachypnea seen in some newborns without other discernible cardiopulmonary abnormality. Several observations suggest that the permeability of the pulmonary blood vessels decreases with maturity: 1) The filtration coefficient of the puppy lung has been found to be approximately ten times larger than that of the mature dog. In addition, the immature lung contains more water than the mature lung. 2) Based on studies of the lymphatic clearance of protein in the canine lung, it has been deduced that the pore radius of the fetal fluid-exchanging vessels is larger than those of the puppy. The larger radius has been attributed to higher vascular pressures’ stretching pores. The permeability of the pulmonary vascular endothelium is greater than the permeability of the alveolar epithelium in utero, as well as postnataally. This explains why extracellular fluids are normally excluded from the alveolar air spaces and why alveolar flooding is a late occurrence in pulmonary edema. It also explains the low concentration of proteins in fetal alveolar fluid compared with lymphatic fluid and plasma (table 1). The presence of protein in the alveoli in disease, e.g., RDS of the newborn, suggests
that an alteration in the integrity of the wall occurs, and is consistent with the observation that the epithelium of the immature lung is more easily disrupted by the stresses of ventilation than that of the mature lung.\textsuperscript{140}

Airway Closure, Grunting, and Constant Distending Pressure

AIRWAY CLOSURE

Studies of the distribution of ventilation show a change in the sequence of emptying of the lung at low lung volumes which has been attributed to closure of some airways.\textsuperscript{143,146} During a vital capacity maneuver, the volume at which closure presumably occurs is recognized by an abrupt increase in the expired concentration of nitrogen (or an inert gas injected during inspiration) and is called "phase IV" or "closing volume" (fig. 14). The closing volume plus the residual volume is now called the "closing capacity" (CC).

Airway closure tends to occur normally in lungs at lower volumes where airways are of smaller diameter. This is especially likely to occur in dependent lung regions because of gravity. Closing lung volumes are greatest in young children and in old age and are least in the teenage years (fig. 15).\textsuperscript{148} This has been attributed to the observation that elastic recoil of the lungs is maximum in the teens and is less in younger and older individuals.\textsuperscript{146,147}

From a functional point of view it is important to relate closing capacity (CC) to functional residual capacity (FRC). When CC exceeds FRC airway closure will occur during tidal breathing, thus impairing gas exchange and increasing the alveolar-to-arterial \textsubscript{O\textsubscript{2}} gradient (A-a\textsubscript{D\textsubscript{O}}\textsubscript{2}). No data on closing volumes in children less than 6 years of age are available. However, extrapolation of data from older children suggests that CC exceeds FRC before 6 years of age.\textsuperscript{149} This would be one possible explanation for the higher A-a\textsubscript{D\textsubscript{O}}\textsubscript{2} and lower \textsubscript{P\textsubscript{a\textsubscript{O}}\textsubscript{2}} seen in infants and young children.

There may be limitations to the ability of mechanical ventilation or constant distending pressure to improve blood–gas exchange depending upon body position and whether respirations are active or passive. During anesthesia or muscle paralysis the supine adult there is cephalad movement of the diaphragm, which is greatest in the dependent (posterior) regions.\textsuperscript{148} This will decrease FRC and enhance the tendency for airway closure and atelectasis in the dependent lung region. Under these conditions, CC exceeds FRC. In the supine adult caudal displacement of the dependent portion of the diaphragm is greater during spontaneous breathing than during assisted or mechanical ventilation. This difference depends on the mechanical advantage of the smaller radius of curvature in the dependent portion of the contracting diaphragm, according to the Laplace relationship. During controlled ventilation the mechanical advantage of the contracting diaphragm is lost. This, together with the gravitational effects on the abdominal contents opposing expansion of the lung, results in a greater distribution of ventilation to the nondependent portions of the lung, which are already well ventilated. During assisted ventilation, while the initial distribution of gas is influenced by the contracting diaphragm, the remaining major part of inspiration is passive, as in the paralyzed patient.
This again results in overventilation of those areas of lung already well ventilated. Similarly, the application of constant distending pressure with mechanical ventilation common by application of positive end-expiratory pressure (PEEP) also results in the greatest distribution of ventilation to the nondependent regions. Hence, despite the use of mechanical ventilation with PEEP there may be little increase in effective ventilation or decrease in airway closure in the dependent regions of the lung. The observed clinical effectiveness of constant distending pressure must be the result of opening of units in the mid-regions of the lung. As a result, there is an overall increase in FRC which exceeds CC. Although it seems likely to us that the results of these studies apply to infants, they will need to be repeated in children before we can be certain of this.

It appears that if the hydrostatic effects of the intra-abdominal contents on thoracic volume could be minimized, ventilation and gas exchange could be improved. In the adult, FRC has been shown to be greatest while resting on the hands and knees and least in the supine position. The position on hands and knees is very similar to the position frequently assumed by children with advanced cystic fibrosis and by the prone infant with flexed knees and hips. This position appears to be best suited to minimize the effects of the abdominal contents on lung volumes and is logistically feasible in children.

There are several groups of diseases in which airway closure is enhanced, resulting in enlargement of closing capacity: 1) conditions that reduce lung volumes, e.g., obesity, ascites, kyphoscoliosis; 2) conditions that alter elasticity, e.g., emphysema; 3) conditions that narrow the airways, e.g., asthma, cystic fibrosis, pulmonary edema.

We believe that the airways of some children with large left-to-right shunts as the result of congenital heart disease are especially prone to airway closure. The large shunts markedly increase mean pulmonary arterial pressure, blood flow, and pressure, resulting in increased fluid filtration from the fluid-exchanging vessels in the lung. The edema fluid which is known to collect around small airways presumably is the cause of airway closure, by preventing the normal tethering action of the lung from holding the airways open. These patients manifest a-

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**Fig. 15.** Difference between functional residual capacity (FRC) and closing capacity in liters as a function of age (±1 SD) is shown. Negative values indicate that airway closure is present during normal tidal breathing. Modified from Mansell et al.
cylator and radiographic evidence of airway obstruction.\textsuperscript{132}

**GRUNTING**

Airway closure and atelectasis are important clinical problems in disease, especially in the neonatal infant. The grunt, so characteristic of many clinical conditions in the neonatal period, was for years interpreted only as a sign of distress or discomfort; more recently it has been appreciated that grunting may help to prevent collapse of the lung. A grunt represents an expiratory maneuver against the closed glottis, and therefore shortens the time during which the lungs are emptying. There are several potentially beneficial effects from grunting, depending on the clinical circumstances. Grunting 1) delays alveolar emptying, thereby increasing the surface area available for gas diffusion; 2) minimizes the time during which airway closure can occur, thereby minimizing time for atelectasis; 3) raises pleural pressure, decreasing venous return and thereby decreasing cardiac output, pulmonary vascular filling, and the hydrostatic forces favoring transudation of fluid into the lung; 4) minimizes extremes of lung volume, thereby conserving surfactant;\textsuperscript{135} 5) improves distribution of inspired air; the effect on ventilation/perfusion relationships is complex and depends upon the circulating pulmonary blood volume and the pressure in the pulmonary vascular bed.

**CONSTANT DISTENDING PRESSURE AND THE CIRCULATION**

Various mechanical techniques have been used to prevent collapse of the lung, each with a bewildering number of terms and abbreviations, e.g., PEEP, CPAP, CPPV, none of which has been universally accepted.\textsuperscript{1} In all, the lowest value of the transpulmonary pressure (the difference in pressure between the airway opening and the pleural space or the distending pressure of the lung) during the breathing cycle is increased. Sometimes this is accomplished by application of positive pressure to the entire head by means of a head chamber with a neck seal\textsuperscript{134} or by direct pressure to the airway opening by means of nasal prongs, a tight-fitting face mask, or an endotracheal tube. Alternately, negative pressure is applied to the chest wall with or without inclusion of other parts of the body, again with some sort of neck or other seal.\textsuperscript{135,134} In either case the patient may breathe spontaneously or ventilation may be controlled mechanically.

While it is possible to achieve constant distending pressure of the lung by application of either positive or negative pressure, the choice may depend upon such considerations as access to or ease of handling the patient, or the effects on the circulation. From a practical point of view, the only two circumstances that produce exactly the same physiologic effects on circulation and ventilation are application of positive pressure to the head using a head chamber and neck seal and negative pressure below the neck on the trunk and extremities. While the effects on pulmonary inflation may be similar when positive pressures are confined to the airway or negative pressures are limited to the chest wall, the effects on the circulation are markedly different.

Maneuvers involved in changing the magnitude of inflation of the lung can alter the circulation in at least two ways: 1) changes in pleural pressure alter venous return to the heart, i.e., positive pressure applied to the airway will tend to increase pleural pressure and decrease venous return, while negative pressure around the thorax will tend to decrease pleural pressure and increase venous return, and 2) as the lung inflates, overall pulmonary vascular resistance initially decreases and then increases in the adult. This results, presumably, from the balance of two opposing effects, i.e., the resistance of the extra-alveolar vessels decreases with pulmonary inflation while the resistance of the capillaries increases. This U-shaped change in vascular resistance is well recognized in the mature lung. Since there is a difference

\textsuperscript{1}There might be less confusion if in addition to indicating the presence of positive end-expiratory pressure (PEEP) or constant positive airway pressure (CPAP), it were also specified whether this was accomplished with spontaneous or mechanical ventilation.
in the amount and distribution of muscle in the pulmonary vasculature of the immature lung, it is possible that the changes in vascular resistance with inflation also may be different. Negative pressure around the chest not only increases the functional residual capacity but also increases venous return from those parts of the body not exposed to negative pressure. When one considers that more than 50 per cent of the total blood volume may be circulated to the head in very immature infants, shifts in the distribution of only a small proportion of the circulating blood volume may result in major increases in pulmonary vascular volume, thus enhancing the tendency towards transudation of fluid into the lung. Conversely, positive pressure applied to the airway opening raises pleural pressure, decreasing the venous return and reducing pulmonary vascular volume and pressure.

The situation is even more complex in the RDS of the newborn, where changes in pulmonary inflation as a result of mechanical ventilation produce changes in $P_{aw}$ which in turn will produce changes in vascular resistance of the pulmonary bed. There is evidence suggesting that infants with hyaline membrane disease have a relatively large compartment with a ratio of ventilation to perfusion ($V_{A}/Q_{A}$) that is so very low that regional $P_{aw}$ is also low, and hence there is intense local vasoconstriction. Because of the large size of this compartment, this leads to an increase in overall pulmonary vascular resistance, with a concomitant increase in true right-to-left shunting through the foramen ovale, the ductus arteriosus, or the lung. These workers have concluded that constant distending pressure increases the ventilation to these low-$V_{A}/Q_{A}$ regions, raising $P_{aw}$, decreasing both local and overall pulmonary vascular resistance, and decreasing true right-to-left shunting.

Thus, the overall effects of either positive or negative pressure will depend not only upon the nature of pulmonary disease and its effect on lung volume and compliance but also on the amount of pressure and the portions of the body exposed to the applied pressure, the volume and distribution of circulating blood, and the position of the right ventricle on the Frank-Starling curve. Variations in the responses of different patients to positive or negative applied pressures must in some measure depend on the inherent stiffness of the lung, airway resistance, blood volume, cardiac function, and regulation of vascular capacitance by the autonomic nervous system.

Mechanical ventilation has been associated with major changes in renal perfusion and total body fluid balance. The normal neonatal primate has been shown to have the same pattern of renal blood flow as the adult, i.e., a predominance of outer over inner cortical blood flow. With the administration of intermittent positive-pressure ventilation in the neonatal primate, there is a decrease in cardiac output, an increase in renal vascular resistance, and a decrease in the proportion of cardiac output perfusing the kidneys. There is also an absolute decrease in both inner and outer cortical blood flow with reversal of the normal pattern. In contrast, in the adult dog, total renal blood flow was not significantly altered following the application of 10 cm H$_2$O positive end-expiratory pressure despite a decrease in cardiac output. However, as in the case of the neonatal primate with intermittent positive-pressure ventilation, positive end-expiratory pressure in the adult reverses the pattern of cortical blood flow. As a result, urinary output, creatinine clearance, and urinary sodium excretion decrease. Inappropriate antidiuretic hormone secretion has been associated with intermittent positive-pressure ventilation and with continuous positive-pressure ventilation in the adult, and may also play a role in the decrease in urinary output seen. Thus, it seems reasonable to conclude that the use of some forms of mechanical ventilation may alter cardiac output, renal perfusion, and the total body fluid balance in the neonatal infant.

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