Environmental Health Perspectives
Vol. 55, pp. 205-226, 1984

Lung Surfactant

by Seamus A. Rooney*

Aspects of pulmonary surfactant are reviewed from a biochemical perspective. The major emphasis is on the lipid components of surfactant. Topics reviewed include surfactant composition, cellular and subcellular sites as well as pathways of biosynthesis of phosphatidylcholine, disaturated phosphatidylcholine and phosphatidylglycerol. The surfactant system in the developing fetus and neonate is considered in terms of phospholipid content and composition, rates of precursor incorporation, activities of individual enzymes of phospholipid synthesis and glycogen content and metabolism. The influence of the following hormones and other factors on lung maturation and surfactant production is discussed: glucocorticoids, thyroid hormone, estrogen, prolactin, cyclic AMP, β-adrenergic and cholinergic agonists, prostaglandins and growth factors. The influence of maternal diabetes, fetal sex, stress and labor are also considered. Nonphysiologic and toxic agents which influence surfactant in the fetus, newborn and adult are reviewed.

Introduction

The alveoli of the lung are lined with a highly surface-active, phospholipid-rich material, pulmonary surfactant, which prevents their collapse on expiration. The existence of surfactant was first suggested by von Neergard (*1*) in 1929 but it was not until some 30 years later that its presence was actually demonstrated when Pattle (*2*) showed that remarkably stable bubbles could be squeezed from a lung cut under water and Clements (*3,4*) showed that lung extracts lowered the surface tension at an air-water interface. In 1959 Avery and Mead (*5*) demonstrated its clinical importance when they found that the lungs of infants who died from the respiratory distress syndrome (RDS) were deficient in surfactant. In the ensuing years the composition and biosynthesis of surfactant has been extensively studied. Since it is now recognized that RDS is a developmental disorder due to immature lungs there has been considerable interest in the control of fetal lung maturation and in the mechanism of surfactant synthesis and secretion as well as in the acceleration of these processes. There has also been interst in surfactant changes in adult lung disease and in the influence of toxic agents on surfactant.

Surfactant is essential for normal lung function in both newborn and adult mammals. Without sufficient surfactant the alveoli would collapse on expiration and this would lead to impaired gas exhange. The surfactant system may be particularly susceptible to pulmonary toxicants. Damage to surfactant or impairment of its production may have a deleterious effect on lung function and may even be incompatible with life. Although the effects of pulmonary toxicants on surfactant biochemistry have not been systematically examined, there is abundant evidence that many such agents do alter the system. However, these agents may not necessarily act directly on the surfactant system but rather affect it secondary to effects on specific lung cells. This paper reviews what is known of surfactant biochemistry and biosynthesis to provide a basis for elucidating possible sites of toxicant action on this vital pulmonary system.

The history of the discovery of surfactant and its relationship to RDS has been detailed in an intriguing review by Comroe (*6–8*). There are also other excellent reviews on the physiochemical (*9,10*), biosynthetic (*11–13*) and developmental (*14–16*) aspects of surfactant.

Composition of Surfactant

The *in vivo* composition of functional surfactant is unknown. Surfactant for *in vitro* study can be obtained by endotracheal lavage with saline followed by differential centrifugation (*17*). Harwood et al. (*18*) examined such material from rats, rabbits, oxen and sheep. All were highly surface-active and consisted of lipid (79–90% by weight) and protein (28–18%) with only a trace of carbohydrate. Surface-active material from dog lung has a similar composition (*19*).

Lipids from rabbit lung lavage consist of 80 to 90% phospholipids, 10% glycolipids and 5% neutral lipids (*20*). Phosphatidylcholine (PC) is by far the most abundant phospholipid. It accounts for 86% of the total phospholipid (*20*). Over half of the PC is disaturated (*21–23*) and palmitic acid accounts for 90% of the saturated fatty acids (*24*). Dipalmitoyl-PC is, therefore, a major component of pulmonary surfactant. Phosphatidylglycerol is the second most abundant phospholipid in surfactant. It accounts for 6 to 11% of the total (*20,25–29*). Surfactant characteristically contains very

*Department of Pediatrics, Yale University School of Medicine, P.O. Box 3333, New Haven, CT 06510.

little phosphatidylethanolamine and sphingomyelin—phospholipids which are present in appreciable quantity in lung tissue (*20*). Phosphatidylinositol, phosphatidylserine and lyso-PC are also only very minor components of surfactant (*20*). The glycolipids in lung lavage have been little studied. Recently Slomiany et al. (*30,31*) reported structures for sulfated and neutral glyceroglucolipids from rabbit lung lavage. The neutral lipids consist of free fatty acids, acylglycerols, cholesterol and cholesterol esters (*18,19,27*).

Dipalmitoyl-PC and phosphatidylglycerol are characteristic components of lung surfactant but they are not exclusive markers for it by any means since they also occur in other, nonsurfactant lung fractions. In addition both disaturated PC (*32*) and phosphatidylglycerol (*33*) also occur in other mammalian tissues, although usually not as abundantly as in lung lavage.

Both dipalmitoyl-PC (*20*) and phosphatidylglycerol (*20,34*) are highly surface-active. The precise nature of surfactant *in vivo*, however, is unknown. It is unlikely to be pure dipalmitoyl-PC because of its poor spreading properties (*35*). Hildebran et al. (*36*) recently reported that monolayers consisting of at least 90% dipalmitoyl-PC with up to 10% cholesterol or monoenoic PC could function as surfactant. Recently, Morley et al. (*37*) reported that a mixture of 70% dipalmitoyl-PC and 30% phosphatidylglycerol was an effective artificial surfactant. A role for protein in surfactant has also been suggested (*38*) although this has been recently disputed (*27,37*). Clearly further work is needed to establish the *in vivo* composition of surfactant. This is particularly important in the development of an artificial surfactant (*37,39–41*) which might be used in the treatment of RDS in the newborn or possibly in adult conditions where surfactant is altered.

Biosynthesis of the Major Lipids of Surfactant

The pathways by which PC and phosphatidylglycerol are synthesized are illustrated in Figure 1. This biosynthetic scheme can be considered in four parts: synthesis of phosphatidic acid from nonlipid precursors; synthesis of PC from choline and phosphatidic acid; synthesis of phosphatidylglycerol from phosphatidic acid and remodeling of the de novo-synthesized PC to form the disaturated species.

Synthesis of Phosphatidic Acid

The first glycerophosphatide in the pathway, phosphatidic acid, is the product of acylation of 1-acylglycerol-3-phosphate which, in turn, is formed from dihydroxy-

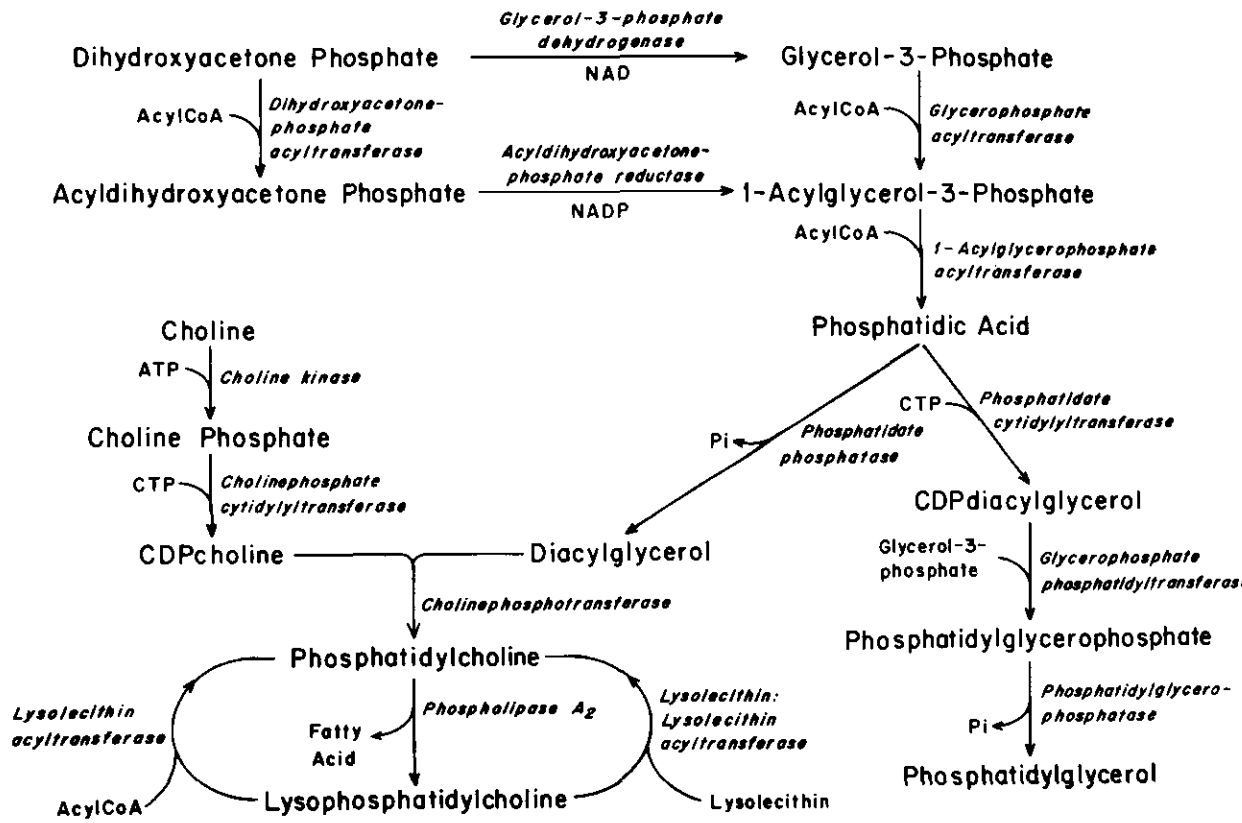

FIGURE 1. Biosynthesis of phosphatidylcholine and phosphatidylglycerol. From Rooney (*42*).

acetone phosphate by either of two mechanisms: initial reduction to glycerol-3-phosphate followed by acylation or initial acylation followed by reduction. There is evidence that both of these mechanisms are operative in the lung (*43,44*). Mason (*45*) reported that the acyldihydroxyacetone phosphate pathway is responsible for synthesis of approximately 60% of PC and phosphatidylglycerol in Type II cells isolated from rat lung. There is evidence that dihydroxyacetone phosphate acyltransferase and glycerophosphate acyltransferase are the same enzyme (*46*). However, 1-acylglycerophosphate acyltransferase appears to be a separate enzyme.

Glucose, glycerol and free fatty acids are incorporated into phospholipids at this stage of the biosynthetic scheme. Glucose and glycogen are metabolized via the glycolytic pathway to dihydroxyacetone phosphate or to acetate and hence fatty acids. Glycerol is converted to glycerol-3-phosphate by glycerol kinase, an enzyme which is present in lung (*47,48*). Fatty acids may be synthesized de novo by the lung or supplied by the blood. Both sources appear to be important. Recent data (*49–52*) suggest that fatty acids synthesized by the lung are incorporated into de novo-synthesized PC and phosphatidylglycerol while exogenous palmitate is incorporated into disaturated PC by remodeling of unsaturated PC (see below).

De Novo Synthesis of Phosphatidylcholine

Choline is phosphorylated and transferred to CDP (cytidine 5′-diphosphate) before reacting with diacylglycerol to form PC. All four enzymes involved in this section of the pathway have been reported to be rate-regulatory in nonpulmonary systems (*53–58*). The rate-limiting step in the lung is not yet known. A rate-regulatory role for cholinephosphotransferase (CPT) was suggested by the finding that this enzyme was induced by glucocorticoids which stimulate PC synthesis in the fetal lung (*59*). This observation has not, however, been consistently made by others (*42,60*). Johnston and co-workers (*61,62*) and Brehier et al. (*63*) presented evidence in favor of a rate-regulatory role for phosphatidate phosphatase (PAPase). However, in those studies, aqueously dispersed phosphatidic acid was used as substrate, and Casola and Possmayer (*64*) have suggested that PAPase assayed with aqueously dispersed rather than membrane-bound phosphatidic acid does not reflect the activity of the enzyme involved in phospholipid synthesis. Recent data suggest a rate-regulatory role for pulmonary cholinephosphate cytidylyltransferase (CP-CYT). The activity of this enzyme increases either at the end of gestation or immedately after birth (*65–72*), when there is a surge in surfactant production. CP-CYT is also stimulated by glucocorticoids (*60,65,73–75*) and estrogen (*74,76,77*)—hormones which stimulate lung PC synthesis.

Most of the above studies have been carried out in preparations of whole lung. It is possible that synthetic rates are controlled differently in different cell types. More precise information on the control of surfactant PC synthesis will be obtained when such studies are carried out on purified Type II cell preparations.

Incorporation of choline via the CDPcholine pathway appears to be the major pathway for de novo PC synthesis in the lung as in most other mammalian systems. There were early reports that synthesis of PC by triple *N*-methylation of phosphatidylethanolamine was particularly important in the case of surfactant (*78–80*). The initial basis for this was the mistaken identification of phosphatidylglycerol as phosphatidyldimethylethanolamine (*20,81,82*). Further studies showed that the methylation pathway is of no more than minor significance in the synthesis of lung PC (*13,83,84*).

Synthesis of Phosphatidylglycerol

Phosphatidylglycerol is also synthesized from phosphatidic acid. Phosphatidate cytidylyltransferase catalyzes the formation of the liponucleotide CDPdiacylglycerol from phosphatidic acid and CTP (cytidine 5′-triphosphate). CDPdiacylglycerol then reacts with glycerol-3-phosphate to form phosphatidylglycerophosphate which is rapidly dephosphorylated to phosphatidylglycerol. Inositol also reacts with CDPdiacylglycerol to form phosphatidylinositol and there is recent evidence from rabbit lung that the level of inositol may control the relative rates of phosphatidylglycerol and phosphatidylinositol synthesis (*85*).

Synthesis of Disaturated PC

Although earlier studies showed that lung disaturated PC was not formed de novo but rather by remodeling of de novo-synthesized 1-saturated-2-unsaturated-PC (*86,87*), recent data (*88–90*) show that disaturated PC can also be synthesized de novo. The relative contribution of these two mechanisms remains to be determined, however.

In the remodeling mechanism, disaturated PC is formed by deacylation of the unsaturated species and subsequent reacylation of 1-saturated-2-lyso-PC (lysolecithin). Deacylation is catalyzed by phospholipase A_2, an enzyme which is present in lung (*91,92*). As illustrated in Figure 1, reacylation can occur by at least two mechanisms—reacylation with acyl CoA, catalyzed by lysolecithin acyltransferase, or transacylation, catalyzed by lysolecithin: lysolecithin acyltransferase, in which two molecules of lyso-PC react to form one molecule each of PC and glycerophosphocholine. There is evidence that both mechanisms operate in the lung but the degree of their quantitative importance has been controversial (*93–99*). Recently, however, it was reported that in adult rat Type II cells the reacylation mechanism is quantitatively more important than the transacylation mechanism (*52,100*).

In addition to deacylation of de novo-synthesized PC by phospholipase A_2, lyso-PC may also be derived from the blood. Van Heusden et al. (*101*) recently reported that, in the rat, bloodborne lyso-PC is incorporated into pulmonary disaturated PC by the reacylation rather than transacylation mechanism. A further source of lyso-PC has recently been reported. Aarsman and van den Bosch (*102*) reported de novo synthesis of lyso-PC by rat lung microsomes from CDPcholine and monoacylglycerol in a reaction similar to that catalyzed by CPT (Fig. 1). The quantitative significance of this pathway is unknown.

Another mechanism for synthesis of disaturated PC from unsaturated PC was reported in rabbit lung (*103*). In this mechanism free palmitic acid exchanges with the oleoyl residue on 1-palmitoyl-2-oleoyl-PC to form dipalmitoyl-PC. This mechanism was also reported in rat lung lamellar bodies (*104*). The precise mechanism of the reaction, however, is not known.

Cellular and Subcellular Site of Surfactant Synthesis

There is substantial evidence that the Type II alveolar epithelial cell is the source of surfactant (*11,105*). A distinct morphological characteristic of Type II cells is the presence of lamellar inclusion bodies. Isolated lamellar bodies have been shown to be rich in phospholipid the composition of which is very similar to that of surfactant (*106*). Although there was early speculation that surfactant was synthesized in lamellar bodies this does not appear to be the case. Isolated lamellar bodies have been shown to lack a number of enzymes necessary for phospholipid synthesis (*24,107,108*). Surfactant PC is synthesized in the endoplasmic reticulum and stored in lamellar bodies prior to release to the alveolar surface. Newly synthesized phospholipids may be transported from the site of synthesis to lamellar bodies by phospholipid transfer proteins. Proteins with the ability to transfer PC and phosphatidylglycerol have been recently demonstrated in the lungs of several species (*109–114*) and in Type II cells isolated from the rat (*115*).

Development of the Surfactant System during Fetal and Neonatal Life

Phospholipid Content and Composition

The fetal lung produces surfactant in increasing quantity towards the end of gestation. In the rabbit, as shown in Table 1, there is a 10-fold increase in the amount of PC and disaturated PC in lung lavage between 27 and 31 (full term) days gestation. There is a further increase of similar magnitude after birth. During the same period the composition of the phospholipids in lung lavage also changes. PC increases while sphingomyelin decreases. This results in a dramatic increase in the PC (lecithin)/sphingomyelin (L/S) ratio.

Since lung fluid contributes to amniotic fluid (*117*) measurement of the L/S ratio in amniotic fluid can be used to predict the degree of maturity of the human fetal lung (*118*). This test is now widely carried out on amniotic fluid obtained by amniocentesis and is used by obstetricians to determine the optimum time for elective delivery (*119,120*). The phospholipids are usually quantitated by densitometry, rather than by phosphorus assay as in Table 1, and under these conditions an L/S ratio of 2 or greater is indicative of fetal lung maturity (*120*). Measurement of amniotic fluid disaturated PC (*120,121*) as well as phosphatidylglycerol and phosphatidylinositol (*120*) leads to even greater reliability in the prediction of fetal lung maturation in normal and complicated pregnancies (*119,120*). Human amniotic fluid phosphatidylinositol has been reported to increase after about 30 weeks gestation and to decline after 35 weeks while phosphatidylglycerol was reported to increase after 35 weeks (*122*). Phosphatidylglycerol was reported to be completely absent in lung effluent from newborn infants with RDS (*123*). Hallman and Gluck (*124*) also reported that phosphatidylglycerol was present in very low amounts prior to term in fetal rabbit lung lavage. In another study in the same species, however, there was little developmental change in lung lavage phosphatidylglycerol (*71*).

Lung tissue PC also increases during fetal development although to a lesser extent than that of lavage. In

Table 1. Developmental changes in the phospholipid content and composition of rabbit lung lavage.[a]

	Phospholipid content, μg P/g lung (dry weight)		Phospholipid composition, % of total lipid phosphorus		
Gestational age, days	Total PC	Disaturated PC	PC	Sphingomyelin	PC/sphingomyelin ratio
27	2.6	1.3	29	38	0.8
29	7.4	3.4	50	11	5
31	25.4	13.4	68	7	10
+1	274	161	79	2.6	31
Adult	264	143	86	1.2	> 50

[a] These data are adapted from the literature (*20,21,71,116*).

the rabbit (*71,116*) and rat (*68*) lung PC increases by about 65% during the last 14% of gestation while disaturated PC more than doubles. During fetal life, lavage PC accounts for only 0.2 to 1.1% of total lung PC (*125*). After birth and in the adult this increases to 10 to 13% (*125*).

Phospholipid Synthesis

The rate of incorporation of precursors, such as glucose (*126*), glycerol (*127*), palmitate (*126*), phosphate (*128*), choline (*60,65,68,126,129,130*) and lyso-PC (*127*) into lung PC increases towards the end of gestation in several species. Most of the incorporation studies were carried out on lung slices. Therefore, they measured rates of incorporation into whole lung PC or disaturated PC and were not specific measurements of surfactant synthesis. Slice studies also suffer from the disadvantage that intracellular pool sizes of the precursor and intermediates are unknown. Pool size differences could alter apparent rates of synthesis. Nevertheless, the increase in the rate of precursor incorporation into PC correlates well with the increase in surfactant as measured by various criteria (*15,129,131*).

Enzymes of Phospholipid Synthesis

The activities of enzymes of pulmonary PC and phosphatidylglycerol synthesis have been measured in the rabbit, rat and mouse during fetal and early postnatal life. There are general similarities in enzyme developmental profiles among the various species. There are also differences but some of these may be due to experimental variation.

Choline Kinase (EC 2.7.1.32). There is little change, or even a slight decrease, in the activity of choline kinase during fetal and early postnatal development in the rabbit (*71,132*), rat (*66,68,133*), mouse (*69*) and human (*134*) lung. In one study, however, the activity of this enzyme peaked 2 to 3 days before term in the rat (*67,135*).

Cholinephosphate Cytidylyltransferase (CP-CYT) (EC 2.7.7.15). There is a developmental increase in the activity of CP-CYT either at the end of gestation or immediately after birth in the rabbit (*70,71*), rat (*66–68,72*) and mouse (*65,69*) lung. Fetal lung CP-CYT activity is stimulated up to 7-fold by phosphatidylglycerol in the rat (*136*), rabbit (*76*) and mouse (*65*). The developmental increase in the activity of this enzyme in rat lung cytosol parallels the increase in phospholipids in the same fraction (*72*). Weinhold's group (*72,137*) has shown that rat lung CP-CYT exists in two forms: an L form of 190,000 molecular weight, which predominates in the fetus, and an H form of 5-50 $\times$ 10^6 molecular weight, which predominates in the adult. The L form aggregates into the H form in the presence of phosphatidylglycerol. The same group (*136*) has recently shown that there is less of the H and more of the L form when the lungs are lavaged prior to homogenization and subcellular fractionation. This suggests that the aggregation occurs during the experimental manipulations involved in preparation of the cytosol fraction. It remains to be established if the aggregation and activation by phosphatidylglycerol is of any physiological significance.

Cholinephosphotransferase (CPT) (EC 2.7.8.2). CPT activity does not change much or even decreases during fetal life in the rabbit (*61,71,81,132*), rat (*68,133*) and mouse (*65*) lung. There is a postnatal increase in the activity of CPT in the rabbit (*70,71,81*) while in the rat adult activities are considerably higher than those of the fetus or newborn (*68,133*). In two studies, however, the activity of lung CPT was reported to peak 1 to 2 days before term in the rat (*67,135*) and mouse (*69*).

Phosphatidate Phosphatase (PAPase) (EC 3.1.3.4). The activity of lung PAPase, measured with aqueously dispersed phosphatidic acid as substrate, increases before term in the fetal rabbit (*60,61*) and mouse (*65*) and after birth in the fetal rat (*68,138*). PAPase activity, measured with membrane-bound phosphatidic acid —which is probably more meaningful in terms of phospholipid synthesis (*64*)—increased before birth in both the fetal rat (*139*) and rabbit (*140*) lung. Johnston and colleagues have reported that PAPase is released from lamellar bodies together with surfactant phospholipids (*141–143*). The activity of PAPase in human amniotic fluid increases during gestation (*144*). The increase precedes the increase in the L/S ratio but is parallel to it (*145*). It has been suggested that measurement of PAPase in amniotic fluid might be used in the prediction of fetal lung maturity (*142,146*). PAPase has also been reported to be associated with surfactant in the dog lung (*147*). The relationship, if any, between the PAPase associated with surfactant and that involved in the synthesis of lung phospholipids, including surfactant, is not known.

Acyltransferase. There is a developmental increase in the activities of 1-acylglycerophosphate acyltransferase (EC 2.3.1.51) (*71*), lysolecithin acyltransferase (EC 2.3.1.23) (*71,132*) and lysolecithin:lysolecithin acyltransferase (*132*) in the fetal rabbit lung. Hallman and Raivio (*148*) and Okano and Akino (*127*) also reported increased activity of the deacylation-transacylation pathway with increasing gestational age in the rabbit and rat lung. In the fetal mouse there is no developmental change in lysolecithin acyltransferase activity but there is a sharp increase in lysolecithin:lysolecithin acyltransferase just before term (*149*).

Enzymes of Fatty Acid Synthesis. The activities of enzymes of de novo fatty acid synthesis have been reported to be unchanged (*150*) or to increase slightly (*151*) during fetal rabbit lung development. The activity of lung lipoprotein lipase, which may be involved in the uptake of fatty acids from the blood, also increases toward the end of gestation and then declines after birth in the rat (*152*).

Phospholipid Transfer Proteins. Engle et al. (*109*) reported maximum activity of a phosphatidylcholine transfer protein 2 days before term in the fetal mouse lung.

Enzymes of Phosphatidylglycerol Synthesis. Activities of enzymes involved in the synthesis of lung phosphatidylglycerol have been measured in the rabbit (*71,153,154*) and rat (*155*) during fetal and neonatal development. In both species there is an increase in phosphatidate cytidylyltransferase (EC 2.7.7.41) activity at the very end of fetal life and this continues into the early postnatal period (*153–155*). The activities of glycerophosphate phosphatidyltransferase (EC 2.7.8.5) and phosphatidylglycerophosphatase (EC 3.1.3.27) combined decreased with increasing gestational age in fetal rabbit lung homogenate (*71*). The same was true of glycerophosphate phosphatidyltransferase alone in both the homogenate and mitochondria but the activity in the microsomes increased (*153*). It has been reported that surfactant phosphatidylglycerol is synthesized in the microsomes rather than in mitochondria (*25*). This has been disputed, however (*156*). Rabbit lung microsomal phosphatidylglycerophosphatase activity increases at the end of gestation (*153*). There was an increase in the activities of rat lung homogenate glycerophosphate phosphatidyltransferase and phosphatidylglycerophosphatase at the end of gestation and in the immediate newborn period (*155*).

In summary, although there are discrepancies in the developmental profiles of the enzymes of lung phospholipid synthesis, the following general pattern does emerge. There is a developmental increase in CP-CYT activity either at the end of gestation or immediately after birth when there is a surge in surfactant production. An increase in enzyme activity might be expected before an increase in product. This, however, has not yet been demonstrated in the case of surfactant. The increase in the rate of choline incorporation into phosphatidylcholine in fetal lung slices does correlate well with increased surfactant in lung lavage (*60,71*). However, enzyme activities are measured *in vitro* under optimal conditions, while *in vivo* they may operate under suboptimal conditions. In addition, all of the enzyme studies have been carried out on whole lung and, thus, may not accurately reflect the situation in the Type II cell.

In addition to CP-CYT, increased activities of CPT and PAPase might also help to account for increased phospholipid synthesis. Finally, there are developmental increases in the enzymes of disaturated PC and phosphatidylglycerol synthesis.

Glycogen

Brandstrup and Kretchmer (*157*) reported an increase in the glycogen content of the fetal rabbit lung during the period 20 to 24 days gestation followed by a decrease after 26 days. Kikkawa et al. (158), in morphological studies on the same species, noticed the inverse relationship between glycogen and lamellar bodies —glycogen disappearance occurred at the time of lamellar body appearance—and speculated that glycogenolysis might be associated with surfactant synthesis. Biochemical studies on the fetal rat (*68,73,159*), rabbit (*60,160*) and mouse (*65*) lung have also shown a temporal relationship between glycogen depletion and increased choline incorporation into PC. The relationship may, however, not be simply that of a precursur product, since in the mouse the increase in choline incorporation preceded the decrease in glycogen rather than the opposite (*65*). Glycogen could clearly provide substrate or energy for phospholipid synthesis. A direct relationship, however, has not been demonstrated.

Influence of Hormones and Other Factors on Surfactant Production by the Fetus

Several hormones and other factors have been shown to accelerate lung maturation and stimulate surfactant production in the fetus (Table 2). One hormone, insulin, has been implicated in delaying fetal lung maturation

Table 2. Physiological agents and factors which stimulate surfactant production in the fetus and newborn.

Hormone or other agent	Species	Reference[a]
Glucocorticoids	Rabbit	(*75,162*)
	Rat	(*73,163*)
	Mouse	(*65,69*)
	Guinea pig	(*164*)
	Sheep	(*165,166*)
	Monkey	(*167,168*)
	Human	(*169,170*)
Thyroid hormone	Rabbit	(*171,172*)
	Rat	(*73*)
	Human	(*173*)
Thyrotropin-releasing hormone	Rabbit	(*174*)
Estrogen	Rabbit	(*77,175*)
	Rat	(*159*)
	Human	(*176*)
Prolactin	Rabbit	(*177*)
Corticotropin	Rabbit	(*178*)
	Sheep	(*179*)
Epidermal growth factor	Rabbit	(*180*)
	Sheep	(*181*)
Fibroblast pneumonocyte factor	Rat	(*182*)
Cyclic AMP (aminophylline)	Rabbit	(*183,184*)
	Rat	(*185*)
	Human	(*186*)
β-Adrenergic agents	Rabbit	(*187,188*)
	Sheep	(*189*)
	Monkey	(*190*)
	Human	(*191,192*)
Cholinergic agents	Rabbit	(*188,193*)
Prostaglandins	Rabbit	(*22*)
Birth	Rabbit	(*194,195*)
	Rat	(*196*)
Stress	Rabbit	(*75,178*)
	Human	(*197,198*)
Labor	Rabbit	(*70,199*)
	Human	(*200,201*)

[a] References are restricted to a maximum of two for each hormone-species combination. The choice of references does not imply that others are less important.

since infants of diabetic mothers have an increased incidence of RDS (*161*) and these infants are hyperinsulinemic.

Glucocorticoids

In 1969 Liggins (*202*) reported that dexamethasone administration to fetal lambs resulted in partial lung aeration when the animals delivered prematurely and suggested that this might be the result of accelerated surfactant appearance. This finding was quickly confirmed by deLemos et al. (*165*), who administered cortisol to fetal lambs and showed increased lung maturation by measurement of lung mechanics and lung extract surface activity. Kotas and Avery (*162*) reported similar findings in the fetal rabbit while Wang et al. (*203*) and Kikkawa et al. (*158*) extended these observations to include accelerated morphological maturation. Extensive biochemical investigations have shown that glucocorticoids increase the amount of surfactant phospholipid in lung lavage (*60,75*), increase the rate of incorporation of choline into PC and disaturated PC in lung slices (*59,60,63,163,197,204*), as well as in lung explants (*73,169*) and cells (*171*) cultured *in vitro*, and stimulate lung glycogen depletion (*60,73,205*).

The effects of glucocorticoids on enzymes of lung phospholipid synthesis have been examined in several laboratories (*59,60,63,65,69,73–75,163,204,206–211*). As in the case of the normal developmental profiles, there are discrepancies in the reported effects of glucocorticoids on individual enzymes. Choline kinase is not stimulated by glucocorticoids (*69,73,75,207*). As shown in Table 3, CP-CYT was stimulated by glucocorticoids in several *in vivo* and *in vitro* studies in the fetal rabbit, rat and mouse. In two studies, however, in the fetal rabbit (*207*) and mouse (*69*), this enzyme was not stimulated while in another study in the rabbit it was actually decreased (*211*). CPT was reported to be stimulated by glucocorticoids in an early study in the fetal rabbit (*59*). This finding was not confirmed in several subsequent studies in the same species (*60,63,75,204,209–211*). However, CPT was stimulated by glucocorticoids in *in vivo* studies on the fetal rat (*163*) and mouse (*65,69*) but not in fetal rat lung explants (*73*). Pulmonary PAPase, measured with aqueously dispersed phosphatidic acid, was stimulated by glucocorticoids in the fetal rabbit (*60,63,204*) and mouse (*65*) but not in fetal rat lung explants (*73*). Glucocorticoids did not significantly stimulate PAPase measured with membrane-bound phosphatidic acid (*204*). There is even less consistency in the reported effects of glucocorticoids on lysolecithin acyltransferase (*69,73,75,204,206,210,211*), lysolecithin: lysolecithin acyltransferase (*60,69,204,211*) and glycerophosphate phosphatidyltransferase combined with phosphatidylglycerophosphatase (*63,73,75,204,209,210*). In one study (*213*), lipoprotein lipase in adult rat lung was stimulated by dexamethasone.

Some of the discrepancies in the effects of glucocorticoids on enzymes of phospholipid synthesis may be due to species differences. There are also differences in the nature of the glucocorticoid and in the dose employed. More important factors, however, probably include variation in the experimental model, in the gestational age when the hormone is administered and in the period of exposure to the hormone. Experimental models have included glucocorticoid administration to the fetus and to the doe as well as exposure of lung explants to these hormones *in vitro*. The hormone has been administered once as well as up to several times over several days. Animals have been sacrificed from one to several days after hormone administration. Despite these variations, however, glucocorticoids consistently stimulated the rate of choline incorporation into PC (*59,60,63,65,73,74,163,204,208,209,211*), increased the amount of surfactant in lung lavage (*60,75*) or accelerated morphological maturation of the fetal lung (*209,210*) in the studies where effects on enzymes were also examined. In only two studies (*69,206*) were no other maturational effects of glucocorticoids demonstrated.

In summary, although there is conflict in the data on the effects of glucocorticoids on enzymes of phospholipid synthesis, the pattern is generally similar to that of the normal development of these enzymes. Enzymes which increase in activity during normal development also appear to be induced by glucocorticoids. These include CP-CYT, CPT, PAPase, lysolecithin acyltransferase, glycerophosphate phosphatidyltransferase and phosphatidylglycerophosphatase. Of these the strongest evidence has been obtained in the case of CP-CYT. This suggests a rate-regulatory role for CP-CYT in the lung. A similar role has been proposed for this enzyme in other systems (*56,58,214,215*). Clearly experiments are needed in which the effects of glucocorticoids on enzymes of phospholipid synthesis are examined in isolated fetal Type II cells. Such experiments might

Table 3. Effects of glucocorticoids and estrogen on fetal lung cholinephosphate cytidylyltransferase activity *in vivo* and *in vitro*.

Hormone	Species	Experimental design	Stimulation, %	Reference
Cortisol	Rabbit	Fetal injection	22	(*75*)
Cortisol	Rabbit	Explants *in vitro*	250	(*208*)
Betamethasone	Rabbit	Maternal injection	50	(*60*)
Dexamethasone	Rabbit	Explants *in vitro*	41	(*74*)
Dexamethasone	Rat	Explants *in vitro*	134	(*212*)
Dexamethasone	Mouse	Maternal injection	37	(*65*)
17β-Estradiol	Rabbit	Maternal injection	62	(*76*)
17β-Estradiol	Rabbit	Maternal injection	66	(*77*)
17β-Estradiol	Rabbit	Explants *in vitro*	39	(*74*)

distinguish between specific effects in Type II cells and those in cells unrelated to surfactant synthesis. Recently Post et al. (*216*) examined the effect of cortisol on phospholipid synthesis in Type II cells isolated from adult rat lung. Cortisol increased the rates of acetate, palmitate, glucose and glycerol incorporation into PC, disaturated PC and phosphatidylglycerol, but not into phosphatidylethanolamine, to a small but statistically significant extent. The rate of choline incorporation into total and disaturated PC was stimulated by 27–29% (*216*). Effects on enzymes were not examined.

Glucocorticoids act directly on the lung since their effects can be demonstrated in fetal lung explants (*73,169*) as well as in fetal (*171*) and adult (*216*) lung cells cultured *in vitro*. In addition, specific glucocorticoid receptors have been demonstrated in the fetal lung (*217,218*) and in adult and fetal Type II cells (*219*).

There is evidence that endogenous glucocorticoids are involved in the physiological control of fetal lung maturation (*220,221*). Metopirone, an inhibitor of cortisol synthesis, has been reported to delay lung maturation in the fetal rabbit (*222*), rat (*164*) and guinea pig (*164*). Glucocorticoids are used clinically in the prevention of RDS in human infants (*14,16,170*), although there is controversy that such use may have deleterious effects on the development of other organs (*223–227*).

Thyroid Hormone and Thyrotropin-Releasing Hormone (TRH)

Wu et al. (*172*) reported that thyroxine administration to fetal rabbits accelerated lung maturation as shown by morphology and surface activity measurement. Accelerated morphological maturation was later confirmed (*210*) and it was also shown that thyroxine increased the amount of PC in lung lavage (*125*). Smith and Torday (*171*) reported that thyroxine increased the rate of choline incorporation into PC in mixed fetal rabbit lung cells in monolayer culture. Gross et al. (*73*) reported a similar finding in fetal rat lung in organ culture. Morphological lung maturation was delayed in thyroidectomized fetal lambs (*228,229*). The L/S ratio in tracheal fluid from these animals was also lower than in that from controls (*229*). RDS is associated with low thyroid hormone levels (*230–232*). Thyroid hormone receptors have been demonstrated in fetal and adult lungs (*233,234*). Das (*151*) reported a temporal relationship between increased thyroid hormone binding and increased fatty acid synthesis in fetal rabbit lung. These data suggest a role for thyroid hormones in fetal lung maturation.

In the adult, thyroxine has also been reported to increase surfactant production. Redding et al. (*235*) reported that administration of thyroxine to adult rats increased the amount of surfactant in lung lavage and increased the number of lamellar bodies in Type II cells. Thyroidectomized animals had fewer lamellar bodies than controls (*235*). In contrast, Mason et al. (*236*) reported that thyroxine administration or thyroidectomy had no effect on the amount of disaturated PC in rat lung. Lung lavage was not examined, however. Post et al. (*216*) reported that throxine had no effect on the rate of precursor incorporation into phospholipids in isolated rat lung Type II cells.

The effect of thyroxine on enzymes of pulmonary phospholipid synthesis was examined in two studies. Gross et al. (*73*) found no change in enzyme activities in fetal rat lung explants. Rooney et al. (*210*) examined the effect of thyroxine administration to fetal rabbits on a limited number of enzymes and observed no effect. In that study, however, thyroxine was administered directly to the fetus and this administration procedure itself can stimulate fetal lung maturation (*75,173,237*). Thus, in that model, effects on enzymes could very well have been missed. Since thyroxine cannot generally cross the placenta (*238*), its effects on the fetus cannot be studied by maternal administration. Two groups sought to overcome this problem by maternal administration of TRH (*174*) and of the thyroid hormone analog 3,5-dimethyl-3′-isopropyl-L-thyronine (DIMIT) (*239*) both of which cross the placenta.

Administration of TRH to pregnant rabbits resulted in increased amounts of surfactant in fetal lung lavage (*174*). There was no effect on the rate of choline incorporation into PC, however, suggesting that the effect might have been on secretion. The mechanism of this action of TRH is not clear. There are at least three possibilities. TRH could stimulate the fetal pituitary to produce thyrotropin and this would stimulate fetal thyroid hormone production. TRH stimulates prolactin production (*240*) and there is evidence that this hormone also stimulates surfactant production. Finally, TRH could act directly on the fetal lung.

Administration of DIMIT to pregnant rabbits increased the amount of phospholipid in fetal lung lavage and increased the rate of choline incorporation into PC in fetal lung minces (*239*). It also reduced fetal lung glycogen content. It had a stimulatory effect on PAPase measured with aqueously dispersed phosphatidic acid. Other enzymes of lung phospholipid synthesis were not assayed.

Estrogen

There was early clinical evidence that estrogen is involved in maturation of the fetal lung and prevention of RDS (*241,242*). Lower estriol levels were reported in the cord blood (*243*) and first voided urine (*244*) of newborn infants with RDS compared to normal infants of the same weight and gestational age. Spellacy et al. (*176*) reported that estrogens were as effective as glucocorticoids in increasing the L/S ratio in human amniotic fluid. Shanklin and Wolfson (*245*) reported that postnatal estrogen administration lowered the incidence of RDS in humans and rabbits. On the other hand, Dickey et al. (*246*) failed to prevent RDS by administration of aqueous estrogens to women in labor. This might well have been because the hormone was administered

too late to be effective. Abdul-Karim and Prior (*247*) reported that the anti-estrogen ethamoxytriphetol (MER-25) delayed morphological maturation of the lung vasculature in fetal rabbits. This was prevented with 17β-estradiol but the effect of 17β-estradiol alone was not examined (*247*).

More direct evidence that estrogen accelerates fetal lung maturation has been recently obtained. Khosla and Rooney (*175*) reported that administration of 17β-estradiol to pregnant rabbits increased the amount of surfactant in fetal lung lavage. Subsequent studies in the same species showed that estrogen increases the rate of choline corporation into PC in fetal lung slices (*76,77*), increases the activities of fetal lung CP-CYT (Table 3) and lysolecithin acyltransferase (*76*), decreases the glycogen content of the fetal lung (*160*) and accelerates its morphological maturation as determined by both light and electron microscopy (*160*). Some of these effects of estrogen have also been demonstrated in explants of fetal rat (*159*) and rabbit (*74*) lung. This suggests that the effect of estrogen is directly on the lung. Estrogen receptors have been reported in adult rat (*248*) and fetal guinea pig (*249*) lung. Recent studies, however, in the human (*250*) and rabbit (*74*) have shown that the estrogen binder in the fetal lung is not the classical estrogen receptor. The role, if any, of the estrogen binder in mediating the effects of estrogen in the fetal lung remains to be established.

In humans, estrogen levels increase during pregnancy (*251*). The rise in plasma estrogens appears to precede the increase in the amniotic fluid L/S ratio (*252*). It is possible that estrogens are involved in the physiological regulation of fetal lung maturation but there is as yet no direct evidence in support of this. Possible use of estrogens to prevent RDS in humans is unlikely because of the known association between diethylstilbestrol in pregnancy and genital cancer in the offspring.

Prolactin

There have been a number of recent reports suggesting a role for prolactin in fetal lung maturation. Hauth et al. (*252*) reported that, in humans, cord plasma prolactin increased with increasing gestational age and preceded the developmental increase in the L/S ratio in amniotic fluid. A similar relationship between plasma prolactin and tracheal fluid surfactant exists in the fetal lamb (*253*). A correlation between cord blood prolactin levels and the incidence of RDS has also been reported (*252,254,255*). Amniotic fluid prolactin levels correlated negatively with the L/S ratio, however (*256*).

More direct evidence for a role for prolactin was provided by Hamosh and Hamosh (*177*), who administered ovine prolactin to fetal rabbits and reported increased lung levels of total phospholipid, PC and disaturated PC. Preliminary data from Gluck's laboratory (*257*) suggested that prolactin stimulates PC and phosphatidylglycerol synthesis in A549 Type II cells. There is also evidence for a prolactin receptor in fetal monkey lung (*258*). On the other hand, two groups have failed to confirm the finding of Hamosh and Hamosh (*177*). Ballard et al. (*253*) administered prolactin to fetal rabbits in experiments very similar to those of Hamosh and Hamosh (*177*) but found no change in lung total phospholipid or disaturated PC and no change in the rate of choline incorporation into PC in lung minces. The same group found that prolactin had no effect on fetal lamb lung maturation (*253*). Van Petten and Bridges (*259*) reported that prolactin had no effect on fetal rabbit lung maturation as determined by pressure volume relationships. Clearly, further work is needed if a role for prolactin in surfactant production is to be established.

Other Hormones and Growth Factors

Sundell et al. (*179*) infused fetal lambs with corticotropin (ACTH) and demonstrated accelerated lung maturation by morphological criteria. Plasma cortisol levels were elevated and it is likely that the ACTH effect was mediated by cortisol. However, a direct effect of ACTH on the fetal lung is also possible (*178*).

Stahlman's group reported that epidermal growth factor accelerates maturation of the fetal rabbit (*180*) and lamb (*181*) as shown by morphology and lung mechanics.

Smith (*260*) reported that a factor from fetal lung fibroblasts (fibroblast-pneumocyte factor, FPF) mediates the effect of cortisol on fetal Type II cells. In the absence of fibroblasts pure fetal Type II cells respond poorly to cortisol (*260*). Administration of partially purified FPF to fetal rats resulted in increased amounts of lung disaturated PC and phosphatidylglycerol and an increased rate of choline incorporation into pulmonary disaturated PC (*182*).

Smith et al. (*261*) also reported that serum from pneumonectomized rabbits stimulated the rate of thymidine incorporation into DNA in human fetal Type II cells. The active agent was reported to be a somatomedin-like compound. Effects on phospholipid synthesis or secretion were not reported.

Cyclic AMP (cAMP)

Administration of aminophylline (a phosphodiesterase inhibitor which increases endogenous cAMP levels) to pregnant rabbits has been shown to have the following effects on the fetal lung: it increases the amount of phospholipid in lavage (*183,184,262*); it increases the rate of precursor incorporation into phospholipids (*263,264*); it decreases glycogen content (*264*); and it accelerates maturation as determined by measurements of lung mechanics (*183,184,262*). Hallman (*265*) also reported that intraperitoneal administration of cAMP to preterm rabbits at cesarean section delivery increased the amount of surfactant in lung lavage. In a human study, antepartum aminophylline was reported to lower the incidence of RDS (*186*).

The effects of cAMP have also been examined *in vitro*. In fetal rat lung in organ culture, cAMP (*185*), aminophylline (*185*) and caffeine (*73*), another phosphodiesterase inhibitor, increased the rate of choline incorporation into PC. In the same model both cAMP and aminophylline decreased glycogen content and inhibited glycogen synthase (*266*). cAMP has also been reported to increase the rate of choline incorporation into total and disaturated PC in A549 Type II cells (*267*). Incubation of preterm fetal rabbit lung slices with cAMP has been reported to increase the rate of precursor incorporation into phosphatidylglycerol (*265*).

These studies suggest that cAMP may stimulate surfactant synthesis. Since cAMP is known to be involved in the mediation of the action of β-adrenergic agonists and such agonists are known to stimulate surfactant secretion (see below) clearly cAMP is also involved in the secretion of surfactant. Barrett et al. (*263*) reported that cortisol inhibited fetal rabbit lung phosphodiesterase activity and increased cAMP levels and speculated that cAMP mediates the effect of glucocorticoids on fetal lung maturation. In addition to cAMP, cyclic GMP has also been reported to be involved in surfactant release (*268*).

β-Adrenergic Agonists

Early clinical data (*191*) suggested that administration of isoxsuprine to pregnant women to delay labor resulted in a reduced incidence of RDS in premature newborns. Similar findings were reported with ritodrine (*269*) and terbutaline (*192*). Several studies have shown that administration of isoxsuprine to pregnant or fetal rabbits increased fetal surfactant production (*187,270–273*). Isoxsuprine also stimulated surfactant production in the fetal monkey (*190*). Epinephrine had a similar effect in the fetal rabbit (*188*) and lamb (*189*). β-Adrenergic agents also stimulated surfactant production in the adult rabbit (*274*) and rat (*275*). The effect of β-agonists was blocked with propranolol (*187,188,274,275*). In many of these studies the β-adrenergic agent was administered for a relatively short period (a few hours at most). Thus, the increased surfactant production was attributed to stimulation of secretion rather than synthesis. Kanjanapone et al. (*276*) reported, however, that isoxsuprine increased the rate of choline incorporation into disaturated PC in fetal rabbit lung slices, suggesting an effect on synthesis. Abdellatif and Hollingsworth (*188*) also suggested that epinephrine increased synthesis secondary to increased secretion.

There is evidence from studies with lung slices and isolated Type II cells that β-adrenergic agents stimiulate PC secretion. Marino and Rooney (*199*) reported that secretion of surfactant increased during the period 29–31 days gestation in fetal rabbit lung slices. Secretion was stimulated by terbutaline at 30 days and by labor at 31 days. The labor-induced stimulation was abolished by propranolol. They concluded that the effect of labor is at least partly mediated by catecholamines which are known to increase at birth (*277*). it is also noteworthy that β-receptors increase toward the end of gestation in fetal rabbit lung (*278,279*) at the same time as the increase in surfactant secretion (*199*). β-Receptor concentrations were increased by glucocorticoids in fetal rabbit lung (*278*), in adult rat lung (*280*) and in human lung cells cultured *in vitro* (*281*).

Dobbs and Mason (*282*) and Brown and Longmore (*283*) reported that β-adrenergic agonists stimulated disaturated PC secretion in Type II cells isolated from adult rat lung. These studies show that β-adrenergic agonists act directly on the Type II cell to stimulate surfactant secretion.

Cholinergic Agonists

Cholinergic agents have also been reported to stimulate surfactant production. Goldenberg et al. (*284*) showed in a morphological study that pilocarpine stimulated surfactant secretion in adult rats. Subsequent studies showed that pilocarpine increased the amount of surfactant in adult lung lavage and that this effect could be blocked by atropine (*275,283,285*). Atropine was reported to block the ventilation-induced increase in alveolar phospholipids in adult (*286*) and newborn rabbits (*195*). In the fetus, pilocarpine has been reported to stimulate surfactant production as determined by pressure volume studies (*187,193*) and to accelerate morphological lung maturation (*287,288*).

Dobbs and Mason (*282*) and Brown and Longmore (*283*) reported that cholinergic agonists did not stimulate disaturated PC secretion in isolated adult rat Type II cells. Brown and Longmore (*283*) showed that cholinergic receptors were functional in these cells so lack of response cannot be attributed to receptor loss or damage during the isolation procedure. Other perturbations during culture, however, cannot be ruled out. Abdellatif and Hollingsworth (*188*) reported that the muscarinic agonist, oxotremorine, stimulated surfactant release in intact newborn rabbits but not in isolated perfused lungs from the same animals. The effect of oxotremorine was blocked by adrenalectomy (*188*). The effects of both pilocarpine (*187*) and oxotremorine (*188*) were blocked by the β-antagonist propranolol. These data suggest that cholinergic agonists do not act directly on the lung or on Type II cells and that their effect in whole animals is mediated by catecholamines which are released by the adrenal medulla in response to the cholinergic stimulation. This, however, does not explain the findings of Brown and Longmore (*283*) who reported that pilocarpine did stimulate surfactant release in isolated perfused adult rat lung, and of Pysher et al. (*289*), who reported that pilocarpine stimulated PC release in fetal rat lung explants. It is possible that fetal and adult lung respond differently to cholinergic agents. Abdellatif and Hollingsworth (*188*) studied isolated perfused newborn rabbit lungs while Brown and Longmore (*283*) studied those from adult rats.

Delahunty and Johnston (*290*) reported that carbamylcholine stimulated PC release in adult, but not fetal, hamster lung slices. Marino and Rooney reported that pilocarpine did not stimulate surfactant release in newborn rabbit lung slices (*22*) and that atropine did not block the labor-induced stimulation of surfactant release in the same model (*199*).

Prostaglandins

Marino and Rooney (*22*) reported that prostaglandin E_2 stimulated surfactant secretion in newborn rabbit lung slices. Indomethacin and flufenamic acid, inhibitors of prostaglandin synthesis (*291*), inhibited secretion (*22*). Indomethacin also abolished the labor-induced stimulation of surfactant secretion in the same model (*199*). Pulmonary prostaglandin synthesis has been reported to increase with increasing gestational age in the fetal rabbit (*292*) and lamb (*293*). Prostaglandins are also known to increase in labor (*294*). These data, therefore, suggest a physiological role for prostaglandins in surfactant production by the neonatal lung.

Prostaglandins may also be involved in surfactant production in adults. Oyarzun and Clements (*274*) reported that inhibitors of prostaglandin synthesis inhibited the ventilation-induced increase in alveolar phospholipids in adult rabbits. Anderson et al. (*295*) reported that prostaglandin $E_{2\alpha}$ stimulated PC release in adult rat Type II cells. Colacicco et al. (*296*) reported that prostaglandin E_2 and $F_{2\alpha}$ stimulated the rates of choline and palmitate incorporation into PC in A549 Type II cells.

Maternal Diabetes

The infant of the diabetic mother (IDM) has an increased incidence of RDS (*161*). Glucose freely crosses the placenta from mother to fetus making the fetus hyperglycemic. In response to this situation the fetal pancreas produces insulin so the fetus is also hyperinsulinemic.

IDM models have been developed in a number of laboratories. These include fetuses of the alloxan-diabetic rabbit (*297,298*) and streptozotocin-diabetic rat (*299,300*) and rhesus monkey (*301*). Lungs from fetuses of diabetic rats and rabbits were less mature than those from normal animals as determined by morphology (*301,302*), pressure volume studies (*297,298*), and surface activity measurement (*298*). They also contained more glycogen than controls (*299,303*). Lung lavage from fetuses of alloxan diabetic rabbits contained less disaturated PC than did that from controls (*297*). Tyden et al. (*300*) reported reduced rates of choline incorporation into PC in fetal lung slices from streptozotocin-diabetic rats. The Harvard group, however, reported no change in the disaturated PC content of lung lavage (*298*) or in the rate of choline incorporation into PC or disaturated PC in lung slices (*303*) in their alloxan-diabetic rabbit model. There were extremely wide ranges in their lung lavage disaturated PC values, however, and it is possible that differences were missed (*298*).

The above animal models are not exact replicas of the human IDM. The human IDM is both hyperinsulinemic and hyperglycemic and is also larger than normal. Although the animal models have elevated fetal blood glucose levels, fetal insulin levels are not elevated and the fetuses are often smaller than controls (*297,298,300*). It is possible that the observed changes in fetal lung maturation in the animal models are due to the hyperglycemia alone. The phospholipid content and composition of lung lavage from fetal rhesus monkeys who were hyperinsulinemic but not hyperglycemic was the same as that from normal animals (*190*). The effect of hyperinsulinemia together with hyperglycermia on fetal lung maturation remains to be determined.

Rhoades et al. (*304*) studied newborns from streptozotocin-diabetic rats. In contrast to the above models, these animals were significantly smaller than controls and were also hypoglycemic. They were probably stressed. Total lung phospholipid was increased, PC was unchanged but disaturated PC was decreased. Lung choline kinase, CP-CYT and CPT activities were increased. CPT activity was 3.5-fold higher in the fetuses from the diabetics than in those from the controls. This enzyme was also reported to be increased by stress in the fetal rabbit (*75*).

There is evidence that insulin and cortisol have opposite effects on the fetal lung. It is possible that insulin interferes with the physiological action of cortisol in normal lung maturation. Sosenko et al. (*305*) reported that the delay in lung maturation in fetuses from alloxan-diabetic rabbits could be abolished by maternal administration of cortisol. Smith et al. (*306*) reported that insulin antagonized the action of cortisol in stimulating choline incorporation into PC in fetal rabbit lung cells *in vitro*. Insulin alone slightly stimulated choline incorporation (*306*), but this is probably attributable to the known anabolic action of this hormone. Antagonism of the action of glucocorticoids by insulin was also reported by Gross et al. (*307*), who showed that insulin abolished the dexamethasone-induced stimulation of acetate incorporation into disaturated PC in fetal rat lung explants. This effect of insulin may be at least partly expressed at the CP-CYT level. Dexamethasone stimulated CP-CYT by 134% but addition of insulin reduced this by half (*212*). In the same model, insulin delayed morphological maturation of the fetal lung and increased lung glycogen content (*307*)—effects opposite to those of dexamethasone.

Neufeld et al. (*308*) reported that addition of insulin to the medium decreased the rate of precursor incorporation into PC in fetal rabbit lung slices after 90 min incubation. It is difficult to determine if this observation has any physiological significance.

Moxley and Longmore (*309*) reported that insulin increased, and diabetes decreased, the rate of glucose incorporation into surfactant and nonsurfactant lipid in

the perfused adult rat lung. These findings may again only reflect the anabolic action of insulin and probably have little relevance to the IDM situation.

Finally, as in the case with other hormones, specific insulin receptors have been reported in adult rat lung (*310*) supporting the notion that insulin has a direct effect on the lung.

Other Factors Which Influence Surfactant Production in the Fetus and Newborn

Birth and Labor. Birth and labor have been reported to stimulate surfactant production. There was a 2- to 4-fold increase in the phospholipid content of lung lavage from newborn rabbits delivered by cesarean section prior to labor at 29–31 days gestation (*70,194*). A similar finding was reported by Lawson et al. (*195*) who measured surface activity. Weinhold et al. (*196*) and Stewart-DeHaan et al. (*311*) reported an increased rate of precursor incorporation into lung PC in premature newborn rats delivered by cesarean section. As discussed earlier, there are increases in the activities of enzymes of pulmonary phospholipid synthesis immediately after birth.

It has long been recognized that there is a higher incidence of RDS among premature newborn infants delivered by cesarean section without labor than among those delivered either vaginally or by cesarean section after labor at the same gestational age (*14,200,312*). The protective effect of labor is more apparent at 37–38 weeks than at 31–33 weeks (*312*), presumably because labor stimulates surfactant release and insufficient surfactant is stored at the earlier gestational age. Recent studies have shown that labor increases the L/S ratio and PC content of human amniotic fluid (*201,313–315*). Animal studies have also shown that labor increases surfactant production (*70,199*). Studies with newborn rabbit lung slices showed that labor stimulated surfactant secretion rather than synthesis (*199*).

There is evidence that the effects of birth and labor on surfactant production are mediated by a number of the hormones and other pharmacological agents discussed previously. For instance, the increase in surfactant production at birth can be prevented with atropine (*194,195*). There is evidence that the effects of labor are mediated, at least in part, by prostaglandins and catecholamines (*199*).

Stress. Stress has also been reported to stimulate surfactant production. Injection of fetal rabbits with saline, while the doe is under general anesthesia, has been shown to increase surfactant production (*75,178,237*). Although glucocorticoids are known to increase in stress, they do not appear to mediate this effect (*60*).

Sex. Recent studies in both humans (*316*) and rabbits (*317*) have shown that the lungs of female fetuses mature earlier than those of males. Female fetal lungs also respond better to glucocorticoids than those of males at the same gestational age (*318–320*).

Surfactant in Adult Human Lung Disease

Petty et al. (*321*) isolated surface-active material from the lungs of a man who developed adult respiratory distress syndrome (ARDS) after massive trauma and hemorrhagic shock. When compared to normals, there were differences in surface compressability properties and in lipid/protein ratios (*321*). Subsequently the same group (*322*) confirmed the difference in surface properties in bronchoalveolar lavage from additional patients with ARDS. Decreased dipalmitoyl-PC levels were also reported in lungs of patients with shock lung (*323*).

Nonphysiological and Toxic Agents Which Influence Surfactant Production in the Fetus and Adult

Glass et al. (*324*) reported absence of RDS in premature infants of heroin-addicted mothers. Taeusch et al. (*325*) reported that heroin administration to pregnant rabbits accelerated fetal lung maturation. However, heroin had no effect on the rate of choline incorporation into PC in cultured fetal rabbit lung cells (*171*). Thus, heroin may act indirectly on the lung possibly via agents released in response to stress.

Metabolite VIII (NA872) of Bisolvon (bromhexine hydrochloride) has been reported to stimulate surfactant production in a number of studies (*221*).

Togari (*326*) reported that injection of fetal rabbits with CDPcholine increased surfactant production. Whether the CDPcholine provides substrate for PC synthesis or the choline moiety is converted to acetyl choline and this stimulates surfactant production is not known.

Colchicine and vinblastine have been reported to inhibit PC secretion in newborn rabbit (*22*) and adult hamster (*327*) lung slices as well as adult rat Type II cells (*328*), suggesting a role for microtubules in surfactant secretion. That microfilaments are also involved in this process is suggested by the finding that surfactant secretion is inhibited by cytochalasin B (*22*).

Karotkin et al. (*329*) reported that maternal phenobarbital administration inhibited surfactant production in the fetal rabbit. Cadmium has also been reported to reduce lung PC and increase RDS in rats (*330*). Aflatoxin B inhibited pulmonary PC synthesis in the fetal rat (*331*).

Many agents have been shown to alter the amount of surfactant in the adult lung (*332*). Exposure of adult rabbits to ozone has been reported to decrease the rate of fatty acid incorporation into lung tissue PC but not into that in lung lavage (*333*). It was concluded that ozone inhibited PC synthesis but stimulated its rate of release into the alveoli. Ozone was also reported to change the fatty acid composition of rat lung lavage PC (*334*).

Hyperoxia has been reported to lead to less surfactant in the rat (*335*), to decreased synthesis of lung PC in the rat (*336*) and rabbit (*337*) and to slightly altered lung lipid fatty acid compositions in the rabbit (*338*). Changes in lung surfactant, however, appear to be secondary to cellular changes (*339–342*). There are species differences in susceptibility to oxygen damage (*343*).

Nitrogen dioxide increased the amount of phospholipid in the adult rat lung (*344*). The greatest increase was in the disaturated PC and phosphatidylglycerol fractions. The rate of palmitate incorporation into PC was also increased (*344*). In another study (*345*), nitrogen dioxide was reported to cause small changes in the fatty acid composition of adult rat lung phospholipids.

Cook and Webb (*346*) reported decreased surface activity in bronchial washings from chronic smokers. Finley and Ladman (*347*) reported a similar finding and showed that lipid content rather than composition was altered. In a more recent study, Low et al. (*348*) reported little difference between smokers and nonsmokers in lung lavage phospholipid. There was no difference in phospholipid concentration but the phospholipid/protein ratio was lower in the smokers (*348*). Pre et al. (*349*) found no difference between smokers and nonsmokers in the PC concentration or in the PC/protein ratio in bronchoalveolar lavage fluid. Exposure of rats to cigarette smoke led to less surfactant in lung lavage (*350*). Lower surfactant levels were also reported in dogs who were exposed to smoke from burning wood or kerosene. (*351*).

Inhalation of gasoline, trichloroethylene or carbon tetrachloride led to lower amounts of surfactant in rat lung lavage (*350*). Chronic exposure of rats to hydrochloric acid has been reported to decrease the rate of choline incorporation into lung PC (*352*). Sulfuric acid fumes produced small changes in the surface activity of rat lung (*353*). Dusts, such as quartz, silica, and chrysotile asbestos, have been reported to increase the amount of total and surfactant phospholipid in the lung (*354–358*). Surface activity, however, was decreased on exposure to silica (*359*).

Inhalation anesthetics have been reported to have little effect on surfactant in the concentrations usually employed (*360–362*). Methoxyflurane, however, did lower surface activity (*363*).

Ethanol consumption has been reported to lower the rate of lung PC synthesis in the rat (*364*). It also reduced the surface activity of lung extracts (*365*).

Paraquat injection was reported to decrease the amount of PC in lung lavage and to decrease the rate of choline incorporation into lung PC in the rat (*366*).

Effects of radiation on surfactant have also been examined (*367–373*). Rubin et al. (*372*) reported an increase in alveolar disaturated PC, a decrease in lung tissue PC and decreased numbers of lamellar bodies in irradiated mice. Radiation also increased the amount of lung lavage phospholipids in mice (*368*) and rabbits (*367*). However, surface activity was reduced (*367,369,371*). The amount of phosphatidylglycerol in lung lavage was also reduced in irradiated mice (*370*). It is possible that radiation causes cell death leading to release of nonsurfactant lipids into the alveoli.

Work in the author's laboratory was supported by grants HD-10192 and HD-11018 from the National Institute of Child Health and Human Development.

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