The ins and outs of respiratory distress syndrome in babies and adults

Respiratory distress syndrome is an important cause of morbidity and mortality in babies and in adults. In the newborn it is usually caused by immaturity of the lungs and mainly occurs in preterm babies. However, maternal diabetes, elective caesarean section, birth asphyxia, and inborn errors of surfactant metabolism may initiate the syndrome in babies born at term [1] and we will therefore use the term 'neonatal respiratory distress syndrome' (NRDS). In adults respiratory distress syndrome (ARDS) is initiated by many causes [2,3,4]. They can be divided into two main groups: (a) direct toxic insults to the lung such as inhalation of smoke, aspiration of gastric contents, and oxidative damage by paraquat intoxication; and (b) generalised or distant primary insults such as shock, sepsis and pancreatitis which trigger lung damage through an inflammatory response [2,3,4]. The pathogenic mechanisms of NRDS and ARDS therefore appear to be different, but there are important similarities; furthermore, ARDS can also develop in the newborn baby [5].

Three major mechanisms play an interlinked role in NRDS and ARDS: decreased surfactant, pulmonary oedema, and toxicity of reactive oxygen species (ROS). We will use input/output models to analyse these three mechanisms and their interaction in respiratory distress syndrome (Fig 1). We will develop a framework which is currently valid for all age groups and which will allow integration of new factors into the pathogenic pathways [6].

Pathophysiological disturbances in respiratory distress syndrome

Atelectasis due to surfactant deficiency is the dominant feature in the baby, and pulmonary oedema due to increased membrane permeability is the dominant feature in the adult. Reactive oxygen species, as a primary cause or as a complication of therapy, may aggravate both problems in NRDS and ARDS. Atelectasis and pulmonary oedema cause respiratory distress by decreasing lung compliance and impairing gas exchange. The diffusion deficit and ventilation perfusion mismatch (intrapulmonary shunting) result in hypoxaemia, hypercapnia, and acidosis. These factors induce pulmonary arteriolar vasoconstriction and thus pulmonary hypertension; in the newborn this can cause right-to-left extrapulmonary shunting across the patent ductus arteriosus and foramen ovale. Disturbances in the metabolism of the eicosanoids (prostaglandins, thromboxanes, leukotrienes), platelet aggregating factor, and ROS can aggravate the pulmonary arteriolar vasoconstriction. The aim of therapy in both age-groups is to provide an adequate oxygen supply to the tissues. Oxygen and ventilatory support are often required and oxygen toxicity and barotrauma are potential complications. Pulmonary vasodilator therapy with β adrenergic blockers may be necessary and may induce systemic hypotension [7,8].

Pathogenesis of alveolar atelectasis and oedema

Intra-alveolar surfactant pool (Fig 2)

Surfactant deficiency is the major factor in the pathogenesis of NRDS in the preterm baby, and also plays a role in ARDS [9]. Type II pneumocytes synthesise pulmonary surfactant, a lipid-protein complex consisting mainly of phospholipids and specific surfactant proteins (SP-A, SP-B, SP-C, SP-D). The surfactant is condensed into highly structured lamellar bodies which are exocytosed into the alveolar space. There they unravel to form the tubular myelin structures from which surfactant then spreads into the phospholipid monolayer of the air-liquid interface. The dominant surface active component at all ages is phosphatidylcholine, containing mainly saturated palmitic acid (C16:0), with smaller amounts of unsaturated fatty acids eg oleic (C18:1), linoleic (C18:2), and arachidonic (C20:4) acid [10]. *In utero* the phosphatidylinositol level falls as gestation advances and is proportionally replaced by phosphatidylglycerol. Surfactant phospholipid and protein synthesis depends on an adequate supply of nutrients such as fatty acids, choline, inositol, and amino acids. Synthesis is stimulated by cortisol and thyroxine, and inhibited by insulin and testosterone [11]. Release of surfactant into the alveolar pool is triggered by β adrenergic stimulation but inhibited by SP-A. *In utero,* cortisol induces development of the β adrenergic receptors on the type II cells, and the surge in the baby's adrenaline level during the stress of a normal vaginal delivery triggers the release of surfactant. SP-B and SP-C help adsorption and spreading of the surfactant film into the air-

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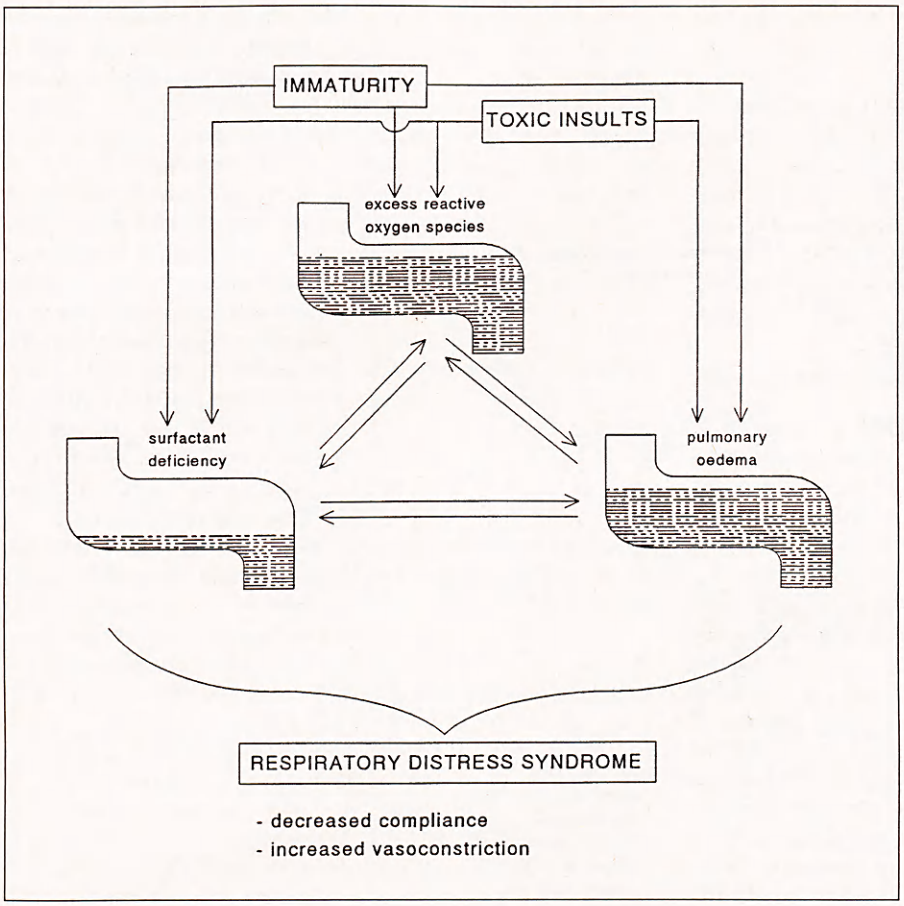

Fig 1. *Schematic presentation of the three factors that contribute to the pathogenesis of respiratory distress syndrome (RDS): a decreased pool of surfactant, an increased pool of pulmonary oedema, and an increased pool of reactive oxygen species (ROS).* Each pool is represented as an input/output model, which is described in detail in the text and in the other figures. Immaturity, resulting in neonatal RDS, and toxic insults, resulting in adult RDS, directly influence the pools of surfactant, oedema, and ROS. The complex interactions between the pools, which play a role in both neonatal and adult RDS, are also shown.

liquid interface. There is constant recycling of this alveolar pool and SP-A stimulates uptake of surfactant by the type II cells. Very little surfactant is lost into the capillaries and lymphatics, or via the airways and macrophage degradation.

Factors that may lower the active surfactant pool in RDS

Dilution of surfactant

The concentration of active alveolar surfactant can be diluted by excess fluid in the alveolar space. The resulting decrease in lung compliance contributes to the transient respiratory distress seen in babies with 'wet lungs' after caesarean sections (see section on alveolar fluid). Lung oedema in ARDS may also produce a similar effect [12]. However, decreased synthesis and/or increased inactivation are the main causes of decreased surfactant activity in both NRDS and ARDS.

Inadequate production of surfactant

Genetic regulation: genetic disturbances in surfactant synthesis may explain the cases of NRDS that occur in apparently mature babies. In a mutant rat strain, impaired glycogen mobilisation decreases surfactant production [13], and in man an inherited deficiency of SP-B has recently been reported in three full-term siblings with severe NRDS [14]. Inhibition of gene expression may also interfere with surfactant production. Macrophages produce tumour necrosis factor (TNF) and this cytokine, which plays many roles in ARDS, decreases the expression of SP-A and SP-B by inhibiting their messenger RNA [15]. Bronchoalveolar lavage specimens reflect the disturbed surfactant synthesis in ARDS patients. Phospholipid composition in ARDS resembles that of the immature baby (decreased phosphatidylcholine and phosphatidylglycerol, increased phosphatidylinositol and decreased SP-A and SP-B) [9].

Hormonal control: the production of surfactant phospholipids and proteins is regulated by various hormones [11,16]. The rise in cortisol in late gestation induces surfactant phospholipid and protein synthesis. Inadequate stimulation of surfactant synthesis by cortisol is a major factor in the pathogenesis of NRDS in preterm babies. Lower thyroxine levels are present in NRDS, which occurs more frequently in babies with congenital hypothyroidism. Clinical trials using maternal administration of combined betamethasone and

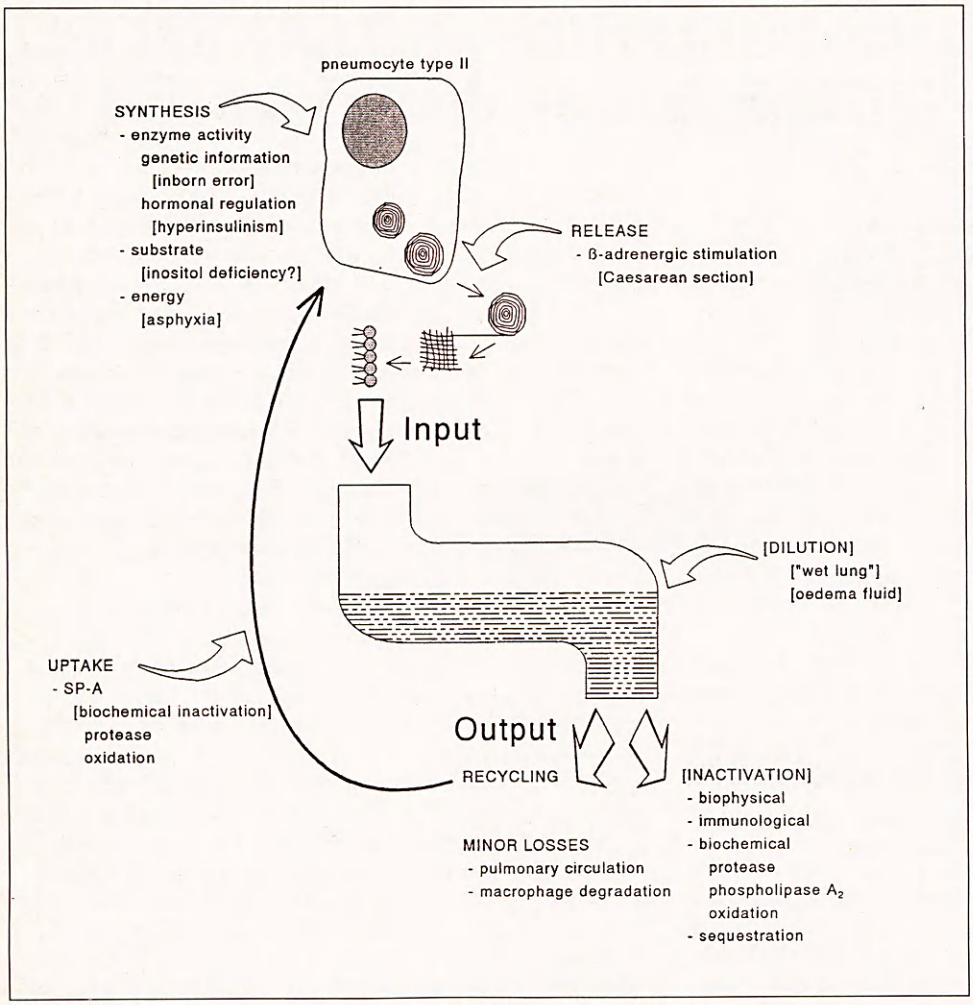

Fig 2. *Input/output model showing physiological mechanisms and pathological factors (in square brackets) influencing the pulmonary pool of active surfactant.* Input of surfactant by a pneumocyte type II is shown, ie factors influencing surfactant synthesis and release. The conversion of the lamellar bodies via the tubular myelin network to the phospholipid film is shown. Output of active surfactant occurs *via* recycling, inactivation, and minor losses. The concentration of surfactant can also be decreased by dilution.

thyrotropin releasing hormone, which pass easily through the placenta, are being performed [17]. Insulin and testosterone both inhibit surfactant production. Babies of diabetic mothers have a greater incidence of NRDS because they develop secondary hyperinsulinism *in utero* and NRDS is more frequently seen in male infants. We are not aware of any evidence suggesting that hormonal control of surfactant synthesis may be disturbed in ARDS.

Nutrient supply: in animals, a maternal diet deficient in calories or essential fatty acids or inositol decreases surfactant production and reduces lung compliance of the newborn [18]. These findings have not yet been applied during human pregnancy, but postnatal supplementation of the babies' diets with inositol does decrease the severity of NRDS [19]. Dietary variations could also influence the quantity and quality of surfactant in the adult and play a role in the therapy of ARDS.

Energy supply: asphyxia neonatorum has long been recognised as a predisposing factor in NRDS [20]. Anoxia decreases the supply of adenosine triphosphate (ATP) and metabolic and respiratory acidosis can also interfere with surfactant synthesis. However, with adequate ventilation, surfactant synthesis recovers rapidly. In the asphyxiated lamb, lung compliance and phosphatidylcholine pool sizes are normal when measured after resuscitation [20]. This may explain why rapid resuscitation of asphyxiated babies also appears to diminish the severity of NRDS [21]. NRDS occurring after asphyxia may therefore call for a more complex explanation. After ventilation, increased ROS production due to oxygen therapy and increased xanthine oxidase activity may play a role. ROS can inhibit ATP and protein synthesis and decrease incorporation of choline and palmitic acid into phospholipid [22,23]. These latter mechanisms could also play a role in ARDS.

Impaired release of surfactant into alveolar space

The poorly developed β adrenergic receptors on the type II cells of the preterm baby may result in decreased surfactant release at birth. Ritodrine, a β adrenergic agent used to inhibit premature uterine

activity, decreases the incidence of NRDS [24]; on the other hand, the impaired adrenaline release in babies after an elective caesarean section increases the incidence of NRDS [16] (see section on alveolar fluid). Inflation of the lungs also induces surfactant release [18], and this may explain why elective intubation immediately after birth decreases the ventilatory requirements of preterm babies with NRDS [21]. Impaired release of surfactant could also occur in ARDS. The number of β adrenergic receptors in mature lung membranes can be decreased by the highly toxic 4-hydroxynonenal which is an end-product of lipid peroxidation [4]. Thus, impaired release is another mechanism whereby excess ROS could impair surfactant metabolism [25].

Excessive loss of surfactant

Inactivation of alveolar surfactant: biophysical inactivation may occur if leaked plasma proteins inhibit phospholipid adsorption into the air-liquid interface by competing for the available space [26].

Autoimmune processes initiated by leakage of surfactant proteins from the damaged lung into the circulation may also contribute to RDS in the baby and adult [27]. SP-B is immunogenic and its monoclonal antibody interferes with tubular myelin formation *in vitro* and causes severe RDS in animals. The latter effect may be due to direct disturbance of surfactant function, but neutrophil-induced damage after immune complex complement activation may also play a role. SP-B antibodies have been detected in the first week after birth in babies who had not been treated with exogenous surfactant.

Biochemical interference may occur due to the presence of aberrant fatty acids, digestion of phospholipid and protein, and peroxidation. Atelectasis after meconium aspiration may be due not only to bronchiolar obstruction, but also to surfactant inactivation by free fatty acids in meconium [28]. In ARDS and NRDS, degradation of surfactant proteins by proteases [29, 30] and of phospholipids by phospholipases [31] may also be important. Neutrophil proteases may digest surfactant proteins [3]. Decreased phosphatidylcholine and increased phospholipase A_2 are found in the bronchoalveolar lavage in ARDS associated with acute pancreatitis, and bacteria can produce phospholipase C [31]. The oxidative mechanisms of surfactant inactivation are discussed in the section on ROS.

Sequestration by fibrin/hyaline membrane: the hyaline membrane in the alveolar space, produced by conversion of leaked fibrinogen to fibrin, is a typical histological finding in RDS in the baby and adult. It may play a role in the pathogenesis by sequestrating the surfactant within the fibrin strands. Plasminogen is present in normal plasma and is converted to the fibrinolytic enzyme plasmin when activators are released from tissues. The concentration of plasminogen is low in babies with NRDS [32], and low concentrations of its activators are found in ARDS [3].

Diminished uptake of surfactant: SP-A stimulates phospholipid uptake by type II cells. Inactivation of the protein by antibodies, neutrophil proteases, and oxidation will interfere with uptake and recycling of surfactant. In RDS damage of alveolar capillary membranes by ROS and proteases may also increase the losses of surfactant phospholipids and proteins into the circulation.

Intra-alveolar fluid pool (Fig 3)

Pulmonary oedema is the major factor in the pathogenesis of ARDS, and evidence is accumulating that it plays a role in NRDS. Hydrostatic and osmotic forces, alveolar-capillary permeability, and lymphatic drainage regulate the movement of fluid in and out of the lungs [33,34]. Hydrostatic pressure of the blood drives water through the endothelial cell junctions into the interstitial space. The endothelial cell-to-cell junctions are relatively permeable and allow water, solutes, and some proteins to pass through into the interstitial space. In contrast, the alveolar epithelium is impermeable to water and proteins and normally very little fluid moves into the alveolar space. The interstitial fluid is reabsorbed into the capillaries at the venous end by the colloidal osmotic gradient or drains into the lymphatics [34]. Protein adhesion molecules cross the phospholipid membrane in the cell wall and attach to opposing molecules of an adjacent cell to form 'tight junctions' (Fig 3). These tight junctions form a network of strands, and a fibre matrix fills the space between these strands. The tight junction network of the epithelium is much denser than that of the endothelium, making the former cells more impermeable to water and proteins than the latter. The adhesion molecules link the cells and oppose the contractile force created by intracellular actin/myosin microfilaments in the complex cytoskeleton. The permeability of the membrane will depend on the balance between the two opposing forces 'opening or closing pores' in the tight junctions. An increase in intracellular calcium triggers contraction, while an increase in cyclic AMP after β adrenergic stimulation induces relaxation of the cytoskeleton. Various mechanisms in RDS can influence the adhesion molecules and the cytoskeleton and thus change the permeability of the alveolar capillary barrier.

Active electrolyte transport mechanisms also normally influence fluid movements in the lung [33,34]. Fluid fills the lungs during fetal life and is essential for normal growth and development of the lungs. Active secretion of chloride ions (Cl^-) into the alveolar space, which creates a positive osmotic gradient, drives this transepithelial flow of fluid. This active production of intra-alveolar fluid ceases at birth. Cyclic AMP released by the adrenaline surge activates a Na^+,K^+ ATPase

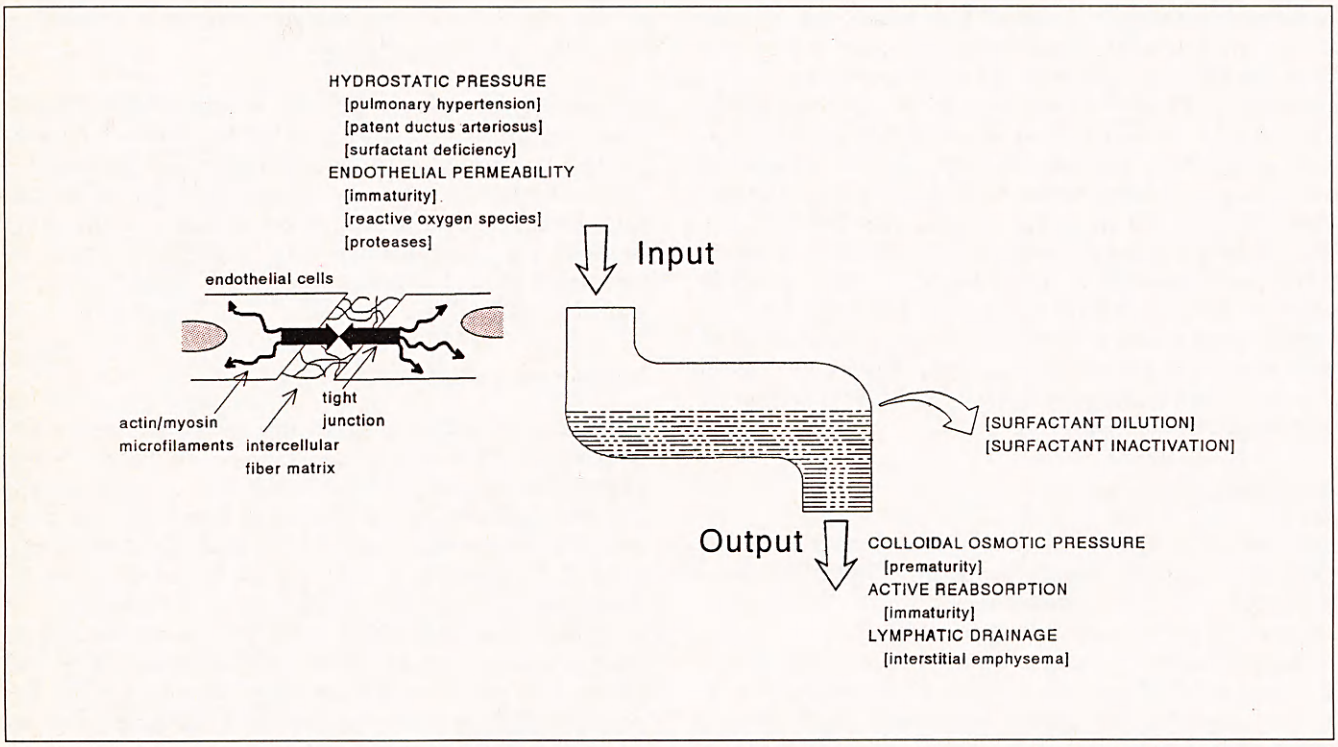

Fig 3. *Input/output model showing physiological mechanisms and pathological factors (in square brackets) influencing the pool of pulmonary oedema.* Input is influenced by hydrostatic pressure and endothelial permeability. A schematic drawing of endothelial cells illustrates the opposing forces that influence permeability, ie tight junctions, actin/myosin microfilaments, and intercellular fibre matrix. Output is effected by colloidal osmotic pressure, active reabsorption, and lymphatic drainage. Large amounts of oedema fluid can result in dilution and inactivation of surfactant.

pump located at the base of the cell, and active reabsorption, which persists throughout life, begins. The Na^+ gradient thus produced in the interstitial space draws Cl^- and water from the alveolus through the epithelial cell junctions. This water then moves into the capillaries or lymphatics.

Factors that may increase the alveolar fluid pool in RDS

Greater inflow

Increased hydrostatic pressure: pulmonary hypertension is common in RDS. In pulmonary hypertension, the arteriolar vasoconstriction is not present in all arterioles and the high pressure is transmitted to capillaries supplied by dilated arterioles: interstitial oedema develops in those parts of the capillary bed [35]. Surfactant deficiency, by raising the surface tension in the alveolar space, synergistically increases the transpulmonary hydrostatic pressure. In the preterm baby the ductus arteriosus may remain patent; in that case when the NRDS improves and the pulmonary pressure begins to fall, left-to-right shunting of blood can develop and alveolar oedema will recur [1].

Increased membrane permeability: high capillary pressure and high distending pressures in ventilated patients may not only 'stretch' the tight junctions but also disrupt the capillary and epithelial cell walls and produce large fluid leaks [35]. The tight junction may also begin to leak excessively because of increased contractility of the cell cytoskeleton or destruction of the adhesion molecules. Leakage of calcium into the endothelial or epithelial cell, because of either ROS-induced membrane damage or increased levels of tumour necrosis factor (TNF), thromboxane and leukotrienes, will increase actin/myosin microfilament contractility [34]. Intercellular space permeability increases in ARDS when neutrophil proteases digest the adhesion molecules and fibrin matrix [34]. Increased leakage of fluid across the membranes can also occur in preterm babies because of disturbances in the tight junction function. Generalised oedema is a well-recognised accompanying clinical finding in NRDS. Generalised and pulmonary oedema could be related to immaturity of the tight cell junctions or β adrenergic receptors [36]. But anoxia due to acute birth asphyxia does not increase pulmonary oedema [20].

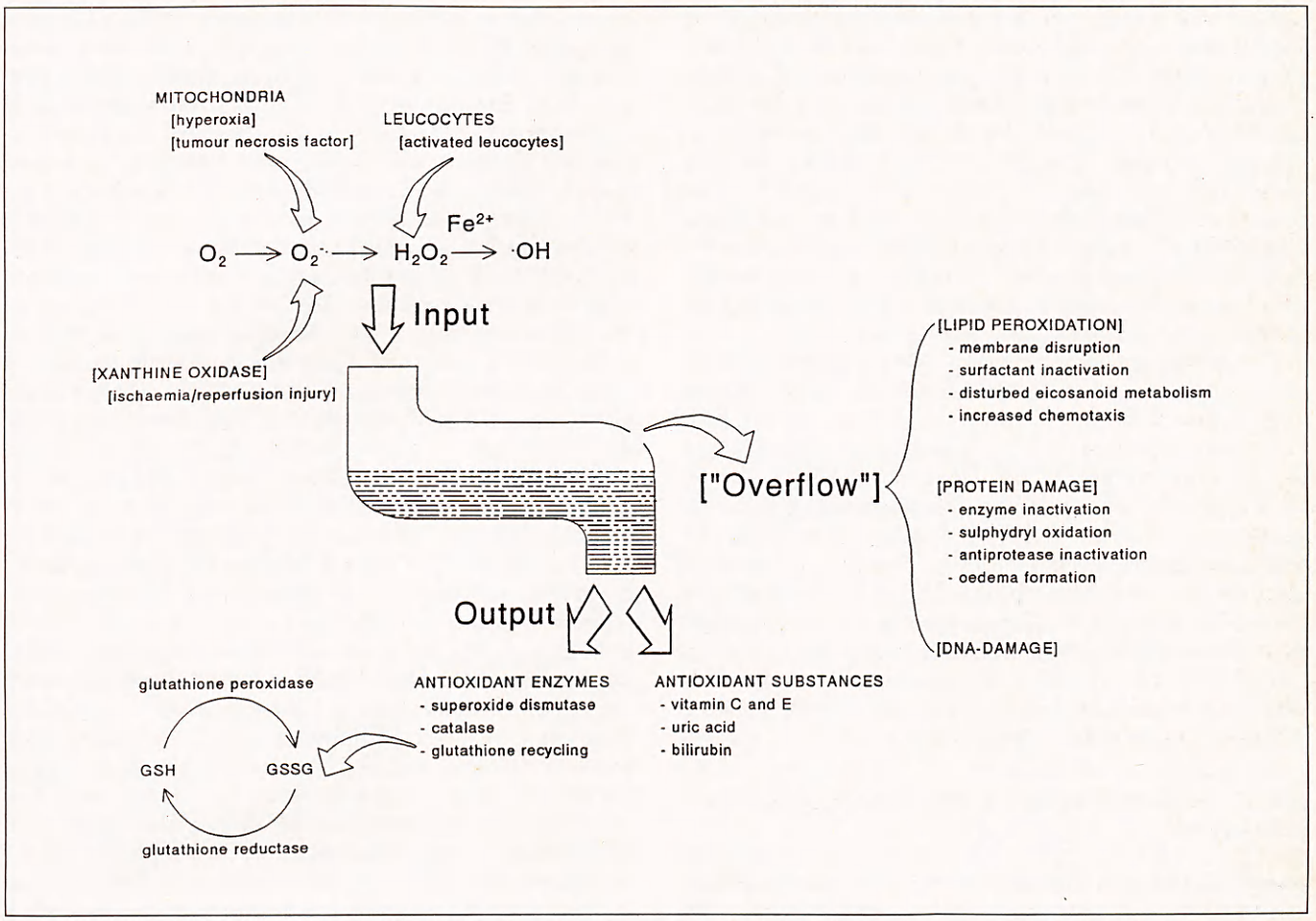

Fig 4. *Input/output model showing physiological mechanisms and pathological factors (in square brackets) influencing the pulmonary pool of reactive oxygen species (ROS).* Mitochondria, leucocytes, and xanthine oxidase produce ROS which are removed by antioxidant enzymes and substances. Excess production eg hyperoxia, presence of non-protein-bound iron (Fe^{2+}), and decreased removal, eg catalase inactivity, results in an 'overflow' of ROS damaging lipids, proteins, and DNA.

Smaller outflow

Plasma protein levels correlate with the gestational age of the baby: the colloidal osmotic pressure is low in preterm babies and particularly in those with NRDS [33]. Therefore the greater flow of fluid into the alveolar space due to the increased transpulmonary hydrostatic pressure is aggravated by decreased reabsorption. The active absorption of alveolar fluid is also hampered in the preterm baby with poorly developed β adrenergic receptors. Caesarean section, by diminishing the adrenaline surge, may also result in a 'wet lung' and aggravate the respiratory distress. Disturbed passive and active water reabsorption may aggravate the high permeability oedema of ARDS, eg protein losses in burns patients, or β adrenergic receptor inhibition by ROS [4]. Decreased lymphatic drainage is probably only a problem in RDS if air leaks, due to mechanical ventilation, block the lymphatics (interstitial emphysema) [37].

Reactive oxygen species pool (Fig 4)

Reactive oxygen species (ROS), eg superoxide radical ($\cdot O_2$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($\cdot OH$), can inhibit the synthesis, release, and activity of surfactant and influence membrane permeability and arteriolar reactivity. ROS thus play a major role in the pathogenesis of ARDS [2], and there is evidence that they are also important in the pathogenesis of NRDS [38].

Molecular oxygen is converted, by stepwise reductions, via $\cdot O_2$ and H_2O_2 to water. $\cdot O_2$ is formed during normal mitochondrial and eicosanoid metabolism, and in disease when neutrophils are activated and hypoxanthine is converted to uric acid by xanthine oxidase. Neutrophils also contain myeloperoxidase which converts H_2O_2 to hypochlorous acid (HOCl). In all cells and extracellular fluids H_2O_2 can be converted to $\cdot OH$, the most reactive oxygen metabolite, if transition metals, eg nonprotein bound ferrous iron, are

present. This does not occur normally because these metals are rigorously bound to protein during transport or storage: eg iron to apotransferrin and apoferritin [39]. In adults plasma transferrin levels are higher and iron levels are lower than in healthy newborn babies, resulting in a greater iron binding capacity (≈60% vs. ≈40%). Ferrous iron (Fe^{2+}) cannot bind to plasma transferrin unless it is oxidised to the ferric form (Fe^{3+}) by caeruloplasmin. High levels of vitamin C, a powerful reducing agent, can antagonise this ferroxidase activity. Vitamin C levels in cord blood are up to three times higher than adult levels [40].

The output of ROS depends on the activity of various antioxidant enzymes and antioxidant substances. Superoxide dismutase removes $\cdot O_2$ by converting it to H_2O_2, which in turn is catabolised to water by catalase and glutathione peroxidase. The latter enzyme is part of the glutathione recycling system oxidising reduced glutathione (GSH) to GSSG which is then reduced back to GSH by glutathione reductase (Fig 4). Antioxidant substances such as vitamin E and C, uric acid, and bilirubin, scavenge ROS and secondary peroxidation products, thereby breaking oxidative chain reactions [40]. Vitamin C, by reducing iron (see above) may also act as a pro-oxidant; however, the clinical significance of its potential double-edged effect is not clear.

Factors that may increase the reactive oxygen species pool in RDS

Raised ROS levels may produce an 'overflow', resulting in oxidation damage to lipids, proteins, and DNA (Fig 4). Lipid peroxidation disrupts cell membranes and inactivates surfactant, and the resulting products, eg malondialdehyde and 4-hydroxynonenal, are highly toxic and chemotactic agents. The changes in peroxide levels influence eicosanoid metabolism: thromboxanes and leukotrienes, powerful vasoconstricting and chemotactic agents that induce pulmonary hypertension and attract large numbers of neutrophils, are produced by the lung [4]. Protein damage includes inactivation of β adrenergic receptors, enzymes, and α_1-antitrypsin (which normally protects the lung and surfactant proteins from neutrophil proteases) [2,3].

Increased production of ROS

Babies produce more $\cdot O_2$ by mitochondrial activity when they are born into the high oxygen environment of terrestrial life; they will produce even more when high ambient oxygen concentrations are required for treatment. Epithelial and endothelial cell mitochondria, after anoxic damage, will also subvert greater amounts of oxygen to $\cdot O_2$ [41]. In ARDS, increased mitochondrial $\cdot O_2$ production can also be induced by tumour necrosis factor [42] released by pulmonary macrophages. Tumour necrosis factor working synergistically with increased thromboxane, leukotrienes, and ROS increases chemotaxis and adhesion of the neutrophils to pulmonary endothelium [43]. This produces, in ARDS, the typical massive pulmonary accumulation of neutrophils which are usually the major source of ROS ($\cdot O_2$, H_2O_2, HOCl). However, ARDS also occurs in neutropenic patients [44], and epithelial and endothelial cells or pulmonary macrophages may then be sources of ROS. In anoxic conditions, eg shock, xanthine dehydrogenase converts to xanthine oxidase, and ATP catabolism releases large amounts of hypoxanthine, the substrate for xanthine oxidase. After resuscitation, xanthine oxidase uses oxygen as the electron acceptor to oxidise hypoxanthine to uric acid, and $\cdot O_2$ is formed. Xanthine oxidase is present in pulmonary epithelium and endothelial cells but leakage of the enzyme from the liver into the plasma [45] may also contribute to the lung damage after ischaemia reperfusion induced injury [2]. Xanthine oxidase induced damage may also contribute to other forms of ARDS. For example, paraquat intoxication appears to increase the conversion of xanthine dehydrogenase to xanthine oxidase by oxidative alteration of sulphydryl groups [46].

H_2O_2 can be converted to the more powerful oxidising species $\cdot OH$, when a source of non-protein-bound iron is present. In the newborn preterm baby plasma transferrin is low, but highly saturated with iron. Iron binding capacity is therefore decreased and non-protein-bound iron can be detected in the plasma. This potentially dangerous pro-oxidant status is aggravated by the babies' low caeruloplasmin and high vitamin C levels, respectively three times lower and higher than in adults, which will maintain the non-protein-bound iron in the dangerous reduced form (Fe^{2+}) [47]. Non-protein-bound iron in plasma of preterm babies oxidises surfactant *in vitro*. Leakage of this plasma into the alveolar space could damage surfactant lipids and proteins, increasing the severity of NRDS and decreasing the effect of surfactant therapy [48]. In contrast, transferrin from bronchoalveolar lavage fluid of adults with ARDS inhibits iron-induced lipid peroxidation [49]. Thus pulmonary oedema in ARDS, despite its detrimental effect on gas exchange, may help prevent lung injury [50]. Nevertheless, iron-induced oxidative damage is believed to play a role in ARDS. Ferritin may be the iron source because, unlike transferrin, it releases iron in the presence of $\cdot O_2$ [51]. The lung, before and after birth, is a major site of caeruloplasmin production and its gene expression can be induced by both inflammation and hyperoxia [52].

Decreased removal of ROS

The antioxidant defences of the lung are made up of the antioxidant systems in the endothelial cells and pneumocytes acting synergistically with the systems in the surfactant, alveolar lining fluid, and blood.

Pulmonary antioxidant enzyme levels are lower in the preterm baby [38], and can be influenced by intrauterine nutrition [53]. The development of these

enzymes parallels the maturation of the surfactant system during gestation; glucocorticoids accelerate both processes. Thyroxine, in contrast to its effect on the surfactant system, may depress development of the antioxidant enzymes [54]. In ARDS, antioxidant enzyme activity may also be depressed. $\cdot O_2$ can inactivate catalase *in vitro* [4], and riboflavin deficiency, due to inadequate intake or excess urinary losses in catabolic patients, impairs glutathione recycling [55]. Vitamin E is the major chain-breaking antioxidant in cell membranes, and plasma and/or red blood cell membrane levels of vitamin E are decreased in preterm babies [56] and adults with RDS [57]. However, supplementation trials in animals and man have not helped to clarify its role in protecting the lung against ROS damage [58]. Uric acid, which is water soluble, is recognised as an important extracellular antioxidant in alveolar fluid and plasma, but recently its role as an intracellular antioxidant has attracted attention. It scavenges the powerful oxidising species $\cdot OH$ and HOCl. Xanthine dehydrogenase/xanthine oxidase activity of pulmonary epithelial and endothelial cells produces large amounts of uric acid. This may help inhibit ROS-induced vasoconstriction, as it has been shown that uric acid prevents oxidative inactivation of endothelial cyclo-oxygenase, which produces prostaglandins [59].

Natural surfactant has significant amounts of superoxide dismutase and catalase; but preparing animal surfactant for therapeutic use inactivates these enzymes [60]. We have shown *in vitro* that addition of vitamin E to commercial surfactant does provide protection against peroxidation damage [48]. Alveolar lining fluid contains all the major antioxidant enzymes and antioxidant substances [58]. High concentrations of reduced glutathione, 140-fold higher than in plasma [61], and catalase protect the alveolar cells against H_2O_2 damage [62]. Uric acid diffusing in from the plasma and locally produced by epithelial and endothelial cells may be particularly important in scavenging HOCl, a powerful oxidising agent produced by neutrophils. These cells accumulate in large numbers in ARDS [2], and they may also contribute to the pathogenesis of NRDS [30].

The antioxidant capacity of the blood contributes to the total protection of the lung against ROS. The powerful plasma antioxidants not only contribute to the chain-breaking antioxidant capacity of the alveolar fluid but also protect endothelial cells from oxidative damage. We have shown that the total peroxyl radical trapping capacity (TRAP), which assesses the interaction between the various plasma antioxidants, is higher in newborn babies than in adults [40]. It gradually decreases, and we suggest that the TRAP may help protect the lung postnatally whilst the tissue's antioxidant enzymes are maturing. Uric acid and vitamin C are the major contributors to the TRAP. Vitamin C regenerates uric acid in plasma and vitamin E in cell membranes and may be an essential part of the antioxidant defences [59,63]. Vitamin C levels fall markedly in the first three days after birth in well preterm babies. This may be due to a decreased input and/or an increased output due to oxidative or urinary losses. Low levels develop in ARDS [64] and we are currently studying postnatal changes in NRDS. Erythrocytes and platelets have high concentrations of catalase and glutathione peroxidase and they may act synergistically with the other systems in protecting the lung against ROS [58]. Erythrocyte catabolism of H_2O_2 by glutathione recycling is more efficient in the newborn, and this may partly compensate for the deficient antioxidant capacity of their lung tissue [55]. Anaemia may adversely affect ROS metabolism in NRDS and ARDS [55].

Greater susceptibility to damage by ROS

The susceptibility of phospholipids in cell membranes and surfactant to damage by ROS would be expected to increase as the concentration of polyunsaturated fatty acids (PUFA) rises [65]. Babies with RDS have lower palmitic acid (saturated) levels associated with increased unsaturated fatty acids (oleic, linoleic and arachidonic) in their pulmonary surfactant [10]. In animal studies, however, supplementation of the maternal diet with linoleic acid and fish oil PUFA clearly protects the newborn animal against oxygen toxicity [66]. The mechanism of this paradox may be that the PUFA supplements are used to build up intracellular reserves which subvert the ROS from oxidising essential structures. The explanation may be more complex because postnatal parenteral nutrition with lipids containing a high PUFA content appears to increase oxygen toxicity [67]. Membrane antioxidant concentrations as well as the amount of oleic acid, a mono-unsaturated fatty acid that inhibits peroxidation, may be explanations [65]. The influence of the composition of the pulmonary fatty acids on the pathogenesis and outcome of ARDS also requires further study.

Current and future therapy in NRDS and ARDS

Impaired gas exchange due to alveolar atelectasis, oedema, and pulmonary arteriolar vasoconstriction is the major therapeutic problem. Supportive therapy aims to maintain adequate oxygen delivery to the tissues. When respiratory support is required, air leaks due to high ventilatory pressures are a common complication. Use of positive end expiratory pressure and high inspiratory/expiratory time ratios to increase alveolar expansion and reduce oedema are recommended in adults. But in the newborn a low inspiratory/expiratory time ratio is now preferred. High frequency ventilation, extracorporeal membrane oxygenation, and liquid ventilation are also being tried in both age groups. Despite these methods, morbidity and mortality are still high in NRDS and ARDS, and other therapeutic approaches specifically to counter the pathogenic mechanisms are being tried. Theoreti-

cally, the possible steps are correction of the inappropriate losses and gains in surfactant, alveolar fluid and ROS. We will only deal with a few of the many possible therapies [3,7,8,58].

The surfactant deficiency may be alleviated in babies by increasing endogenous production by antenatal hormone therapy [17,24], or in all age groups by exogenous replacement therapy [9,68]. Antioxidant therapy [48] or removal of inhibitory proteins using liquid ventilation with fluorocarbons [69] may prevent inhibition of surfactant activity. The excess production of ROS due to oxygen therapy can be reduced with careful non-invasive monitoring. Inhibition of xanthine oxidase activity with allopurinol is effective experimentally [58]. Diminishing recruitment of neutrophils by using monoclonal antibodies to tumour necrosis factor may decrease ROS and protease-induced damage. Exchange transfusions and iron chelating agents may decrease iron-induced ROS damage [48]. Administration of parenteral antioxidant enzymes in liposomes may increase their intracellular uptake, and acetylcysteine therapy increases intracellular glutathione concentrations. As well as these pharmacological manoeuvres, attention to nutritional factors, such as the fatty acid content of parenteral feeds, may decrease peroxidation damage of the lung. Glucocorticoid therapy, although not successful in ARDS [8], does decrease lung permeability in babies [36]. β adrenergic drugs, eg pentoxifylline, may decrease lung permeability in RDS in all age groups [34]. Systemic administration of pulmonary vasodilator drugs is complicated by generalised hypotension but inhalation of nitric oxide could be a useful alternative in ARDS and NRDS [70,71]. Oxidative damage to the lung tissue, surfactant, and red blood cells by nitric oxide, a ROS, is a potential problem but the first results are encouraging.

RDS results from a complicated interplay of many factors, and we have concentrated only on the main pathogenic mechanisms. Comparing them in babies and adults may lead to a better understanding of the syndrome and its complications. This overview attempts to create a model that will allow cross-fertilisation of current and future ideas on the pathogenesis and therapy of respiratory distress syndrome in all age groups.

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