Aetiology of hyaline membrane disease

The demonstration that the lungs from infants with hyaline membrane disease (HMD) have abnormal surface properties¹ sparked off a decade of intensive study on the structure and mechanical aspects of the lungs in this condition. Douglas Gairdner played a major role in a series of classical papers on the subject which virtually brought this era to a close. The first paper gave a detailed comparison of the different methods which can be used to evaluate the surface properties of the lung in the perinatal period.² The others described the cellular structure and lecithin content of the lungs from perinatal deaths, particularly from babies dying with HMD.^{3, 4}

This work clearly established the sequence of structural and functional events in the lungs of infants with HMD associated with surfactant deficiency. The earliest change was shown to be an interstitial oedema with localised necrosis and desquamation of alveolar epithelial cells and absence of osmiophilic granules in the type II cells. Progressive development of hyaline membranes and the initiation of repair phenomena with return of osmiophilic granules and normal surface properties were described in detail. It was recognised that hyaline membranes could develop in some cases despite normal lung surfactant and that lack of surfactant occurs, though rarely, in the term infant. In conjunction with quantitative estimates of lung lecithin content, this provided a formidable amount of new information which complemented and amplified the work published during the preceding decade.

Changing directions in HMD research

Since that time the directions of research into the perinatal lung and HMD have altered in response to two major advances. The first of these was the demonstration by Liggins that prenatal glucocorticoid administration to fetal lambs allowed them to survive if born prematurely.⁵ This has prompted widespread research into the pharmacology and endocrinology of fetal lung maturation. The use of prenatal corticosteroid administration to mature the preterm infant lung *in utero*, thus preventing the development of HMD, was subsequently introduced,⁶ although relative benefits and hazards are still the subjects of arguments.⁷ The second major advance was the discovery by Gluck and co-workers that infants at risk of developing HMD could be detected

prenatally by measurement of lecithin/sphingomyelin ratios in fluid obtained by amniocentesis.⁸ The twin possibilities of being able to diagnose and treat surfactant deficiency before birth have not unnaturally preoccupied medical research workers to the exclusion of the more fundamental questions about how and why the condition arises in particular circumstances.

In this, as in other fields of medical research, real advances are episodic and each one provokes a flurry of subsidiary activity centred on the particular area of the problem highlighted by the initial work, rather than on attempts to integrate it with all other aspects of the problem. It is justifiable to ask whether we are any closer to understanding the aetiology of HMD than we were 10 years ago.

Control of fetal lung development

The problem of the aetiology of HMD is of course just a part of the far wider problem of control of fetal lung development in general. The mammalian fetal lung develops as a hollow fluid-filled organ that must be capable of rapid transformation into an efficient air-filled gas-exchange system within minutes of birth. The human lung differs from that of other mammalian species in the ability to perform this feat at any time in the last trimester of pregnancy.

Recent work on the rabbit indicates that normal mammalian fetal lung growth requires the integration of neuromuscular and secretory activities.⁹ Secretion of lung liquid appears to provide a moulding force for the developing lobule which is probably enhanced by the swings in intrathoracic pressure associated with fetal respiratory movements. There is evidence that agents such as corticosteroids which cause premature structural and biochemical maturation of the lungs may also retard their growth.¹⁰ Diversion of substrate to surfactant production could well reduce the quantity available for cell proliferation. There may therefore be a biological advantage in the lung remaining functionally immature, provided that biochemical maturation can rapidly be induced when delivery becomes imminent. To allow efficient transition to an air-breathing state one might postulate the presence of one or more early warning systems to trigger biochemical lung maturation at the onset of labour.¹¹ HMD would then arise as a result of failure to activate these systems or the inability of the target tissue to respond.

Trigger mechanisms for biochemical lung maturation

It is well established that endogenous glucocorticoid production is capable of inducing the enzymes necessary for surfactant synthesis¹² and specific cortisol receptors have been demonstrated in the fetal lung.¹³ The glucocorticoid mechanism may adequately explain the advanced lung maturation seen in various forms of fetal stress including infection¹⁴ or recurrent antepartum haemorrhage.¹⁵ Although most animal species have a surge in cortisol production near the end of pregnancy it is not yet clear how important this mechanism is for normal human fetal lung maturation.¹² Infants with congenital absence of the adrenals or anencephaly¹⁶ may be born with lungs which show normal surface properties. It is also unclear how much of the wide variation in lung maturity at any gestational age^{3, 17} can be accounted for by the variable activation of this mechanism. Are there specific pathways for triggering lung maturation by methods other than cortisol release?

There is evidence that thyroxine can promote lung maturation¹⁸ as can pharmacological agents such as pilocarpine.¹⁹ An additional, possibly important, pathway is the autonomic nervous system.²⁰ Infusion of catecholamines in lambs causes inhibition of lung liquid secretion and release of surfactant.^{21, 22} It is not yet established whether surfactant synthesis is increased but it would be intellectually satisfying to have a link between removal of lung liquid and enhanced surfactant production since these would be sensible activities for the fetal lung when faced with imminent discharge into a gaseous environment.

Prolonged rupture of the membranes is associated with advanced lung maturation in the human.^{23, 24} This may provide a nonspecific stress which induces lung maturation directly by the glucocorticoid mechanism, or such stress might be the result of secondary infection of the liquor. It is interesting to speculate whether the intimate relationship between the fetal airways and the amniotic fluid may allow triggering of some more direct mechanism for biochemical lung maturation after rupture of the amniotic sac.

Conclusions

The main structural and functional features of HMD associated with surfactant deficiency have been well understood for a number of years.

The problem of aetiology which remains to be resolved is what determines that a particular infant develops this condition of apparent immaturity, while another infant of considerably lower maturity does not.

It is suggested that the solution of this problem demands greater understanding of the way that the fetal respiratory system interacts with its environment and of the mechanisms which influence the balance between growth and biochemical maturation of the fetal lung.

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