My immediate reaction when asked to present a history of hyaline membrane disease (HMD) was that I was too young for such a task! Upon reflection, I concluded that this was not true. As a medical student in the late fifties, I recall the numerous theories proposed for the pathogenesis of the disease. Later (about 20 years ago), I prepared a talk on HMD while a house officer at Hopkins. Fibrinolysin deficiency and surfactant deficiency were the two new and favorite theories of the day and, with the passage of time, the former has slipped into well deserved oblivion. Treatment was of course extremely primitive in those days but Bob Usher had begun to make systematic biochemical measurements and the "Usher Regime" was the approach of the day.[1,2] How rapidly we have progressed since then! With the exciting new possiblity of both prevention or replacement therapy for HMD the future looks promising.

In this chapter I propose to review some historical aspects of nomenclature and diagnostic criteria, pathogenesis, artificial ventilation, prevention and replacement therapy.

THE DARK AGES

NOMENCLATURE AND DIAGNOSIS
Considerable disagreement on nomenclature and diagnostic criteria for HMD existed in the fifties. Because of the many theories of the etiology of the condition, many terms were used to describe similar pathological findings: myelin formation in lungs; congenital aspiration pneumonia; asphyxial membrane; desquamative anaerosis; congenital alveolar dysplasia; vernix membrane; hyaline membrane; hyaline-like membrane; and hyaline atelectasis. On July 21, 1959 an informal international meeting of 34 experts (clinicians and pathologists) was held in Montreal at the time of the IX International Congress of Pediatrics, chaired by Dr. Clement Smith. The purpose was to establish clinical criteria for diagnosing and assessing the severity of the disease. In addition, those factors affecting prognosis were to be enumerated. A fascinating discussion ensued. An attempt was made to define the syndrome more accurately, I gather by Dr. Mary Ellen Avery, but presented by Dr. C. D. Cook. Following are the criteria included:

Clinical

- History of prematurity
- History of intrauterine distress
- Family history of respiratory distress in other siblings
- Diabetes

Physical

- Birth weight of prematures
- Increased respiratory rate
- Retraction
- Cyanosis
- Subnormal temperature-will occur in any sick infant
- Hypotonia

Laboratory

- pH, fall
- PCO2, increase
- Placenta, absence of findings
- X-ray of chest helpful

Pathologic

- Atelectasis
- Hyaline membrane
- Edema
Physiologic measurements

- Functional residual capacity, decreased
- Lung compliance, markedly decreased
- Blood pressure, fall

Biochemical measurements

- Surface tension changes
- Absence of fibrinolytic activity in lungs

Although there was little unanimity at this meeting, these diagnostic criteria have subsequently been modified to include the clinical presentation of respiratory distress plus a radiologic picture of HMD.

It is of interest that at this meeting nomenclature was considered in detail and of 22 voting, 15 voted for the term, idiopathic respiratory distress of the newborn; 4 voted for pulmonary syndrome of the newborn; and 3 voted for the term, hyaline membrane syndrome. If one excludes the chairman as non-voting, it can only be assumed that 11 of the participants left because of the lateness of the hour (the meeting apparently adjourned about midnight!). Note that the term, hyaline membrane disease, was not considered for this vote. Currently the term, idiopathic respiratory distress syndrome (IRDS), continues to be used by some, although there is ample evidence that the disease is caused by surfactant deficiency. Some clinicians thus use the term, respiratory distress syndrome (RDS). My preference is still hyaline membrane disease, as long as we bear in mind that the hallmark of the disorder is atelectasis and it is this which leads to the characteristic clinical picture.

THEORIES OF PATHOGENESIS (B.A.M.)

B.A.M. (Before Avery & Mead) many theories of pathogenesis were proposed to explain HMD.[5] Much was made of the membrane in the early days. One leading theory was that the membrane consisted of aspirated material from amniotic fluid and that upon breathing air this became impacted distally. Obstruction of distal airways was considered the mechanism of the atelectasis. Against this theory was the failure to see membranes in infants who died within the first hours of life. Asphyxia was also implicated in the pathogenesis since those infants who died with HMD were more likely to have low Apgar scores.[6] Asphyxia of fetal animals is known to cause HMD even in the term fetus.[7] Thus, asphyxia may play a role in altering surface tension in the neonatal lung. However, B.A. M., it was suggested by some that perinatal asphyxia could cause heart failure and it was heart failure that was the primary problem. In addition to perinatal asphyxia, it was suggested that heart failure could be caused by an abnormal degree of shunt through the ductus or foramen ovale, a low pH, or because of a shift of intracellular potassium to the extracellular fluid spaces. Two controlled trials of digitalis failed to demonstrate any effect on mortality in infants with HMD.[8,9]
Decreased blood volume was implicated in the pathogenesis of the disease, since early clamping of the umbilical cord was associated with a greater mortality. If cord clamping was delayed until after the first breath, with the infant held below the level of the placenta, mortality from the disease was reduced.\[10\]

Disturbed autonomic regulation was implicated because of the observation that many infants with HMD had low blood pressure, cool extremities and edema. The consequence of a decreased blood volume, shock or heart failure could lead to hypoperfusion of the pulmonary vascular bed. This led to the concept by Chu et al.\[11,12\] that pulmonary hypoperfusion and lung ischemia might be the primary problem in HMD. They reported some success with the use of acetylcholine to vasodilate the pulmonary arterioles but none when using aerosolized d-palmitoyl lecithin, a major component of pulmonary surfactant. This concept of a primary problem with the pulmonary circulation in the pathogenesis of HMD has not withstood the test of time and scientific evidence. Persistent neonatal pulmonary hypertension, the so-called persistent fetal circulation syndrome, is now well recognized as a distinct clinical entity not associated with HMD.

Fifteen to 20 years ago deficient fibrinolytic enzymes were suggested as a primary problem accounting for the presence of the membrane.\[13,14\] In addition, fibrinogen was shown to inhibit pulmonary surfactant. A controlled trial of aerosolized and intravenous urokinase activated fibrinolysin was apparently successful in reducing mortality from HMD.\[15\] Again, it is clear now that the deficiency described was a result of our lack of appropriate ventilatory support for these sick infants at that time and is not a primary defect.

THE AGE OF ENLIGHTENMENT

ANNO AVERY & MEAD

The classic studies of Avery and Mead reported in 1959 clearly established that surfactant deficiency was present in the lungs of infants dying of HMD.\[16\] In fact, Peter Gruenwald, a dozen years earlier, had proposed that high surface tension might cause the atelectasis in HMD.\[17\] He also correctly concluded that the membrane was "an eosinophilic red herring." What foresight he had! The magnificent contributions of John Clements to the understanding of the physiology and biochemistry of surfactant, and the demonstration of high surface tension in the lungs of infants with HMD by Avery, Mead and Pattle, set the stage for improved treatment of the disorder and subsequently the possibility of prevention of HMD.\[16,18,19,20\]

ARTIFICIAL VENTILATION

Dr. Stahlman has addressed this subject in detail in this book. However, I wish to make a few personal observations. Technological advances now make it possible to measure arterial blood gases and pH on
minute quantities of blood. In the 60's this was not possible. The Astrup technique introduced in the early 60's at last made it possible to measure capillary pH, and by equilibrating the infant's blood with two different PCO's, the infant's PCO$_2$ and bicarbonate concentration could be estimated. This was a major advance. Now of course, the ability to estimate arterial PO$_2$, PCO$_2$, or pH on small blood samples is being replaced by transcutaneous electrodes which allow continuous measuring of these parameters. There was a gradually increasing ability to artificially ventilate the small infant. The development of respirators specifically designed for newborn infants continues to the present day.

Another major advance was the introduction of distending pressure in 1971 by George Gregory.[21] Distending pressure probably has decreased the incidence of one serious complication, bronchopulmonary dysplasia. However, the use of distending pressure during artificial ventilation (PEEP) doubled the incidence of lung rupture in a series that we reported some years ago[22] (Tables 1 and 2). We are still plagued by lung rupture as a frequent complication of artificial ventilation.[23] I will leave discussion on newer techniques of ventilation to Dr. Stahlman. The continued relatively high mortality of infants with HMD who require artificial ventilation lends support to the notion that prevention of the disease and replacement therapy should be the major approaches to treatment in this decade.

PREVENTATIVE THERAPY

A controlled trial of ante-partum glucocorticoid demonstrated that lung maturation was accelerated and the incidence of HMD was reduced by 80% in the newborn infant between 26 and 32 weeks gestational age. This was first reported by Liggins and Howie in 1972 (Table 3).[24] Since then, numerous studies, including the recently completed NIH study, have confirmed these results. Glucocorticoid may not be the optimal agent to use in this regard for two reasons. Some investigators have concerns about possible long term effect of steroids on growth of the lung. Additionally, it is now clear that that particular steroid is only effective in the female of the species and the male lung is not responsive.[25,26] This is a fascinating observation which requires a better understanding of the mechanism of male non-responsiveness. Other agents such as DIMIT (a synthetic thyroid hormone), which crosses the placenta, may be less selective for the female but this remains to be proven.[27] Thus, the last decade or so has seen the exciting emergence of techniques aimed at preventing HMD. One can look forward to a refinement of our knowledge in this area and the emergence of more effective preventative techniques.

SURFACTANT REPLACEMENT THERAPY

Initial reports of significant improvement in the clinical course of infants with severe HMD, following the installation of surfactant, are most encouraging. Fujiwara[28] instilled a liquid surfactant into the trachea of infants with HMD which was obtained from tracheal washings of cow lung and modified to exclude most of the protein (Fujisurf). The British have used a dry powder insufflation of a combination of Dipalmitoyl lecithin and diacylphosphotidylglycerol (7:3 ratio, w/w).[29] This approach could prove to be a major advance in our therapy of those infants with HMD whose lungs cannot be matured in
Indeed, one might speculate that replacement therapy will succeed artificial ventilation as the therapy of choice in the future, thereby avoiding the serious complications associated with prolonged ventilation of these tiny infants.

In summary then, we have passed through a fascinating era in the past twenty years or so. The pathogenesis of HMD is now well understood, and there have been significant advances in our ability to treat these infants. The future holds tremendous promise in preventative therapy. Where that is not obtainable, replacement therapy—and the avoidance of prolonged artificial ventilation and its complications—seems an attractive possibility. I look forward to the next twenty years with great excitement.

Table 1

Prevalence of Bronchopulmonary Dysplasia in Infants with HMD

<table>
<thead>
<tr>
<th>Group</th>
<th>1968-1969</th>
<th>-1973</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiological diagnosis only</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Histological diagnosis only</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Histological and radiological diagnosis</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>21 (36.2%)</td>
<td>10 (17.2%)</td>
</tr>
</tbody>
</table>

*Group 1 infants treated with IPPB

**Group 2,A infants treated with IPPB plus PEEP

***Group 2,B spontaneously breathing infants on continuous negative pressure (CNP)
Table 2

Prevalence of Alveolar Rupture in Infants with HMD

<table>
<thead>
<tr>
<th>Group</th>
<th>1968-1969</th>
<th>-1973</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1*</td>
<td>2,A**</td>
</tr>
<tr>
<td>Developed prior to respirator therapy</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>(5.2%)</td>
<td>(8.6%)</td>
</tr>
<tr>
<td>Developed during respirator therapy</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>(20.7%)</td>
<td>(39.7%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>15</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>(25.9%)</td>
<td>(48.3%)</td>
</tr>
</tbody>
</table>

*Group 1 infants treated with IPPB

**Group 2,A infants treated with IPPB plus PEEP

***Group 2,B spontaneously breathing infants on continuous negative pressure (CNP)

Table 3

Influence of Steroid Therapy on Incidence of HMD*

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Betamethasone Treated Group</th>
</tr>
</thead>
</table>

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| Interval between treatment and delivery 2 to < 7 days | 33.3% | 3.6% |
| Gestational age at delivery 26 to < 32 weeks | 69.6% | 11.8% |

*Adapted from Liggins and Howie[24]

REFERENCES


