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Hyaline membrane disease

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Introduction

From reports in literature and personal communications, the respiratory distress syndrome of the newborn (commonly called hyaline membrane disease) forms the largest cause of death in the newborn period. The figures for Kandang Kerbau Hospital for the period 1961 to 1964 shows that the major cause of death is intra-cranial haemorrhage, but for the first four months of 1965, hyaline membrane disease is now well in the lead as the most common cause of death. These differences can only be speculated upon but the trend here seems to be approaching that of statistics in Western countries.

In the past in Kandang Kerbau Hospital newborn infants exhibiting the features of respiratory distress were managed inadequately by administration of oxygen *via* a funnel which in most cases were inadequate to even relieve the cyanosis of the syndrome. This resulted in a very high mortality rate of the syndrome: estimated at about 95%. It seemed that this major cause of neonatal deaths needed to be be studied and more adequate measures were called for to try to salvage a few of these infants. Added interest on the disease resulted with the visit of the Research Team from the U.S. which brought to the forefront the various clinical features, biochemical and physiological changes, ideas on pathogenesis and various lines of therapy of the disease.

Following their departure a line of management of these cases which would take into account the limited facilities at our disposal was contemplated and that suggested by Dr. Robert Usher in Montreal (1961) with regard to correction of the acidosis of the condition was decided upon.

This present series of cases is presented from the point of view of the general incidence and

TABLE I

Major causes of death in premature newborn infants in K.K.H. 1964 & 1st 4 months of 1965:

	1964	%	**1965**	%
Total deaths	623		143	
Intracranial haemorrhage	128	20.5	26	18.2
Hyaline membrance disease	122	19.6	42	29.4
Prematurity	112	17.9	28	19.6
Bronchopneumonia	76	12.2	11	7.7

patterns of the syndrome as seen in Kandang Kerbau Hospital and the effects of correction of acidosis by the use of sodium bicarbonate solution.

Materials & Method

The period of study in this series of cases is from August 1, 1964, to April 30, 1965, inclusive. Only those infants delivered in Kandang Kerbau Hospital are included. The selection of the cases are based on the following criteria:

Criteria for the diagnosis of H.M.D.

I. **Clinical:** Silverman-Anderson rating of 2 or more, *persisting* for a period of at least 24 hours and excluding any known causes for respiartory distress *e.g.*

(i) Respiratory system: aspiration syndrome, bronchopneumonia, emphysema, pneumothorax, pulmonary haemorrhage, diaphragmatic hernia, congenital lung cysts, obstruction of respiratory passage;

(ii) CNS: intracranial haenorrhage

(iii) Cardiovascular system: cardiac failure from congenital heart disease, peripheral circulatory collapse

(iv) Blood: anaemia of newborn; haemolysis (*e.g.* blood incompatibility of newborn)

II. **Pathological:** features of resorption atelectasis with the presence of hyaline membrane microscopically.

All babies showing respiratory distress were examined by the paediatric officer at Kandang Kerbau Hospital and the clinical diagnosis of hyaline membrane disease was made by him based on the criteria enumerated and with the aid of other clinical, radiographic and biochemical findings. The pathological diagnosis was made by a pathologist from the Pathology Dept. of the University of Singapore.

TABLE II

Silverman-Anderson Rating

Score	0	1	2
(1) Movements of chest & abdomen	Both rise with inspiration	mild upper chest lag during inspiration	marked upper chest lag during inspiration: see-saw movement
(2) Intercostal retractions	Nil	Just visible	Marked
(3) Xiphoid retractions	Nil	Just visible	Marked
(4) Movement of chin	Nil	Chin descends with inspiration but lips closed	Chin descends with inspiration and lips held opened
(5) Grunt	Nil	Heard only with stethoscope on chest wall	Heard without stethoscope

No distress : Score O.
Maximal distress : Score 10.
(Silverman & Anderson : Ped. 17:1, 1956)

Infants showing respiratory distress soon after birth but passing off before 24 hours were excluded. Where there was any doubt as to the presence of any of the other known causes of respiratory distress and the diagnosis was not clarified either at autopsy, or with prolonged observation, the case was excluded.

All babies with cliniclally diagnosed respiratory distress were treated as follows:—

i) Nursing in an incubator with the temperature of the incubator raised so as to maintain the body temperature of the infant at 96-97° F.

ii) Oxygen was given to relieve cyanosis and, if needed, up to 100% O_2 concentrations were used *via* an enclosed hood.

iii) Oral feeds were not started until the infant was sufficiently recovered to take the feeds without difficulty and these feeds were given by an oesophageal tube.

During the period from November 1, 1964, to March 18, 1965, all cases of clinical hyaline membrane disease in addition were placed on intra-venous fluid therapy according to the schedule suggested by Usher consisting of 10% dextrose solution and varying concentrations of sodium bicarbonate dependent on the blood pH.

TABLE III

Capillary pH	NaHCO3 concentration
more than 7.30	5 mEq. per 100 ml.
7.20—7.30	10 mEq. ,, ,, ,,
7.10—7.20	15 mEq. ,, ,, ,,
less than 7.10	25 mEq. ,, ,, ,,

Rate of infusion: 65 ml. per kg. per day.

Those cases of hyaline membrane disease delivered during the periods August 1, 1964 to October 31, 1964 and from March 19, 1965 to April 30. 1965, serve as the control series to those on bicarbonate therapy. A case was deemed to have recovered when the Silverman-Anderson rating was zero and the infant was not cyanosed when breathing air.

Results & Comments:

TABLE IV

Hyaline Membrane Disease: Aug. 1, 1964 to April 30, 1965.

Total number	:	183
Number on bicarbonate therapy	:	102
Number not on bicarbonate therapy	:	81

TABLE V

Mortality of H.M.D. according to birth weights

	1000 Gm or less (2lb. 2.5 oz. or less)	1001 Gm—1500 Gm (2 lb. 2.6 oz.—3 lb. 4.8 oz.)	1501—2000 Gm (3 lb. 4·9 oz.—4 lb. 6.4 oz.)	2001—2272 Gm (4 lb. 6.5 oz.—5 lb.)	2273 Gm or more (more than 5 lb.)
HCO_3 Therapy					
Total:	5	24	47	15	11
No. died:	4	17	24	7	9
Mortaliy:	80%	70·8%	51.1%	46.7%	81.6%
Control					
Total:	4	28	29	15	5
No. died:	4	21	20	10	2
Mortality:	100.0%	75.0%	69.0%	66.7%	40.0%

TABLE VI

Overall Mortality

	Total	Deaths	Mortality
HCO_3 therapy	102	61	59.8%
Control	81	57	70.4%

Standard Error = 7.0

Difference in Mortality = 10.6%
= less than 2 × S.E.

This is *NOT* significant

Comments on HCO_3 Therapy:

There are several shortcomings in this series of cases that are presented with regard to the effects of bicarbonate therapy on hyaline membrane disease.

1) The series of cases under bicarbonate therapy were obtained from the period November 1, 1964, to March 18, 1965, and those in the control group were from different periods. of time. These two groups as a result may not be entirely comparable. The distribution according to birth weights showed a much higher number of cases of the weight range 1501-2000 Gm. in the bicarbonate therapy group than in the control although the numbers for the other groups were roughly equal.

2) There may be seasonal variations of the disease so that more severe cases occur at certain periods of the year than at others and as a result the mortality may be affected adversely in the group with more severe cases. This, however, has not been proven and the two groups have been studied with regard to severity of the disease and they were found to be fairly equally distributed among the groups.

3) The aetiology and pathogenesis of the disease have not been unravelled and as a result we may be dealing with two or more different types of disease. Unless the two groups of cases are selected with this in mind, there may be a more severe type of disease predominating in one group than in the other.

4) As regards bicarbonate therapy, frequent checks on blood pH and frequent adjustments of bicarbonate concentrations were suggested by Usher. As this entailed full-time personnel in the form of laboratory technicians and nursing staff, the control of therapy that was enforced here was based on 24-hourly blood pH determinations.

This, however, should not affect the results very much.

5) Admittedly, an additional number of infants may be salvaged with more adequate staff and closer observations of the ill-infants but this would form only a small proportion and would affect both groups.

In considering all these factors, no bias could be found in the two groups which would affect the outcome of bicarbonate therapy more favourably and it is considered that intra-venous therapy with alkali-solution does not significately alter the prognosis in hyaline membrane disease. This is contrary to the report of Usher (1961) who claims an overall mortality, with this schedule, of 25% as compared to 45% before institution of this schedule in the Royal Victoria Hospital, Montreal.

Seeing that there is no significant difference between the two groups of cases, the second part of the study of hyaline membrane disease in Kandang Kerbau Hospital *viz.* the pattern and incidences of the disease observed here will now be considered.

TABLE VII

Incidence of H.M.D.

Total number of H.M.D. : 183

Total number of H.M.D. among prematures : 167

Total live births (1/8/64 to 30/4/65) : 28,699

Total premature live births (1/8/64 to 30/4/65): 1414

Incidence of H.M.D. in all live births : 183 in 28,699 = 6.4 per 1,000

Incidence of H.M.D. in all premature live births : 167 in 1414 = 118 per 1,000

Incidence of H.M.D. in all full-term live births : 16 in 27,285 = 0.6 per 1,000

(Criterion for prematurity : Birth Weight of 5 lb or less)

TABLE VIII

Sex Distribution of H.M.D.

Period from Aug 1, 1964 to April 30, 1965
Total live births : 28,699
Males : 14,794
Females : 13,905
Proportion Males : Females = 1062 : 1000
Total H.M.D. : 183
Males : 106
Females : 77
Proportion Males : Females = 1377 : 1000
Standard error = 3.6
Male preponderance in population = 6.2%
Male preponderance in H.M.D. = 37.7%
Difference of 31.5% = 8.75 × S.E.
This is highly *significant*.

TABLE IX

Racial distribution of H.M.D.

Chinese	157
Malays	14
Indians	10
Others	2 (1 Eurasian : 1 Nepalese)
Total:	183

TABLE X

H.M.D. in relation to type of delivery

Type of delivery	No. of cases	%
N.D.	128	69.9
Breech	25	13.7
Caesarian section	21	11.5
Compound	1	0.5
Unknown	8	4.4
	183	100.0

There is a significant sexual bias towards males in the incidence of hyaline membrane disease. There is no racial bias as the figures shown are approximately the proportions of the live-births for the different races.

There is a significant incidence with relation to caesarian section as the caesarian rate in

TABLE XI

Incidence of H.M.D. diagnosed at autopsy by birth weight

B.W.	Total live births	Total deaths	Autopsies	H.M.D.	H.M.D. per 100 births	H.M.D. per 100 deaths	H.M.D. per 100 autopsies
1000Gm or less	52	51	41	7	13.5	13.7	17.1
1001-1500Gm	166	132	104	33	19.9	25.0	31.7
1501-2000Gm	526	140	136	37	7.0	26.4	27.2
2001-2272Gm	670	47	38	10	1.5	21.3	26.3
Total	1414	370	319	87	6.15	23.5	27.3

Kandang Kerbau Hospital is about 2-3% as compared to the hyaline membrane disease incidence contributed to by caesarian sectioned cases of 11.5%.

The low incidence of hyaline membrane disease among the infants below 1000 Gm. is probably explained by their very short survival in most cases so that hyaline membranes have not had time to form. Otherwise, the incidence of hyaline membranes per 100 deaths and per 100 autopsies are about similar for the different weight groups.

TABLE XII

H.M.D. diagnosed at autopsy per 1000 live births

		Full Term	Prem
Total births	28,699	27,285	1,414
H.M.D.	94	7	87
HMD per 1000 live births	3.3	0.3	61.5

The low incidences of Avery & Oppenheimer (1960) and Chuang (1962) in proportion to total births and total deaths are explainable by the low autopsy indices of these two series. More comparable figures are those of the percentage in relation to the total autopsies: it varies from 25.5% of Avery & Oppenheimer (1960) to 36.9% of Latham (1955).

It will be seen that compared to the report of Latham (1955) whose autopsy index was 82.1%, the incidence of hyaline membrane disease per 1000 premature births is about the same for his series and for the present series.

The overall incidence is about the same apart from Latham's series. Both Latham (1955) and Potter (1950) found very high incidence among full-term infants compared to Chuang's series (1962) and the present one. Incidence among premature infants is comparable between the present series and that of Latham but decidedly lower in Potter's and Chuang's series. As these incidences are based on autopsy diagnosis, they would be dependent on the autopsy index.

TABLE XIII

Comparison of H.M.D. diagnosed at autopsy in various centres among prematures

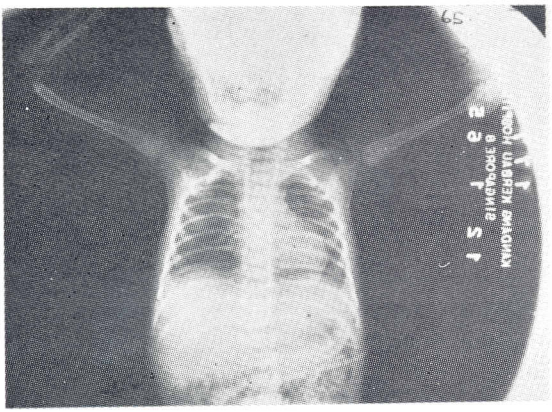
	Prem. mortality	HMD per 100 births	HMD per 100 deaths	HMD per 100 autopsies	Autopsy Index
Present series	26.2%	6.15	23.5	27.3	86.2
Latham et al (Baltimore 1937-49)	19.9%	6.02	30.3	36.9	82.1
Avery & Openheimer (Baltimore 1954-58)	21.2%	3.90	18.4	25.5	72.2
Chuang (Hawaii 1958-60)	18.2%	3.50	19.3	35.5	53.5

TABLE XIV

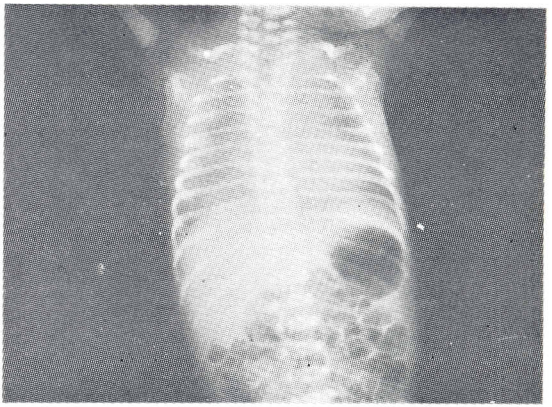
H.M.D. diagnosed at autopsy per 1000 live births

	All live births	Full-term	Prem.
Present Series	3.3	0.3	61.5
Latham et al (Baltimore 1937-49)	4.7	1.1	60.2
Potter	3.4	1.0	40.5
Chuang (Hawaii 1958-60)	3.2	0.2	35.1

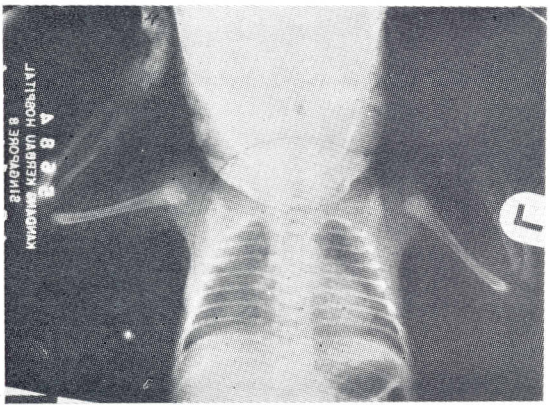
FIGURE 1



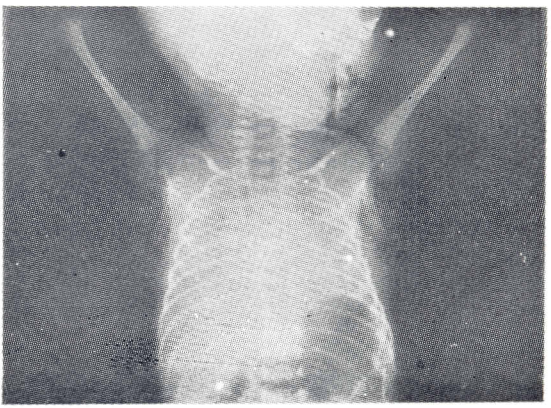
Class I. Classification of chest X-ray changes in HMD



Class III. Classification of Chest X-ray Changes in HMD



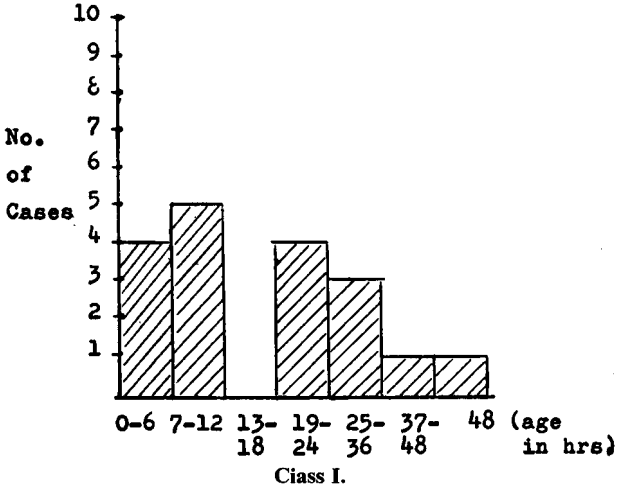
Classs II. Classification of chest X-ray changes in HMD



Class IV. Classification of Chest X-ray Changes in HMD

FIGURE 2

Age at which Chest X-ray was taken



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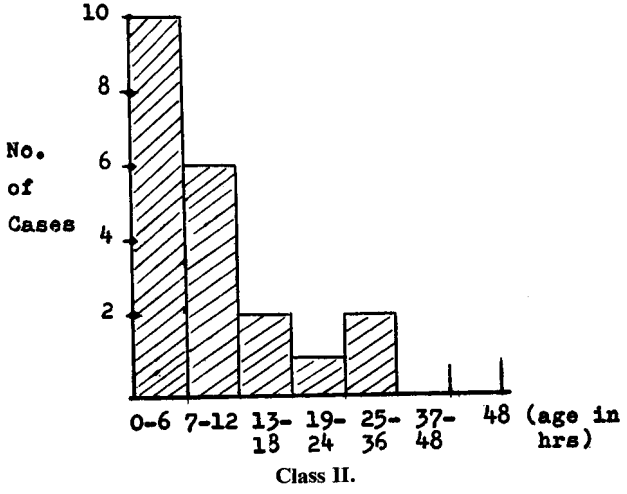

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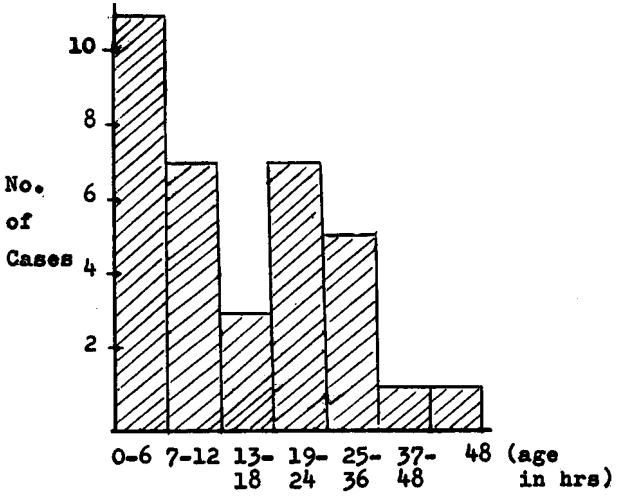

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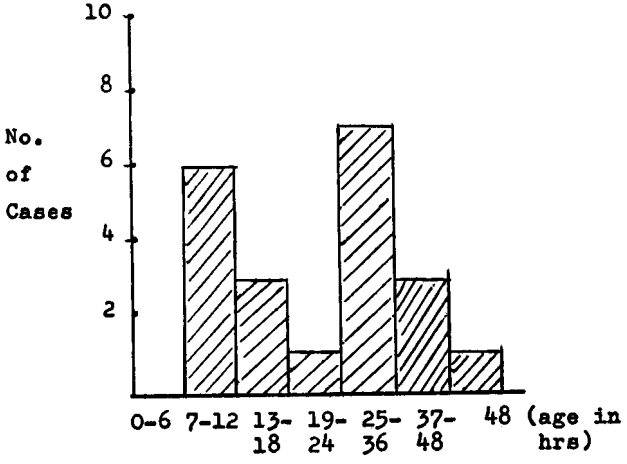

Class IV.

One important finding of the present study was the relationship of the chest X-ray to the prognosis of hyaline membrane disease.

The classification of the chest X-ray changes was into four classes as described by Bauman & Nadelhaft (1958):

Class I : Radioluscent lung fields without prominent pulmonary markings

Class II : Generalised mild increase in pulmonary markings or density outside the usual range of fine, coarse or mixed patterns

Class III: Generalised moderate increase in pulmonary markings or density outside the usual range of dine, coarse or mixed patterns

Class IV: Generalised marked increase in pulmonary density or markings of fine, coarse or mixed patterns

(After Bauman, W. A. & Nadelhaft, J: Ped. 21:813, 1958)

There were 95 infants submitted to chest X-ray study in this series. These X-rays were classified by a radiologist (Dr. J.C.K. Yin) who

had no idea whatsoever of the outcome of the infants so that there was no prejudice in the classification.

Table 15 shows a significant correlation between chest X-ray classification and the mortality rate: those with class I X-ray findings having the best prognosis with the mortality rising rapidly with the higher classification.

TABLE XV

Correlation between Chest X-ray classification and mortality from hyaline membrane disease:

Chest X-ray Class	No. of Cases	No. died	Mortality
I	18	1	5.6%
II	21	6	28.6%
III	35	18	51.4%
IV	21	20	95.2%

It was not possible to obtain chest X-rays of all babies at birth or soon after. Most of these cases had only one X-ray done and most of them were done as soon as possible. Those cases done at one or two days old represented cases delivered for instance just before a week-end and could only have the X-ray done on the following Monday. Nevertheless it will be seen in Fig. 2 that for each class of chest X-ray the changes were present at ages varying from less than 6 hours to over 2 days.

The conclusions that may be arrived at with regard to the chest X-ray findings are:—

1. The different X-ray changes are stages of the same disease.
2. The X-rays represent two or more different disease processes with different prognoses.
3. A combination of (1) and (2).

Summary:

1. A study of 183 cases of hyaline membrane disease over a period of nine months is presented.
2. The effects of combating the acidosis of hyaline membrane disease with sodium bicarbonate solution was assessed and found to be not significant in improving the mortality rate of the disease in Kandang Kerbau Hospital.
3. The incidence of the disease in Kandang Kerbau Hospital is comparable to that reported from other centres.
4. New observations noted in these series were a significant sexual bias towards males in the incidence of the disease and chest X-ray correlation with prognosis of the disease.

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