DISEASES OCCURRING AMONG PREMATURE BABIES

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The chief diseases causing mortality and morbidity among premature babies are shown in table 1.

TABLE 1

Diseases Causing Mortality and Morbidity in Premature Babies

Disease	Death	Defect
Idiopathic respiratory distress	Yes	—
Intracranial birth injury and asphyxia	Yes	Hydrocephalus Cerebral palsy Convulsions Mental deficiency, etc.
Congenital malformations	Yes	Various
Infections	Yes	Various
Hyperbilirubinemia	Yes	Cerebral palsy Hightone deafness Mental deficiency
Retrolental fibroplasia	—	Blindness

Compared with babies born at term, premature babies are more prone to:

1. birth injury and asphyxia,

2. being born with a congenital malformation, the malformation causing premature birth,

3. infection.

Prevention, diagnosis and treatment of these diseases is the same for premature babies as for babies born at term but the greater prevalence of these conditions among premature babies must be recognized.

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Although idiopathic respiratory distress and hyperbilirubinemia can both occur in babies born at term, they are essentially diseases of prematurity and these will be dealt with in detail.

In premature babies respiratory distress may be caused by:

1. primary atelectasis (usually in babies weighing less than 900 grams at birth),

2. secondary atelectasis associated with such conditions as pneumonia, birth aspiration, pulmonary hemorrhage, intra-cranial hemorrhage, pneumothorax, diaphragmatic hernia, etc.,

3. heart failure, or

4. it may be 'idiopathic.'

At the Ninth International Pediatric Congress in 1959 "idiopathic respiratory distress" was suggested as a clinical diagnosis to cover atelectasis from all causes which cannot be separated out during life.

Idiopathic Respiratory Distress Syndrome

The signs of idiopathic respiratory distress syndrome are set out in table 2. Unless improvement commences, death usually occurs

TABLE 2

SIGNS OF IDIOPATHIC RESPIRATORY DISTRESS SYNDROME	
RESPIRATION	Respiration rate increased Respiration labored, with inspiratory dilation of alae nasi and expiratory grunt Poor air entry Epigastric, intercostal (and often sternal) retraction Periods of apnea, with cyanosis Moist sounds heard in lungs
EDEMA	Usually develops
HEART	Heart rate becomes slow Heart failures may occur with enlargement of liver
B. P.	May fall (radial pulse becomes difficult to feel)
BODY TEMPERATURE	Tends to fall
CEREBRAL ANOXIA	May develop Baby becomes quiet, atonic and unresponsive to stimuli Respirations become slow and gasping

during the first 48 hours of life. If the baby does not die recovery is generally complete. In fatal cases the lungs show distention of the bronchioles and alveolar ducts with collapse of the alveoli, edema, and interstitial pulmonary hemorrhage. Often eosinophilic hyaline membranes line the distended alveolar ducts and bronchioles. Edema of the leptomeninges is usually present and intraventricular and subarachnoid hemorrhages frequently occur. Edema of the subcutaneous tissue is usually present.

Gitlin and Craig[1] have shown that hyaline membranes consist mainly of fibrin and it is now believed that pulmonary edema is the main cause of the respiratory distress.

Causes of Pulmonary Edema

These are not yet known but possible causes are listed in table 3.[2-9] The effects of birth weight, maturity, birth asphyxia and hypothermia are shown in table 4 (the effects of birth asphyxia and hypothermia were the same in *each* birth weight group.)

TABLE 3

Possible Causes of Pulmonary Edema and Respiratory Distress
I. Prematurity
a. Increased permeability of capillaries
b. Poor recovery of plasma protein by lymphatics after normal postnatal shift of plasma from circulation to tissues[2]
c. Deficiency of fibrinolysins for removal intra-alveolar fibrin clots[3]
d. Decreased lung compliance due to deficiency of mucoprotein which reduces alveolar cohesion[4]
II. Birth Asphyxia
a. Increased permeability of capillaries
b. Aspiration of liquid and fibrinogen of edema fluid converted into fibrin by thromboplastin of liquid[5]
III. Hypothermia
a. Increased permeability of capillaries
IV. Administration of High Concentrations of Oxygen[6,7]
V. Heart Failure
a. Heart failure[8]
b. L-R shunt through patent ductus arteriosus[9]
VI. Late Tying of Cord in Premature Babies
At 20 weeks gestation one half total fetal blood is in placenta
At 40 weeks gestation one fifth total fetal blood is in placenta

TABLE 4

SOME FACTORS INFLUENCING FORMATION OF HYALINE MEMBRANES FROM THE SORRENTO PREMATURE BABY UNIT (277 BABIES)

	NUMBER OF BABIES	PERCENT OF BABIES WITH HYALINE MEMBRANES (PM)
BIRTH WEIGHT up to 1500 Gm.	72	29.2
1501-2000 Gm.	112	9.8
2001-2500 Gm.	93	5.4
MATURITY		
up to 30 weeks	39	35.9
31-34 weeks	135	11.9
35 weeks and over	103	6.8
BIRTH ASPHYXIA		
Present	90	21.2
Absent	187	9.6
RECTAL TEMPERATURE ON ADMISSION		
up to 92 F. (33.5 C.)	40	35.0
over 92 F.	237	9.7

Reduction of Incidence of Idiopathic Respiratory Distress

This entails the reduction of the incidence and degree of prematurity; the prevention of birth asphyxia and hypothermia; and the avoidance of high concentrations of oxygen.

Treatment

The air passages must be kept clear. The "head-up" position allows the lung bases to expand more easily.

Oxygen should be given if the child is cyanosed but care must be taken to avoid retrolental fibroplasia. If continuous oxygen is required, keep the concentration below 30 per cent. If this does not keep the baby pink, give pure oxygen by face mask until the baby becomes pink, but after ten minutes remove the mask and allow the infant to become slightly cyanosed (and the ophthalmic arteries to relax) before reapplying the mask. This must be repeated as often as necessary.

Keep the infant warm (rectal temperature above 95 F. or 35 C.). A relatively high humidity is usually helpful.

Feeding should be delayed until the respiratory distress is over; but intravenous glucose must be given if acidosis develops.

Antibiotics should be given to prevent secondary infection. Digitalis must be given if heart failure develops. (Digoxin 0.05 mg./pound or 0.1 mg./Kg., in 3-4 divided doses over a period of 12-24 hours, followed by a daily maintenance dose of 0.01 mg./pound or 0.02 mg./Kg.) Stimulants can be given if required e.g. caffeine sodium benzoate 7.5-15 mg. or nikethamide (250 mg. in 1 ml.) one quarter to one half ml. as required.

Hyperbilirubinemia of Prematurity

Premature babies have immature livers which fail to conjugate indirect-active bilirubin with glucuronic acid to form direct-acting bilirubin.[10] This is due to a deficiency of transferase enzyme required for conjugation.[11] Indirect-acting bilirubin accumulates in the blood and at a critical level it passes the blood-brain barrier. This barrier is more permeable during the early days of life, especially in premature babies. Exposure of the brain cells to bilirubin results in a deficient oxygen uptake and so to brain damage,[12] especially in the basal nuclei, i. e. kernicterus.

The reported incidence of hyperbilirubinemia among premature babies varies considerably in various centers (3 per cent to 39 per cent).[13] The incidence depends on many factors, see table 5. [14,22]

The reported incidence of kernicterus (in untreated jaundice) has also varied a great deal (2.4 per cent to 31 per cent).[12] The early signs of kernicterus include lethargy, reluctance to feed and eye-rolling. These are followed by head retraction, vomiting, cyanotic attacks, a high-pitched cry, an expressionless face and alterations in muscle tone. The mortality rate of untreated kernicterus is high. Babies who survive appear to improve at first but later development is disappointing. The most severely affected babies become rigid, have convulsions and bouts of pyrexia and these babies usually die during the first year of life. Less affected babies develop varying degrees of rigidity, choreo-athetosis, deafness, emotional instability and mental retardation.

Prevention of Hyperbilirubinemia

This entails avoidance of all the factors set out in table 5.

Prevention of Kernicterus

Various methods of treatment for hyperbilirubinemia have been suggested.

1. Exchange transfusion. There is some doubt as to what the

TABLE 5

FACTORS INFLUENCING INCIDENCE OF HYPERBILIRUBINEMIA OF PREMATURITY

I. PRENATAL

1. Race (premature babies are more mature for weight, if mean birth weight is low)
2. Familial immaturity of enzyme system [11]
3. Maternal diabetes
   - Intra-uterine anoxia [15]
   - Thyrotoxicosis
   - Hepatic cell damage [16]
4. Drugs taken by mother, e. g.
   - Vitamin K [17]
   - Sulfonamides [18]

II. BIRTH

1. Birth asphyxia
   - Liver cell damage
   - Blood brain barrier more permeable

III. POSTNATAL

1. Increased hemolysis, e.g.
   - Hemolytic disease
   - Vitamin K [19]
   - Infection
2. Increased permeability of blood brain barrier, due to
   - Prematurity
   - Anoxia (anemia, respiratory distress, birth asphyxia)
   - Infection
3. Damage to liver cells, by
   - Anoxia
   - Hypoglycemia
   - Infection
   - Hypothyroidism [20]
4. Competition for albumin (premature babies have relatively low levels of serum albumin) e. g. by
   - Sulfonamides [21]
5. Concentration of serum bilirubin increased by dehydration, due to
   - Infection [22]
   - Late feeding

critical level for transfusion should be. The danger of kernicterus certainly increases as the level of serum bilirubin goes up. (See table 6.) [23,24] Provided no special factors are present, i. e. conditions increasing the permeability of the blood-brain barrier, or substances competing for the serum albumin, etc., a safe critical level would seem to be 20 mg. per 100 ml. indirect-acting bilirubin.

TABLE 6

Association Between Concentration of Serum Bilirubin and Incidence of Kernicterus In Premature Babies

Author	Number of Infants	Serum Bilirubin (mg%)	Kernicterus		Follow up
			No. of Cases	Incidence	
Crosse [23] (1958)	68	<22	—	—	1 year minimum
	21	22 - 27	4	19 %	
	3	>30	1	33 %	
Koch [21] (1959)	31	<20	—	—	2 years (only 1/2 cases followed)
	14	20 - 30	2	14 %	
	4	30 - 40	3	75 %	

Transfusion is time-consuming and expensive, and the risks include infection and death; but in experienced hands results are excellent. Tolle [25] states that the risk of death from transfusion is four times the risk of kernicterus, but that is very different from the author's experience. (See table 7.)

2. Corticosteroids. These have been used with varying success in hemolytic disease [26] but it was originally believed that glucuronic conjugation was necessary for elimination of corticosteroids, and for this reason they might even be harmful. However, it is now known that ACTH is excreted mainly as 6-beta-hydroxy-hydrocortisone. [27] The use of ACTH was started in the Birmingham units early in 1959 and the results have been promising. (See table 8.) Murano [28] published good results with corticosteroids in August 1959.

The action of ACTH is not clear. It is known that the fetus has a greatly enlarged suprarenal which involutes rapidly after birth. It is therefore likely that a baby who is born prematurely may suffer from a lack of secretions from the suprarenal gland. [29]

TABLE 7

RELATIVE RISKS OF KERNICTERUS AND REPLACEMENT TRANSFUSION PREMATURE BABY UNITS, CITY OF BIRMINGHAM		
	JULY 1955-JUNE 1957 (2 YEARS)	JULY 1957-DEC. 1958 (18 MONTHS)
Babies admitted	1320	1060
Expected cases of kernicterus (1.08 % of admission) dead spastic	10 + 4 = 14	7 + 3 = 10
Transfused babies Total Number transfused in order to save each case of kernicterus	92 6.6	80 8.0
Results : Total Transfusion Transfusion death Cases of kernicterus (all spastic)	115 1 5	97 1 0

3. Other suggestions. These include the administration of Periston N,[30] the use of ultraviolet light,[31] the administration of glucuronic acid (now known to displace bilirubin from the serum albumin and increase the danger of kernicterus), and the administration of

TABLE 8

JAUNDICE AND ACTH SORRENTO PREMATURE BABY UNIT, CITY OF BIRMINGHAM		
	JAUNDICED BABIES (SERUM BILIRUBIN 5 MG. PER 100 ML. AND OVER)	
	Number	Number transfused
No ACTH	65	21
ACTH	67	4

intravenous salt-free serum albumin.[32] This last method has been used in animals only, but might prove useful.

Management of Hyperbilirubinemia

1. Watch every premature infant for the development of jaundice.

2. If jaundice develops, estimate the serum bilirubin level. The use of Gossett's[33] icterometer will reduce the number of laboratory serum bilirubin estimations necessary. Except during the first 36 hours of life (when it is wise to do a laboratory estimation on every baby developing jaundice) it is unnecessary to take blood unless the icterometer shows a degree of jaundice up to Number 3 or more.

3. Keep all jaundiced babies well hydrated.

4. Give ACTH if the serum bilirubin (indirect-acting) reaches 3 mg. on the first day, 4 mg. on the second day, or 12 mg. on the third day or after. Give 10 units twice a day for 3 days (or longer if jaundice not subsiding) then reduce dosage (5 units b. d. for 1 day, 2.5 units b. d. for 1 day and 2.5 units once for 1 day). Antibiotic cover should be given, e. g. penicillin 125,000 I. U. every 12 hours and streptomycin 40 mg./Kg./day divided into 2 doses at 12-hourly intervals.

5. If serum bilirubin reaches 20 mg. per 100 ml. replacement transfusion should be performed by experienced personnel in suitable surroundings.

If birth asphyxia, respiratory distress, anemia, infection, etc. are present; or if sulfonamides have been given, a transfusion might have to be considered at a lower level of serum bilirubin.

6. Continue to estimate the serum bilirubin level until it begins to fall. Repeat the replacement transfusion if the level rises again to 20 mg. per 100 ml.

Prognosis

This should be guarded if the serum bilirubin level reached 18-20 mg. per 100 ml. In tissue cultures, damage to the brain cells begins at 20 mg. per 100 ml. and the majority of the cells are killed at 40 mg. per 100 ml.[34] so probably some brain damage occurs even before kernicterus develops.

Every jaundiced baby should be followed up to the age of at least one year, to exclude brain damage and high tone deafness.[35]

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