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This review was written with the aim of highlighting specific neonatal problems in Hong Kong. It was based on the local publications obtained from Medline search, Hong Kong Index of Paediatric Publication published by the Hong Kong Paediatric Society in October, 1997, hand searching of abstract books published for local paediatric meetings as well as personal communication. This review also contained original works done by this author in phototherapy of neonatal jaundice, respiratory sequelae of bronchopulmonary dysplasia and inborn errors of metabolism. This brief review can not, of course, cover all the problems pertinent to neonatologists in Hong Kong. Hopefully, this work could serve as a handy reference for those working in this area and encourage others to continue the fine tradition established by our predecessors into the new millenium. I extend my sincere thanks to Professor Chap-yung Yeung, my Master course supervisor. He guided me through the complex maze of neonatology with provoking questions. Without his unfailing support, this review could not have been produced. Special thank is due to Ms Clara Hung, my personal secretary to her valuable help.

Daniel K. K. Ng
Hong Kong, China, 1999
CHAPTER 1: JAUNDICE IN NEONATES

Introduction

Neonatal jaundice (NNJ) is the commonest problem in Hong Kong neonates (vide infra). It is most likely to be unconjugated hyperbilirubinemia. Neonatal cholestasis would not be discussed in this chapter.

Epidemiology

Yeung\(^1\) found that neonatal jaundice accounted for 14.5% of admissions to the hospital paediatric department in 1971. By 1983, this condition only accounted for 7.8% of paediatric admissions.\(^2\) This dropped to only 5% of admission in 1996\(^3\). Similar downward trends are observed in China, Taiwan and Singapore(personal communication). Degree of jaundice was found to be lower in higher socio-economic group\(^3\). (Table 1). Poor hygiene, over-crowding, increased herbal consumption, less access to proper medical treatment were suggested to be responsible. The rate of kernicterus dropped from 1.8% of NNJ in 1966 to 0% in 1992-96\(^3\).

Table 1. Effect of socio-economic environment on frequency of neonatal jaundice in Hong Kong.

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Socio-economic class</th>
<th>No. infants</th>
<th>SB&gt;171 umol/L</th>
<th>SB&gt;256.5umol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Lower</td>
<td>198</td>
<td>78.8%</td>
<td>12.6%</td>
</tr>
<tr>
<td>B</td>
<td>Higher</td>
<td>100</td>
<td>32%</td>
<td>5%</td>
</tr>
</tbody>
</table>
Clinical Features

Li & Chau\(^4\) studied 131 jaundiced infants in 1967 and this group included 57 with indirect hyperbilirubinemia. Haemolysis and haematoma accounted for 46. 18 developed kernicterus. Amongst them, 14 were glucose-6-phosphate dehydrogenase deficient. 14 were kernicteric on admission and all but one died in this group. Yeung\(^1\) reported a series of 1,811 infants with NNJ in 1973. No specific causes were found in 57.9\% of this group of patients. The commonest known etiology for NNJ was ABO incompatibility, which was found in 22.9\% of patients. However, overt features of haemolysis was present in only less than a third of those who developed moderately severe jaundice\(^4\). G-6-PD deficiency was found in 13.4\%.

Li et al\(^5\) studied the relationship between early immunization and jaundice in 200 full-term Chinese newborns with birth weight over 2,500 grams in 70/71. Those with G-6-PD deficiency, significant cephalohematoma, significant bacterial infections were excluded. They found no significant difference between control group, BCG vaccination group, smallpox vaccination group, polio vaccination group and the group that received all three vaccines. They also assessed if occurrence of jaundice was associated with occult intrauterine infections. They used cord blood IgM level of 20mg/100 ml and above as indicative of occult intrauterine infections. They found no significant difference in SB level between the group with IgM >= 20mg/dL and the group with IgM < 20 mg/dL. Li et al\(^5\) found SB level to be over 205 umol/l in 54\% of their study population of 200 full-term Chinese neonates and 1\% to have SB level over 342 umol/l. SB level was noted to peak on day 4 and day 5 of life.
Fok et al\(^6\) studied a group of healthy Chinese term babies (N= 1,238) in 1983/84 (Table 2). Clinical jaundice was detected in 89%. Moderate/severe jaundice, ie SB>204 umol/l, was found in 23.9% of babies not associated with G6PD deficiency nor ABO blood group incompatibility with mothers. Subgroup analysis showed higher percentage in infants with ABO blood groups incompatible with that of the mother and infants with G6PD deficiency, 95.2% and 95.8% respectively. The mean age of peak serum bilirubin was 83 hours for ‘physiological’ jaundice, 81 hours for those with ABO blood group incompatible with that of the mother and 87 hours for those with G6PD deficiency.

Factors that were found to be associated with a higher peak SB level in the ‘physiological’ jaundice group included male sex, elder siblings who had a history of neonatal jaundice, breast-fed infants with or without supplementation with formula feed.

**Table 2** Distribution of peak SB levels and incidence of phototherapy among the infant groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Clinical Jaundice</th>
<th>Absent or minimal &lt;120</th>
<th>Mild 120-204</th>
<th>Moderate / severe &gt;204</th>
<th>Phototherapy</th>
<th>Peak SB level (µmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%*</td>
<td>N</td>
<td>%*</td>
<td>n</td>
<td>%*</td>
</tr>
<tr>
<td>1</td>
<td>1004</td>
<td>87.3</td>
<td>228</td>
<td>22.7</td>
<td>536</td>
<td>53.4</td>
</tr>
<tr>
<td>2</td>
<td>143</td>
<td>95.2</td>
<td>14</td>
<td>9.8</td>
<td>68</td>
<td>47.5</td>
</tr>
<tr>
<td>3</td>
<td>91</td>
<td>95.8</td>
<td>9</td>
<td>9.9</td>
<td>37</td>
<td>40.7</td>
</tr>
</tbody>
</table>

Group 1: non-specific jaundice, Group 2: ABO incompatibility, Group 3: G6PD deficiency
*Percentage of total number in each group.
* P<0.01 when compared with Group 1
**P<0.01 when compared with Group 1 and male infants in Group1.
Pathogenesis

Lau et al.\textsuperscript{7} reported in a letter that they found evidence of increased bilirubin production in Chinese babies with ‘physiological’ jaundice. They analysed pulmonary carbon monoxide excretion rate (VeCO) which reflected total bilirubin production. In 20 infants with ‘physiological’ jaundice, mean VeCo was 15.7 +/- 4.2 uL/kg/h in contrast to the mean VeCO 11.4 +/- 1.7 uL/kg/h found in 18 infants with no jaundice; P<0.01. Increased bilirubin production is likely to be responsible for the high incidence of NNJ in Hong Kong Chinese.

Law et al\textsuperscript{8} examined cord blood in 111 infants who were admitted to the neonatal unit before day 3 after birth. They were admitted for NNJ or for observation because of prolonged leakage of liquor, birth trauma or high birth weight (>4.0 kg). None had polycythemia, sepsis, G6PD deficiency or other blood group incompatibilities. The cord blood were retrieved for analysis of alpha-fetoprotein (cAFP), AFP variant that is nonreactive to concanavalin (CNAFP), bilirubin (cBIL), albumin (cALB), glutamyltransferase (cGGT) and transferrin (cTRF). SB was checked from day 3 to day 6 by heel prick. A serum bilirubin concentration of 200 umol/L was used as the cutoff value to distinguish the nonhyperbilirubinemic from the hyperbilirubinemic infants. Only cAFP, cCNAFP, cCNAFP/cAFP ratio and cBIL were found to be significantly higher in hyperbilirubinemic group than nonhyperbilirubinemic group. cAFP and cCNAFP were found to have a high correlation coefficient; r=0.9415, P<0.001. Hence, cCNAFP were excluded from further statistical analysis. Stepwise multiple regression affirmed that cAFP and cBIL contributed to post-partum peak serum bilirubin concentration, r=0.504, P<0.0001. No significant correlation existed between cBIL and cAFP. The authors
concluded that a combination of cAFP and cBIL can be used to predict development of ‘physiological’ jaundice and the results suggested that both liver immaturity and increased bilirubin production were associated with development of ‘physiological’ jaundice. The question remain why Hong Kong Chinese have more bilirubin production and more immature liver than Caucasian.

Sung et al.\textsuperscript{9} studied glucaric acid excretion in 122 full-term Chinese babies with ‘physiological’ jaundice. 100 were born by caesarean section and 22 were born by normal vaginal delivery. D-glucaric acid was shown to be a sensitive index of hepatic microsomal enzyme induction in adults and children. They measured urine D-glucaric acid / creatinine ratio daily for first 5 days of life. They found statistically significant higher ratio of D-glucaric acid / creatinine on Day 1 & 2 in those that developed jaundice. This result raised doubt about the hypothesis that liver immaturity play a role in physiological jaundice. However, this result may not negate the hypothesis that babies with ‘physiological’ jaundice had immature liver function because D-glucaric acid excretion may not be useful in assessing liver maturity in the newborn.

**Kernicterus**

The incidence of kernicteric deaths in Queen Elizabeth Hospital dropped from 20% of all paediatric death in 1966 to 9.6% in 1971. In one series, 8.6% (156/1811) of term infants admitted into hospital developed kernicterus in 1968-71\textsuperscript{1}. The serum bilirubin of the infants with kernicterus ranged between 381 umol/l (22.3mg/dl) and 855 umol/l (50mg/dl) with an average 605.3 umol/l (35.4 mg/dl) in this series. Twenty-nine of the kernicterus infants died and most of them had not been transfused. With the improvement of socio-
economic condition in Hong Kong as well as a better educated public, the percentage of kernicterus dropped to 0.63% in 1981-82. In the ‘90s, only 1 to 2 cases were seen every 3 to 4 years in Queen Mary Hospital. The rate of brain toxicity from serum bilirubin above 20mg/dl (342 umol/L) were 26.5% and 5.5% for 1971 series and 1981/82 series respectively. Of the three patients that developed kernicterus in 1981-82, two were associated with glucose-6-phosphate dehydrogenase and there was no demonstrable cause in one infant and her bilirubin level was only 398 umol/l (23.3mg/dl). The last patient illustrated the point that it would be dangerous not to do exchange transfusion for severe hyperbilirubinaemia not associated with haemolysis in this part of the world. It can be seen from (Table 3) 12 cases of kernicterus occurred in the group with non-specific cause. This group may otherwise be labelled as physiological jaundice which is obviously a misnormer. It was suggested by Yeung to adopt the term ‘non-specific jaundice’ to describe raised SB level with no known causes rather than using the misleading term ‘physiologic jaundice’.

**Table 3**  Kericterus in hyperbilirubinaemic Chinese infants

<table>
<thead>
<tr>
<th>Associated condition</th>
<th>Infants</th>
<th>Kernicterus deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td></td>
</tr>
<tr>
<td>ABO incompatible</td>
<td>51/157</td>
<td>2/29</td>
</tr>
<tr>
<td>G6PD deficient</td>
<td>58/130</td>
<td>4/26</td>
</tr>
<tr>
<td>Cephalhaematoma</td>
<td>3/12</td>
<td>0/12</td>
</tr>
<tr>
<td>Non-specific</td>
<td>40/275</td>
<td>1/26</td>
</tr>
<tr>
<td>Total n</td>
<td>152*/574</td>
<td>7/83</td>
</tr>
<tr>
<td>%#</td>
<td>26.5</td>
<td>8.4</td>
</tr>
</tbody>
</table>

*Average serum bilirubin=35.4 mg/dl (range=22.3-50), 605.3 μmol/l (range 381-855) for 1969-71 and 1981-82 respectively. # percentage of kernicterus among those with serum bilirubin >=342 umol/L
Herbs

Yeung\textsuperscript{3} reported use of herbs in a survey of 125 pregnant women in 1982. 45\% took herbs, ‘12 Tai Pau’ being the most popular. He also found 75\% of neonates were given some herbs, Chuen Lin and Ngau Huang being most popular in a survey of 250 cases in 1972. Similar survey found a lower incidence of 38\% in 1982 (Table 4).

Fok et al\textsuperscript{11} found 54\% of expectant mothers took some Chinese herbs, eg Angelica Sinensis, Panax Ginseng, Radix Glycyrrhiza and Nelumbo Nucifera, after conception in their study of NNJ in Tsan Yuk Hospital in 1983/84. They found no significant association between maternal herb consumption and the mean peak SB levels. This was attributed to the fact that none of the mothers took herbs during the third trimester and no one took Chuan-Lien, Nga-Huang, Leh-Mei-Hua.

Table 4 Chinese herbs commonly used in neonatal period\textsuperscript{2}

<table>
<thead>
<tr>
<th>Herbs</th>
<th>1972(%)</th>
<th>1983(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Chuan-Lien’</td>
<td>50.9</td>
<td>28</td>
</tr>
<tr>
<td>‘Nga-Huang’</td>
<td>35.9</td>
<td>23.2</td>
</tr>
<tr>
<td>‘Leh-Mei-Hua’</td>
<td>30</td>
<td>14</td>
</tr>
<tr>
<td>Others</td>
<td>25</td>
<td>32</td>
</tr>
<tr>
<td>None</td>
<td>25</td>
<td>62.4</td>
</tr>
<tr>
<td>Infants Surveyed (n)</td>
<td>220</td>
<td>125</td>
</tr>
</tbody>
</table>

Yeung et al\textsuperscript{12} reported the in-vitro effect of a popular Chinese herb, ‘Yin-chen’ (Artemisia scoparia). This herb was manufactured in intravenous form and it was suggested to be given for treatment of jaundice. The dosage was 25-50 ml of the extract to be diluted with saline and to be infused over 15-20 minutes. The extract was incubated with pooled cord serum at different concentrations. Free bilirubin was assayed by the horseradish peroxidase method. They found that Yin-chen produced a significant increase in free bilirubin level compared
with control for a given bilirubin/albumin molar ratio. Similar study was performed with ‘Chuen-lin’ (Coptis chinensis/japonicum)\textsuperscript{13}. Similar results of raised free bilirubin by displacing bound bilirubin were obtained. Subsequently, Yeung\textsuperscript{3} summarized the effect of Chuen-lin, Ngau Huang and Yin-chen. He performed in-vitro study of effect of Chuen-lin and Yin-chen on bilirubin-protein binding in cord blood sample as well as in-vivo test of effect of Ngau-huang on bilirubin-protein binding. He found all three herbs were highly effective in displacing bilirubin from its albumin binding. Both Chuen-lin and Yin-chen were found to have a strong dose-response relationship. This result showed that these herbs were effective to decrease the SB level by displacing bilirubin from serum. This unbound bilirubin would be deposited in the brain and other organs. This of course would be more harmful than bilirubin in the serum.

**Indomethacin and bilirubin-albumin binding**

Lam et al\textsuperscript{14} reported an in vitro experiment studying the effect of indomethacin on bilirubin-albumin binding. Lyophilised indomethacin powder was added to 2 ml aliquots of pooled cord blood serum to make up concentrations of 1500 ug/l, 3000 ug/l and 4500 ug/l. The blood concentration of indomethacin after an oral dose of 0.2mg/kg was shown to be 27-1500 ug/l. Free bilirubin was measured by using horseradish peroxidase. The concentration of free bilirubin was determined from the initial rate of bilirubin oxidation measured by direct spectrophotometry of the incubated mixture after a timed exposure to peroxidase and hydrogen peroxide. The bilirubin to protein titration curve was compared with a normal serum control containing no indomethacin. No difference was found with the amounts of free bilirubin between the indomethacin treated serum and normal serum. It was suggested by the authors that the lack of competition between bilirubin and indomethacin for albumin
binding may be due to presence of different binding sites for these two chemicals under usual therapeutic conditions. However, the authors cautioned that the in vitro study was conducted in physiological pH whereas ill-preterm infants were often acidotic and hypoxaemic.

**Transcutaneous bilirubinometer**

Fok *et al*\(^\text{15}\) compared the Airshield-Minolta transcutaneous bilirubinometer’s readings (TcB readings) with serum bilirubin(SB) level as measured by the AO Unistat bilirubinometer. 259 full-term neonates with jaundice were recruited. 202 neonates were not treated before the measurement whilst 57 were receiving phototherapy during the measurement. The transcutaneous readings were obtained from both the forehead and mid-sternum.

TcB readings from the sternum were consistently lower than the forehead readings for the same SB level. Sternum reading correlation with SB was also slightly better than forehead readings (r =0.91;P<0.001 versus r = 0.86;P<0.001). Exposure to photolight significantly reduced the correlation between TcB indices and SB levels. The correlation coefficient dropped to 0.26 for TcB readings from the sternum and to 0.79 for those from the shaded area of the forehead. This rendered TcB index unreliable in those given phototherapy. This study showed that using forehead TcB index of >=22 would include all neonates with SB level >= 255 umol/l (15mg/dl) , ie sensitivity=100% and specificity was 66%. They also found that haematocrit level contributed little to the regression formula.

Sung *et al*.\(^\text{16}\) studied 63 clinical jaundiced term babies who presented to the Kwun Tong MCH clinic in the first two weeks of life between June and September 1983. They found
good correlation (r=0.847) between TcB index and SB level. TcB index was the mean reading of the duplicate TcB readings over glabella in this study. Using TcB index of >=21 to detect SB level >221, they found 100% sensitivity and 88% specificity.

Leung et al\textsuperscript{17} studied 66 Chinese term babies who presented with jaundice after being delivered in their hospital between March and April, 1982. TcB index was taken as the mean of two readings. TcB index was obtained at four sites: forehead, sternum, abdomen and right thigh. They found correlation between TcB index and SB level to be 0.89 (forehead), 0.92 (sternum), 0.84 (abdomen), 0.87 (thigh). They also found a highly reproducible results with coefficient of variation less than 3.5% after obtaining five consecutive readings in each of four patients.

\textbf{Phototherapy}

Phototherapy was first used in Hong Kong in 1969. Lau et al\textsuperscript{18} studied efficacy of continuous versus intermittent phototherapy in 34 full term normal birthweight babies with ‘physiological’ jaundice that required treatment, ie SB between 190 umol/l and 205 umol/l. The babies were divided into 3 groups- group A (n= 13) underwent continuous phototherapy, group B(n=9) received four hours of phototherapy followed by four hours off, group C(n=12) underwent one hour of phototherapy and three hours off. Irradiance was checked regularly and was maintained at 350 uW/cm\textsuperscript{2} +/- 5%. SB level were determined every 6 to 8 hourly. The three groups had comparable birthweight, gestational age and initial SB level. The change in SB level with time was represented by a bilirubin growth curve which was constructed by the least square method. A polynomial of third degree (SB= a+bxT+cxT\textsuperscript{2}+dxT\textsuperscript{3} where SB= interpolated serum bilirubin level;
a, b, c, d = coefficients of the polynomial equation; and T = time) was found to be a satisfactory mathematical model. No significant difference was found in peak SB level, rate of decline of SB level amongst the three groups. Significant difference (p<0.001) was found in total hours of irradiation in these three groups. The mean hours of irradiation for group A, B and C were 89.9 hours, 43.4 hours and 25.0 hours respectively. This result supported the hypothesis that the rate-limiting step in photodegradation of bilirubin in vivo was the migration of photoproducts out of the skin. The time required for this step has been estimated to be one to three hours. This intermittent phototherapy regime allowed saving of energy, better bonding with mothers.

Chung et al.\textsuperscript{19} studied stool frequency in 68 jaundiced babies who received phototherapy. The mean daily stool frequency during and after phototherapy were 4.34 and 3.53 respectively. The difference was neither clinical nor statistically significant. They also examined for evidence of lactase deficiency by looking at change of capillary blood glucose level after a dose of lactose, 2 gm/kg. In all 10 patients, the rise in blood glucose was above 20 mg/dl before, during and after phototherapy. They concluded that no evidence of lactase deficiency existed during or after light treatment.

This author conducted a study\textsuperscript{20} to compare the effectiveness of Bilibed\textsuperscript{TM} (phototherapy unit underneath the patient) with conventional overhead phototherapy. Bilibed does not require use of incubator nor use of eyepatch. Chinese term infants aged less than 2 weeks with normal hemoglobin were included if SB level was greater than 220 umol/l in first 2 days of life or greater than 240 umol/l after 48 hours of life. 20 term babies were recruited. Nine were randomized to Bilibed group and eleven in conventional group. The two groups had comparable birth weight, gestational age, initial SB level. Phototherapy was stopped
when SB level dropped below 220 umol/l. The conventional treatment group had statistically significant lower bilirubin at end of therapy, 181.3 umol/l vs. 200.2 umol/l. However, there was no difference in total phototherapy time, total drop in bilirubin, rate of bilirubin drop, bilirubin rebound after stoppage. Nursing time for preparation was significantly shorter with Bilibed, 6.7 minutes vs. 20.5 minutes. Parents were asked to state their preference before discharge. 14 preferred Bilibed and 6 preferred conventional phototherapy. The average daily cost for conventional phototherapy was $43.9, $42.6 for nursing time and $1.32 for equipment. The cost for Bilibed was $38.1, $13.9 for nursing time and $24.2 for equipment. The authors concluded that Bilibed™ was as effective as conventional phototherapy and Bilibed was cheaper and more acceptable to parents.

**Phenobarbitone therapy**

Yeung & Field21 studied use of phenobarbitone in 93 Chinese neonates with SB level between 10-20 mg/dL in first two weeks of life. 117 cases were recruited as control. Treatment group received phenobarbitone syrup orally at a dose of 5mg eight hourly for normal birth-weight and 6mg/kg/day for low birth-weight until SB level dropped below 10mg/dL. 45% of control cases required exchange transfusion(ET) whilst only 4% of treated cases required ET(p<0.001). This led to subsequent study of prophylactic phenobarbiton by Yeung et al22 involving 133 term infants. Primigravida mothers of blood group O and Rh+ve with no complications of pregnancy were allocated consecutively in turn to one of three study groups - group 1: control, group 2: mothers given phenobarbitone 30mg every night commencing at 38 weeks’ pregnancy and continuing until delivery, group 3: infants were given syrup phenobarbitone 5mg 8 hourly from 6 to 8 hours after birth for 3 to 5 days until the serum bilirubin showed a tendency to fall to levels below 10
mg/100ml. Those with G6PD deficiency, pyruvate kinase deficiency, cephalohematoma were excluded. In infants without ABO incompatibility, SB level in the phenobarbitone treated infants was significantly lower than control from the third day onward. In those with ABO incompatibility, the SB level was significantly lower in the phenobarbitone treated infants than the control group by the second day. SB level of the treated infants were significantly lower than those of the infants of treated mothers from day 4 for Group O infants and from day 6 in those with ABO incompatibility. Comparing control group and ‘treated mother’ group, the treated group had significantly lower SB level by day 3 for group O infants but no significant difference was observed for those with ABO incompatibility. SB level remained significantly lower for two more days after cessation of treatment. Phenobarbitone prophylaxis is an effective method to prevent kernicterus in areas where phototherapy is not readily available.

Yeung & Yu studied the bromsulphalein(BSP) clearance in NNJ that were treated with phenobarbitone. 40 full-term newborns were studied during the first 2 weeks of life. All were without clinical manifestation of other diseases or evidence of acute haemolysis. 20 were assigned to treatment group who received phenobarbitone syrup orally in the dosage of 5 mg 8-hourly. The 20 infants not receiving the drug served as controls. BSP tests were performed on admission and repeated 24 hours later. They found that BSP clearance of the first, which was related to uptake by liver, and second phase, which was related to liver excretion, was increased significantly, comparing 1st and 2nd day (p<0.025). Similar increase was seen in the control group but the increase was not significant (p= 0.2 to 0.49). The result suggested that phenobarbitone improved both hepatic uptake and excretion of BSP. Similar mechanisms might account for its effect on bilirubin level.
Yeung reported a study looking at the effect of phenobarbitone, which was given as therapy for NNJ, on blood glucose level for NNJ. 46 babies were recruited into the study. All were full-term normal birthweight first-born blood group O infants born to mothers with similar blood group. Those with G6PD deficiency or sepsis were excluded. Treatment group received syrup phenobarbitone 5mg 8 hourly for 3 days starting 6 to 8 hours after birth for 3 days whereas control group received no medication. In the control group, a significant inverse correlation was found between the blood sugar and the serum bilirubin level. Similar inverse correlation was observed in the treatment group but the correlation did not reach statistical significance. Treatment group had a statistically significant decrease in serum bilirubin level starting from day 3 as well as a statistically significant increase in blood sugar level starting from day 3. It was postulated by the author that phenobarbitone raised blood sugar level through enzyme induction or enhancement of liver function which was also responsible for lowering the serum bilirubin level. Liberal use of oral phenobarbitone prophylaxis from 1970 to 1986 by the local maternal and child health centres was noted to be important to decrease the incidence of severe NNJ that require ET.

**Exchange transfusion (ET)**

ET was first performed by Dr. SC Wu in Tsan Yuk Hospital, Hong Kong in 1960 for hyperbilirubinemia (Personal communication). Tsao & Yu studied the effects of giving albumin before and during ET and compared them with controls. They found that the reserve dye-binding capacity was immediately increased but early priming decreased the efficiency of ET due to expansion of plasma volume. They concluded that ET should be performed as soon as possible after giving albumin. Ngai and Yeung reported an in vitro study looking at cell survival 1) at different times of exposure to bilirubin 2) the effect of
adding albumin to increase binding capacity 3) effect of removing free bilirubin. They found that adding albumin was much better than simple removal of free bilirubin in improving cell survival. The reason is probably albumin helps remove bilirubin bound to cell surface whereas removing free bilirubin would do nothing to the membrane-bound bilirubin. This beneficial effect was greater when intervention occurred in first hours demonstrating that bilirubin toxicity occurs in two phases. The initial phase of toxicity, probably at the membrane level, could be reversed. The second phase was irreversible when bilirubin entered intracellular compartment. The requirement for ET dropped dramatically in last 30 years\(^3\). It was not uncommon to perform five ET on one ‘call day’ in the 70s. Now ET is hardly done more than once a month in any particular department.

Fok et al\(^{27}\) reviewed their experience in using peripheral vessels for exchange transfusion from 1984 to 1989. 87 neonates underwent ET for severe NNJ and 127 for polycythaemia. The technique employed cannulation of radial artery with a 24 gauge Angiocath (Deseret Pharm.) and a peripheral vein with a 22 or 24 gauge Angiocath. Simultaneous withdrawal and replacement of blood or plasma were carried out at a rate of 5-10 ml/min. They successfully performed exchange in 201 infants (95% success rate). Minor complications occurred in 8 infants, blocked or dislodged catheters in 6 and subcutaneous extravasation in 2. No adverse cardiorespiratory events occurred and no ischaemia of the limbs were observed. This study showed that peripheral exchange transfusion was a definite alternative to exchange transfusion through umbilical venous catheter. For all its advantages, the main deterrent to peripheral exchange transfusion is probably the perceived difficulty of cannulating the radial artery. With supervision and encouragement from the attending neonatologist, this reluctance could be overcome.
Conclusion

The last three decades saw tremendous progress in the management of neonatal jaundice in Hong Kong. Health education of a better-educated public, ready access to medical care provided by the Mother & Child Health Center, use of oral phenobarbitone, availability of phototherapy, steady blood supply for exchange transfusion are the important elements that will continue to play a vital part in the future. A further refinement in the provision of phototherapy to allow better mother-baby bonding will be needed. Adoption of intermittent phototherapy instead of continuous phototherapy should be seriously considered. A clinical trial comparing phenobarbitone, phototherapy or even tin-meso-protoporphyrin in terms of cost-effectiveness, parents’ preference would be a challenging but worthwhile project. The advent of university-based Chinese traditional medicine should encourage further research into use of herbal medicine in neonatal jaundice.
Reference


CHAPTER 2: ERYTHROCYTE GLUCOSE-6-PHOSPHATE

G6PD catalyzes the entry step of G6P into the pentose phosphate shunt for production of NADPH which is important in protecting red cell membrane. In the Chinese, about five G6PD variants account for the majority of the enzymes characterised. The G6PD gene, located on chromosome Xq28 region, is 18 Kb long consisting of 13 exons transcribed to a 2.269 Kb messenger RNA with 1.545 Kb of coding regions. The commonest variant in South China, G6PD Canton, was found to be due to a G to T substitution in nucleotide position 1376 leading to mutation in amino acid position 459, arginine to leucine. Routine screening for G6PD deficiency has been adopted in Hong Kong. G6PD deficiency was found to be high in South China and Indochina (Table 1).

Table I – G6PD Deficiency in South East Asia (Male)

<table>
<thead>
<tr>
<th>Population Groups</th>
<th>Number Tested</th>
<th>G6PD Deficient</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taiwan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mainland Chinese</td>
<td>282</td>
<td>5</td>
<td>1.77</td>
</tr>
<tr>
<td>Taiwanese Chinese</td>
<td>343</td>
<td>1</td>
<td>0.29</td>
</tr>
<tr>
<td>Hakka Chinese</td>
<td>1535</td>
<td>84</td>
<td>5.47</td>
</tr>
<tr>
<td>Hong Kong</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult Chinese</td>
<td>200</td>
<td>11</td>
<td>5.50</td>
</tr>
<tr>
<td>Newborn Chinese</td>
<td>1379</td>
<td>61</td>
<td>4.42</td>
</tr>
<tr>
<td>Kwangtung (Quangdong)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult Chinese</td>
<td>1048</td>
<td>90</td>
<td>8.60</td>
</tr>
<tr>
<td>Malaya</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aborigines</td>
<td>607</td>
<td>103</td>
<td>17.00</td>
</tr>
<tr>
<td>Chinese</td>
<td>747</td>
<td>28</td>
<td>3.80</td>
</tr>
<tr>
<td>Malays</td>
<td>550</td>
<td>14</td>
<td>2.60</td>
</tr>
<tr>
<td>Indonesia</td>
<td>446</td>
<td>5</td>
<td>1.10</td>
</tr>
<tr>
<td>Thailand</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Various Provinces</td>
<td>1577</td>
<td>189</td>
<td>11.98</td>
</tr>
<tr>
<td>Filipinos</td>
<td>1205</td>
<td>86</td>
<td>7.10</td>
</tr>
</tbody>
</table>
Yeung and Lee reported the use of a semi-automated method to assay red cell G6PD activities. Only 20 ul packed cells are required and 21 tests can be done at once in 20 minutes. They compared it with the WHO-37° manual method and found a highly significant correlation (r=0.98; p<0.005). They also found highly reproducible result (coefficient of variation = 1.4% to 2.6%). They examined 2,723 fresh cord blood samples from Chinese infants, 1379 boys and 1344 girls. Amongst the boys, the enzyme level separated into two groups. A small group of 61 (4.42%) infants had level less than 3IU/g Hb and were obviously deficient. The other large group showed enzyme level to be distributed along a normal bell shaped curve ( mean +/- SD = 15.4 +/- 2.7 IU). Using 3 SD as cut-off value for normal, enzyme level below 7.3 IU/g Hb would be classified as deficient state. 6 infant girls were found to have enzyme level less than 3 IU suggesting they were homozygous deficient subjects. This represented an incidence of 0.45% (6/1344). Eighteen girls had enzyme levels between 3.1 and 7.3 IU/g HB suggesting they were heterzygous deficient. Fluorescent spot test showed suspicious result in 6 of these 18 girls and normal result in the other 12 girls. However, fluorescent spot test showed complete correlation with this new test in those with enzyme level < 3IU/g Hb and those with enzyme level > 7.3 IU/g Hb.

Lam et al reported the results of the neonatal screening programme in Hong Kong in 1986. It was started in 3/84 to screen for congenital hypothyroidism and G6PD deficiency. It covered all newborns delivered in the 23 government maternity homes, three obstetric units in two major government regional hospitals and eight government subvented hospitals. Cord blood was collected from the placental side and 2.5 ml blood was put in EDTA bottles for G6PD screening. All male neonates were screened while females were screened on a selective basis. A total of 23,304 male were screened from 3/84 to 6/85. 1,041 were found
to be deficient in fluorescent spot test. Thus, the incidence of G6PD deficiency in male newborns is 4.47%.

Yeung\(^6\) reported 11.4% of infants (80/704) who developed bilirubinaemia above 10mg/dl were associated with erythrocyte G6PD deficiency. G6PD deficiency was associated with higher incidence of severe hyperbilirubinemia compared to other causes. Two of the four infants who developed kernicterus were also from the G6PD deficient group. They tended to run a more prolonged course of jaundice and acute haemolysis often occurred beyond the first week of birth. Infection, herb exposure and inhalation of naphthalein vapour were associated with significantly higher incidence of severe hyperbilirubinemia necessitating exchange transfusion among G6PD deficient infants. Among infants with low haemoglobin levels suggestive of haemolysis very little abnormality could be detected from the peripheral blood smear besides a fairly high number showing evidence of thrombocytosis and occasional Heinz bodies.

Chan et al\(^7\) studied haemolysis in G6PD deficient patients who suffered from typhoid fever. They injected G6PD deficient cells into normal subjects in the early stage of typhoid fever. They found that it was typhoid fever that caused haemolysis and not chloramphenicol. Chan observed similar phenomenon in those with viral hepatitis\(^3\).

In G6PD deficient individuals, their tissue G6PD enzyme levels are also lower than normal in the leucocytes, platelets, liver, kidneys and adrenals.\(^3\) Since there are alternative pathways for the generation of NADPH in nucleated cells, most of these subjects do not suffer from any other cellular dysfunction. Chan\(^3\) tested the production of cortisol by the
adrenals and the metabolism of cortisol as well as the bromsulphalein excretion by the liver and found these to be normal.

In some variants of G6PD deficiency with leucocyte G6PD level less than 2%, proneness to infection similar to chronic granulomatous disease was observed. Neutrophils did not kill non-hydrogen peroxide producing bacteria, eg S. aureus. Patients with leucocyte G6PD level which are 25% of normal or greater have been shown to have no increased susceptibility to infection or decreased bactericidal activity. Lau et al reported an 11-year-old boy with recurrent skin abscesses and lung abscess with methicillin sensitive Staphylococcus aureus. They found G6PD level to be 0.5 IU/gm Hb in rbc and around 9% of normal in wbc. Detailed investigations of his neutrophil function did not reveal any significant abnormality. Serum Ig level were all normal. They suggested that wbc G6PD activity between 9% and 25 % is probably the minimal level for normal neutrophil function.

Conclusion

G6PD deficiency is a fine model of success of scientific medicine. It illustrated the path from disease, i.e. hemolysis, to identification of enzyme defect, i.e. G6PD, to gene defect, i.e. G to T substitution in G6PD Canton to pilot screening program showing it to be a common disease in Southern Chinese to adoption of universal screening program in the whole territory. It is a superb example of collaboration between clinicians, scientists and government. It serves as an example of successful screening program.
Reference


CHAPTER 3: NEONATAL RESPIRATORY DISORDERS

Bronchopulmonary dysplasia (BPD)

This author prepared a review of BPD under the guidance from Prof. CY Yeung during the course. It was subsequently published in the Education Bulletin of the Hong Kong Paediatric Society (Appendix 1). A retrospective study was conducted by this author to look at prevalence of asthma in those previously diagnosed as bronchopulmonary dysplasia. Attempt was made to identify perinatal risk factors for development of asthma. All Chinese preterm infants, i.e.<32 weeks, who were oxygen dependence for more than 28 post-natal days, were recruited. Those with congenital heart disorders, renal or liver failure, immunodeficiency syndrome, cerebral palsy were excluded. Those with recent respiratory tract disease within one month were not challenged with hypertonic saline excluded. A total of 55 children were recruited (Male : Female = 29 : 26). Mean gestational age was 28.38 +/- 3.89 weeks. 25 infants were less than 1001 gm at birth and 22 were between 1001gm and 1500 gm. Mean duration of supported ventilation was 29 days. For those with birthweight less than or equal to 1,000gm. The mean duration of supported ventilation was 36.4 days compared to 24.3 days for those with birthweight between 1,001 gm and 1,500 gm. A BPD study data sheet was filled in when they returned for assessment (Appendix 2). Those who refused to return in person would have the questionnaire administered by phone. They were regarded as having current asthma if the answer to any of the questions #2, #7, #8 was yes or signs of asthma as determined by the author or spirometry that showed
significant change in forced expiratory volume in one second (FEV 1) to either hypertonic saline or bronchodilator. A detailed review was prepared by this author et al with regard to the use of hypertonic saline in diagnosing asthma\textsuperscript{1a}.

Mean duration of follow-up was 5.4 years +/- 2.34 years. Spirometry and hypertonic saline challenge test were successfully performed in seven children only as other children could not perform a satisfactory spirometry. Most were too young to be able to blow hard and long enough to allow a satisfactory assessment. All had normal baseline spirometry. Only one child showed hyper-responsiveness to hypertonic saline amongst the three asthmatic children who completed the spirometry successfully. This was similar to the sensitivity published locally and overseas (Appendix 3). In contrast, 24 (44\%) had symptoms or sings of current asthma and 30(55\%) had symptoms suggestive of past asthma. The prevalence of current asthma and ever asthma was much higher than the general incidence of 9.3\% having wheeze in the preceding 12 months, 21.7\% having nocturnal cough and 7.7\% ever had the diagnosis of asthma respectively in a local survey of 3,618 6-7 year-old using the same questionnaire\textsuperscript{1}. Family history of atopy, i.e. asthma, allergic rhinitis, eczema, urticaria, was found in 15 out of 50 families (30\%). Logistic regression analysis was performed for risk factors for current asthma. Birth month was found to be significantly associated with current asthma. Those who were born early in the year were significantly more likely to have current asthma. This result was similar to that of another study that showed girls who were born in summer were less likely to develop asthma\textsuperscript{2}. No significant relationship was found between current asthma and other risk factors that were analyzed. These included gestational age at birth, birth weight, pneumothorax, presence of patent ductus arteriosus and heart failure, duration of supported ventilation ( intermittent positive pressure ventilation, IPPV, and continuous positive airway pressure, CPAP), duration of nothing by
mouth, duration of absent protein intake, use of surfactant, presence of failure to thrive at the corrected age of one-year, respiratory syncytial virus infection, use of home oxygen, maternal antenatal smoking, education and occupation of mother, education and occupation of father, number of elder siblings, family history of atopy and presence of smoker at home. Chest deformity was present in 12 out of 31 children that were examined (39%). Growth failure at the corrected age of 1-year, defined as body weight less than 3rd percentile, was found in 17 out of 48 patients (35%). Eleven of these seventeen infants (53%) had normal weight at last follow-up whilst 6 had impaired growth (4 in height and weight, and 2 in weight only). Home oxygen was required in 18 of the 54 infants (33%). No association was found between requirement for home oxygen and growth at 1-year (p = 0.7566). This was rather surprising as those BPD infants that required home oxygen probably had more severe disease. It would be reasonable to assume that those with severe disease would be more likely to have growth failure. The lack of association could be due to either overuse of oxygen or under-use of oxygen. It is more likely to be under-use of oxygen as 24 hours oxymetry analysis was not routinely employed before discharge. Electrocardiography was available in 40 patients and none showed evidence of right ventricular hypertrophy. However, one worrying fact is the persistence of interstitial haziness in 25 out of 40 (63%) who had chest radiograph. It would be important to assess if this group of children would have earlier and more marked decline in pulmonary function when compared with those without BPD later on in life. Long term follow-up into adulthood is required in this group of children. Early education about avoidance of smoking and importance of physical exercise is essential.
Use of systemic steroid in BPD

Systemic steroid has been established as a useful treatment for bronchopulmonary dysplasia. Yeh et al\textsuperscript{3} undertook a multicenter randomized, double-blind clinical trial of early use of systemic steroid in prevention of BPD. 262 preterm infants were recruited. Dexamethasone was administered intravenously from day 1, 0.25 mg/kg every 12 hours for first week and tapered off over next three weeks. Infants in the treatment group had significantly lower incidence of BPD. However, significantly more infants in the treatment group had either bacteremia or clinical sepsis. There was no difference in mortality between the groups. Yeh et al\textsuperscript{4} published a follow-up study of the treatment group one year later. 133 children (70 control, 63 treatment group) were studied at the age of 2-year. The dexamethasone treated boys were significantly shorter and thinner and the treatment group had a significantly higher incidence of neuromotor dysfunction. They concluded that early use of systemic dexamethasone given in their regime could not be recommended at this stage. Lin et al\textsuperscript{5} studied the early use of dexamethasone in preventing BPD in one centre in Taiwan. 40 infants were recruited (birth weight from 500 to 1,999 gm) and they all had severe RDS. Dexamethasone (0.5 mg/kg/day for 1 week, then tapered over 3 weeks) was given within 12 hours of life. They found significantly lower incidence of BPD in the treatment group. No difference was found in mortality, incidence of sepsis or intraventricular haemorrhage between the two groups. A meta-analysis of 5 studies in other centers showed a statistically significant reduction in BPD or death (relative risk of 0.8, 95% C.I.0.64, 1.00).\textsuperscript{6} The main difference between these studies and the studies in Taiwan was the duration of dexamethasone, <3 days vs. 3 weeks respectively. It could well be appreciated that early use of systemic steroid for prevention of BPD was a potentially useful treatment modality that required further refinement and data gathering.
Ng et al\(^7\) reported adrenal response after a course of systemic steroid in a group of VLBW infants with BPD. Inclusion criteria were: 1) a gestation of less than 32 weeks and a birth weight below 1500 g, 2) dependence on mechanical ventilation and/or supplementary oxygen of more than 40% on day 14 of age together with chest radiographic findings consistent with the changes of BPD, 3) commenced on a full 3-week course of systemic dexamethasone, and 4) did not receive postnatal inhaled corticosteroid treatment. Infants were excluded if they had concurrent hypoglycemia, systemic infection, NEC or major surgery in the preceding week. The dexamethasone was given in a 3-week dose-tapering course: 0.6mg/kg/day for the first week, 0.3mg/kg/day for the second week, 0.15mg/kg/day for the third week. Dexamethasone was given via a nasogastric tube once full enteral feeding was established. Adrenal response was measured by hCRH (human corticotropin releasing hormone) stimulation test before dexamethasone treatment, at the end of the course and 4 weeks after steroid treatment had ended. 23 VLBW infants were enrolled. The mean gestational age was 26.5 weeks +/- 0.4 and the mean birth weight was 905g +/- 54. 3 died before the end of the study and 2 were discharged before the final hCRH stimulation test. ACTH and cortisol level was significantly suppressed immediately after the end of dexamethasone treatment. Both levels returned to pretreatment level 4 weeks later with the only significant difference found in the 60 minutes serum cortisol concentration (p=0.02). This study showed that the pituitary gland recovered its function 4 weeks after high dose dexamethasone treatment whilst the adrenal glands still have mild impaired response. The result was similar to other similar studies\(^8,9,10\). This would suggest that steroid replacement therapy would not be routinely necessary in face of stress if dexamethasone treatment was stopped more than one month before.
Corticosteroid is well known to cause gastroduodenal ulcers with haemorrhage and perforation. Ng et al\textsuperscript{11} reported two cases of ileal perforation in preterm infants treated with dexamethasone for bronchopulmonary dysplasia. The first case was a 625 g 24 weeks gestation male infant who developed abdominal distension on day 7 of dexamethasone. Abdominal radiograph showed pneumoperitoneum. Laparotomy revealed a distal ileal perforation 10 mm in diameter. No evidence of NEC was found. The second case was a 26 weeks’ gestation 855 g male infant. Routine chest radiograph revealed pneumoperitoneum on day 4 of dexamethasone treatment. A 3mm perforation was found in mid-ileum in laparotomy. Again no evidence of NEC was found. Both cases responded well to simple resection and ileostomy. The authors stressed that both cases were clinically well and cautioned the readers that high index of suspicion for bowel perforation was warranted in those patients receiving high dose corticosteroid.

**Inhalation device**

Medication can be delivered directly to the lung by either nebulizer or metered dose inhaler(MDI) through spacer in neonates. MDI through spacer is a more speedy and convenient method with similar efficacy. All spacers were equipped with a one-way valve to prevent rebreathing. It was observed that the valve did not actually open during inspiration in small infants. Fok et al\textsuperscript{12} conducted a study to see if the valves in two spacers, aerochamber and babyhaler, impaired albuterol delivery to a group of spontaneously breathing, oxygen dependent preterm infants (n=20). The first ten were recruited for the evaluation of neonatal Aerochamber and the second ten for Babyhaler. Each infant was given two puffs of albuterol twice 4 hours apart, one with the valve intact and the other with the valve removed. Clinical parameters including heart rate, respiratory rate, $\text{SaO}_2$, transcutaneous $\text{O}_2$ and transcutaneous $\text{CO}_2$ were monitored. Heart rate was consistently
raised in all infants after being given albuterol. Respiratory systemic resistance and compliance were measured before and after albuterol for both spacers with and without valves. After removing the valves of either Aerochamber or Babyhaler, the same dose of aerosol resulted in 50% or 100% greater decrease in resistance respectively. There was no significant difference in respiratory system compliance. The authors postulated that decreased compliance was more related to collapsed alveoli. The absence of extensive collapse in the studied infants probably accounted for the lack of difference between groups. They also measured the aerosol particulate size at the exit port of the two spacers both with and without valves. The particles size was only slightly larger in the spacer without valve but all readings were well within the respirable range of 1-5 µm. They concluded that removal of valves in these spacers would improve the effectiveness of MDI aerosols in newborns and small infants.

**Meconium aspiration syndrome**

Lam et al\(^{13}\) studied a group of infants delivered through meconium-stained liquor (MSL) at Tsan Yuk Hospital from January 1995 to December 1995. Inclusion criteria were delivery through meconium stained amniotic fluid, birth weight > 2500 gm and gestational age >34 weeks. Meconium aspiration syndrome (MAS) was defined as the development of respiratory distress in the first 6 hours after birth not explained otherwise and an abnormal chest radiograph. 437 infants (13%) of the 3360 live births were delivered through MSL. 10 were excluded from final analysis because of incomplete data or the turbid amniotic fluid was attributed to intra-uterine infection. The occurrence of thick, moderate, thin MSL was 37.4%, 29.2% and 33.4% respectively. 49 infants (11.5%) developed MAS. When comparing the perinatal characteristics of these 49 infants with those MSL without MAS, MAS was more likely to be associated with thick MSL, apnoea before intubation and lower
Apgar score at 5 minutes (8 vs. 10). 8 (16%) out of the 49 infants developed air leak complications on chest radiograph. 6 infants required mechanical ventilation for progressive respiratory failure (severe MAS). Thick MSL and requirement for intermittent positive pressure ventilation were significant risk factors for severe MAS. No mortality was reported in this series. The importance of this paper lied in 11.5% of MSL infants developed MAS even under the study setting which would be the ‘gold standard’ of perinatal care. This strongly suggested that MAS is not entirely preventable by the best intervention at birth or intense perinatal monitoring and intervention.

Lam et al\textsuperscript{14} reported preliminary favourable result of use of surfactant lavage in a small group of MAS, n=6, recruited from 1996 to 1997. They compared this group with 6 historical control treated in the same centre from 1994-1995. The two groups had similar demographic data and similar severity. They all had severe MAS necessitating mechanical ventilation with an oxygenation index of $\geq 15$ within 6 hours of life. The neonates were treated with tracheobronchial lavage with 15 ml/kg of diluted surfactant solution (Survanta) at a phospholipid concentration of 5mg/ml administered in 2-ml aliquots. They found significantly shorter duration of ventilation, 55 vs. 131 hours, and shorter duration of oxygen supplement, 4 days vs. 20 days. No mortality was seen in the treatment group whilst 2 deaths occurred in the control group. The main drawbacks of this study was the small number and the use of historic control. However, this pilot study provided data supporting the theoretical advantage of surfactant lavage in MAS. Thig should encourage conduction of a multi-centre randomized controlled trial into this area.
Congenital diaphragmatic hernia

Lee et al\textsuperscript{15} reviewed their experience in managing congenital diaphragmatic hernia in Hong Kong. Nine babies were managed their centre (PWH) from 1984 to 1987. 7 presented at birth with respiratory distress. 7 babies had left Bochdalek hernia (BH), one had right BH and one had Morgagni hernia. 6 babies required pre-operative positive pressure ventilation. Only one baby died because of accidental leakage of air from the tubing connection. The mortality was 14% amongst those that presented within first 24 hours of life. This compared favourably with the reported mortality of 25 to 75% in overseas centers at that time. The authors attributed it to the meticulous care offered in the NICU before and after the operation.

Lee et al\textsuperscript{16} published their experience of managing 21 patients in QMH from 1988 to 1996. All had BH, 17 left-sided and 4 right-sided. 3 presented as incidental finding in chest radiograph after neonatal period. 8 required endotracheal intubation and positive pressure ventilation at birth. These eight patients underwent repair operation between 10 to 24 hours of life. 10 other patients underwent operation beyond first day of life. 15 survived their peri-operative period. The overall peri-operative mortality was 29%. 3 died without operation, one had Patau’s syndrome, one died of streptococcal septicaemia and one died of severe respiratory failure. They found that maturity beyond 37 weeks and absence of symptoms within the first day of birth were significantly associated with improved survival. For those that required ventilatory support, oxygenation index (OI= mean airway pressure x FiO2 x 100 / PaO2) >20 and ventilation index (VI= respiratory rate x mean airway pressure) >1000 were associated with significantly increased mortality. Actually all those who had OI >20 or VI> 1000 died in this series. QMH’s series had a higher mortality than that from
PWH. Direct comparison was not possible as the two series might have different severity mix which could not be derived from the published data. Creation of a territory-wide registry would help solve the problem.

**Nasal CPAP**

Wong et al\(^7\) reported a fatal case of vacular air embolism whilst a preterm infant was receiving nasal prong CPAP at 5 cm water and a gas flow of 10L/min. He was born with RDS and responded well to surfactant. He was extubated on day 5. Nasal CPAP was started and he had an acute deterioration 6 hours later with bradycardia and unrecordable blood pressure. Large number of gas bubbles were aspirated from the umbilical vein catheter. Chest radiograph showed bilateral pneumothoraces and extensive vascular air embolism. He remained in critical condition with refractory seizures and disseminated intravascular coagulation and finally succumbed on day 13. The CPAP machine (Infant flow nasal CPAP system, Electro Medical Equipment Ltd. Sweden) was found to working normally and intravenous fluid infusion system was demonstrated to have no evidence of leakage. The authors suggested that the air leak occurred when the infant exhaled forcefully against the positive pressure during one of his agitation episode. This rare complication should not detract one from using CPAP which is a very safe procedure. However, judicious use of sedative and analgesic would help ensure a smooth clinical course.

**Inhaled steroid**

Fok et al reported the early use of inhaled corticosteroid in preterm infants with RDS in a randomized double blind control trial. They recruited preterm infants with RDS requiring ventilation within 24 hours of age. 27 were given a 14 day course of fluticasone propionate, 250 mcg/puff at 2 puff 12 hourly through a spacer, Aerochamber. 26 neonates were
recruited as controls. The treatment group had higher successful rate of extubation by 14 days (17/27 vs 8/26, p=0.038). The treatment group also had better respiratory compliance. However, no difference in mortality, requirement for systemic steroid after day 14 of age and occurrence of chronic lung disease were detected.

**Conclusion**

Increasing survival rate of very low birth-weight and extreme low birth-weight infants were followed by a higher incidence of bronchopulmonary dysplasia. Further research into prevention of bronchopulmonary dysplasia is urgently needed. Follow-up study into the longterm outcomes, e.g. growth, asthma, is important for neonatologists, paediatric and adult respirologists. A territory-wide registry of meconium aspiration syndrome, congenital diaphragmatic hernia would help standardize the report format allowing comparison of outcome in different centres. Use of surfactant in diseases other than RDS, comparison of different kinds of surfactant, actual impact of high frequency oscillation, comparison of different higher frequency ventilators provide a fertile ground for future research.
Reference:

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CHAPTER 4: INBORN ERRORS OF METABOLISM IN NEONATES

Introduction

Inborn errors of metabolism are rare disorders that mimic much commoner conditions like sepsis especially during the neonatal period. Hence, a working knowledge about inborn errors of metabolism is essential for those working with neonates otherwise the true diagnosis could be missed resulting in serious and undesirable consequences.

Practical biochemistry for cell energy production $^{1,2}$ (Fig. 1)

Carbohydrate

Glucose is the final common step leading to the process of energy generation from all carbohydrate. All exogenous carbohydrates like fructose, galactose, lactose, sucrose, starch, and endogenous carbohydrate, ie glycogen, are converted to glucose for generation of energy. Glucose would be converted to pyruvate in glycolysis. Pyruvate, a 3-carbon ketoacid, is converted to acetyl CoA which is fed into the Krebs cycle for generation of the reduced form of nicotinamide adenine dinucleotide (NADH). NADH is carried through oxidative phosphorylation for generation of adenosine triphosphate (ATP). ATP is the currency of energy at the cellular and molecular level.
Fat

Fat is composed of a 3-carbon backbone (glycerol) coupled to long chain fatty acids with varying degrees of saturation. Majority of energy is stored in long chain fatty acids. In a process of beta-oxidation, successive 2-carbon units are removed from the fatty acids. The 2-carbon unit is acetyl CoA which is fed into Krebs cycle for NADH and ATP production.

Protein / amino acids

Amino acid is comprised of two components, the amino group and an organic acid backbone. The amino group is metabolized in the form of ammonia, which is converted to urea through the urea cycle in the liver. Different organic acids are metabolized somewhat differently. However, acetyl CoA, pyruvate and ketones are the common end products.

Hong Kong Data (Table I)

Selected areas of inborn errors of metabolism were reported from Hong Kong. The author conducted an informal survey of various public hospitals to assess the number of cases of inborn errors of metabolism. In one hospital, QMH, the data was retrieved for patients with discharge diagnoses compatible with those listed in Table 1 from 1987 to 1997. For other hospitals, individual hospital contact person was requested to survey his/her colleagues for number of patients with diagnoses listed in Table 1. As all these diagnoses are unusual, it is unlikely that doctors responsible would forget. This informal survey would reflect the cumulative incidence over the past years. The true incidence must be higher as a number of cases would have been missed and a number of cases would be treated in private hospitals. Assuming these cases were recruited over ten years, the average
annual incidence of inborn error of metabolism as defined here would be around 9 cases per year in public hospitals. Given an average annual birth rate of 78,000 and assuming all affected babies born in private hospital were referred to public hospitals, the incidence of inborn errors of metabolism as listed in Table 1 would be at least 1.1 per 10,000 live birth. In Hong Kong, the commonest inborn errors of metabolism are glycogen storage diseases followed closely by organic acidurias. Urea cycle disorder would come third. Amongst organic acidurias, multiple carboxylase and ketothiolase deficiencies occurred more frequently than others. In China, regional screening programs for PKU have documented an incidence of 1/16,500 in Beijing, 1/17,000 in Shanghai. A pilot screening project for PKU was done in Hong Kong and no PKU was found. In Guangzhou, the incidence was estimated to be 5 per 100,000.

**Clinical Clues**

A history of consanguinity increases the risk of genetic diseases from 2 to 4%. As the placenta serves as an effective hemodialyser, affected infants are usually normal at birth and remain well for the first few days. Previous stillbirths or unexplained neonatal deaths would further increase the suspicion. Most of these disorders are due to protein intolerance and the affected infant often improves when feeding is withheld only to relapse with resumption of feeding. Affected neonates often present with poor feeding, depressed conscious level and convulsion. Besides the characteristic odour of isovaleric acidaemia, glutaric aciduria type II, maple syrup urine disease and cataracts in galactosaemia, specific signs are often lacking. The single most important indicator of an inborn error is altered neurologic status disproportionate to systemic symptoms and signs of the presumed etiologies, e.g. sepsis, asphyxia.
Types of clinical presentations

1) acute encephalopathy
2) diffuse liver disease
3) specific phenotypes

Acute encephalopathy (Table II, Fig. 2)

Acute encephalopathy is the commonest clinical manifestation of inborn errors of metabolism. It is usually due to diffusible small molecules and is often associated with hepatomegaly. Most of these disorders are due to defects of catabolic pathways including pathways of amino acid or organic acid degradation, defects of fatty acid oxidation, defects of ureagenesis, disorders of pyruvate metabolism and defects of the mitochondrial electron transport chain. These infants are usually well during the first few days after an uneventful pregnancy and a normal delivery. Unexpected deterioration occurs with poor feeding, vomiting, poor weight gain, increasing lethargy progressing and seizures to coma. Differential diagnoses include infection, malformation, trauma, intoxication.

Suggested initial metabolic screening

This includes blood pH, blood gases and glucose, plasma electrolytes, and renal and liver function tests. Urine is checked for glucose and ketones. For those with metabolic acidosis, the anion gap should be determined. Anion gap greater than 25mmol/l makes organic acidaemia a likely cause.

Plasma ammonia level should be checked and it is raised in organic acidopathies and urea cycle defects as well as in liver disease and sepsis (Figure 3). Lactic acidosis is a difficult
but important problem. It is important to remember that plasma lactate and pyruvate would be raised by two to three fold in the presence of venous obstruction by crying, tourniquet or restraint. The most important difference is to differentiate primary from secondary lactic acidosis causes by hypoxia, cardiac disease, infection or convulsions. Persistently raised level of lactate and pyruvate alert one to suspect primary pyruvate metabolism defects. Hypoglycemia is seen in disorders of carbohydrate or fat metabolism. Heavy ketonuria is unusual in the neonatal period and its detection should be immediately followed by organic acid analysis. Urine should be checked for reducing substance.

The laboratory should be provided with full details of diet and drugs when metabolic screen is requested. Where possible a blood sample must be taken before any blood transfusion. Amino acids concentrations are estimated in blood and urine by high performance liquid chromatography. One-dimensional thin layer chromatography differentiates at least five reducing sugar residues simultaneously in urine: lactose, galactose, glucose, fructose and xylose. Gas chromatography-mass fragmentography is used for organic acid analyses. Urine orotic acid level should be checked if plasma ammonia concentration is high.

**General management for suspected severe inborn errors of metabolism**

Fluid replacement and correction of acid-base and electrolytes imbalance is the important first step. Often large doses of bicarbonate is necessary and steady infusion is usually preferred. For those with resistant acidosis, a range of treatment options are available. This includes peritoneal dialysis, high-flow hemofiltration at 300ml/hr to 600ml/hr ultrafiltrate removal or continuous venous-venous hemofiltration with dialysis (CVVHD) or exchange transfusion. Assisted ventilation is often required to prevent hypoxia or hypercapnia.
Adequate glucose, using 15-20% glucose with insulin (1 IU/3 g glucose, or 0.05 unit/kg/hour) is employed to promote anabolism after first 24 hours.

A combination of vitamins in pharmacological doses are often given intravenously to sick infants while awaiting results because several inborn errors of metabolism have vitamin responsive forms. A typical megavitamin cocktail is listed in (Table 3).

**Role of carnitine in inborn errors of metabolism**

Carnitine is an amino-acid derivative. It has several important functions including:

1. the transfer of long chain fatty acids across the inner mitochondrial membrane for oxidation;
2. esterification of potentially toxic acyl-CoA metabolites which impair the citric acid cycle;
3. gluconeogenesis;
4. urea cycle and fatty acid oxidation in acute clinical crisis, facilitation of branched chain alpha-ketoacid (metabolites of branched chain amino acids) oxidation.

75% of our daily carnitine requirement is derived from diet. Breast milk, dairy products and red meat are rich sources of carnitine. The rest of the daily carnitine requirement is derived from endogenous production in liver and kidneys with conversion from lysine or methionine.

Carnitine is excreted in kidneys with active absorption across proximal tubules. The absorption threshold is 40 μmol/L.
Clinical conditions that benefit from carnitine supplement

1. Primary carnitine defects occur with abnormal carnitine transport from plasma to cells. Clinical features include cardiomyopathy and muscle weakness.

2. Secondary carnitine deficiency occurs:
   (a) in a range of inborn errors of metabolism and acquired disorders. Fatty acid acyl-CoA dehydrogenase deficiency states - SCAD, MCAD, LCAD. Organic acidurias - glutaric aciduria type I, methylmalonic acidemia, isovaleric acidemia, homocystinuria are the main inborn errors of metabolism that give rise to carnitine deficiency.
   (b) Acquired conditions include Fanconi syndrome, renal tubular acidosis, prolonged total parenteral nutrition, short gut syndrome, extreme prematurity, chronic valproate treatment.

3. Carnitine deficiency is confirmed by plasma free carnitine concentration less than 20umol/L

4. Carnitine insufficiency is diagnosed when the ratio of plasma acylcarnitines (total carnitine-free carnitine) to free carnitine is less than 0.4. This reflects that carnitine is insufficient to buffer toxic acyl-CoA compounds.

5. Carnitine should be given when deficiency or insufficiency state is diagnosed. 100mg/kg/day is given for simple deficiency. 200-800 mg/kg/day is given for those with urinary loss. Intravenous carnitine preparation is 1gm in 5ml and oral preparation is 330mg per tablet or 1gm per 10ml oral solution. Side effects include diarrhea, fishy odor, transient hair loss and skin rash.
Specific causes of acute encephalopathy

1. **Amino acid diseases:**

Maple syrup urine disease is a classical example of 16m. The defects lie in the branched chain 2-keto acid dehydrogenase complex. This results in a failure to catabolise the branched chain amino acids - leucine, isoleucine and valine. The incidence is reported at 1 in 180,000 world-wide. Four cases were reported from 1983-1994 in Hong Kong. One more case was diagnosed in Queen Mary Hospital during this period, giving a minimum incidence of 1 in 175,800 for Hong Kong Chinese.

There are five clinical types with classical form being most severe and the only form that presents during neonatal period. Clinical features include lethargy, poor sucking, alternate hypotonia and hypertonia, dystonic posture, seizure and cerebral edema. The urine smells like maple syrup or burnt sugar. Urine would be positive for 2, 4 dinitrophenylhydrazine (DNPH) test and raised level of branched amino acids especially leucine is found in blood, urine and CSF.

In the acute phase, peritoneal dialysis is instituted to remove toxic metabolites. Long term management involves dietary adjustment with branched chain amino acids free formula plus a small prescribed amount of leucine, isoleucine and valine as deficiency of these three amino acids may lead to severe dermatitis resembling acrodermatitis enteropathica. Liver transplant provides definitive cure.
2. **Organic acidopathies**

Accumulation of organic acids occur in many disorders in the metabolism of amino acids, carbohydrate and lipids. 15 cases of organic acidurias were reported in one series from one centre in Hong Kong from 1989 to 1995\(^5\).

Propionic acidaemia is a prime example. The defect lies in biotin-dependent propionyl-CoA carboxylase which converts propionyl-CoA (an intermediate metabolite of isoleucine, valine, threonine, methionine) to methylmalonyl-CoA. Clinical features include lethargy, poor feeding. Ammonia level is raised with marked ketoacidosis. Raised glycine level is also found. Hence, this disorder is also known as ketotic hyperglycinaemia. Acute management include peritoneal dialysis or hemodialysis, trial of biotin and protein restriction. Carnitine decreases the toxic effect of acyl coenzyme A ester within the cell by conjugating with these compounds to from acylcarnitine esters, which are excreted through the kidney.

In isovaleric acidaemia, glycine conjugates with isovaleryl groups for excretion. Hence, glycine supplementation leads to metabolic correction\(^10\). Forced diuresis with intravenous volume loads of 200 ml/kg/day of 10% dextrose with adequate sodium and calcium supplement with or without diuretic administration is the treatment of choice in acute metabolic deterioration of methylmalonic acidaemia because the clearance of methylmalonic acid by peritoneal dialysis is less than the renal clearance\(^12\).

For propionic acidaemia, synthetic amino acid devoid of isoleucine, valine, threonine and methionine is advised. Liver transplant is an alternative treatment.
3. **Fatty acid metabolic defects**

Long chain fatty acid couples with carnitine to enter the mitochondria whereas medium chain and short chain fatty acids enter the mitochondria readily. Long-chain, medium-chain and short chain acyl-CoA dehydrogenases are the first enzymes in the beta-oxidation of fatty acids for production of ketone bodies which serve as fuel for the brain and muscle after prolonged fasting. MCAD is the commonest defect in this group with incidence of 1/10,000-15,000. These disorders usually present after three months of age when longer interval of feeding is introduced. Clinical features include fasting non-ketotic hypoglycemia, coma, hepatomegaly, sudden infant death syndrome, cardiac hypertrophy, muscle hypotonia and recurrent Reye-like syndrome. Investigation reveals hyperuricaemia, hyperammonaemia, decreased total plasma carnitine, increased esterified carnitine and dicarboxylic aciduria. Treatment involves avoidance of prolonged fasting and carnitine administration may be beneficial by augmenting urinary excretion of toxic acyl-CoA intermediates.

4. **Urea cycle disorders**

Ammonia is formed from the catabolism of amino acids, cytosine, adenosine and amines and by gut bacteria. Ammonia is highly toxic to the central nervous system although the mechanism is unclear. As ammonia is highly toxic, it is rapidly converted to urea in the liver by a series of reactions termed the urea cycle. Ammonia enters the urea cycle in the liver mitochondria and ends with the production of urea in the cytoplasm.
Clinical features include encephalopathy, liver failure, respiratory alkalosis, pulmonary haemorrhage and intracranial haemorrhage. The plasma urea may be low but the most important investigation is the plasma ammonia concentration. Measurement of plasma amino acids, primarily citrulline level, and urine orotic acid level is helpful to determine the defective enzymes involved. Plasma citrulline level is in excess of 1000uM/L in arginosuccinic acid synthetase deficiency. Its level is between 100 and 399 uM/L in argininosuccinase deficiency. Citrulline is found in absent to trace amount in both ornithine transcarbamylase deficiency and carbamyl phosphate synthetase deficiency. However, urinary orotic acid concentration is high in ornithine transcarbamylase deficiency but low in carbamyl phosphate synthetase deficiency. Specific enzyme assay is possible in erythrocytes, leucocytes, skin fibroblasts or liver biopsy. Severe hyperammonaemia is a medical emergency. All dietary protein must be withdrawn and intravenous glucose started. Peritoneal dialysis is an effective way to bring down ammonia level. It is often the preferred method despite its inferior ammonia clearance compared with haemodialysis which is technically more difficult. Ten per cent arginine hydrochloride (6ml/kg/day), sodium benzoate (250mg/kg/day) and sodium phenylacetate (250 mg/kg/day) given intravenously are used to promote ammonia excretion by alternative pathways\textsuperscript{12}. Long term management includes protein restriction, arginine supplementation for argininosuccinate synthase deficiency and argininosuccinate lyase deficiency. Sodium benzoate and sodium phenylacetate or butyrate are employed to provide an alternative pathways of nitrogen excretion in some of the urea cycle disorders.
5. **Transient hyperammonemia of newborn**

The mechanism is not known. It usually occurs in the first 24 hours of life with respiratory distress in premature babies. Treatment is similar to urea cycle disorders.

6. **Primary lactic acidaemia (Figure 4)**

The essential feature is raised lactate level with or without acidosis in the absence of cardiac, pulmonary failure nor sepsis, i.e. tissue hypoxaemia. The incidence of primary lactic acidosis is not known and it was estimated that 250 new cases were recognised in the US per year\(^{14}\). Causes include disorders of oxidative phosphorylation, pyruvate oxidation and Krebs cycle enzymes as well as defects of gluconeogenesis.

a. **Disorders of oxidative phosphorylation, pyruvate oxidation and Krebs cycle enzymes.**

This group of disorders is characterised by progressive neuromuscular deterioration, seizures, dystonia, spasticity. Most cases involve inherited or spontaneous mutations in the pyruvate dehydrogenase complex (PDC) or in one or more enzymes of the respiratory chain.\(^{15}\) PDC is a series of linked enzymes located in the inner mitochondrial membrane. PDC mutations are very heterogeneous. Most arise within the coding region of the alpha-subunit of PDC, the gene of which is located on chromosome X.\(^{14}\). Most defects in oxidative phosphorylation involve mutations of mitochondrial DNA which is exclusively maternally inherited. Mitochondrial DNA mutations are associated with diverse phenotypic expression.
Measurement of serum lactate, pyruvate, hydroxybutyrate and acetoacetate provide helpful clues in determining sites of defects. A lactate/pyruvate ratio of more than 20 and a ketone body ratio, i.e. hydroxybutyrate/acetoacetate, of more than 2 is suggestive of defect in oxidative phosphorylation or pyruvate carboxylase. If lactate/pyruvate ratio is less than 10, defect in pyruvate dehydrogenase complex is suggested. If lactate/pyruvate ratio is more than 20 and ketone body ratio less than 2, Krebs cycle disorder is likely. Other investigation include neuro-imaging demonstrating cystic lesions in basal ganglia, brainstem and cerebral hemisphere. Enzyme activity may be measured in various tissues, including cultured skin fibroblasts, lymphocytes, skeletal muscle.

Megadoses of thiamine (200-1000mg/day) and lipoic acid (50-500mg/day) could be tried but success is rare. Ketogenic diets have been observed to reduce hyperlactaemia and to improve short term neuromuscular function in infants and children with proved PDC deficiency. Success of ketogenic diets depend on providing alternative source of acetyl CoA. Dichloroacetate (DCA) is shown to be effective in primary lactic acidosis. It inhibits PDC kinase, thus ‘blocking’ PDC in its unphosphorylated, catalytically active form. It is orally active and readily crosses the blood-brain barrier and other plasma membranes. Initial high dose up to 100mg/kg per day can be given either intravenously or orally. Serum lactate usually fall at least by 20% within six hours of the initial dose. Those who fail to achieve a 20% fall are unlikely to have therapeutic benefit from DCA and probably should not be retreated. Responders should be maintained on daily dose of 25-50 mg/kg. Daily dose of thiamine of at least 1mg/kg body weight is indicated for those
on chronic DCA administration to decrease the incidence of peripheral neuropathy. DCA is usually well tolerated with neuropathy, elevated transaminase level as the main side-effects.

b. **Defects of gluconeogenesis**

Defective enzymes include pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose-1, 6-diphosphatase, glucose-6-phosphatase. Glucose-6-phosphatase deficiency (von Gierke disease) is the commonest disorder amongst this group.

Clinical features include hepatomegaly and fasting hypoglycemia. Impaired glucose formation will leads to accumulation of pyruvate and lactate. Pyruvate is also converted to acetyl-CoA which in turn will be converted to fatty acid and ketones.

Treatment consists of correction of hypoglycemia and acidosis during acute phase.

Slow release glucose preparation, e.g. uncooked cornstarch, has been found useful for long term management.

c. **Disorders of mitochondrial electron transport chain proteins**

Defects of the electron transport chain results in impairment of electron transport leading to decreased ATP production. The inheritance is either autosomal recessive or maternally inherited. The maternal inheritance stems from the fact that mitochondrial DNA is derived from the mitochondria from ovum and sperm does not contribute to the mitochondria found in the zygote. Severe defects present in the neonatal period with encephalopathy and lactic acidosis. Milder defects present later with
chronic encephalopathy and other neurological deficits like ophthalmoplegia and optic neuropathy. Raised lactate level is found in CSF. This will be diagnostic if meningitis and seizure are excluded. Blood lactate to pyruvate ratio is also helpful and it is only suggestive if the ratio exceeds 25. Muscle biopsy should be obtained for ultrastructural and biochemical analysis.

If all tests are normal and seizures predominate, one should consider nonketotic hyperglycinemia and pyridoxine-dependent epilepsy.

Nonketotic hyperglycinemia

It is a severe autosomal recessive neurological disorder. The defects lie in one of four proteins (P,H,T,L) of the glycine cleavage system. Glycine is an inhibitory neurotransmitter in spinal cord but is an excitatory are in cerebral cortex. It also activates N-methyl-D-aspartate receptors (NMDA) thereby augmenting excitatory synaptic transmission. Preventing this effect on NMDA receptors might be of therapeutic value as activation of NMDA receptors causes an excessive calcium influx into neurones and may finally lead to cytolysis.

Clinical features include rapidly progressive hypotonia, obtundation, seizure, apnoea and characteristic hiccup within the first days of life. The type of can vary from Seizures include abnormal eye movement and myclonic seizures to generalized tonic-clonic convulsion. Elevation of cerebral spinal fluid (CSF) glycine to plasma glycine ratio is the diagnostic test as plasma glycine may be normal.
Hypomagnesaemia should be corrected if it is found. Strychnine, a potent antagonist of glycine at the inhibitory glycine receptors given at dosage of 0.2 to 1 mg/kg/day divided in six doses, may be helpful in mild cases to decrease muscular hypotonia. Ketamine intravenous infusion at 0.1 mg/kg/hour for four weeks followed by oral ketamine 1 mg/kg/day divided in 6 doses is found to be helpful in one case report to decrease convulsion frequency.\textsuperscript{17}

Neurological outcome is poor but early use of ketamine may possibly be helpful to improve the outcome.

**Pyridoxine-dependent epilepsy**

The defect probably lies in glutamic acid decarboxylase. Clinical features include serious seizures with no other identifiable disorders. Clinical and EEG response to pyridoxine should be sought. Trial of pyridoxine 75 mg bid for 3 weeks should be attempted even if there is no immediate response.

**Specific phenotypes**

**Neonatal jaundice**

Neonatal jaundice glucose-6-phosphate dehydrogenase (G6PD) deficiency results in decreased production of NADPH which is important to protect red cell membrane against oxidative stress and subsequent hemolysis. G6PD deficiency affects 400 million people worldwide.\textsuperscript{19} G6PD deficiency is a X-linked recessive condition. 4.42% of Hong Kong
Chinese male and 0.4% of Chinese female are affected. Heterozygous female is also at increased risk\textsuperscript{20} of.

They are prone to hemolysis by oxidant drugs, infection e.g. umbilical sepsis. Even for those without demonstrable hemolysis, moderately higher bilirubin level still tends to develop. G6PD level may also be low in leucocyte, platelet, liver, kidneys and adrenals in affected individuals. Usually no organ dysfunction is seen because of the presence of alternate pathways in nucleated cells for the generation of NADPH.

**Ambiguous genitalia**

Salt-losing congenital adrenal hyperplasia presents in the neonatal period with dehydration, shock and hyper-pigmentation. Females would present with ambiguous genitalia resulting from excessive androgen production. The commonest defect is 21-hydroxylase deficiency. Plasma 17 hydroxy-progesterone level is elevated.

**Lysosomal disorders**

The lysosome is a single membrane bound organelle in all cells, containing numerous enzymes. These enzymes function to degrade macromolecules for recycling. A few cases have been reported to present during the neonatal period as hydrops fetalis. Otherwise, they usually present later in life, eg mucopolysaccharidoses, sphingolipidosis. There is no effective treatment available for most of these disorders. There have, however, been some successes for a few disorder, for example, enzyme replacement therapy for Gaucher disease and bone marrow transplantation for Maroteaux-Lamy syndrome.
Peroxisomal disorder

Peroxisome is a single membrane bound organelle found in all cells except mature red blood cells. It has both anabolic a catabolic functions. Anabolic functions include synthesis of plasmalogen (ether phospholipid found in cell membrane especially myelin), cholesterol and bile acid. Catabolic functions include oxidation of a number of amino acids and organic acids.

Three kinds of defects have been reported.

1. **Defects of peroxisomal biogenesis**
   
   No peroxisome is found in this group of disorders. Cerebrohepatorenal syndrome (Zellweger Syndrome) was the first disorder in this group to be reported. Clinical features include dolicocephaly, high narrow forehead, large fontanelle, prominent epicanthic fold, deformed ears and cataract. Neurological abnormalities include marked hypotonia, delayed motor development and structural brain lesion. Liver cirrhosis and renal cysts are other associated features. Most patients die within 6 months. A number of related disorders have been described and it has been estimated that at least ten genes in which mutation may lead to failure of peroxisomal assembly.

2. **Peroxisomes present with some enzymes being defective**
   
   Peroxisomes are identified but the function of several peroxisomal enzymes is abnormal. Rhizomelic chondrodysplasia punctata is a prime example. Clinical features include dysmorphic facial features, proximal limb shortening and seizure. Development is delayed and growth is suboptimal. There are at least four
biochemical abnormalities resulting in raised phytanic acid level in blood and plasmalogen deficiency in tissue. Very long chain fatty acid level is not raised, in contrast to other peroxisomal disorders. Most cases die in early infancy.

3. **Single peroxisomal enzyme defect**

Single enzyme deficiency is found in the otherwise normal looking peroxisomes. Severe type may resemble Zellweger Syndrome. Mild type may present with progressive dementia and behaviour change with variable adrenal insufficiency, e.g. X-linked adrenoleucodystrophy. Investigations include assay for plasma very long chain fatty acid ratios, liver biopsy for ultrastructural analysis for peroxisomal morphology. Tissue or skin fibroblast can be cultured for specific enzyme analysis.

**Maternal PKU**

It is usually found in mother with poorly controlled phenylketouria. High phenylanine levels act as teratogen and affected babies would present with microcephaly, growth retardation, congenital heart defect especially ventricular septal defect.

**Diffuse liver disease**

Causes include galactosaemia, glycogen storage disorders and tyrosinemia type I.

**Galactosaemia**

This is due to galactose - phosphate 1-uridyl transferase deficiency. Clinical features include *E. coli* sepsis in neonate, cataract, hemolysis, hypoglycaemia and prolonged
jaundice. Urine for reducing substance is often negative. Urine chromatography for galactose should be performed in suspected case. Erythrocytes galactose-6-phosphate uridyl transferase activity can be measured by a commercially available assay kit. Dietary restriction of lactose and galactose is advised. Subtle defects of intellectual function are often found despite good dietary compliance.

**Glycogen storage disorders**

Common defects include glucose-6-phosphotase in type I and debranching enzyme in type III. Features include hepatomegaly, hypoglycemia, hyperuricaemia, hyperlipidaemia and lactic acidosis. Hypoglycaemia can be prevented by frequent feeds during the day and continuous nasogastric feeding at night, in infancy and early childhood. Raw cornstarch (2g/kg every six hours) has been shown to be effective in preventing hypoglycaemia in older children with glycogen storage disease type I as well as decreasing the hyperlipidaemia, hyperuricaemia and lactic acidaemia\(^{21}\).

**Hereditary tyrosinemia**

This involves defect in fumaryl acetoacetase, which is the last enzyme in the tyrosine catabolic pathway. Acute form presents with severe hepatocellular dysfunction, hepatomegaly and acute neurologic crises that began at mean age of 1 year. Chronic form presents with progressive liver failure, hepatocellular carcinoma and porphyria-like syndrome. Investigations show generalised amino aciduria, elevated liver transaminases and markedly raised serum alpha-fetoprotein level. Raised succinylacetone level in urine is diagnostic. The enzyme deficiency can be demonstrated in lymphocytes and cultured skin fibroblasts.
NTBC (nitro-trifluoromethylbenzoyl-cyclohexane), a pesticide derivative, brings down serum succinylacetone level and improve clinical symptoms. The oral dose is 0.1 to 0.6mg/kg/day. Liver transplant is recommended as a long term measure to decrease chance of hepatocellular carcinoma.

**Management when death seems inevitable**

Post-mortem examination must be carried out as soon as possible after death so that biochemical studies can be made on tissues that have not undergone enzymatic self digestion. If post-mortem examination is declined, limited biopsy study including liver, muscle and skin should be obtained. Serum should be frozen together with as much urine as possible.

Samples for biochemical studies should be snap-frozen (in dry ice or liquid nitrogen) and stored at -70°C until assay\textsuperscript{10}.

**Conclusion**

As a group, inborn errors of metabolism are not uncommon. They would usually masquerade as sepsis during neonatal period. It is therefore important for neonatologists to have a working knowledge about this group of disorders in order to diagnose them early. This would often mean a relatively normal life versus a severely handicapped one or even death for those that are diagnosed late. A central registry of inborn errors of metabolism reported in standardized format is desirable to provide data about the need of new screening programme in Hong Kong. A core group of clinical biochemists should join hands to provide a one-stop service for clinicians.
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**Figure 1**  Schematic representation of various metabolic pathways involved in energy production

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<td>complex I-V &amp; Coenzyme Q</td>
<td>for electron transport (oxidative phosphorylation)</td>
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**Note:**
- PC = pyruvate carboxylase, PDH = pyruvate dehydrogenase
- ATP = adenosine triphosphate (energy currency of cells)
- MSUD = Maple Syrup urine disease, PKU = phenylketouria
- MELAS = myoclonic epilepsy, lactic acidosis syndrome
- MCAD = medium chain acyl-CoA dehydrogenase deficiency
- MAD-S = multiple acyl-CoA dehydrogenase deficiency - severe
- Krebs cycle = citric acid cycle = tricarboxylic acid cycle (TCA cycle)
- Carnitine is essential for entry of long chain fatty acid into mitochondria

Words in italics represent examples of diseases.
# Table 1

Local Cumulative Occurrence in Hong Kong Public Hospitals up to 1997

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## Sources of data

QMH : discharge diagnosis from 1987-1997


CMC : Pang CP, et al., 1994 + personal communication

PMH, KWH, QEH, YCH, PYEH, TMH : personal communication
**Table 2**  
Acute encephalopathy

<table>
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<th>IEM that present as encephalopathy during neonatal period</th>
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<td>1) amino acidopathies (e.g. maple syrup urine disease)</td>
</tr>
<tr>
<td>2) organic acidopathies (e.g. methylmalonic aciduria)</td>
</tr>
<tr>
<td>3) hyperammonaemia (e.g. ornithine transcarbamylase deficiency)</td>
</tr>
<tr>
<td>4) inherited causes of lactic acidosis (e.g. pyruvate dehydrogenase deficiency)</td>
</tr>
<tr>
<td>5) encephalopathy with prominent seizures (e.g. nonketotic hyperglycinaemia)</td>
</tr>
</tbody>
</table>
Figure 2  Acute encephalopathy

encephalopathy in a previously well neonate with normal glucose/Na/ Ca

↓ infection screen
  +ve consult neurologist Dx
  -ve Treat infection metabolic acidosis

No increased anion gap raised ammonia level
  +ve yes no no Abnormal brain CT scan
  -ve yes no no
  yes yes no no
  yes yes no no
  yes yes no no

1. organic acidosis
2. amino acid disorders

Primary lactic acidosis pyridoxine response
  +ve -ve

hepatomegaly pyridoxine dependent epilepsy raised CSF/serum glycine
  +ve -ve

glucogenesis defect e.g. type 1 GSD mitochondrial disorders
  +ve -ve
  - ve

- pyruvate disorders
- Kerbs cycle enzyme defects
- respiratory chain disorders

non-ketotic hyperglycinemia
**Table 3**  
A typical megavitamin cocktail

<table>
<thead>
<tr>
<th><strong>Ingredient</strong></th>
<th>(mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>thiamine</td>
<td>30</td>
</tr>
<tr>
<td>riboflavin</td>
<td>200</td>
</tr>
<tr>
<td>biotin</td>
<td>100</td>
</tr>
<tr>
<td>nicotinamide</td>
<td>600</td>
</tr>
<tr>
<td>pyridoxine</td>
<td>100</td>
</tr>
<tr>
<td>vitamin B12</td>
<td>1</td>
</tr>
<tr>
<td>folic acid</td>
<td>15</td>
</tr>
<tr>
<td>ascorbic acid</td>
<td>3000</td>
</tr>
<tr>
<td>pantothenic acid</td>
<td>50</td>
</tr>
<tr>
<td>carnitine</td>
<td>300</td>
</tr>
</tbody>
</table>
Figure 3  Approach to hyperammonemia

ammonia level (> 170 umol/L)

- anion gap > 25 mmol/L
- respiratory alkalosis
- characteristic urine smell
- premature
- + urine ketone +ve
  + plasma citrulline
  + urine orotate
  + abnormal amino acid
  + DNPH test +ve
  + profile
  + 1st day of life

Organic acidosis

urea cycle disorder

amino acid disorder

transient

hyperammonemia

Figure 4  Approach to primary lactic acidosis

acute encephalopathy + lactic acidosis
+ no evidence of cardiac or pulmonary failure
+ no evidence of sepsis

cystic lesion in basal ganglia

brainstem / cerebral hemisphere

pyruvate or citric acid cycle enzyme defect

fasting hypoglycemia

hepatomegaly

raised CSF lactate

not associate with meningitis or seizure

mitochondrial cytopathy
Neonatal Pneumonia

Yeung and Tam\textsuperscript{1} studied the diagnostic value of gastric aspirate in neonatal pneumonia. They aspirated the gastric content after 4 hours of fasting in 4 groups of neonates: (1) 9 infants with necropsy evidence of bronchopneumonia (2) 10 infants with respiratory distress and radiological evidence of lung mottling (3) 7 neonates with some respiratory symptoms but not all features of group 2 (4) 24 healthy babies. The gastric aspirate was sent for culture as well as Wright’s and Gram’s stain. They found that polymorph in excess of 75\% was a good indication of chest infection. They found the gastric aspirate culture to be useless in differentiating infection from normal controls. This result would be most helpful in areas without ready access to X-ray and other diagnostic tests like C-reactive protein, echocardiography.

Neonatal meningitis

Yeung\textsuperscript{2} reported a series of 20 neonatal bacterial meningitis admitted to the Queen Elizabeth Hospital. 16 had gram negative infections and 4 had gram positive infections. Upon initial diagnosis, all neonates were started on intramuscular gentamicin 8mg/kg/day and intravenous ampicillin 200-400 mg/kg/day. Intrathecal gentamicin 4mg was given daily for 7 days, 2mg for LBW infants. If the offending pathogen was identified to be gram positive, intrathecal methicillin 25 mg daily would be given for staphylococcal infection.
and penicillin 10,000 units daily for pneumococcal and streptococcal infections. In those who showed persistent growth after 48 hours of therapy, intrathecal administration was changed from the lumbar subarachnoid to the intraventricular route. 6 of the 16 infants with Gram-negative infections were found to have ventriculitis and were treated with daily intraventricular antibiotics. It took 2 to 12 days to sterilize CSF in this group of patients. Intrathecal antibiotic was continued until the CSF showed all of the following changes: negative growth for at least 3 days, no demonstrable organism on gram smear and a decrease of polymorph to less than 50%. Infants who showed signs of increased intracranial pressure and features of midbrain compression were treated with intramuscular dexamethasone 1 mg 8 hourly for 3-5 days after starting antibiotics. The mortality rate was 20%. The four fatal cases died within 48 hours of admission, one Gram-positive and three Gram-negative infections. Follow-up assessments were available on 9 of the 16 surviving infants ranging from 3 months to 30 months. 6 infants were normal, 2 had minor neurological deficit and one had cerebral palsy and marked mental retardation. Of the other 7 survivors who defaulted, 5 were clinically normal at the time of discharge from hospital. This series reminded us the importance of early diagnosis of ventriculitis in neonatal meningitis. This paper is especially important today when the incidence of neonatal meningitis is much less (personal observation) and paediatricians had little experience in intrathecal antibiotics.

**Staphylococcal infection**

Tam and Yeung reported a survey of *staphylococcus aureus* infection (SAI) in their neonatal unit from 1976-85. They found 42 cases of SAI during that period. The overall incidence was 7.1/1000 admissions. Seven cases occurred during the period 1976-80 and 35 cases during 1981-85. Of the 42 cases, 13 were due to methicillin-sensitive *S. aureus*
(MSSA) while 29 were due of methicillin-resistant *S. aureus* (MRSA). Sites of infection are listed in Table 1.

<table>
<thead>
<tr>
<th>Sites of infection</th>
<th>MSSA</th>
<th>MRSA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septicaemia</td>
<td>12</td>
<td>29</td>
<td>41</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>2</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Meningitis</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Infected urachal cyst</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Parotitis</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Vancomycin, fusidic acid and amikacin were found to be active against all MRSA isolates. For erythromycin, 10/12 MSSA and 18/28 MRSA were sensitive. For co-trimoxazole, 9/11 MSSA and 23/25 MRSA were sensitive. For gentamicin, 6/9 MSSA and 3/29 MRSA were sensitive. MRSA infection was associated with significant longer hospital stay than that of MSSA, 64 days vs. 40 days. However, the mortality was similar between these two groups, 9.5%.

**Fungal infection**

Leung et al[^1] conducted a retrospective study of systemic candidiasis in babies admitted to neonatal intensive care unit (NICU) and special care baby nursery (SCBN) from 1983-88.

Diagnosis was based on the finding of one or more of the following: a positive blood culture, a positive suprapubic urine culture, a positive culture of a normally sterile body fluid such as cerebrospinal (CSF) or pleural fluid or postmortem histopathological demonstration of Candida infection. 21 Chinese infants were identified. 13 male and 8
female infants were affected. The mean birth weight was 1,653 g and mean maturity was 32 weeks. The mean age of onset was 31 days. 15 infants (71%) had onset of disease within 28 days of life. The mean body weight at onset of disease was 1,665 g. The overall incidence of systemic candidiasis in infants admitted to NICU was 2.4% and the incidence was 4.8% in very low birth weight (VLBW) infants. All patients had received intensive care prior to onset of systemic candidiasis. 71% developed systemic candidiasis whilst in the NICU.

Blood culture was positive in 14 out of 20 patients and suprapubic urine culture was positive in 15 out of 19 patients. CSF culture was positive in 3 out of 9 patients. Candida albicans accounted for 18 cases (86%), Candida tropicalis and Candida guilliermondii each accounted for one case and the remaining case was unidentified. Kidney was the most susceptible organ, 11 out of 21 patients (52%). Lung and pleura was involved in 10 patients (48%). Postmortem examination of the brain revealed granulomatous fungal lesions in all the fatal cases.

Medical treatment was attempted in 16 infants (76%). Almost all received amphotericin B intravenously and 5-fluorocytosine orally at standard maximum daily dose of 1 and 150 mg/kg. The mean duration for sterilization of blood was 8 days, of CSF 9 days, of urine 12 days and of surface swabs 11 days. 13 out of 21 infants (62%) died and 8 of whom had no treatment prior to death. Of the 16 treated infants, Candida was eradicated in 10 who completed treatment and the rest died before completion of treatment. For the 5 untreated infants, the mean duration from onset to death was 10 days.

This case series presented a local picture that was similar to that of literature. Incidence, demographic data were similar. Mortality in those with birth weight >1500 gm was
comparable other series. However, mortality in those with birth weight <= 1500 gm was higher (67% vs. 30-40%). This was probably related to delay in diagnosis of systemic candidiasis in a sick VLBW babies. The mean delay was 9 days (range: 4-21 days). This report would prompt the local neonatologist to have a high index of suspicion for systemic candidiasis. The authors also emphasized the importance of suprapubic urine as indicator of systemic candidiasis.

Nicholls, Yuen and Saing\textsuperscript{5} reported a case of \textit{Malassezia furfur} infection in a neonate in 1993. The patient was a 3.5 kg neonate with exomphalos. He was initially thriving with total parenteral nutrition given through Broviac catheter. Septicaemia developed with blood culture grew \textit{M. furfur}. He died on day 37 of life. \textit{M. furfur} was found in pericardial fluid, liver, blood and lung tissue taken postmortem.

**Group B Streptococcus (GBS) infection**

Liang ST \textit{et al}\textsuperscript{6} 168 mother-infant pairs in Tsan Yuk Hospital from 1983-84. The mothers were randomly selected from antenatal clinic. Cultures were taken from endocervix, rectum and perineum after 37 weeks’ gestation. Cultures were taken from the ears, nose, throat and umbilicus of the infants within 72 hours of delivery. Infants whose mother was known to be a GBS carrier were examined daily for evidence of neonatal infection. No prophylactic antibiotic was used.

Maternal carriage rate of GBS was 19 % when multiple sites were cultured (32/168). This was similar to overseas series of 5 – 30 % published during that period. The genital carriage rate was 7.4% in Hong Kong. 12 babies born to these mothers were colonized with GBS.
The vertical transmission was 37.5% in this study. The figure were 30-75% from overseas centers. This group of mother had significantly longer duration of rupture of membrane of 17 hours (p<0.05), more incidence of intrapartum fever (17%, p<0.05), higher incidence of premature/prolonged rupture of membranes (42%, p<0.05). These neonates had significantly lower birth weight (mean 2,904g, p<0.05). The difference was due to the inclusion of 2 infants who were small for dates. Two babies from the mothers carrying GBS developed symptoms suggestive of GBS sepsis but blood and CSF cultures were negative for GBS in both. Both were treated with antibiotics and responded well.

A total of 33 babies were found to be colonized by GBS giving an overall colonization rate of 19.6%. 21 out of these 33 babies were born to mother negative for GBS. These babies probably acquired GBS nosocomially and serotype 1c, III/R, 1b were most frequently isolated. Those born to mother positive for GBS carried GBS serotypes III, 1a. The concordance of serotypes in those mother infants pairs that were both positive for GBS was 88%. All serotypes were represented but there was an absence of type II. This was distinctly different from the 24% carriage rate of type II in a Caucasian population. No infants suffered from GBS sepsis in this series. This low attack rate of sepsis was compatible with the low attack rate of 0.58/1,000 live birth reported from the same center. Yuen et al⁷ reported the incidence of early onset Group B septicaemia to be 0.2 per thousand livebirths in Princess Margaret Hospital in an eight year review in 1986.
**Viral infection**

Tam et al. studied the prevalence of “TORCH” antibodies, IgG and IgM, in 439 consecutive cord blood samples of varying gestation. The prevalence of IgG against rubella, CMV and HSV were all above 85%. The prevalence was constant throughout different gestational ages. The prevalence for IgG against toxoplasma was low: 5.9% for gestational age <= 32 weeks, 14% for those between 32 and 36.9 weeks, 21% for those >= 37 weeks. This significant rise in prevalence suggested the possibility of acquiring the infection throughout pregnancy. A large scale longitudinal study would help to assess this possibility. Meanwhile, pregnant women should be warned not to eat raw meat, poultry, eggs or drinking unprocessed fresh milk. Virus IgM was done in those with total IgM >=20mg/dl or total IgA>=3mg/dl. A total of 70 infants had virus specific IgM tested. None was positive except one baby who was positive for rubella IgM. This infant turned out to have typical features of congenital rubella syndrome.

**Hepatitis B vaccine**

Wong et al. studied the use of hepatitis B vaccine +/- hepatitis B Ig in babies born to mother who carried HbeAg. 315 HbeAg positive mother were screened out from 9,072 pregnant women, 3.5%, from 6/81 to 9/83. 216 infants were born to the 262 mothers who agreed to participate in the study when the study was terminated. 21 infants were excluded – 8 with birthweight less than 2500g, 8 with Apgar score less than 7, 2 with congenital abnormalities, 1 born after prolonged rupture of membrane, 1 stillborn, and 1 infant brought to hospital 3 hours after birth. 6 infants were withdrawn from the trial by their parents before the treatment had been started. Enrolled infants were randomized to one
of four groups - Group 1: heat-inactivated hepatitis B vaccine and hepatitis B Ig within one hour of birth followed by vaccine at 1, 2, 6 month and HBIg at 1, 2, 3, 4, 5, 6 month, Group 2: vaccine at similar schedule and HBIg at birth only, Group 3: only vaccine was given at similar schedule, Group 4: placebo only. In each of the three treatment groups, the persistent carrier state arose much less frequently than in the placebo group (p<=0.0001). The difference between the attack rates in groups I and III also reached statistical significance (p=0.03). Group 2 did better than group 3 but this difference was not significant (p=0.09). Group 1 and 2 had similar cumulative incidence of chronic carrier.

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbsAg carrier</td>
<td>2.9%</td>
<td>6.8%</td>
<td>21.0%</td>
<td>73.2%</td>
</tr>
<tr>
<td>Protective rate</td>
<td>96.0%</td>
<td>90.7%</td>
<td>71.3%</td>
<td>NA</td>
</tr>
</tbody>
</table>

86 samples of cord blood (64.7%) were found positive for HbsAg but no correlation was found between the presence of HbsAg in cord blood and chronic carrier state in group 4. Transient hepatitis B infection, ie transient HBs antigenaemia or positive HbsAb, was found in 8 babies in group 4. The anti-HBs titre was similar in all treatment groups. No adverse effects were noted. This study paved the way for universal HB vaccination of all newborn infants in Hong Kong in 1988. Ip et al\textsuperscript{10} published a follow-up study in 1989. 188 infants were recruited to the three treatment groups and 47 were recruited to placebo group. They found higher rate of persistent HB infection in the treatment groups: 9.2% in group 1, 14.4% in group 2, 24.3% in group 3, 69.6% in placebo group. This indicated a continuous horizontal infectivity pressure. They further deduced that vaccination offered an additional 46% protection over natural protection whilst one dose of HBIg or multiple doses offered another 10% and 5% respectively. They also reported intrauterine infection in 2% of studied population. 7% failed to respond to immunization.
Lau et al\textsuperscript{11} studied immunogenicity of HB vaccine in 132 preterm infants with birthweight less than 1750gm from 9/89 to 3/91. 99 infants completed the study. They were assigned to two groups- group 1 received HB vaccine when body weight reached 1000 gm, group 2 received HB vaccine when body weight reached 2000 gm. Full term normal infants were recruited as control group. Second dose was given 1 month later and third dose was given 4 months after the second dose. Venous blood was taken 4 to 6 weeks after the second and third dose of HB vaccine. Seropositivity was defined as an HbsAb titer $\geq 10$ mIU/ml. Results were listed below.

### Seropositivity rates and geometric mean titers after the second and third doses of HB vaccine

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seropositivity rate (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After third dose*</td>
<td>78.9</td>
<td>90.5</td>
<td>100</td>
<td>0.0012</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(66.1, 78.9)</td>
<td>(77.4, 97.3)</td>
<td>(91.7, 100)</td>
<td></td>
</tr>
<tr>
<td>After second dose+</td>
<td>58.3</td>
<td>69.8</td>
<td></td>
<td>0.0012</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(44.9, 70.9)</td>
<td>(55.7, 81.7)</td>
<td>(78.9, 99.9)</td>
<td></td>
</tr>
<tr>
<td>HbsAb titer (mIU/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After third dose++</td>
<td>61</td>
<td>262</td>
<td>679</td>
<td>0.0007</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(27, 138)</td>
<td>(101, 680)</td>
<td>(265, 1742)</td>
<td></td>
</tr>
<tr>
<td>After second dose#</td>
<td>5</td>
<td>13</td>
<td>83</td>
<td>0.0009</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(2, 11)</td>
<td>(5, 30)</td>
<td>(24, 281)</td>
<td></td>
</tr>
</tbody>
</table>

*For pairwise comparison after third dose: group 3 versus group 1, $p=0.001$; group 3 versus group 2, $p=0.038$; group 2 versus group 1, $p=0.124$

+ For pairwise comparison after second dose, group 3 versus group 1, $p=0.001$; group 3 versus group 2, $p=0.023$; group 2 versus group 1, $p=0.142$

++By Fisher protected least significant difference, for comparison after third dose:
  group 3 versus group 1 and group 2 versus group 1, significant at 0.05 level

# By Fisher protected least significant difference, for comparison after second dose:
  group 3 versus group 1 and group 3 versus group 2, significant at 0.05 level

Group 2 had statistically higher HbsAb titre than group 1 although the difference in seropositivity rate did not reach statistic significance. Control group had a much better seropositivity rate and HbsAb titre. It was suggested by the authors that HB vaccination
should be delayed until infants reach 2000gm. Even than the failure rate after three doses of HB vaccine was still 10%. For those preterm infants born to mother with positive HbsAg or HbeAg positive status, a fourth dose may be considered between 9 and 12 months of age.

**Markers of sepsis**

Ng et al\(^\text{12}\) studied the use of IL-6, TNF, IL-1, CRP and E-selectin in diagnosing late onset neonatal sepsis (>72 hours of age). VLBW infants who were >72 hours of age with signs, symptoms, biochemical or haematological abnormalities suggestive of sepsis were recruited for 6 months beginning in June, 1995. Full sepsis screen was performed together with serial measurement of above-mentioned chemical markers on day 0, 1, 2, 4 and 7. Three groups of infants were recruited, Group 1 (n=35): confirmed infection, Group 2 (n=46): non-infected group, i.e. negative cultures results plus clinical improvement after stoppage of antibiotics, Group 3 (n=20) : well VLBW infants as control. Clinical characteristics were summarized in Table 1 and episodes of infection were summarized in Table 2.

**Table 1** Clinical characteristics of the study populations

<table>
<thead>
<tr>
<th></th>
<th>Infected group</th>
<th>Non-infected group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of infants</td>
<td>35</td>
<td>46</td>
<td>20</td>
</tr>
<tr>
<td>Gestational age (weeks)*</td>
<td>29.3 (2.6)</td>
<td>29.6 (2.4)</td>
<td>29.0 (2.7)</td>
</tr>
<tr>
<td>Birthweight (g)*</td>
<td>1175 (290)</td>
<td>1192 (266)</td>
<td>1106 (299)</td>
</tr>
<tr>
<td>Apgar scores:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 minute &lt; 7</td>
<td>17</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>5 minute &lt; 7</td>
<td>6</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>(days)*+</td>
<td>34.2 (29.3)</td>
<td>25.2 (32.7)</td>
<td>39.1 (15.2)</td>
</tr>
</tbody>
</table>

+ Episodes of suspected infection; *values are mean (standard deviations).
Table 2  Characteristics of the episodes of infection (n=45)

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Episodes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A Gram positive septicaemia (n=25):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>3</td>
<td>Osteomyelitis (x 1)</td>
</tr>
<tr>
<td>MRSA</td>
<td>7</td>
<td>NEC with peritonitis (x 2)</td>
</tr>
<tr>
<td>CONS</td>
<td>12</td>
<td>Meningitis (x 1)</td>
</tr>
<tr>
<td>Streptococcus agalactae</td>
<td>1</td>
<td>Meningitis (x 1)</td>
</tr>
<tr>
<td>Streptococcus faecalis</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>B Gram-negative septicaemia (n=12):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klebsiella sp</td>
<td>4</td>
<td>Meningitis (x 2); meningitis with NEC (x 1)</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>5</td>
<td>Osteomyelitis (x 1); NEC (x 1); died (x 1)</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>3</td>
<td>NEC (x 1)</td>
</tr>
<tr>
<td><strong>C Fungal septicaemia (n = 4):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida albicans</td>
<td>4</td>
<td>Meningitis (x 2); ventriculitis (x 1)</td>
</tr>
<tr>
<td><strong>D Other confirmed septic episodes (n=4):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEC</td>
<td>1</td>
<td>Infection responded to imipenem</td>
</tr>
<tr>
<td>? Gram negative septicaemia</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

CONS = coagulase negative staphylococci;
MRSA = methicillin resistant Staphylococcus aureus;
NEC = necrotising enterocolitis

101 episodes of suspected sepsis were investigated in 68 preterm VLBW infants. 45 episodes were confirmed, 44.6%. Of the infection episodes, 55% was due to Gram positive organisms, 27% due to Gram negative organisms, 9% due to fungi and 9% due to unidentified organisms. By minimising the number of misclassified cases on days 0 and 1, they determined the best cutoff values to be : IL-6 (31 pg/ml), TNF alpha (17 pg/ml), IL-1 beta (1pg/ml), CRP (12mg/l), E-selectin (64 ng/ml). These values were similar to the recommendations of the manufacturers. IL-6 had higher sensitivity (0.89) and negative predictive value (0.91) than other markers in late onset sepsis of VLBW infants. CRP had highest specificity and positive predictive value, 1.0, but lower sensitivity and negative
predictive value. 24 and 48 hours after onset of infection, CRP had the best sensitivity and specificity.

The authors calculated that combining CRP and IL-6 on day 0 together with either TNF alpha on day 1 or CRP on day 2 provided the best overall sensitivity (98%) and specificity (91%). In contrast to adult data, this study showed that neither IL-1 beta nor E-selectin were useful in VLBW infants.

Only one of 45 infected cases had normal values in all biochemical markers. This was a case of ventriculitis due to C. albicans. The authors speculated that was probably due to the fact that the infection was chronic, localized and low grade.

**Hypoglycemia**

Yeung\(^{13}\) looked at the relationship between hypoglycemia and sepsis. From 12/68 to 1/70, all neonates with overt clinical features of sepsis were screened for blood sugar levels on admission. Hypoglycemia was defined as blood sugar level less than 30mg/dL in the first 3 days of life, less than 40mg/dL thereafter for term infants and below 20mg/dL for low birth weight infants. Blood sugar was determined by the modified method of Asatoor and King. 56 infants were recruited into the study. 17 (30%) were found to be hypoglycemic. The commonest infection was umbilical sepsis (6/17) and septicaemia (4/17). 8 of them were symptomatic for hypoglycemia. 6 of them had persistent hypoglycemia despite calorie intake of 100-140 kCal/kg/day. This suggested increased utilization of glucose as the cause of hypoglycemia in neonatal sepsis. Of the 17 infants, 13 were normal birth weight suggesting that impairment of gluconeogenesis as another factor in hypoglycemia in
neonatal sepsis. They also found that hypoglycemia is more likely to occur in gram negative infection than gram positive infection (OR=20, p<0.01). This finding tallied with the previous reported finding of McFadzean and Yeung\textsuperscript{14} who found severe hypoglycemia in E. coli sepsis. Yeung et al\textsuperscript{15} did a follow-up study in 15 neonates who presented with infection, 8 umbilical sepsis and 5 septicemia, pneumonia. Exclusion criteria included gestation < 38 weeks, small for gestational age, maternal diabetes mellitus. 20 healthy infants were recruited as control. Intravenous glucose tolerance tests were performed after 3 to 5 hours of fasting. Glucose (1gm/kg as 50% dextrose) was given within 2 minutes. Serial capillary blood samples were taken at intervals of five minutes for 30 minutes. The rate of glucose disappearance(K\textsubscript{G}) was expressed as the percentage of glucose disappearing from the plasma in one minute. K\textsubscript{G} of infected neonates and healthy controls were 3.941 +/- 0.863 and 1.788 +/- 0.375 respectively (p=0.0001). K\textsubscript{G} was reassessed one week after appropriate antibiotics treatment in infected babies. All had significantly lower value and four had normal value. Hypoglycaemia was present in 5 of the 15 infected neonates after 3 to 5 hours of fasting. Plasma insulin level at fasting, 5 and 15 minutes after glucose were measured in 4 infected babies and 3 healthy control. No difference was found. Intravenous glucagon tests were performed in six control and five infected neonates four hours after the glucose tolerance test. No difference was found. These results suggested that hypoglycemia in neonatal sepsis was due to increased peripheral glucose utilization.

**Massive pulmonary haemorrhage**

Yeung\textsuperscript{16} reported a series of 35 neonates with proven fatal infection. Massive pulmonary hemorrhage, defined as confluent hemorrhages in more than two lobes of the lung, was demonstrated in 19 of the 35 neonates at postmortem examination although clinical
evidence of pulmonary hemorrhage was only evident in nine of these nineteen patients. Eight of the nineteen infants showed features of disseminated intravascular coagulation (DIC). Antemortem evidence of fibrin clots were found in all but one of the nineteen patients. Evidence of vasculitis in the lungs was demonstrated in 2 infants with massive pulmonary hemorrhage. This study reminded us that DIC was common in sick septic neonates and pulmonary hemorrhage was a common manifestation of DIC. Early detection and timely treatment may help improve the outcome.

**Unusual infection**

Wong et al\(^{17}\) reported two neonates who presented with fulminant sepsis leading to multi-organ failure secondary to Coxsackie B1 infection. Both mothers developed fever around the time of delivery. Both died within ten days of life. Most fatal coxsackie infections were due to coxsackie B2 to B5. Coxsackie B1 was a rare cause. Myocarditis and meningoencephalitis were the prominent symptoms in previous reports but features of severe sepsis, disseminated intravascular coagulation and massive liver necrosis was the dominant picture in this local series.

Wong et al\(^{18}\) reported a case of Campylobacter infection in the mother which resulted in severe neurologic damage in the baby. The mother had Campylobacter fetus subspecies fetus gastroenteritis at 33 weeks gestation. She was not given antibiotics as she was well by the time the culture was known. A repeat stool culture 2 weeks later showed no pathogens. Thick meconium was noted on artificial rupture of membrane at 37 weeks gestation after onset of labour. A female 2.4 kg baby was delivered with evidence of severe asphyxia neonatorum. Blood culture grew Campylobacter fetus subsp. Fetus. The same organism
was isolated from stool. Examination of CSF showed evidence of bacterial meningitis. CSF culture was negative as it was obtained after initiation of penicillin and cefuroxime. The clinical course was complicated by development of haemorrhagic infarct leading to rapid head enlargement. Craniotomy was done on Day 24 of life for evacuation of a subdural hematoma. She improved gradually and follow-up examination at the age of 10 month revealed severe spastic left hemiplegia and alternate convergent squint and delayed development. This case illustrated the typical course of severe C. fetus subsp. fetus infection in the neonate. It served to remind the serious nature of C. fetus in the stool in late pregnancy. Appropriate antibiotics treatment in the mother might have averted the adverse outcome.

Li et al.\textsuperscript{19} reported a 7-week old infant with congenital tuberculosis that presented with hepatosplenomegaly, generalized lymphadenopathy, DIC. The baby was born by an illegal immigrant from mainland China. He was initially misdiagnosed as malignancy. Tuberculosis was diagnosed after lymph node biopsy revealed active caseous tuberculosis. Unfortunately, he died within 4 days of admission before initiation of appropriate treatment. Post-mortem examination showed disseminated tuberculous foci in lungs, liver, spleen, adrenal glands, bone marrow and lymph nodes. Chest X-ray of mother showed pleural effusion suggestive of pulmonary tuberculosis. Lam et al.\textsuperscript{20} reported another case of tuberculosis in a 2-week-old baby girl who presented with respiratory distress and hepatomegaly. She was born by an occupational therapist working in an outpatient clinic. Chest radiograph was done for the mother’s cough. Unfortunately, the nodular opacity with central cavity was initially missed. Tuberculosis was diagnosed after gastric aspirate of the baby showed abundant acid-fast bacilli. The patient was treated with isoniazid, rifampicin and amikacin with good response. The baby developed gangrene of left big toe for no
apparent reason. This case illustrated the importance of detailed examination of the mother when faced with disease in neonate as well as highlighting the fact that tuberculosis is an endemic problem in Hong Kong. The present cases run a course similar to those reported in the literature with mortality of 50%.

**Conclusion**

Universal hepatitis B vaccination is an important achievement for Hong Kong people in the field of infection. The challenge for neonatologists in the new millennium would undoubtedly be the emergence of multi-drug resistant organisms, e.g. vancomycin-resistant enterococci, vancomycin-resistant staphylococci, muti-drug resistant tuberculosis. Those sick neonates with multiple invasive monitors dictate a low threshold of use of broad-spectrum antibiotics. This would encourage growth of the so-called ‘super-bug’ in an area with most susceptible patients which called for use of even newer antibiotics and the cycle continue. Stopping this vicious cycle require the use of more non-invasive monitoring, infection markers that provide result within minutes, speedy and sensitive detection of pathogens in different specimens. Research into these areas would be important.
Reference:
9. Wong VCW, Ip HMH, Reesink HW, Lelie PN, Reerink-Brongers EE, Yeung CY, Ma HK. Prevention of the HbsAg carrier state in newborn infants of mothers who are chronic carriers of HbsAg and HbeAg by administration of hepatitis-B vaccine and hepatitis-B immunoglobulin. The Lancet 1984;921-926


17. Wong SN, Tam AYC, Ng THK, Ng WF, Tong CY, Tang TS. Fatal coxsackie B1 virus infection in neonates. Paediatr Infect Dis J 1989;8:938-641


Lo et al\textsuperscript{1} reviewed a series of 2,404 Chinese children (ages 1 day to 14 years) with cardiac catheterization in Hong Kong from 1/73 to 12/85. They found coartation of aorta with or without ventricular septal defect was the most common acyanotic congenital heart disease that presented as heart failure in newborn. Among these, 39% had isolated coartation, 33% were associated with a supracristal VSD and 17% with perimembranous VSD.

Leung et al\textsuperscript{2} reviewed neonatal congenital heart diseases admitted to the Grantham Hospital, the only paediatric cardiac surgery centre, from 1981 to 1990. 782 symptomatic neonates with congenital heart malformation were admitted during this period. This represented an incidence of 1.02 per 1,000 live births. Demographics were summarized in Table 1. Outcome of different congenital heart diseases were summarized in Table 2

\textbf{Table 1}  
Demographics of the Neonates with Congenital Heart Diseases

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>484</td>
<td>62</td>
</tr>
<tr>
<td>Female</td>
<td>298</td>
<td>38</td>
</tr>
<tr>
<td>Ethnics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>760</td>
<td>97</td>
</tr>
<tr>
<td>Canasians</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Maturity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mature</td>
<td>676</td>
<td>86</td>
</tr>
<tr>
<td>Premature</td>
<td>106</td>
<td>14</td>
</tr>
<tr>
<td>Body Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2.5 kg</td>
<td>628</td>
<td>80</td>
</tr>
<tr>
<td>&lt;2.5 kg</td>
<td>154</td>
<td>20</td>
</tr>
<tr>
<td>Presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1\textsuperscript{st} Week</td>
<td>642</td>
<td>82</td>
</tr>
<tr>
<td>2\textsuperscript{nd} Week</td>
<td>811</td>
<td>0.5</td>
</tr>
<tr>
<td>3\textsuperscript{rd} Week</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>4\textsuperscript{th} Week</td>
<td>33</td>
<td>4.5</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>503</td>
<td>64</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>148</td>
<td>19</td>
</tr>
<tr>
<td>Tachypnoea</td>
<td>78</td>
<td>10</td>
</tr>
<tr>
<td>Rhythm Disturbance</td>
<td>28</td>
<td>4</td>
</tr>
<tr>
<td>Associated anomalies (extra cardiac)</td>
<td>102</td>
<td>13</td>
</tr>
</tbody>
</table>
This probably underestimated the true incidence because a number of congenital heart diseases, eg ventricular septal defect, would not require admission nor referral to Grantham Hospital during neonatal period. A subsequent study was published by Sung et al with data from Prince of Wales Hospital covering 1987 to 1989\(^3\). Among 20,928 babies born alive, 492 were referred by paediatric medical officer who examined all babies within 2 to 3 days after birth. 221 babies were found to have congenital cardiac malformation by either echocardiography or autopsy. Echocardiography missed one case of patent ductus arteriosus. Excluding 82 premature babies with PDA and 6 babies with transient tricuspid regurgitation, 133 cases of structural cardiac malformation were found, giving an incidence of 6.35 per 1,000 live births (Table 3). This is most likely an under-estimate of the true incidence because a number of cases would have been missed during the initial clinical examination, e.g. small VSD, ASD.

<table>
<thead>
<tr>
<th>Study Group</th>
<th>RVOT Obstruction</th>
<th>LVOT Obstruction</th>
<th>Left to Right Shunt</th>
<th>TGA Complex</th>
<th>Common Mixing</th>
<th>Misc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=782</td>
<td>n=285</td>
<td>n=173</td>
<td>n=119</td>
<td>n=96</td>
<td>n=65</td>
<td>n=44</td>
</tr>
<tr>
<td>Discharged</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(70%)</td>
<td>(75%)</td>
<td>(42%)</td>
<td>(88%)</td>
<td>(93%)</td>
<td>(52%)</td>
<td>(66%)</td>
</tr>
<tr>
<td>Died</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(30%)</td>
<td>(25%)</td>
<td>(58%)</td>
<td>(12%)</td>
<td>(2%)</td>
<td>(48%)</td>
<td>(34%)</td>
</tr>
<tr>
<td>Well</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(33%)</td>
<td>(22%)</td>
<td>(18%)</td>
<td>(65%)</td>
<td>(56%)</td>
<td>(27%)</td>
<td>(7%)</td>
</tr>
<tr>
<td>“At Risk”</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(16%)</td>
<td>(27%)</td>
<td>(8%)</td>
<td>(5%)</td>
<td>(9%)</td>
<td>(9%)</td>
<td>(23%)</td>
</tr>
<tr>
<td>Lost</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(9%)</td>
<td>(10%)</td>
<td>(5%)</td>
<td>(11%)</td>
<td>(7%)</td>
<td>(3%)</td>
<td>(13%)</td>
</tr>
<tr>
<td>Died</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(14%)</td>
<td>(16%)</td>
<td>(11%)</td>
<td>(7%)</td>
<td>(21%)</td>
<td>(13%)</td>
<td>(23%)</td>
</tr>
<tr>
<td>Total Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(44%)</td>
<td>(40%)</td>
<td>(69%)</td>
<td>(19%)</td>
<td>(28%)</td>
<td>(62%)</td>
<td>(57%)</td>
</tr>
</tbody>
</table>

Table 2  Outcome of the Neonates of Various Groups
Table 3 Number of patients and incidence per 10,000 live births in each major diagnostic category.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
<th>Incidence per 10,000 live births</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSD</td>
<td>60</td>
<td>29.6</td>
</tr>
<tr>
<td>PS</td>
<td>16</td>
<td>7.6</td>
</tr>
<tr>
<td>PAD</td>
<td>13</td>
<td>6.2</td>
</tr>
<tr>
<td>TOF</td>
<td>10</td>
<td>4.8</td>
</tr>
<tr>
<td>CT</td>
<td>7</td>
<td>3.3</td>
</tr>
<tr>
<td>ASD</td>
<td>5</td>
<td>2.4</td>
</tr>
<tr>
<td>DIV</td>
<td>3</td>
<td>1.4</td>
</tr>
<tr>
<td>AVSD</td>
<td>3</td>
<td>1.4</td>
</tr>
<tr>
<td>TAPVC</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>PA+IVS</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>HLH syndrome</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Ebstein’s malformation</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>COA</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Miscellaneous*</td>
<td>8</td>
<td>3.8</td>
</tr>
<tr>
<td>Total</td>
<td>133</td>
<td>63.5</td>
</tr>
</tbody>
</table>

Compared with other published series in English literature, Hong Kong had significantly higher incidence of pulmonary outflow obstruction. Hong Kong had more left ventricular outflow obstruction and left to right shunt but critical aortic valve stenosis was rare. We had less TGA and common mixing but none of these reach statistic significance.

**Echocardiography**

Leung et al assessed the role of echocardiography in neonates in a prospective study. They compared the diagnosis of echocardiogram which was reviewed by all three paediatric cardiologists together with the gold standard of cardiac catheterization or necropsy. 96 consecutive neonates were recruited from 10/83 to 4/85. Cardiac catheterization was carried in all babies except seven who were moribund on admission. These seven cases died subsequently and necropsy was carried out. A total of 536 cardiovascular anomalies were
diagnosed at cardiac catheterisation and at necropsy. Echocardiography correctly identified 512 anomalies, i.e., sensitivity of 95.5%. Seven false positive diagnoses were made by echocardiography, i.e., specificity of 98.6%. The management of 12 babies (12.5%) could not be planned on the basis of clinical and echocardiographic findings alone. In 76 out of the remaining 84 babies (79%), the proposed management plan did not require alteration after catheterisation. Echocardiography provided complete diagnosis in 67 (69.8%) babies. Most errors occurred in extracardiac vascular anomalies. This study confirmed the commonly held belief that echocardiography/pulsed Doppler ultrasound and a team of experienced cardiologists would decrease markedly the need for catheterisation. A follow-up study was done by the same group from 7/85 to 12/86. 140 consecutive neonates were recruited. 612 cardiovascular anomalies were identified by angiographic, surgical or autopsy findings. There were 23 missed or uncertain diagnoses (sensitivity = 96%) and 10 wrong echocardiographic findings (specificity = 98%).

**Treatment**

1) **Right ventricular outflow tract obstruction**

Leung et al. reviewed 62 consecutive neonates with pulmonary atresia and intact ventricular septum from 1979 to 1990. Since 1984, tripartite assessment of the right ventricle was introduced with the help of high resolution echocardiography. This approach allowed identification of those with small right ventricles and narrow infundibula for whom biventricular repair was not contemplated. Hence, they divided the patients into 2 groups: group 1 before 1984 (n=23) and group 2 after 1984 (n=39). All babies in group 1 underwent catheterization and primary ventricular outflow reconstruction by transannular pericardial patch enlargement irrespective of their right ventricular size or presence of sinusoidal coronary arterial
communications. In group 2, transventricular pulmonary valvotomy or shunt operation were performed during the neonatal period. This was followed by right ventricular outflow reconstruction in nine, ballon valvuloplasty in 8, Fontan operation in 2. Eight required no further intervention after the neonatal intervention. Total mortality in group 2 (10/39) was lower than group 1(12/23), p<0.01. The tripartite classification with surgery tailored to right ventricle size and the improved ICU care over the years undoubtedly contribute to the decrease in mortality.

2) **Left ventricular outflow obstruction**

Of the 173 babies, 98 and 25 had coarctation and interrupted aortic arch respectively, 50 had hypoplastic left heart. Conservative management was implemented for those with hypoplastic left heart sequence and all 50 babies died. Repair for those amenable to surgery include subclavian flap aortoplasty or end-to-end anastomosis with or without Gortex graft interposition.

Introduction of echocardiography in late 1982 facilitated the management in this group of sick babies as a number of babies died shortly after cardiac catheterization previously. Advent of interventional cardiac catheterization further advance the service. Amongst the 64 survivors, 12 developed re-coarctation. Ballon angioplasty was successfully performed in 11 of them.

3) **Left to right shunt**

Persistent arterial duct (n=51, 43%) and ventricular septal defect (n=48, 40%) were the commonest lesions for this group. Medical treatment by fluid restriction, diuretics and indomethacin successfully closed off 18 ducts while 31 required surgical ligation.
4) Transposition of great vessels

92 of the 96 neonates underwent balloon septostomy. The other four had an adequate atrial septal defect. Since 1983, septostomy was performed under echocardiographic guidance in the intensive care unit. Venous switch operation (n=39) was then performed at around 1 year of age. Four (4/39, 10%) died after the surgery. From 1989 to 1994, arterial switch operation was performed on 29 neonates. The early neonatal and late mortality were 7 and 14% respectively.

5) Common mixing

The commonest group was total anomalous pulmonary venous connection (n=38). Medical treatment alone was offered to 29 babies while operations, corrective or palliative, were performed on 36 neonates. Eight of the 33 neonatal survivors underwent further corrective surgery. Leung et al\textsuperscript{7} reported a follow-up study in abstract covering the period from 1991 to 1995. They reported a statistically significant improvement in the overall neonatal and surgical survival when compared with the previous report from the same centre (p<0.001). The best improvement was seen in repair of aortic coarctation.

\textbf{Patent ductus arteriosus (PDA)}

Nandi\textsuperscript{8} described a new technique of ligation of PDA. The standard technique at that time was dividing the ductus between clamps, followed by suturing. Nandi employed a new technique of first suturing with continuous horizontal mattress sutures after applying ductus clamps. This was then followed by division of ductus. The same needles were used to suture the cut ends with a continuous over-and-over stitch. This procedure minimised the
problem of bleeding. The initial suture lines prevented the divided ductal ends from retracting under the clamps. Nandi reported his series of 29 patients and none had postoperative complication. This technique would still be applicable today in cases where transvenous placement of occluder was not available or contradicated. Cheung et al\(^9\) reported the results of 40 consecutive patients who underwent percutaneous transcatheter occlusion of the PDA with the Rashkind occluder system (umbrella) in Grantham Hospital between 1991 and 1993. The mean age was 5.8 +/- 3.6 years. The mean procedural and screening time were 97 +/- 34 minutes and 19 +/- 10.7 minutes respectively. Successful placement of the umbrella was possible in all except 1 patient. Embolization occurred in one patient when the umbrella was dislodged into the right pulmonary artery and was subsequently retrieved with the wire loop. 36 patients were discharged on the day following the procedure and the rest within 48 hours. Residual shunt was found in 21 out of 38 (54\%) patients whose records were available at 24 hours and fell to 23\% at the end of the first year. The only significant difference between those with residual shunt and those without was the size of the duct. The larger duct was more likely to have residual shunt. The avoidance of thoracotomy scar, the shorter hospital stay without need for ICU stay makes transcutaneous occlusion of PDA the method of choice.

So et al\(^10\) studied the efficacy of enteral indomethcin in closing patent ductus arteriosus (PDA) in preterm infants. 60 preterms infants were found to have PDA from 3/87 to 8/89. 10 babies had surgical ligation because of contraindications to indomethacin therapy. 6 had small PDA that closed spontaneously. 3 babies were too ill to receive any treatment for PDA. Elevated urea and creatinine in the absence of frank oliguria (urine output <1ml/kg/h) was not considered contraindication. The remaining 41 babies were enrolled and given enteral indomethacin of 0.2mg/kg at 12 hourly interval for three doses. Indomethacin
powder was obtained from the commercially available 25mg capsules and then mixed with lactose by trituration, a mixing method. The mixture was suspended in 2-3 ml of 5% dextrose solution just before use. The mean birthweight was 1322 grams and mean gestational age was 29.7 weeks. Indomethacin was given at a mean age of 8.6 days. Overall success rate of duct closure was 71% and this was similar to that of intravenous indomethacin (79-82%). Although all treated infants developed oliguria, they made an interesting observation that those with raised creatinine before indomethacin treatment returned to normal level after treatment. This study would encourage those without access to intravenous indomethacin to try enteral indomethacin.

Ng et al\textsuperscript{11} compared oral sulindac, a relatively renal-sparing cyclo-oxygenase prostaglandin inhibitor, with intravenous indomethacin in closing PDA in preterm infants. Eight infants were recruited into each treatment group. Infants with congenital heart disease, those on high frequency oscillatory ventilation, those suspected to have severe infection and those with unstable clinical condition were excluded. The two groups of infants were matched for gestational age (+/- 1 week) and birthweight (+/- 100g). Indomethacin was given at 0.2mg/kg per dose for three doses for those weighted above 1250g. For those $<1250g$, the second and third dose were reduced to 0.1mg/kg/dose. Sulindac was given as 3mg/kg per dose 12 hourly for 4 doses. One failure was seen in sulindac group compared with 100% success in indomethacin. Sulindac treated group showed no significant change in urea and creatinine concentration whilst indomethacin treated group showed significant but reversible changes. The trial was terminated prematurely because one infant in the sulindac group died from severe acute haemorrhagic gastritis. This was actually an unexpected finding as sulindac was found to have less gastrointestinal side effect than indomethacin in adult. Hence, indomethacin remained the drug of choice in treatment of PDA.
Milne MJ et al\textsuperscript{12} studied the closure time of ductus arteriosus in 45 consecutive neonates admitted to the neonatal unit of Prince of Wales Hospital. They were divided by gestational age into 3 groups: group 1, n=15, <35 weeks; group 2, n=15, 35 to 37 weeks, group 3, n=15, >37 weeks. The mean closure time as defined by absence of shunting as detected by continuous wave Doppler was 105 +/-179, 33 +/- 15 and 46 +/- 39 hours for group 1,2,3 respectively. No statistic significance was found between these groups if those with RDS were excluded. No relationship was found between duct closure time and birth weight, maturity, oxygen therapy, Apgar scores. Closure time of ductus arteriosus was significantly longer in the presence of RDS, 178 +/- 250 vs. 40 +/- 35 hours, p<0.002. They found that the best predictor of ductal closure was peak ductal velocity. All infants with peak ductal velocity <1m/s had closure time in excess of 176 hours.

Sung et al\textsuperscript{13} studied the effect of maternal use of topical prostaglandin E2 gel on closure of ductus arteriosus. 51 full term babies were enrolled. 29 were born to mothers who had received a 3mg PGE2 pessary to ripen the cervix before induction of labour. The mean time interval between application of the gel and delivery was 13 hours. 22 controls were born to mothers who did not receive PGE2. Serial Doppler echocardiography studies were done within 12 hours of birth and every 12 hours subsequently until closure of ducts. The median closure time were 28 hours and 15 hours in the treatment group and control group respectively (p<0.05). Maternal and cord PGE2 were measured immediately after clamping and cutting of the cord. There was no difference between control and treatment group. This was probably related to the rather long time lapse of 13 hours between application and measurement. Multiple logistic regression found no significant contribution of birth weight and cord blood PGE2 concentration in predicting closure time. This study showed that topical use of PGE2 gel prolonged ductal closure time. However, no clinical significance
was found in any of the subjects. This study did not include a detailed summary of the haemodynamic description of the ductal shunting which would be more important than the exact time of closure of ductus arteriosus.

**Conclusion**

A lot of data were collected from Grantham Hospital in the last two decades. The pattern of congenital heart diseases is well established. Follow-up studies showed steady improvement in outcome. The next decade would see other hospitals taking increasing role in the surgical management of congenital heart disease. It is important for these hospitals to adopt a standardized documentation so as to allow comparison of outcome in different centres. This would allow early detection of problems. Paediatric cardiologists would play an increasingly curative role with the advent of interventional cardiac catheterization. Again meticulous documentation and long term follow-up is essential to provide support for evidence-based medical practice.
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Lau et al\textsuperscript{1} reported the experience in Princess Margaret Hospital and Tsan Yuk Hospital from 1980 to 1984. 19 cases (11 premature, 5 small for date and 3 normal weight term neonates) were diagnosed. The overall incidence was 0.3 per 1000 live births and that for low birthweight infants was 4.1 per 1000. The overall mortality was 58\% which compared unfavourably with the reported rates of 20 to 40\%. Only 1 out of 8 infants who underwent operation survived. Severe hypoxia was found in 9 cases. Overfeeding with either too much volume or too concentrated formula was found in 5 infants. Two VLBW infants developed NEC between 3 to 4 weeks after birth and both received large dose of intravenous vitamin E supplement. This observation was in line with the reported association between prophylactic vitamin E treatment and subsequent sepsis and NEC. The authors also highlight the low rate of breast feeding (10\%) during that time. The findings of hypoxia, improper feeding regimes, vitamin E overdose were still relevant in today’s practice. The rate of breast feeding is higher in 1990s, 41\% breast feeding rate on discharge from hospital was reported in 1997\textsuperscript{2}. However, it still needs to be improved with concerted effort of obstetricians and paediatricians.

**Organism**

Chan et al\textsuperscript{3} reported the culture results in 125 patients with NEC before commencement of antibiotics from 1988 to 1992. 59 infants(47\%) belonged to Bell’s Stage I, 48(38\%) to Stage II, 18(15\%) stage III. Male to female ratio was 67 : 58. Mean birth weight was 1700g.
Mean gestational age was 32 weeks and mean age at presentation was 10 days. Culture results from blood, pharyngeal aspirate, nasogastric aspirate, umbilical swab, umbilical catheter were analysed. 20 patients underwent laparotomy had peritoneal swabs taken. Positive cultures were present in 45 patients (36%) with 55 positive specimens. Positive cultures were obtained in 17 patients (29%) with Stage I, 15(30%) in Stage II, 13(72%) in Stage III. The commonest organisms were Enterobacter (29%), E.coli(14.5%) and Klebsiella(13%). All three belonged to the same family Enterobacteriaceae or enteric bacilli. They are not vigorous invaders of normal human tissue but are opportunistic human pathogens. From the antibiotics sensitivity pattern reported, gentamicin plus cefuroxime would cover most of the cultured organisms.

Wong et al\(^4\) reported an outbreak of NEC due to Citrobacter sensitive only to amikacin and imipenem in their NICU. Four cases were involved. All were preterm male babies (mean gestational age of 27.4 weeks) and low birthweight (mean weight of 1070 gram). All had antenatal dexamethasone. Last three cases were diagnosed within a 24 hour period about one week after the onset of the first case. The last three cases all had a fulminant course with pneumoperitoneum and extensive gut involvement within one day. Only the index case survived. The authors shared with the readers preventive measures adopted. This included repeated emphasis on handwashing, use of fresh expressed breast milk, slow advancement of enteral feed, administration of oral immunoglobulin (500mg/day), use of amikacin as first line antibiotics in face of clinical sepsis during that period. They reported successfully ending the outbreak. This case report highlighted the tragic results of NEC outbreak and outlined the possible measures to contain the outbreak.
**Breast milk**

Administration of breast milk to VLBW infants is usually through expressed breast milk. Care should be exercised for the collection process. Ng *et al* reported a pair of extreme low birthweight twins who developed fatal necrotizing enterocolitis. Twin A developed acute NEC on day 40 after 36 days of expressed breast milk from mother. Blood culture and peritoneal swab grew *S. epidermidis*. Resection of the gangrenous segments with primary anastomosis was performed. Enteral feeding with pregestamil was resumed three weeks after operation. NEC recurred and two small perforation in an ischaemic segment of the terminal ileum was found and oversewn. He sustained grade IV intracranial hemorrhage during this episode and dies a week later (day 68). Twin B was started on mother’s EBM on day 4. He developed septicaemia due to *S. epidermidis* on day 8. Despite clinical improvement with intravenous vancomycin, repeated blood culture on day 15 and 17 continued to yield the same organism. Extensive investigation failed to find the occult source of infection. He developed NEC on day 30. Resection and primary anastomosis was performed and feeding was resumed three weeks later. NEC recurred and he died of multi-organ failure. Three consecutive samples of mother’s EBM taken between day 21 (9 days prior to onset of NEC for twin B) and day 40 (day of onset of NEC for twin A) showed heavy growth of *S. epidermidis* with similar antibiotic resistance pattern as those obtained from the twins. There was no similar *S. epidermidis* infection during the same period. It seemed likely that the contaminated breast milk was the most likely cause of the septicaemia and NEC in the twins. This case report highlight the importance of ensuring proper collection and storage of breast milk collection. It also raises the important question whether routine culture of expressed breast milk is necessary. In view of its rarity, it probably should not be done unless evidence for its cost-effectiveness is available. These
two cases also highlight the importance of common sense. When twin B developed NEC on day 30 together with evidence of infected breast milk and persistent bacteremia, twin A should be taken off the infected breast milk. This might prevent him from getting NEC on day 40. When twin B died of recurrent NEC after reintroduction of milk three weeks post-operation, twin A should not be restarted on feeding on the same schedule 10 days later.

**Congenital heart disease**

Leung et al. examined the risk factors associated with NEC in neonates with congenital heart diseases (CHD). Nine (7%) of 133 neonates with CHD developed NEC between 1/85 and 12/86. Three possible risk factors were identified: PGE2 infusion (p=0.02), apnea (p=0.008), hypotensive episodes (p=0.0008). Notable factors that were found not to be associated with increased risk for NEC included cardiac catheterization, presence of patent ductus arteriosus, left ventricular outflow obstruction, cardiac surgery and aortic clamping. This study failed to find the usual risk factors for NEC to be applicable to this group of patients. This may not be all that surprising as this group of neonates were mainly full term infants and the number of NEC in this series was too small for it to have enough power to identify the possible risk factors. Identification of PGE2 as risk factor remind one to be careful not to overdo it.
Conclusion

NEC is a disease of concern to all neonatologists as it could occur in a cluster or run a fulminant course. It is essential to know the prevalent organisms in one’s locality. Hence, a meticulous search for organisms in all affected cases and careful reporting of involved organisms to a central registry would help guide management. Breast feeding in VLBW infants is even more important in the context of NEC. It is important to have a concerted effort helping the mother collect breast milk for tube feeding the sick premature babies. Further research into prevention of NEC is important.
Reference:


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Biliary atresia

5’-nucleotidase was noted to increase in diseases associated with bile duct proliferation. Yeung\(^1\) postulated that it would be increased in biliary atresia but not in neonatal hepatitis syndrome. He compared the level of 5’-nucleotidase in biliary atresia and neonatal hepatitis syndrome. The serum 5’-nucleotidases were estimated by the method of Campbell. 27 neonatal hepatitis syndromes and 9 biliary atresia cases were recruited. All the biliary atresia cases were confirmed by liver biopsies and all neonatal hepatitis syndrome showed clinical recovery in follow-up. He found that the level in biliary atresia was 58.5 +/- 22.7 and that in neonatal hepatitis syndrome was 14.0 +/- 5.8. The difference was highly significant (p<0.0005). The average age of enzyme assay was 12.7 weeks for neonatal hepatitis syndrome and 15 weeks for biliary atresia.

Fung et al\(^2\) reviewed a series of 82 patients with infantile cholestasis from 1972-1982. 41 patients had extrahepatic biliary atresia (EHBA) and the other was neonatal hepatitis syndrome (NNH). Male to female ratio was 1.9 in the NNH and 0.46 in the EHBA group and this difference was highly significant (p<0.01). They found that maximum gamma glutamyl-transpeptidase (GGTP) level was significantly higher in EHBA group than that of NNH group, 1133 vs 275 umol/ml. Interestingly, they found no difference in 5’ nucleotidase level between these two groups of patients. This discrepancy might be due to different time of assay for 5’ nucleotidase. The same authors published another study comparing 17 babies with EHBA and 19 babies with NNH\(^3\). They demonstrated that GGTP
level and its rate of rise were higher in the EHBA group. A similar study was published by Liu et al\(^4\) in Taiwan and they found similar result with GGTP.

Lau and Ong\(^5\) reported their experience in managing 89 consecutive infants with biliary atresia from 1955 to 1981. All infants had biliary atresia confirmed by laparotomy or by postmortem examination. There were 34 male and 55 female. Kasai-type procedure (hepatic portojejunostomy and hepatic portocholecystostomy) were introduced since 1975. From 1955 to 1975, 67 infants were diagnoses as biliary atresia. 12 were offered surgery-10 choledochojejunostomy, 1 choledochoduodenostomy and 1 cholecystojejunostomy. Only 3 patients in the choledochojejunostomy were still alive at the time of publication. The cure rate for the whole group was 4.5%. 17 infants were diagnosed as biliary atresia from 1975 to 1981. 12 underwent Kasai-type procedure. 6 out of the 12 infants had post-operative disappearance of jaundice. The apparent cure rate in this group is 35.3%. All infants, who had apparent cure of jaundice after operation, had post-operative attacks of cholangitis. All had varying degrees of hepatosplenomegaly. This paper highlighted the initial impact of Kasai operation in Hong Kong and the secondary problems of persistent hepatic fibrosis and portal hypertension.

Saing et al\(^6\) presented the subsequent experience in the same center. 45 infants were managed by them from 1979 to 1986. One presented too late and surgery was not attempted. 5 were referred from other centers after failed initial portoenterostomy. Amongst the 39 infants who were first operated on in their center, 27 (69%) had extended bile drainage. This success rate was comparable with that in other centers with extensive experience. Amongst the five infants who were initially operated on in other centers, three were re-operated. Two out of these three showed extended bile drainage. Cholangitis occurred in 20
children (45%). Five developed bleeding from esophageal varices and were successfully treated with endosclerosis.

**Congenital renal anomalies**

Lam et al\(^{6a}\) reported a series of 60 fetuses with prenatal ultrasonographic renal abnormalities out of 19,301 pregnancy screened (0.31%). 6 fetuses had major renal abnormalities, e.g. multicystic kidney, gross hydronephrosis, and were aborted. 12 fetuses were diagnosed to have major renal abnormalities late in pregnancy and were not aborted. They all died in early neonatal period. Post-mortem examination confirmed the prenatal diagnosis in all these cases. Among the remaining 42 fetuses, 37 had hydronephrosis and 5 had either multicystic dysplastic kidneys or renal agensis. Amongst the 37 hydronephrosis infants, five had mild hydronephrosis, 11 had transitional hydronephrosis, 5 had extrarenal pelvis, 4 had persistent non-progressive hydronephrosis with good renal function, 5 had pelviureteral junction obstruction, 5 had vesicoureteral reflux, 2 had vesicoureteral junction obstruction and one each of Prune Belly syndrome and bilateral megacalyses. Hence, around half of isolated hydronephrosis diagnosed antenatally would have an excellent prognosis. They also reported the excellent accuracy of DTPA renal scan with the diuretic nephrogram in differentiating obstruction from non-obstructing hydronephrosis. Only one false negative out of 33 negative results.

Mya\(^7\) reviewed their series of antenatally diagnosed hydronephrosis that was confirmed postnatally. 20 neonates were recruited with a male to female ratio of 14 to 6. 9 had bilateral hydronephrosis and 11 had unilateral lesion (9 left, 2 right). Ultrasonography, diuretic 99Tc DTPA scan, intravenous urography, voiding cystourethrogram and DMSA
were carried out in all patients. Panendoscopy was done in 9 infants. Pyeloureteric junction obstruction was the commonest lesion (6 definite and 7 doubtful). Vescicoureteric junction obstruction was found in 2 patients. There were two duplex kidneys, one dysplastic kidney with posterior urethral valve, one ureterocele. Seven kidneys were diagnosed as normal after extensive investigation and 3 were diagnosed as prominent pelvicalyceal system with no definite diagnosis. The results were comparable with that of other reported series. This paper gave a nice summary of the diagnostic make-up of an increasingly common problem for neonatologists in Hong Kong.

**Computed tomography in surgical neonates**

Tam et al. reported the use of direct sagittal CT scan in neonates. 12 babies were recruited – 6 imperforate anus, 2 tracheoesophageal fistula (TOF), 3 sacrococcygeal teratoma, 1 laryngeal cyst. The babies were placed with the long axis of the body in the plane of gantry of the CT scanner, which had an aperture diameter of 70cm. A scout view was use for localization and one 5 mm thickness slice was performed along the midline, one or two additional parasagittal slices 5 mm apart were also done to each side of the midline. The direct sagittal CT scans were interpreted preoperatively and conclusions were subsequently correlated to operative findings. For imperforated anus, the blind rectal pouch was delineated by a well-defined meconium-tissue interphase. The pubococcygeal line could be accurately drawn. The cases were classified correctly into high types (3) and low types (3). Operative findings confirmed the accuracy of direct sagittal CT. For TOF, the gap between the two esophageal segments were accurately determined by CT scan and showed clearly the air-filled fistula. For sacrococcygeal teratoma, direct sagittal CT scan allowed an accurate delineation of pelvic involvement and the size of tumour.
cyst, direct sagittal CT scan allowed a clear definition of the subglottic extension. This simple study showed the importance of clinical common sense, altering slightly a usual practice allowed a much better return in diagnostic accuracy.

**Cholodochal cyst**

Choledochal cyst was more common in Orientals as shown by the abundant literature from Japan and Southeast Asian countries. Saing et al\(^9\) reviewed 68 patients with choledochal cysts that presented under 12-year of age from 1955 to 1990. Female to male ratio was 3 to 1. 23 (34%) presented before 1-year. The commonest clinical features were jaundice (74%), mass (59%) and pain (42%). The classical triad of jaundice, mass and pain was present in only 25% of cases. Radical cyst excision and hepatico-jejunostomy (Ex-H-J) was the standard procedure at the time of writing. Leakage occurred in 6/66 patients and one died of this complication. 4 developed fatal fulminant cholangitis. All these early complication occurred before early 1960’s when choledochocysto-duodenostomy was offered. Cholangitis was the commonest late complication during follow-up. One child died of biliary cirrhosis and liver failure preceded by repeated attack of cholangitis after Roux-en-Y cystojejunostomy (RY-J). She was the only late mortality in this series. Comparing the results of different procedures offered in this period, they found Ex-H-J to have the best outcome (92% full recovery), RY-J being second best (80% full recovery). The worst procedure was partial cyst excision, choledochorrhaphy and choledocho-duodenostomy which was associated with 50% chance of cholangitis. The authors stressed the need for radical excision in review of the possibility of malignant change in the retained cyst as well as the safety of this procedure.
Infantile hypertrophic pyloric stenosis

Tam et al\textsuperscript{10} reported their preliminary experience in endoscopic balloon dilatation of pyloric stenosis using balloon of 10 to 15 mm diameter. Three cases were reported with 2 success and one failure. They subsequently reported a series of 12 patients\textsuperscript{11}. Ballon was inflated by fluid to a pressure of 45 PSI for 10 minutes after being inserted into the narrowed pyloric canal. Five were successfully treated whilst seven failed and required Ramstedt’s operation. They concluded that endoscopic guided balloon dilatation could not be recommended as standard treatment of infantile hypertrophic pyloric stenosis.

Hirschsprung’s disease

Saing et al\textsuperscript{12} reported on the use of the disposable stapler to perform very low colorectal anastomosis in Hirschsprung’s disease. With this stapler, they could achieve anastomosis 2-3 cm above the anal verge. This compared favourably with previous reports of 3-7 cm. This technique was successfully performed in 7 infants. Tam et al\textsuperscript{13} studied the neuron-specific enolase (NSE) in different level of the gut in fetuses of different gestational age. NSE was a specific marker for neurons. 28 normal fetuses, which were obtained from spontaneous abortion or elective termination, were studied. They found that NSE immunoreactivity was most advanced in the pylorus, less so in the colon and least in the ileum. This suggested that the enteric nervous system proceeded from both ends to the middle of the gut. This would support the hypothesis of a dual gradient of neuronal development in contrast to the classical view of a craniocaudal migration of neuroplasts. Tam reported another study looking at NSE and substance P, marker of peptidergic innervation\textsuperscript{14}. He examined 28 fetuses, 10 normal postnatal gut tissue obtained from postmortem, normal tissues from 9
infants during laparotomy as well as tissue from 6 infants with Hirschsprung’s disease and 28 infants with infantile pyloric stenosis. Substance P followed the same development pattern of NSE, i.e. foregut most developed and ileum least developed. In Hirschsprung’s disease, NSE was absent in the aganglionic colon and substance P activity was markedly diminished in the affected segment. Even in the distal aganglionic colon, substance P activity was decreased compared with control. In biopsy specimens obtained from patients with infantile hypertrophic pyloric stenosis, NSE was present in normal amount in the pylorus but substance P quantity was much diminished. Tam et al\textsuperscript{15} reported the use of wholemount immunohistochemistry in defining the enteric nerve fibres in Hirschsprung’s disease. NSE and vasoactive intestinal peptide, VIP, were used as markers. They made the important discovery that the hypertrophied nerve fibres in aganglionic bowel were in complete disarray and these fibres had an external origin, penetrating the aganglionic rectum by accompanying blood vessels. In a subsequent study, Tam et al\textsuperscript{16} employed substance-P and met-enkephalin as markers to study the peptidergic innervation in Hirschsprung’s disease. They found that the peptidergic efferent fibres were markedly diminished in aganglionic segment whilst the afferent fibres were normal. These nerve fibres were also disorganised in the ganglionic segment of Hirschsprung’s disease (HD). This may account for some of the clinical failures in patients with HD after apparently adequate resection of the aganglionic gut.
Conclusion

Neonatal surgical problems are challenging for both neonatologists, for diagnosis, and surgeons, for intervention. Hong Kong has seen a steady improvement in outcome as documented by Saing and his group in Queen Mary Hospital. With increasing number of paediatric surgeons and improved NICU service, further improvement should be assured. However, cost-benefit analysis should be considered in light of constraint in resources. Establishment of recognized paediatric surgery centres and proper networking with other hospitals would be an important step. Research into the genesis of different congenital surgical problems would certainly make progress with the advance in molecular biology.
Reference:


Fok\textsuperscript{1} reported a prospective study of basic growth parameters of 8445 Chinese infants born at gestation ranging from 27 to 42 weeks recruited from Tsan Yuk Hospital, Princess Margaret Hospital and Prince of Wales Hospital from 1982 to 1986. Only those babies born to mother who were certain of the date of last menses were included. Those born to mother with complications likely to affect intrauterine growth were excluded. Infants with gross malformations and chromosomal abnormalities, multiple birth were also excluded. The data differed significantly from that previously reported by Ip\textsuperscript{2}. Ip’s data was significantly higher for those with gestational age $\leq 37$ weeks and lower in those $> 37$ weeks gestation. As Ip’s study was a retrospective one that relied exclusively on hospital records, this probably included a lot of mothers who were unsure of date. Prospective nature of Fok’s study made it a more reliable estimation of the true intrauterine growth in Chinese. Fok’s data was found to be similar to Chinese infants in Singapore, Japanese infants and American infants born at an altitude of 3000 metres (Lubchenco chart) but was significantly less than that of European, Australian and American infants born at sea level. The authors made the interesting observation that Lubchenco chart was used for many years in most maternity and neonatal centres in Hong Kong as the standard reference despite the difference in ethnic origin and altitude of the two places. Fok’s study showed that it was actually a correct and wise decision. This reflected the clinical wisdom of our predecessors.

Lam et al\textsuperscript{3} studied the postnatal growth of a group of low birthweight infants. 181 low birthweight infants were recruited from 1988 to 1993. Low birthweight was defined as
below 2500g or birthweight below the third centile after adjustment for length of gestation and gender. All infants were followed up for a period of 6 to 18 months. The infants were divided into two groups: small for gestational age (SGA), n=70 and appropriate for gestational age (AGA), n=111. Most AGA were born prematurely whilst most SGA were born term. No catch-up growth was observed in the SGA group when compared with the AGA group. It also showed that growth in both groups of infants fell off from the National Center for Health Statistics growth curve after 6 months of age. This was similar to previous observation by Field, Davis, Karlberg.

Davies et al reported in a letter their results measuring the ratio of mid-arm circumference to occipitofrontal circumference (MAC/OFC) in normal term Chinese babies. This ratio has been suggested as a marker of intrauterine growth retardation. 175 term normal birth weight babies (95 boys; 80 girls) were recruited. The ratio was determined at a mean age of 7 days. The mean ratio (SD) was 0.31 (0.02). This was significantly higher than the value of 0.29 found in black, Asian and white babies (p<0.001). This was probably related to the smaller head size of Chinese. A subsequent study was published from the same centre by Lee et al. 95 Chinese term babies (46 boys, 49 girls) with birth weight below the 10th centile for gestation or clinical signs of wasting (laxity of skinfolds, lack of muscle bulk, dry skin) were recruited. 83 (87%) neonates had a MAC/OFC ratio less than or equal to 0.27. MAC/OFC is undoubtedly cheap to obtain. It remains to be seen if it provides additional clinically useful information for nutritional assessment in neonates besides the basic parameters, i.e. head circumference, body length, body weight.

Herbal medicine was commonly used in Hong Kong. ‘12 Tai Pau’ was one of those herbal mixtures commonly used during pregnancy. Yeung et al studied the effect on rat fetal growth with ‘12 Tai Pau’. 18 rats were assigned to smoking group and 18 were assigned to
control. They were further divided into two groups with one receiving ‘12 Tai Pau’ and the other sterile water. The dose of ‘12 Tai Pau’ was around 4 times the usual dose for human by weight. They found statistically significant fetal weight reduction in the smoking rat when compared with non-smoking rats. When those smoking rats were given ‘12 Tai Pau’, the fetal weight was significantly higher than those given sterile water. However, this increase was not enough for the smoking rats’ fetus to catch up with that of non-smoking rats. For the non-smoking rats, administration of ‘12 Tai Pau’ had no significant effect on fetal weight. Lam et al\(^{10}\) conducted a retrospective case-controlled study looking at effect of smoking on birth weight from 1988 to 1990 in Tsan Yuk Hospital. 13,563 deliveries occurred during this period and 213 (1.57%) pregnant women were past or current smokers. 0.28% were heavy smokers (>20 cigarettes per day). The growth data was summarised in table 2. It could be seen that smoking was associated with a mean reduction of 200 gram in weight, 0.3 cm in head circumference, 1 cm in body length as well as 55% increased chance of admission to special care baby nursery. It would be interesting to compare birth weight of neonates born to smoking mother with or without history of taking ‘12 Tai Pau’.

**Table 2  Condition of Infant at Birth**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Group (n=852)</th>
<th>Study Group (n=213)</th>
<th>1990 Hospital data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth-weight (g)</td>
<td>3,220</td>
<td>3,017</td>
<td>P&lt;0.005</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>(385)</td>
<td>(408)</td>
<td>3,208</td>
</tr>
<tr>
<td>Small for dates babies</td>
<td>60 (7.0%)</td>
<td>27 (12.7%)</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Low birth-weight babies (&lt;2, 500g)</td>
<td>59 (6.9%)</td>
<td>31 (14.6%)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>33.6</td>
<td>33.3</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>(2.0)</td>
<td>(1.4)</td>
<td>*</td>
</tr>
<tr>
<td>Supine body length</td>
<td>49.9</td>
<td>48.8</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>(2.5)</td>
<td>(3.2)</td>
<td>*</td>
</tr>
<tr>
<td>Admission to special care baby nursery</td>
<td>153 (17.9%)</td>
<td>60 (28.2%)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Congenital abnormality</td>
<td>24 (2.8%)</td>
<td>8 (3.7%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* = data not available in our computer or annual report
Conclusion

Construction of distribution curve of growth parameters in different gestational age is an important basic achievement for Hong Kong neonatologist. Further prospective studies into the longterm growth and its relation with weaning diet for both AGA and SGA babies would be interesting. Again the use of herbal medicine in intrauterine growth retardation would be an exciting area to be engaged by enthusiastic clinical researchers.
Reference:
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4. Field CE, Baber F. Growing up in Hong Kong. Hong Kong University Press, Hong Kong, 1975.
CHAPTER 10: OUTCOME OF NEONATAL INTENSIVE CARE

Introduction

Yeung gave a detailed account of neonatal intensive care service in Hong Kong. The first Neonate to be ventilated in Hong Kong was a preterm Indian baby with severe RDS in late 1968. He was ventilated by an old Bennett respirator borrowed from the Medical Unit. Preparation for neonatal intensive care (NIC) started in Tsan Yuk Hospital from 1975. Full NIC was not operational until 1980. In 1982, the service was reorganized in QMH to provide a combined neonatal and paediatric intensive care service. Training programs, local and overseas, for intensive care personnel were initiated. Appropriate equipments and trained medical and nursing staff were provided. This model was recommended by the Royal College of Paediatric & Child Health as a cost-effective model. Similar model was adopted in Kwong Wah Hospital in Hong Kong.

Local mortality figures

Lau et al reported the neonatal mortality rate (NMR) to be 7.03 per 1000 in a retrospective analysis of 43,798 live births in 5 major units in Hong Kong during 1980/81. The essential figures were summarized in Table 1. For the same birthweight mix, the mortality rate was calculated to be 4.8 per 1000 using the published figures of the Maternity Unit at the Cambridge University, England. The incidence of VLBW was 6.9 per 1000 compared with 14.1 in the UK, 7.4 -16.6 in Australia. The incidence was 4.63 per 1000 in Tsan Yuk
Hospital from 1985 to 1987. It was 12.5 per 1000 in Prince of Wales Hospital in 1991. The incidence in Shanghai and Beijing were even lower, 1.9 and 1.6 per 1000 respectively. The low incidence was attributed to low incidence of smoking, hypertension, obesity in Chinese. With the increasing affluence and adoption of ‘Western’ lifestyle, one may expect the incidence of VLBW to increase throughout the year. This was actually the case when the data from the hospital authority was analysed. The incidence of VLBW infants was 10.08 per 1,000 live birth in all public hospitals from 1995 to 1997.

Table 1 The total number and percentage of births and deaths in various birth weight groups

<table>
<thead>
<tr>
<th>Birth Weight Group (g)</th>
<th>500-999</th>
<th>1000-1499</th>
<th>1500-1999</th>
<th>2000-2499</th>
<th>&gt;=2500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per thousand of Births</td>
<td>1.4</td>
<td>5.5</td>
<td>11.9</td>
<td>55.7</td>
<td>925.5</td>
</tr>
<tr>
<td>NMR</td>
<td>852</td>
<td>327</td>
<td>99</td>
<td>16.7</td>
<td>2.0</td>
</tr>
<tr>
<td>Corrected NMR*</td>
<td>852</td>
<td>289</td>
<td>58.7</td>
<td>6.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Percentage of deaths*</td>
<td>25.3</td>
<td>31.5</td>
<td>14.0</td>
<td>6.8</td>
<td>22.4</td>
</tr>
<tr>
<td>Number of Deaths</td>
<td>52</td>
<td>78</td>
<td>51</td>
<td>38</td>
<td>81</td>
</tr>
<tr>
<td>Lethal Congenital</td>
<td>0(0)^</td>
<td>13(16.6%)</td>
<td>22(43.1%)</td>
<td>24(63.2%)</td>
<td>35(43.2%)</td>
</tr>
<tr>
<td>Anomalies ^</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Failure#</td>
<td>27(62.0%)</td>
<td>51(78.5%)</td>
<td>19(65.5%)</td>
<td>4(28.5%)</td>
<td>15(38.0%)</td>
</tr>
<tr>
<td>Infection#</td>
<td>6(11.5%)</td>
<td>14(21.5%)</td>
<td>6(20.7%)</td>
<td>3(21.4%)</td>
<td>6(10.8%)</td>
</tr>
</tbody>
</table>

The overall NMR (7.03 per 1000) was based on 43 798 births and 306 deaths (including 6 cases whose record were missing).

*NMR and percentage of total deaths excluding lethal congenital anomalies

^Total number and percentage of death (in brackets) of various birth weight groups

#Total number and percentage of death in various birth weight groups excluding lethal congenital anomalies

When lethal congenital anomalies were excluded, VLBW group accounted for 56.8% of mortality. The unexpected finding was the relatively large percentage (22.4%) of deaths occurring in infants weighted more than 2499g. Asphyxia as defined by Apgar score of
less than 6 at 1 minute was assessed to be a significant cause of mortality in 75% of normal birthweight infants. Asphyxia was considered to be one of the main causes of death in 31.6% of total deaths. The authors compared the mortality with the Maternity Unit of the University of Cambridge, England. They found that mortality rate in the VLBW was 100% higher and for normal birthweight was 64% higher. This paper was valuable in highlighting the problems facing neonatologist at that time. Neonatal intensive care was reorganized in Tsan Yuk Hospital and Queen Mary Hospital in early 1980s. Lau & Fok\textsuperscript{10} reported the changing mortality in their centre with the introduction of full neonatal intensive care programme. They looked at data collected from Tsan Yuk Hospital from 1978 to 1983. The birth rates were consistent during this period (range from 6,277 to 7,129 births per year). Corrected neonatal mortality dropped from 540/1000 in 1978 to 100/1000 in 1983 for those weighted between 1000g to 1499g. Corresponding figures for 1500g to 2499g dropped from 29/1000 to 5/1000 in 1983. The authors emphasized the importance of having a dedicated team of medical and nursing staff being the most important factor behind the success in their centre. A similar result was observed when Yeung\textsuperscript{1} reviewed the results obtained in Queen Mary Hospital. The mortality rate in the 1 – 1.5 kg group improved from 797 per 1000 (1975-80) to 108 per 1000 (1981-86). For extreme low birth weight group, the mortality rate dropped from 826 per 1000 to 656 per 1000\textsuperscript{1}. Further improvement was achieved in the same centre when Tang et al\textsuperscript{5} reported a combined neonatal and post-neonatal mortality of 550 per 1000 ELBW infants and 100 per 1000 for those between 1000 and 1500g with a mean follow-up period of 33 months. Cheung et al\textsuperscript{6} reported neonatal mortality of only 1.3 per 1000 total birth despite they had 4.2 per 1000 of ELBW and 6.8 per 1000 of VLBW.
Yuen et al\textsuperscript{11} reported the pattern of neonatal mortality in a one-year cohort in 1986. There was 7532 birth from 1/7/83 to 30/6/84. 54 were stillbirth, i.e. 7.2 per 1000 total birth. The early neonatal death rate and late neonatal death rate were 7.4 and 1.3 per 1000 livebirths respectively. The distribution of birthweight, lethal congenital anomalies were summarised in Table II. The major causes of death were summarized in Table III.

**Table II** The number of livebirth, lethal congenital anomalies and the survival rate of babies less than 1750g at birth

<table>
<thead>
<tr>
<th>Birth Weight (gram)</th>
<th>N</th>
<th>Per 1000 livebirths</th>
<th>Lethal congenital anomalies</th>
<th>Neonatal death</th>
<th>Post-neonatal death</th>
<th>Percentage survival*</th>
</tr>
</thead>
<tbody>
<tr>
<td>[750</td>
<td>6</td>
<td>0.8</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>751-1000</td>
<td>14</td>
<td>1.9</td>
<td>0</td>
<td>7</td>
<td>1</td>
<td>43</td>
</tr>
<tr>
<td>1001-1250</td>
<td>17</td>
<td>2.3</td>
<td>1</td>
<td>9</td>
<td>1</td>
<td>44</td>
</tr>
<tr>
<td>1251-1500</td>
<td>38</td>
<td>5.1</td>
<td>3</td>
<td>14</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>1501-1705</td>
<td>40</td>
<td>5.3</td>
<td>2</td>
<td>8</td>
<td>1</td>
<td>82</td>
</tr>
</tbody>
</table>
* excluding lethal congenital anomalies

**Table III**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Neonatal Death</th>
<th>Postneonatal Death</th>
<th>Total infant Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hyaline Membrane Disease</td>
<td>36</td>
<td>4</td>
<td>40 (56%)</td>
</tr>
<tr>
<td>2. Lethal Congenital Anomalies</td>
<td>16</td>
<td>0</td>
<td>16 (23%)</td>
</tr>
<tr>
<td>3. Infection</td>
<td>4</td>
<td>0</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>4. Surgical Conditions</td>
<td>3</td>
<td>0</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>5. Necrotising enterocolitis</td>
<td>1</td>
<td>2</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>6. Pneumoperitoneum</td>
<td>2</td>
<td>0</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>7. Birth Asphyxia</td>
<td>2</td>
<td>0</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>8. Meconium Aspiration Pneumonia</td>
<td>1</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>65</td>
<td>6</td>
<td>71</td>
</tr>
</tbody>
</table>

Hyaline membrane disease was the commonest cause of death accounting for 56% of death. Severe perinatal asphyxia was present in 40% of this subset of patients. The survival rate of VLBW babies, excluding lethal congenital anomalies, was 48% in this series. The
survival rate improved to 85.6% in the neonatal period in Kwong Wah Hospital from 1991 to 1994 with total number of VLBW being 100 for this period\textsuperscript{12}. They also reported an interesting cluster of pneumoperitoneum in 5 babies\textsuperscript{11}. They had no signs of necrotizing enterocolitis. They suspected it to be due to rectal perforation by over-zealous insertion of rectal thermometer. The outbreak stopped after proper insertion technique of not more than 3 cm insertion was given to nurses.

From 1995 to 1997, there were 110,825 live births in Hong Kong Hospital Authority hospitals\textsuperscript{9}. The neonatal mortality was 2.67 per 1,000 live births. The incidence of VLBW infants was 10.08 per 1,000. The VLBW mortality was 177 per 1,000. VLBW accounted for 67\% of neonatal mortality. The concomitant increase in incidence of VLBW and decrease in neonatal mortality and VLBW mortality confirmed the continuous improvement in Hong Kong neonatology service. This served to answer the caution raised by Lau et al\textsuperscript{13} that the satisfactory crude neonatal mortality of Hong Kong had more to do with the biologic advantage of Hong Kong Chinese, i.e. lower rate of lethal congenital anomalies and VLBW.

**Major handicap**

Yuen et al\textsuperscript{14} reported a follow-up study of 29 VLBW survivors who were born between 1983 and 1984. The mean follow-up period was 19 months. Major handicap was found in 2 out of 5 ELBW survivors, 40\%, and 2 out of 24 VLBW survivors, 8\%. They noticed severe hyaline membrane disease in 3 out of 4 infants who had major handicap and suggested that may be an important risk factor for major handicap.
Tang et al\textsuperscript{5} reported the outcome among the surviving VLBW infants born in Tsan Yuk Hospital from 1985 to 1987. They found major handicap in 2 out of 6 ELBW survivors, 33% and 3 out of 41 VLBW survivors, 7.3%. They defined major handicap as abnormalities which in the long term would significantly affect one’s ability to lead a normal life or to obtain satisfactory employment.

Goh et al\textsuperscript{15} reported the neurodevelopmental outcome in a group of low birth weight infants, n=528. Mean birth weight was 1.46 +/- 0.58 kg. Mean gestation age was 30 +/- 3 weeks. 12% of referred children had minor mental handicap which was defined as mild mental retardation or mild delay or limited intelligence. 8% had major mental handicap which was defined as moderate or severe mental retardation, moderate or severe delay. Visual impairment was found in 24 (4.5%). Sensorineural hearing loss was found in 18 (3.4%) and 23(4.3%) had epilepsy.

Yuen et al\textsuperscript{16} reported a prospective study of 211 VLBW babies born in 1993 in 10 Hong Kong public hospitals. 36 out of these 211 (17%) were found to have one of the following problems, developmental quotient <80 or cerebral palsy or impaired hearing or vision when assessment was done at 18-month. The same cohort will be reassessed at 5-year.

Yuen et al\textsuperscript{12} reported a retrospective study of the prevalence of major disabilities, i.e. Griffith Developmental Scale <70, visual acuity <6/60, hearing impairment requiring hearing aid, motor impairment imposing the need of aids, in a 2-year follow up study of 100 VLBW infants born in Kwong Wah Hospital. The prevalence was 3.2%.

Lam et al\textsuperscript{17} studied 45 term neonates with severe birth asphyxia, i.e. 1 min Apgar scor <3. Three babies were excluded because of lethal congenital abnormalities. Mean birth weight
was 3.2+/-0.24 kg. Mean follow up period was 2.5 years. The overall mortality was 10%. 6 babies suffered from neurologic sequelae (4 mild, 1 moderate, 1 severe handicap). Five babies were in deep coma and repeated seizure within first hour of admission to NICU. Of these five babies, 4 died and 1 had severe handicap. They also found that those required ventilation support for more than 24 hours were at high risk of neurologic sequelae.

Yung et al\textsuperscript{18} reported a follow-up study of a group of 46 babies who suffered from stage 2 & 3 hypoxic ischaemic encephalopathy. 5 died in the neonatal period. Mean age of assessment for cerebral palsy and global developmental delay were 30 months. 20 (43% of survivors) suffered from physical or mental dysfunction. 16 had cerebral palsy (8 quadriplegia, 5 hemiplegia, 1 diplegia, 2 dyskinesia). 4 had moderate to severe global developmental delay. They found that significant perinatal risk factors for adverse neurodevelopmental outcome included fetal bradycardia, extended Apgar scores at 20 minutes, prolonged mechanical ventilation, the need for inotropic support and multiorgan involvement.

Lam et al\textsuperscript{19} studied the incidence of retinopathy of prematurity (ROP) in a group of preterm babies, i.e. < 1500 gm and <32 weeks gestation from 1993 to 1995. 75 infants were recruited. The main birth weight was 1192 +/- 233 gm and the mean gestational age was 29.4 +/- 2.5 weeks. Ophthalmologic examination was performed at 32-34 weeks and repeated every 2 weeks until the retina became fully vascularized without retinopathy. ROP was found in 18 infants (24%). 5 had stage 3+ disease and were offered cryotherapy. Amongst these five children, visual assessment at 1 \( \frac{1}{2} \) year showed normal visual outcome in 4 and severe myopia in one. All these five patients were born less than 1000 grams or less than 26 weeks gestations. When stepwise logistic regression analysis was applied, only
the duration of mechanical ventilation, RDS with surfactant replacement therapy, indomethacin treatment and BPD were found to be related to ROP.

**Cerebral palsy**

Lui\(^{20}\) reported that 34% of her series of 248 children with cerebral palsy were due to perinatal hypoxic-ischaemia. In a comprehensive analysis of data collected in a large child assessment centre in Hong Kong, 38.4% of the cerebral palsy children had history of perinatal problem.\(^{21}\) Goh et al\(^{15}\) reported CP rate to be 12.5% in those children referred to her center for developmental follow-up before 1992. The rate dropped to 9% for those referred from 1993 to 1994. This drop might mean a genuine decrease in cerebral palsy rate in those low birth weight or referral of more asymptomatic children. They found that the main significant risk factors for CP were grade 3 or 4 intraventricular haemorrhage and the need for mechanical ventilation (p<0.001).

**Conclusion**

A lot of improvement has been achieved in achieving better survival for sick babies since 1968 when the first ventilation of neonate was reported. Steady decline in mortality in those infants with different birth weight was reported from different hospitals. It would be important for the neonatologists to maintain the standard of service. We should now be prepared to take on the much more difficult task of documenting the morbidity associated with neonatal intensive care. A critical analysis into the total cost to the community is much needed to prove or disprove the point that a lot of resources are devoted to prolong the suffering of a non-productive child and his family.
Reference:

1. Yeung CY Development of neonatal intensive care in Hong Kong. HKJ Paed. 1996;1:82-85


5. Tang TS, Yeung CY. Outcome among surviving very low birth-weight infants. HKJ Paed 1992;9:144-149


9. Hong Kong Hospital Authority’s statistics.

10. Lau SP, Fok TF Impact of intensive care on neonatal survival at Tsan Yuk Maternity Hospital HKJ Paed 1985;2:131-7


A lot had been achieved in the last 3 decades for neonatology. Kernicterus has become a rarity. G-6-PD deficiency induced hemolysis is now unusual with the universal screening program and the accompanying education program. Success of saving very premature babies is followed by an increased incidence of chronic lung disorders. Research into prevention strategies is urgently needed. Long term follow-up studies of this group of children would be helpful to identify risk factors for chronic lung disorders as well as shedding light on the growth problem faced by them. Inborn errors of metabolism (IEM) are the occasional surprise for neonatologists. A standardized protocol for approaching this problem would be helpful for neonatologists. A central registry of important disorders like IEM, outcome of congenital heart disorders, congenital diaphragmatic hernia, Group B streptococcal septicaemia, NEC would be important for neonatologists interested in reviewing their standard of service or for public health measures. Growth of SGA babies is an interesting area worth pursuing especially in term of dietary intervention. Outcome of the neonatology service in terms of mortality and more importantly morbidity is most important to assess the cost-effectiveness of our service. Preliminary result was published to this direction. Further publications would be eagerly awaited for by all those involved in delivery of neonatology service. There are areas that have been neglected in the past. Major congenital anomalies would be an important area, which consume significant resources, worthy of more research. Among this, the commonest problem would be Down’s syndrome. Hong Kong neonatologists should take advantange of our international status as
well as Hong Kong status being a Special Administrative Region of China to conduct collaborative studies with other centers in China in different areas of neonatology that benefit this country as well as international community. A likely area would be trial of surfactant made in China. Role of herbal medicine in neonatology is an exciting area for clinical researchers. This would be helped by the establishment of academic staff in traditional Chinese medicine in different universities. In the new millennium, many challenges await the neonatologists who should look for opportunities for advancing the course of neonatology.
Appendix I

BRONCHOPULMONARY DYSPLASIA

Summary:

1. Bronchopulmonary dysplasia (BPD) is a chronic lung disorder resulting from a multitude of insults upon an immature lung. Different clinical definitions have been proposed.

2. Antenatal steroid and rescue use of surfactant before 2 hours of life decrease the incidence of bronchopulmonary dysplasia.

3. Early use of systemic steroid before 8 days of life for those still on ventilators is helpful.

4. Systemic steroid for treatment of established BPD has no impact on mortality but it does decrease duration of hospitalization and oxygen dependence.

5. Use of diuretics and bronchodilators have short term benefits but long term use beyond 10 days has not been studied.
Introduction

Northway (a radiologist) first describe this entity in 1967 and describe the 4 stages of BPD-

Stage I : 2 to 3 days of life and similar to RDS
Stage II : 4 to 10 days of life with complete opacification of both lung field
Stage III : 10-20 days of life with cystic area of translucency
Stage IV : hyperinflation with large cystic area and interstitial changes

The study population described by Northway was more mature with birth weight more than 1500gm. This population is different from the extreme low birth weight seen in today’s practice.

Definition

1. Oxygen dependence at 4 weeks of age and typical radiological changes following at least 3 days of assisted ventilation in response to respiratory failure in the neonatal period\(^1\).
2. Oxygen dependence at 36 weeks’ postconceptional age with radiological findings and history of assisted ventilation in those with birthweight less than 1500 grams\(^2\).

This definition increase the positive predictive power of ongoing respiratory problems.
Incidence

1. Generally reported at 20% (4.2% to 40%) of ventilated neonates
2. Up to 85% in those between 500 and 699 grams but decrease to 5% in those over 1500 grams.

The increased incidence is probably due to improved survival of VLBW babies

Etiologies

1. Respiratory distress syndrome (RDS)
2. Oxygen toxicity
   Inhalation of elevated oxygen leads to production of reactive oxygen species and release of chemotactic factors with subsequent damaging effects. The premature infants are more prone to these damages because of its lower level of antiproteases, eg. Alpha 1- antitrypsin, and antioxidant enzymes such as catalase.
3. Volutrauma/barotrauma
   Maldistribution of ventilation due to differences in regional time constant result in alternate area of overdistension and collapse.
4. Endotracheal intubation
   Endotracheal intubation impaired tracheal mucous flow and may lead to unrecognized microaspiration and nosocomial pneumonia.
5. Sepsis
   The potential role of nosocomial pneumonia in the pathogenesis of BPD is unknown. Colonization with *Ureaplasma urealyticum* in the respiratory tract of neonate is associated with higher incidence of BPD.
6. **Fluid overload**

Infants given 200ml/kg/day from week 1 to 4 had higher incidence of BPD than infants given 150ml/kg over the same period.

**Pathology**

- BPD represents a continuum of altered lung repair and function secondary to multitude of injury to immature lung tissue.
- Classical description: three stages
  
  Reparative (1-2 weeks)
  Subacute fibroproliferative (2-4 weeks)
  Chronic fibroproliferative (>4 weeks).
- Gross pathology of the lung: a heterogenous cobblestone appearance, representing alternating areas of atelectasis or marked scarring with hyperinflation.
- Airway changes include squamous metaplasia of large and small airways, fibrosis, submucosal edema with hyperplasia of submucosal glands, peribronchial smooth muscle hypertrophy.
- Parenchymal disease include atelectasis, decreased number of alveoli (alveolar simplification) and alveolar septal fibrosis.
- Pulmonary vasculature changes include decreased number of small pulmonary arteries, intimal proliferation, smooth muscle hypertrophy, distal extension of smooth muscle, adventitial thickening and occasional thromboembolic occlusion.
Pathophysiology

- Increased airway resistance secondary to airway hyper-responsiveness, mucosal edema, increased mucus secretion, tracheomalacia or bronchomalacia.
- Decreased compliance secondary to fibroproliferation.
- Pulmonary edema due to disruption of alveolar-capillary unit, increases pulmonary blood flow due to PDA, fluid overload, pulmonary hypertension.

Clinical features

- Tachypnoea, shallow breathing, retractions, cough, paradoxic respirations, wheezing with scattered or diffuse rhonchi.

Prevention

1. Antenatal steroids

   Antenatal steroids decreases the incidence of RDS and the requirement of assisted ventilation. They also increase the concentration of antioxidant enzymes in the preterm lung. Thus, it appear to decrease the incidence of BPD.

2. Antenatal thyrotropin-releasing hormone (TRH)

   Animal models have shown significant synergy between TRH and steroids for antenatal shown similar result. However, further trials did not confirm the finding.

3. Surfactant

   Surfactant rescue treatment neither increase nor decrease incidence of BPD but it decreases overall mortality. There is generally no difference in BPD rates when truly
prophylactic therapy is compared with rescue therapy. However, the OSIRIS study (n=6774) showed that very early use of synthetic surfactant (i.e. <2 hours) is associated with significantly less BPD than delayed treatment (i.e. >2 hours) (7.9% vs 11.2%)\(^3\).

4. **Inositol**

Inositol is a nutrient that promote endothelial cell growth as well as lung epithelial cell differentiation. Inositol supplementation was shown to be associated with increased survival without BPD\(^4\).

5. **Early postnatal steroids**

Meta-analysis of 5 evaluable studies of the effects of steroid commenced prior to 8 days of age showed a relative risk for death or BPD of 0.8 (95%CI 0.64, 1.00). This suggests that the early use of postnatal steroids may be effective in decreasing the combined incidence of death or established BPD. Further trials to evaluate the effect of early use of postnatal steroids are warranted\(^5\).

6. **Superoxide dismutase**

Superoxide dismutase is an important antioxidant. Radiographic signs of BPD was successfully reduced in one trial in which repeated subcutaneous doses of bovine superoxide dismutase were given to preterm infants\(^6,7\).

7. **Vitamin A**

Previous studies have shown lower serum retinol concentrations in infants with BPD compared with controls. Intramuscular vitamin A was effective in reducing BPD incidence in 2 studies while another study showed no effect\(^8,9,10\).

8. **Vitamin E**

A randomized blinded trial (n= 268)showed no benefit\(^11\).
9. **Permissive hypercapnia**

Two retrospective studies showed increased incidence of BPD with low to normal level of \( \text{PaCO}_2 \)\textsuperscript{12,13}. While one preliminary randomized study with a ventilatory strategy of aiming for a \( \text{PaCO}_2 \) of 45 to 55 mm Hg, compared with 35 to 45 mm Hg during the first 72 hours of life, showed a tendency to a decreased diagnosis of BPD and a significant decrease in the duration of ventilation\textsuperscript{14}.

10. **Synchronized ventilation**

One randomized controlled trial (N=90) showed that in infants less than 1000 gm at birth, treatment with synchronized ventilation reduced BPD compared with standard IMV (47% versus 72%; \( P<0.05 \)).

11. **High-frequency ventilation**

Two studies using high volume strategy showed reduction in BPD rates compared with conventional ventilation. However, most other studies that used low volume strategies failed to demonstrate significant benefits.

12. **Fluid restriction**

Three studies showed that relative fluid restriction decreased the rates of BPD.
**Treatment**

1. **Oxygen**
   - Maintain SpO2 between 92 and 96% at all time.
   - Infants who show no steady clinical improvement should be assessed for undetected hypoxaemia, poor compliance with oxygen, chronic aspiration due to gastroesophageal reflux, unrecognized structural cardiac or pulmonary abnormalities.

2. **Ventilator management for established BPD**
   - Slower ventilator rate with longer inspiratory and expiratory time may allow better gas distribution and decrease air-trapping.
   - Tracheomalacia is often found in older BPD patients. Higher level of PEEP may be required and is best titrated with flexible bronchoscope or fluoroscope.
   - Tracheostomy should be considered for those likely to require long-term ventilation as it decreases airway scarring, less noxious oral stimuli, enhance interaction between patient and caregivers.
   - Home ventilation may be provided in selected cases with stable medical conditions, clear care plan, appropriate equipment support, arrangement of home nursing care, identification of emergency services, appropriate home environment, suitably informed parents. Home visits are essential for programs to be successful.

3. **Nutrition**
   - Energy expenditure is at least one third higher than control group but energy intake tend to be lower. Hence, nutritional intervention is widely considered to be of great importance.
4. **Diuretics**

- Frusemide was found to be effective in improving lung mechanics. Alternate-day therapy (4mg/kg qid for 8 days) is found to be effective and yet without the metabolic side effects of chronic frusemide therapy.

- Inhalation of frusemide (1mg/kg stat dose) resulted in improvement in lung mechanics in one study but no improvement in another study.

- Thiazide diuretics showed similar short-term improvement in lung mechanics with less urinary calcium losses.

- Risk and benefits of long term use of frusemide as well as long term impact with short term use is not well known.

5. **Steroids**

- Published reports showed no increase in nosocomial infection rate.

- Meta-analysis of 13 randomized controlled trials showed no statistically significant decrease in mortality in the treatment group, RR =0.75 (95% CI 0.5, 1.1)

- All studies did show a reduction in duration of oxygen therapy and a reduction in duration of hospitalization.

- Inhaled steroid, either by nebulization or by metered dose inhaler, was reported to be effective in improving lung function in three publications\textsuperscript{15}.

6. **Brochodilators**

- Either salbutamol or ipratropium shown to be effective in improving lung mechanics. The use of metered dose inhaler via a spacer may be better than jet nebulizer. However, long term impact on growth or mortality is not available. Cardiac hypertrophy had been reported with long term use of beta-adrenergic agents. Some BPD patients may have paradoxical worsening of respiratory distress
and air-trapping. This is due to loss of central airway tone essential to maintain patency of malacic trachea in some cases.

- Oral / iv theophylline and oral caffeine have been used in BPD patients with short term benefits but long term responsiveness and potential adverse effects are not known.

7. **Cromolyn and ketotifen**
   - Small uncontrolled trials showed some benefit.

8. **Respiratory syncytial virus immune globulin**
   - Monthly prophylactic treatment with 750mg/kg during RSV season reduce incidence of RSV infection and hospitalization.
   - Standard intravenous gamma globulin is not effective.

9. **Physiotherapy**

**Long term sequelae**

1. **Cardiovascular system**
   - Systemic hypertension occurs in 11 to 43 % of BPD patients, mostly occur after 2 to 4 months of age. It tends to be mild and transient. Exact etiology is not known.
   - Isolated LVH in the absence of systemic or pulmonary hypertension is reported in a significant number of BPD patients. Strong association with death had been reported.
   - Large systemic-to-pulmonary collateral vessels were reported in infants with BPD. It may be associated with pulmonary hypertension. High flow through the collaterals may contribute to pulmonary hypertension and recurrent pulmonary
oedema. Embolization of collaterals in symptomatic cases had been reported to be helpful.

2. **Chest**

- Infants with BPD are prone to recurrent respiratory infections. At least 50% of BPD children were hospitalized during the first two years of life.
- 25% of BPD infants develop respiratory failure requiring mechanical ventilation.
- Avoidance of smoking and large day-care settings, routine immunization plus HiB and influenza vaccines for index case and family members.

3. **Growth failure**

- Reasons: decreased intake, increased energy expenditure secondary to increased respiratory effort, impaired energy metabolism due to insulin resistance induced by raised level of catecholamines brought about by hypoxia, hypercarbia, poor cardiac functions, stress, use of bronchodilators and diuretics.
- Treatment: correct underlying causes, gastrostomy feeding, fundoplication if indicated.

4. **Neurodevelopment**

- Subnormal head circumference at 8 months of age is a strong predictor of poor cognitive function at 8 year of age.
- Cerebral palsy was reported in 13% of BPD children and neurodevelopmental problems in 27%.
- The neurodevelopmental outcome may be related to extreme prematurity rather than severe lung disease.
5. **Late mortality**
   - Usually occur in those infants younger than 4 months of age after discharge from hospital.
   - Risk factors include ventilation > 6 months, recurrent cyanotic spells, use of multiple medications (diuretics, theophyllin, bronchodilators), left and right ventricular hypertrophy.
   - Possible mechanism include surge in pulmonary artery pressure, prolonged bradycardia after brief hypoxia.

6. **Long term pulmonary outcome**
   - Older children with BPD generally lack significant respiratory symptoms but airway hyper-responsiveness often persist and mild exercise intolerance is common.

**Prognosis**

Mortality: 40% in stage IV BPD and most of them occur during initial hospitalization.

Post-discharge death rate of 11.2% was reported.

Morbidity: For those <1000gm, mean duration of oxygen supplement and assisted ventilation are 84 days and 76 days respectively.
Reference:


Bronchopulmonary dysplasia study data sheet
(amended 5/98)

Name______________________                  OPD#_________________________
Study #____________________                   Maturity_______________________
Birth order_____________                           Month of birth________________
Age ______________

**Family background**

mother’s education : 1) primary 2) secondary 3) tertiary 4) post-graduate
father’s education : 1) primary 2) secondary 3) tertiary 4) post-graduate
mother’s occupation at the time of delivery
1) housewife 2) unskilled labour 3) semi-skilled labour 4) skilled manual labour
5) skilled non-manual labour 6) semi-professional 7) professional/management
father’s occupation
1) unemployed 2) unskilled labour 3) semi-skilled labour 4) skilled manual labour
5) skilled non-manual labour 6) semi-professional 7) professional/management
Monthly family income at the time of delivery
1) <5,000 2) <10,000 3) <15,000 4) <20,000 5) >20,000

**Risk factors**

*Birth weight: <1kg  <1.5kg  <2.5kg  >2.5kg  *duration of assisted ventilation___
*oxygen>40% ___ days  *duration of protein deprivation___ days
*surfactant : yes  no  : type_____________ *# of doses_____________
*use of systemic steroid during first 8 weeks of life : yes  no
*use of nebulized steroid or puff during first 8 weeks of life : yes  no
*growth failure in 1st year : yes  no  *pneumothorax : yes  no
*PDA : yes  no  with  heart failure : yes  no
*duration of inotropes : _______ days  *duration of NPO: _______ days
*total i.v. fluid(1st five days) : ____________
*antenatal smoking : yes  no
*number of elder siblings: ____
### OPD record

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<td></td>
</tr>
<tr>
<td>*recurrent wheeze (1st 2 years)</td>
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<td></td>
</tr>
<tr>
<td>*use of inhalational steroid ever</td>
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<td>*home oxygen use ever</td>
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### Physical signs

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<tbody>
<tr>
<td>*Chest deformities</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>*Expiratroy wheeze</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

### Investigations

<table>
<thead>
<tr>
<th>Question</th>
<th>baseline</th>
<th>post-saline</th>
<th>post-terbutaline</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Spirometry</td>
<td>FEV1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FVC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*CXR : hyperinflation</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>interstitial haziness</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>*ECG: RVH:</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>*pulse oximetry</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: current asthma Yes / No
Table 1  Core questionnaire wheezing module for children

1. Has your child ever had wheezing or whistling in the chest at any time in the past?  
   Yes [       ]  No [       ]  
   **IF YOU ANSWERED ‘NO’ PLEASE SKIP TO QUESTION 6**

2. Has your child had wheezing or whistling in the chest in the last 12 months?  
   Yes [       ]  No [       ]  
   **IF YOU ANSWERED ‘NO’ PLEASE SKIP TO QUESTION 6**

3. How many attacks of wheezing has your child had in the last 12 months?  
   None [       ]  1 to 3 [       ]  4 to 12 [       ]  More than 12 [       ]

4. In the last 12 months, how often, on average, has your child’s sleep been disturbed  
   Due to wheezing?  Never woken with wheezing [       ]  
   Less than one night per week [       ]  One or more nights per week [       ]

5. In the last 12 months, has wheezing ever been severe enough to limit your child’s  
   speech to only one or two words at a time between breaths?  Yes [       ]  No [       ]

6. Has your child ever had asthma?  Yes [       ]  No [       ]

7. In the last 12 months, has your child’s chest sounded wheezy during or after  
   exercise?  Yes [       ]  No [       ]

8. In the last 12 months, has your child had a dry cough at night, apart from a cough  
   associated with a cold or a chest infection?  Yes [       ]  No [       ]
Certificate of Consent

To: All participants of bronchopulmonary dysplasia study

Your child was born few years ago prematurely and we read from the record that he/she still required oxygen supplement at 4-week of age. We would like to determine if your child is still suffering from airway problem resulting from the premature birth today. A doctor will see you and your child to ask questions about your child’s airway symptoms. A thorough examination will be conducted to look for chest signs. Afterwards, your child will be asked to blow into a machine that measure the lung function of your child. Later, your child will be asked to breathe through a mask that will produce mist from salty water. This is to test if your child’s airway is hyper-responsive or not. Your child may cough with the salty water mist and sometimes may complain chest tightness. A reliever puff will then be given to see if your child airways respond to the reliever puff. At all times, the doctor will be with your child to ensure his/her well-beings. Your child will be asked to blow into the machine after inhaling the salt water mist and reliever puff.

By participating in this study, you benefit by having a detailed assessment of your child’s respiratory system by an experienced doctor and the information generated by this study will also help doctors improve the delivery of service to premature babies.

Only the researchers in the University will have access to the medical information and that if there are publications arising from this study, the confidentiality of your personal medical information will be strictly maintained. The undersigned doctor will take the responsibility for the custody of this personal medical information and for its security and proper use.

Your participation in the study will not entail compensation of any sort.

Parental statement

I have read the foregoing statement, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to enrol my child as a subject in this study and understand that I have the right to withdraw from the study at any time.

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Parent’s signature           doctor’s signature             witness’s signature

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Relationship with parent
參加『支氣管肺發育不全追蹤研究』
同意書

簡介：
由於閣下的孩子出生時早產而需接受四星期氧氣協助，我們希望能夠知道你的
孩子直至目前是否仍在因此而患有呼吸道疾病。我們的醫生將會詢問及檢查
您的孩子，然後作吹氣運動測量度孩子的肺功能。為測試孩子呼吸道的反應，
我們會要求孩子戴上盛有鹽水的氧氣罩，孩子可能因此而咳嗽或感到胸緊。
研究人員隨即給與噴霧緩解，以便觀察孩子呼吸道之反應。全部過程均有醫
生陪伴以確保安全。最後，孩子需再次對儀器吹氣量度肺功能。

參加此項研究，不需任何費用，你可得到資深醫生對你的小孩的呼吸系統所
作的詳細評估。研究所得的資料亦有助改善早產兒的服務，造福社會。

研究人員用於評估的資料絕對保密，以下簽名的醫生專責這些個人資料的保
密和適當的使用。

參與此項研究是無損傷的。

我已閱讀上述內容，而且我也有充分機會提出疑問，並得到滿意的解答。我
願意讓我的孩子參加此項研究，並清楚我可以在任何時候退出該項研究。

研究參加者：

...................................................

簽名

用正楷填寫姓名

身份證號碼：

...................................................

住址：

...................................................

負責醫生：

...................................................

簽名

用正楷填寫姓名

証人：

...................................................

簽名

用正楷填寫姓名

日期：

...................................................