

The Changing Pattern of Neonatal Jaundice in Chinese

A Hong Kong Experience

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Significant changes in the pattern of childhood diseases have occurred over the past few decades in Hong Kong^[1]

One of the most dramatic changes has been in neonatal jaundice (NNJ) in Chinese infants.^[2] This is particularly obvious on reviewing the experience of our own Department which has a long interest in studying and monitoring this condition in Hong Kong. This article outlines the experience on NNJ in Hong Kong Chinese over the past 30+ years.

Admission Statistics

Figures 1 and 2 show the admission statistics and the relative paediatric work load, due to neonatal jaundice, of our department at Queen Mary Hospital. The hospital has been the major referral hospital on Hong Kong Island throughout this study period. Many factors could have affected the referral pattern and fluctuations of admissions.

Apparently, the relative work load from NNJ has declined significantly through these years, from around 20% of all paediatric admissions in late 1960s down to only 5% in recent years (fig. 1). However, waves of influx of NNJ cases have occurred in cycles of about 10 years.

During the initial years (1963-1966) of the Department's operation, rapidly progressive building up of referrals was obvious. A peak was reached by 1971 which coincided with the Department's intensified research inter-

est^[3-8] on the condition. This research has resulted in the successful implementation of phenobarbitone therapy for the condition from late 1968 to 1971^[3,5,6,8] and other jaundice related conditions such as glucose-6-phosphate dehydrogenase (G-6-PD) deficiency 4 and blood sugar changes.^[7]

This was followed by popular use of phenobarbitone prophylaxis in the Maternal and Child Health Centres (MCHC) which could have been responsible for a decline of NNJ admissions in the following years. Since then there have been two other smaller waves of influx of jaundiced neonatal patients. The first of these two waves coincided with a resurgence of research interest on jaundice of the Department, this time to study the effects of herbal medicines,^[9] and the second appears to coincide with

an influx of migrants to Hong Kong from China.

Severity of Neonatal Jaundice

The severity of neonatal jaundice has also been dramatically reduced during these years.

Kernicterus (fig. 2), the most severe sequela of neonatal jaundice, has become a rarity in recent years. Although some local paediatricians attributed this to the introduction of phototherapy to Hong Kong, the author has observed that it was due to the introduction of phenobarbitone prophylaxis^[3,5,10,11] and the control of several important environmental factors^[10-12] which have been identified to be adversely affecting the severity of jaundice.

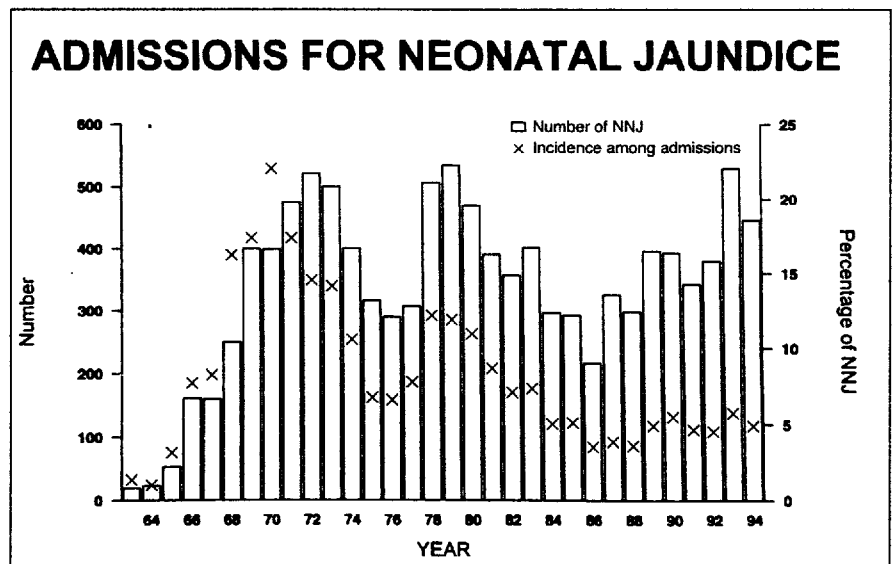


FIG. 1. Admission for neonatal jaundice to Queen Mary Hospital, Hong Kong. NNJ = infants with neonatal jaundice.

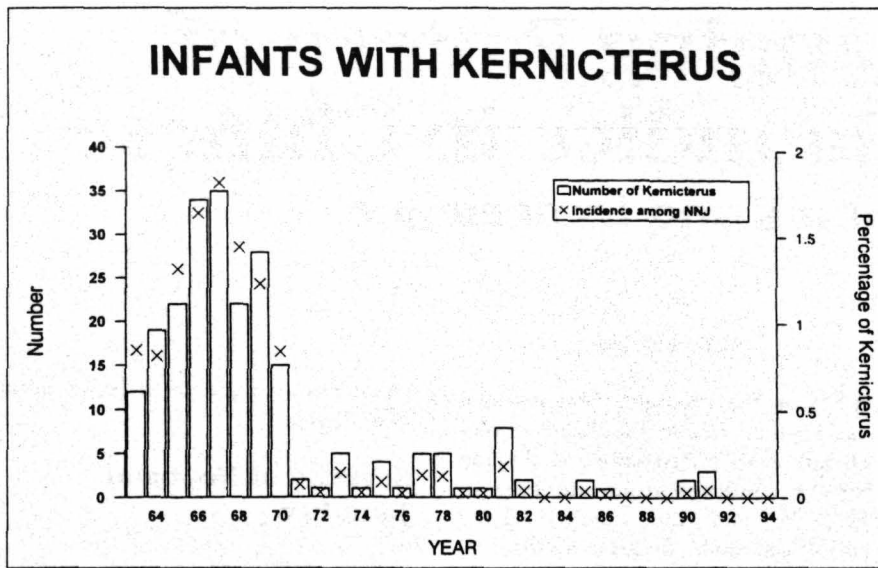


FIG. 2. Infants admitted with kernicterus. NNJ = infants with neonatal jaundice.

Upon the documentation of the efficacy of oral phenobarbitone prophylaxis,^[3,5,6,8,10,11] the MCHC adopted a policy to use phenobarbitone liberally for the prophylaxis and treatment of NNJ from 1971 to 1986. As the MCHC provided services for more than 90% of the neonatal infant population in the territory, it is conceivable that a large number of infants would have been so treated. However, phototherapy units only started to become sparingly available in the 2 major referral hospitals, Queen Mary (QMH) and Queen Elizabeth Hospitals (QEH), in 1970 and 1972, respectively.

These hospitals and other newer paediatric units in the territory were still requesting the health authority to purchase more phototherapy units to cope with NNJ patients in the early 1980s. The sharp decline of both the incidence and the severity of NNJ thus appeared not to be related to the introduction and availability of phototherapy at all.

Over a 3-year period of comprising data collected from the 2 major paediatric units at QMH and QEH of Hong Kong, the author has found a strong association between the consumption of herbs and the severity of neonatal jaundice^[10,11] (table I). After an

absence of 8 years, he has returned to conduct some laboratory studies and has shown that a number of the commonly used Chinese herbs are highly capable of displacing bilirubin from its protein binding,^[9,12-16] thereby increasing the risk of tissue damage including brain damage^[17] (fig. 3). For the first time, therefore, an explanation is offered for the high prevalence of kernicterus seen in early days. An incidence of 8.6% kernicterus was observed among jaundiced infants referred to the 2 major hospitals for

management in 1968 to 1971.^[10]

This high prevalence of kernicterus among term infants is 'unheard of' in the Caucasian communities, a feature which is, however, also observed in nearly all Southeast Asian communities.^[18-23] A significant decrease of kernicteric neonates has occurred; only 1 to 2 cases are seen every 3 to 4 years in the recent few years (fig. 2).

In earlier studies, the high rate of nonspecific hyperbilirubinaemia in Chinese was found to be related to the lower socio-economic status of the infants^[2,10,11,12] (table II). Although the exact reasons contributing to severe jaundice in these infants have not been clearly identified, a number of potential problems have been well known. These have included overcrowding, poor sanitation and hygienic conditions in their homes, which would increase pollution and contaminations of various kinds. Relative lack of proper medical facilities, easy access to self prescriptions and herbal usage,^[9,12-16,24] and high prevalence of infection of both the overt and sub-clinical forms^[25-28] would also aggravate the problem.

Further, strong traditional beliefs and practices^[11-13,24,29,30] including the belief of protecting the umbilicus 'from exposure' often resulted in people with low health education standards resorting to using various unsanitary or even contaminated materials to cover the

TABLE I. Herbal consumption and neonatal jaundice in Chinese^[10]

Infants	Moderate ^a jaundice	Severe ^b jaundice	With brain damage
ABO incompatibility	76/241	53/130	39/58
G6PD deficient	70/414	48/157	23/51
LBW	5/65	2/7	2/4
Cephal-haematoma	4/40	3/12	1/3
Nonspecific	209/1051	105/275	25/40
Total ^c	364/1811 20.1%	211/581 36.3%	90/156 57.7%

a = Serum bilirubin > 10 mg/dl.

b = Serum bilirubin > 20 mg/dl (342 μmol/L).

c = History of herbal consumption within 24 hours of referral to our hospitals for treatment.

LBW = Low birthweight.

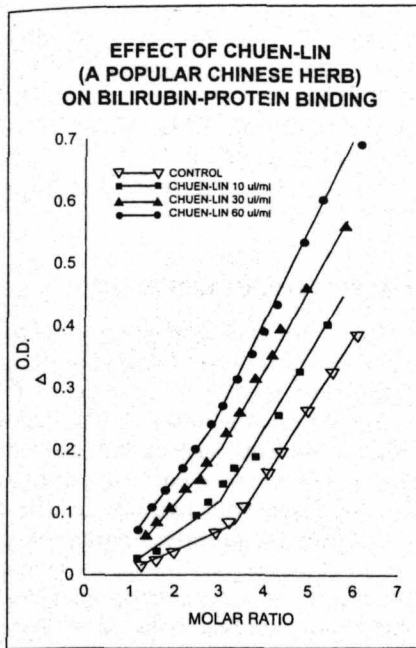


FIG. 3. Effect of Chuen-Lin (a popular Chinese herb) on bilirubin-protein binding.

umbilicus. This often invites infection or over-colonisation resulting in endotoxaemia which opens the 'blood-brain barrier' to cause brain damage^[27,28] in addition to increasing haemolysis and impairing liver function to aggravate the severity of jaundice^[2,10,11,12,31,32] in the infants.

It took the author nearly 2 years, on his return to Hong Kong in late 1980, before he could undo this traditional practice of 'covering up the umbilicus', even in his own hospitals. Even the head nurses strongly believed that if they were not covering the umbilicus with sterile gauzes and a dressing around the abdomen, the parents would apply their own 'unsanitary and contaminated materials'. Little did people realise that whatever sterile material they put on, the umbilical stump would become contaminated within a short while. By covering it up, they produced a perfect temperature and nutritive environment for the contaminated bacteria to over-grow and to cause infection and other toxaemic effects.

The decline of both kernicterus

related deaths and neurologic sequelae among the survivors have been so marked that recent young trainees now have a hard time to believe and understand the efforts and work load spent on this condition in earlier years. In one hospital (QEH), in the early 1970s, it was not uncommon to perform 5 exchange transfusions in a single night on emergency take. Indeed, among the early admissions to the first special school ever established in Hong Kong for handicapped children, the John F. Kennedy Centre, the overwhelming majority of admissions were survivors of kernicterus. In sharp contrast, in 2 hospitals (Queen Mary and Tsan Yuk) combined nowadays, we hardly ever have to do 5 exchange transfusions a month, although the criteria for exchange transfusions using bilirubin level and other risk factors of brain damage have not changed much. The majority of handicapped children requiring special schooling these days are certainly not those survivors of brain damage syndrome from bilirubin.

Nonspecific Hyperbilirubinaemia

Earlier studies have shown that Chinese newborns were more severely jaundiced than other ethnic infants.^[2,3,6,10-12,18,20-22] Most of them did not demonstrate definitive causes apart from possible sepsis.^[10,12] Some work-

ers considered this as an 'exaggerated physiologic jaundice'^[18] in the Chinese newborn. The author suggested that this should be termed 'nonspecific jaundice' to ensure that the condition should not be taken lightly.^[2,10] The jaundice is clinically obvious on the second or third day of life; it peaks on day 5 and persists through the first 7 to 10 days. The level of the bilirubinaemia is significantly^[2,10] higher than those reported in 'physiologic jaundice of newborn'^[33] (fig. 4). In fact, brain damage or kernicterus occurred repeatedly in this form of nonspecific hyperbilirubinaemia.^[2,10] More work was needed to be done to identify the causes and to reduce its potentially damaging consequences.

As stated earlier, lower socio-economic conditions were found to be significantly associated with the intensity of nonspecific jaundice^[2,10] (table II). It has strongly indicated that genetic or ethnic predisposition was not a contributing factor but rather other problems related to low socio-economic status are important. As the socio-economic condition improved, the author predicted a significant decline of both the severity and frequency of neonatal jaundice in Hong Kong.^[10] Indeed, this has materialised,^[2] as can be noted for the number of newborn infants requiring phototherapy treatment in our maternity units and the rarity of kernicteric infants in recent few years.

TABLE II. Frequency of peak serum bilirubin levels in Chinese newborns in two public hospitals on Hong Kong Island (1969)

Hospital	Infant number	Peak bilirubin level in mg/dl			
		>10	>15	>20	Total > 10
A1	45	25	12	3	40/45
A2	44	20	6	0	26/44
B	45	18	4	0	22/45

Note:

In-born infants from 2 local hospitals; Hospital B > Hospital A in socio-economic status. All infants were healthy, > 37 weeks, > 2.5kg; with Apgar scores > 8, blood Group 0, Rh D+, G6PD normal and with no bruises. 44 newborns (A2) in Hospital A were treated with oral phenobarbitone 5mg, tid x 3 days from birth; this resulted in significant reduction of hyperbilirubinaemia.^[5]

TABLE III. Common herbs frequently given to Chinese newborns to 'cleanse the babies of toxins of pregnancy'

Herb	1972 (%)	1983 (%)
Chuen Lin	50.9	28
Ngau Huang	35.9	23.2
Wax roses	30	14
Others	25	32
None	25	62.4
Infants surveyed	220	125

Survey in Hong Kong.^[10-12]

Haemolytic Diseases of the Newborn

It is interesting to note that even the severity of haemolytic diseases of newborn has declined similarly to the overall pattern described above. ABO incompatibility set-up has remained the first ranking in frequency of occurrence in this group of neonatal jaundice; this is followed by erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency.^[2,3,4,10-12] As the severity of the jaundice has declined, the pattern of ABO incompatibility becomes more obviously clustered into 3 distinctive clinical forms.^[2]

One group of patients, constituting more than three-quarters of the total of mother-infant pairs with ABO incompatible set-up have their pattern and level of the jaundice, is indistinguishable from those with nonspecific neonatal jaundice; although the occasional mother may have demonstrated positive antibody titre during pregnancy and some babies' cord blood may even demonstrate a weakly positive Coombs'.

Another group of infants which constitute about 15% of the total showed rapidly rising bilirubinaemia and declining haemoglobin levels from birth although they show no abnormalities in their clinical findings nor deviant cord blood haematologic parameters at birth. Something seems to have triggered the A or B antigenic structures of the red cells to rapidly interact with the existing hyperimmunoglobulin, as evidenced by positive Coomb's tests. There appears to

exist either an inhibitory mechanism or functional immaturity of the antigenic structure before birth.

The third group comprises of a small minority who may show evidence of an intrauterine disease of iso-immunisation, demonstrating mild anaemia and mild jaundice at birth together with cord blood parameters showing a haemolytic element. The condition may progress rapidly after birth necessitating exchange transfusions despite phototherapy. Somehow, our records have not revealed a single case of hydrops fetalis due to ABO iso-immunisation.

G6PD deficiency has remained an important cause of neonatal jaundice in the Southern Chinese population.^[2-4,10-12,34-36] It is often the most severe form of haemolytic diseases in the Chinese newborn. Male infants demonstrate a deficiency rate of 4.42% while the similar degree of severe deficiency in females is round 0.45%.^[14] Female heterozygous condition exists in as much as 9.6%.^[14] Acute haemolytic crises are much less common nowadays although they have continued to occur following sepsis, herbal consumption, especially with Chuen-Lin, and accidental exposure to clothings soaked with naphthalene vapour such as the mothers' overcoats.^[2,12,34]

All G6PD deficient newborns are given labels and warning notes against certain drugs and herbs including naphthalene. However, mothers sometimes forget their own clothes which have been exposed to naphthalene when holding babies in their arms. Acute haemolysis occurs suddenly,

often taking the health professionals unprepared, resulting in irreversible brain damage or kernicterus.^[2,6,10-12,34-36] This has also become a rare occurrence in Hong Kong these days although I realise that this is still a problem plaguing many parts of Southeast Asia.

Rh Iso-Immunsation

Rh iso-immunisation is very uncommon among Southern Chinese in Hong Kong, since 99.9% are RhD positive.^[37] Other minor Rh blood groups have caused problems, such as RhE antigen. This has been observed occasionally to be associated with hydrops fetalis, a condition frequently results from severe RhD iso-immunisation in the West. In most developed communities, RhD iso-immunisation has now been prevented by hyperimmune globulin prophylaxis.^[38] Clinicians, however, should still be on the lookout for both Rh-D and minor blood groups causing iso-immunisation diseases in the jaundiced Chinese newborn.

This may be particularly important when there is influx of Northern Chinese emigrating to various parts of the world including Hong Kong, as

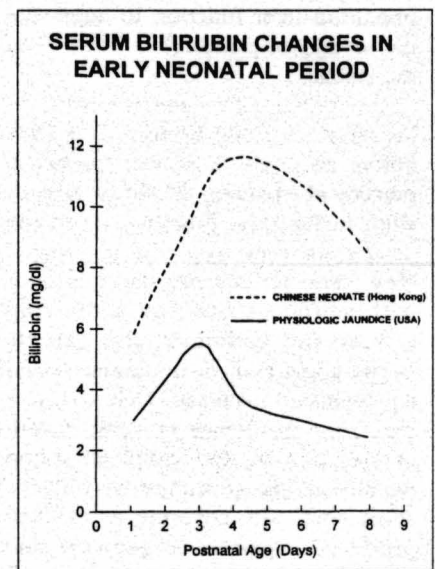


FIG. 4. Postnatal changes of serum bilirubin levels in Chinese and American (physiologic jaundice) term infants.

TABLE IV. Radioactivities (C^{14} bilirubin) in Gunn rat tissues (12-paired studies)

Tissue per gram	Injection of		P-value
	Control ^a	Gantrisin	
Serum before	6969b	6629b	> 0.3
Serum after	6694	2332	< 0.001
Brain	178	278	< 0.005
Fat	1267	1970	< 0.005

a = Dextro-saline.

b = C^{14} Δ ALA 10 μ Ci per dose.

Figures in counts per minute. p-values by paired t-tests.

RhD negative population is not uncommon in Northern China^[39] and hyper-immune globulin prophylaxis is not an adopted practice in China.

Hydrops Fetalis Due to Haemolytic Diseases

α -Thalassaemia major remains the major known cause of hydrops fetalis in Chinese^[40] as the estimated frequency of carriers of the mutation is around 4% in the Southern Chinese population.^[41] Since the introduction of prenatal diagnosis service in 1982 in our hospital, there has been a gradual decrease of this condition in our neonates. With heightened public awareness through a newly introduced thalassaemia screening and health education programme, we expect a more rapid and progressive decline of the condition in the near future. Recently, we have seen a couple of cases of hydrops due to Miltenburger antigen (unpublished). Studies are underway to identify the incidence of Miltenburger in the local Chinese population.

Jaundice of Prematurity

Despite the dramatic decrease of jaundice among term infants, and increasing survival of the low birthweights, premature infants do not constitute the main bulk of jaundiced neonates necessitating management in our hospital.^[2] In fact, in several previous major studies in our unit, low birthweight infants did not only constitute the small minorities among jaundiced neonates, they even had

lower serum bilirubin levels during the first 7 days of life compared to the term infants.^[2,10,42] One observational explanation^[42] made was the completely different environment and management regimen between term and preterm Chinese infants in the unit. The term infants were roomed-in with their mothers in the rather sub-standard postnatal wards. Bacterial contamination and even infection was frequent; many mothers had home-made food and herbal teas even while they were in the hospital. In contrast, all low birthweights were, by hospital policy, kept in a nursery away from their mothers and visitors. Under the management policy prevailing at that time,^[42] these low birthweight infants were least handled even by health professionals. Apart from continuous naso-gastric feeding and occasional scalp IV drip, hardly any had received intra-umbilical catheterisation or monitoring. These minimal handling routines had apparently reduced contaminations and minimised infections which could have produced jaundice and increased risk of brain damage.^[27-30] There was also no exposure to herbal medicine. These could have some effects on their lower prevalence of hyperbilirubinaemia compared with term infants^[42] besides having lower frequency of hypoglycaemia^[42,44] compared to their counterparts in the West.^[44]

NNJ Due to Other Causes

With progressive improvement of obstetric care, large cephalhaematoma

or other forms of concealed haemorrhages have become less common these days. Similarly with less birth asphyxia due to improved obstetric care, the heme oxygenase activities would be less activated.^[45] This would, in turn, lead to less occurrence of hyperbilirubinaemia in the newborn also.

In the 1960s, 65% of Chinese mothers breast-fed their own infants all through the first 3 months.^[25] In contrast, the rate of breast-feeding in the first 4 weeks had dropped to only 5% in the early 1980s.^[12] This change in breast-feeding practice in Hong Kong could have accounted for the decrease of neonates requiring treatment for protracted jaundice in recent years.^[11,12,46] It could not, however, account for the decline of the severity of neonatal jaundice as such.^[46,47]

Neonatal Conjugated Hyperbilirubinaemia

Conjugated hyperbilirubinaemia (conjugated bilirubin > 2% of total serum bilirubin and $\geq 34 \mu\text{mol/L}$) used to be a relatively common occurrence in the past. Over a period of only 1 year (1969-70), a series^[48] from 1 paediatric unit comprised of 27 neonates with 'neonatal hepatitis syndrome' and 9 biliary atresia. All infants studied were term neonates although a third of them were small-for-dates, suggestive of some intrauterine factors like infection syndrome as aetiology. Both biliary atresia and 'cholestatic syndromes' in the Chinese infants have become much less prevalent in the past few years. Instead, over the past 15 years we have observed increasing number of immaturely born (< 32 weeks' gestation) neonates who develop cholestatic jaundice, very often following total parenteral alimentation.

Management of Neonatal Jaundice

Hong Kong has witnessed a progressive change of symptomatic management of moderately severe neonatal jaundice. In the early years, oral phe-

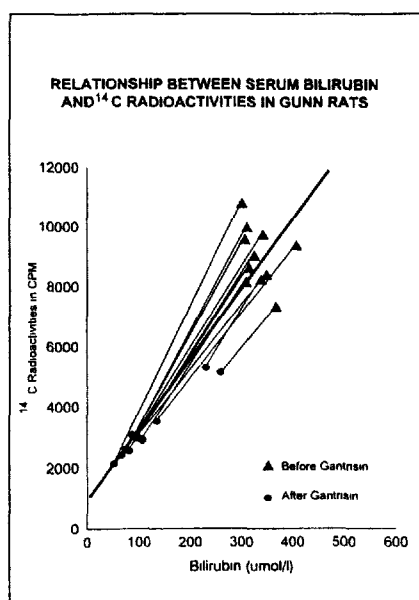


FIG. 5. Serum bilirubin levels in Gunn rats before and 30 minutes after treatment with gantrisin.

nobarbitone remained the mainstay as an enzyme induction therapy after its therapeutic benefit was proven by control studies.^[3,5,6,8,10]

Questions had been raised as to its effectiveness in infants of other ethnic origins.^[49,50] Chinese infants who were given the therapy by mouth had reported improvement;^[3,5,6,8,10] this contrasted its relative ineffectiveness in the Caucasian babies who were given the treatment by systemic route.^[51] Little did people realise that oral phenobarbitone has its first pass effect at the hepatocytes and therefore the therapeutic effect should be most obvious. Intramuscular injection of phenobarbitone, however, necessitates high doses, way beyond those used for treating neonatal jaundice, before the therapeutic serum level can be reached which would in turn build up sufficient tissue level to be effective. Phenobarbitone is thus effective provided it is given by the oral and not by the intramuscular or systemic route.

Questions have also been raised regarding its potential long-term side effects.^[49,52] In a recent long-term follow-up study,^[53] it has been demonstrated that oral phenobarbitone has

produced hardly any adverse effects as the initial worries had suggested. These questions and arguments therefore should not negate the benefit of oral phenobarbitone as a therapeutic agent for neonatal jaundice at all, especially when the cost of treating the bulk of NNJ cases has to be taken into consideration, such as in some Southeast Asian countries.

Phototherapy had been in use for a number of years overseas^[53,54] before it was introduced to Hong Kong mainly because of the cost involved in purchasing the phototherapy units. In 1971 we converted a room in our hospital to a phototherapy room by installing home-made phototherapy light units along the walls of the room so that babies in the cots could be parked under these lamps for a less expensive way of light treatment. Gradually the Government became more willing to purchase some mobile phototherapy units which later became more readily available to the hospitals. At the maternal and child health centres, doctors had continued to use oral phenobarbitone as prophylaxis or therapy routinely till 1986.

Meanwhile, a very aggressive educational programme commenced in the MCH in 1981, teaching the importance of hygiene and sanitation, exposure of the umbilicus to keep it dry to prevent colonisation and infection, and total abstinence from herbs. All these measures have significant impact in reducing the severity of jaundice both in the haemolytic and non-haemolytic situations.

Phototherapy using white light was the initial advocate for symptomatic treatment of jaundices.^[53,54] Many changes have evolved including exchanging white light for green light^[55-57] and blue light to improve the efficiency.^[57] More recently, the fiberoptic blue light blanket^[58] has revolutionised the approach to phototherapy in that the jaundiced infants are no longer required to be separated from the mother and put under the phototherapy lamp. Instead the light blanket is wrapped around the baby in the mother's arms or inside a crib staying

by the mother's bedside. So far, this light blanket has been proven to be equally effective.

Although tin-meso-protoporphyrin^[59,60] has been shown to be highly effective in controlling bilirubinaemia in the neonates, we have not yet adopted such drug for trial. It might be interesting to compare this form of therapy with oral phenobarbitone for both cost-benefit and long-term side effects when such a therapeutic trial is organised for Chinese infants.

Exchange transfusions have remained the standard treatment for the severely and rapidly progressive haemolytic jaundiced neonate. Its used in the non-haemolytic hyperbilirubinaemic term infants have been challenged by several workers. Some have argued that the level of bilirubinaemia indicating a need for exchange transfusion in the non-haemolysing term infants may be extended well beyond 20 mg/dl to 25 mg/dl or even higher.^[56,61,62] Some of the arguments put forth relate to the fact that term infants hardly ever suffer from kernicterus.^[56-64]

Many authors have not taken into considerations many of the factors which increase the chances of brain damage from bilirubin which have continued to exist in Southeast Asian communities. For example, a significant proportion of mothers still give their newborn infants herbal medicine to 'clear the babies of various pregnancy related toxin'.^[2,10-13,24-26] (table III). Many of these herbs have been found to displace bilirubin from protein binding,^[12-16] thus increasing the risk of brain damage (fig. 3).^[17] The cord care in term infants has continued to be a potential health hazard in many communities because of the 'strong traditional belief of covering up the umbilicus'.^[24,29,30] Chances of endotoxaemia in opening the blood-brain barrier are increased.^[25-28]

Kernicterus has continued to occur in term infants in many Southeast Asian countries^[18-23] (personal contacts also). It is therefore not advisable to follow advocates in the Western literature without fully understanding the local implications. It would be advis-

able to exchange transfuse the term infant at 20 mg/dl when the index of suspicion of herbal exposure and/or umbilical contamination is high. For preterm infants, the much lower level for exchange may even be necessary. When other factors such as low serum albumin or significant acidosis etc are also present.

It must be pointed out that in China, health care workers have continued the usage of various herbs to treat neonatal jaundice.^[9,12-16] Many have been claimed to be highly effective. Some herbs have been manufactured as extracts to be used systemically rather than given in their usual brewed-tea forms. One such therapy, Yen-Chen IV extract,^[15] has recently been found to be highly potent in displacing bilirubin protein binding, thereby increasing the risk of brain damage (table IV). In an animal model, we have demonstrated that agents which are potent in displacing bilirubin are also effective in reducing the serum bilirubin level of the Gunn (fig. 5).^[16,17] In a similar therapeutic situation, therefore, one would expect that the patient so treated would be less jaundiced following treatment. However, we have demonstrated that the displaced bilirubin has deposited onto the brain and the fatty tissues (table IV). It is therefore highly undesirable to use such therapies on small infants without obtaining scientific proof of their efficacy and toxicity first. In the interest of the infants other herbal extracts should also be tested scientifically to prove their efficacies or otherwise before their use. I certainly hope that we should not produce any harm to babies through scientific illiteracy.

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