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Singapore Kernicterus: A Review and The Present Position

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INTRODUCTION

Since Wong (1957) first gave prominence to causes of neonatal hyperbilirubinaemia besides the classical ones of Rh and ABO incompatibility, prematurity and sepsis, much has been published with regard to these hitherto unknown causes, which are particularly seen in Singapore and often referred to as Singapore kernicterus. In 1960, Smith and Vella suggested that all these "cryptic" cases of severe jaundice were due to deficiency of an erythrocytic enzyme, glucose-6-phosphate dehydrogenase, a deficiency which would favour haemolysis of the patients red cells in the presence of exogenous triggers, especially drugs. Since then, such cases of jaundice in association with G-6-P.D. deficiency, have been described elsewhere than Singapore (Doxiadas et al, 1961, Fessas et al, 1962; Freier et al, 1965; Yue and Strickland, 1965). Equally, there have been reports that in certain populations and areas where G-6-P.D. deficiency exists, severe neonatal jaundice was not associated with such a deficiency (Capps et al, 1963; Szeinberg et al, 1963). However, in Singapore, Wong (1963, 1964a, 1964b and 1965) showed that all the "cryptic" cases were not associated with G-6-P.D. deficiency and postulated that there is another group which he termed "liver immaturity" cases where there is a transient depression of liver glucuronyl transferase activity in the new-born period, resulting in failure of conjugation of the toxic indirect bilirubin to the non-toxic direct or conjugated bilirubin. Wong (1965) further postulates that even in the G-6-P.D. cases, there is in Singapore an associated element of liver immaturity. The liver immaturity could possibly have been due to the peculiar intake of native herbs by breast-feeding post-partum mothers or forced feeding of such herbal concoctions to their newborns. Brown and Wong (1965) demonstrated that such liver immaturity is seen only in the local infants and was absent in British infants delivered in Singapore under similar medical management of the pregnant mother, the only difference between the 2 groups being the local habit of the use of traditional herbal drinks.

When this point in the hyperbilirubinaemia work in Singapore was reached, a project was undertaken in 1965 mainly for the purpose of reducing, if possible, the infant mortality from kernicterus. The size of the problem can be seen when the commonest causes of death in infants admitted to the Department in General Hospital are examined. Table I shows that the third commonest cause of death in all admissions

Table I

Total Deaths 0-10 yr. (1964)	
Disease	**No. Deaths**
Pneumonia	63
Congenital heart disease	45
Kernicterus	29
Gastro-enteritis	23

from birth to 10 years in kernicterus, being exceeded only by deaths from bronchopneumonia and congenital heart disease. However, when deaths of all infants admitted to the Department under the age of 1 week, are considered, then Table II shows that kernicterus is, by far, the commonest cause of death.

Table II

Deaths Under Age of one week (1963 & 1964)			
Disease	**1963**	**1964**	**Total**
Kernicterus	30	22	52
Pneumonia	8	5	13
Congenital heart disease	4	5	9
Intracranial haemorrhage	0	8	8
Tetanus	4	1	5

The mode whereby this vital problem could be tackled by examining all the causes of neonatal

hyperbilirubinaemia in Singapore (Wong, 1965) is shown in Table III:

Table III

Cause	No. Cases	%
G6PD deficiency	80	43
Liver immaturity	50	25
ABO incompatibility	29	16
Sepsis	13	8
Prematurity	9	6
Rh incompatibility	4	2
TOTAL:	185	100

From the above it can be seen that there are definite genetic causes, i.e. such cases tend to recur in the same family, viz. G6PD deficiency, ABO and Rh incompatibility, the combined incidence being 61%. The status of liver immaturity is still undecided, as to whether it is genetic or due to herbal drugs, but whichever it may finally turn out to be, such cases *tend* to occur in the same family for even if environmental in origin, the "environment" will most probably be operative in subsequent births in the same family. Therefore, if one includes this category, the percentage of cases which may recur in the same family becomes 61 + 25 = 86%, i.e. in almost 9 out of 10 cases, one may except that such families are always at risk with regard to neonatal hyperbilirubinaemia and hence potential kernicterus. Why does one take so much trouble in elucidating the peculiar causes in this country? Is it not sufficient to keep every baby born in Singapore under close medical supervision in a hospital for a period of 10 days (the period when kernicterus can occur) and do serum bilirubins if jaundice is intense and then carry out an exchange transfusion if necessary to prevent kernicterus? A simple calculation will immediately convince ourselves why this is impossible. At the present rate of about 100 births a day in K.K. Hospital alone, just such a procedure will require 100x10=1,000 beds or cots! This is almost equivalent to the whole bed complement of General Hospital, Singapore alone and when one considers in addition, the staff needed to ward so many babies for 10 days, the cost, personnel availability and space conspire to make this apparent simple solution totally impracticable.

How then can one solve this problem with the services available? In other words, any plans envisaged should cover the following:

1. Nil or minimal increase in bed space in hospitals;

2. Nil or minimal increase in staff personnel;

3. Should be simple enough and yet effective.

THE PROJECT

Since the greatest single cause in G6PD deficiency and since almost 90% of cases of kernicterus are expected to recur in the same family, the following simple plan was put into operation since the beginning of 1965:

1. Estimation of cord G6PD in all newborns in KKH

There are several methods for estimation of this enzyme — the most popular and simple so far being the Motulsky's screening method using brilliant cresyl blue as indicator. However, even this method takes about 2 hours for completion of the test, and is a qualitative test, viz. the result being expressed in terms of deficient, intermediate or normal values of the enzyme. The mode of inheritance and interpretation of results of G6PD deficiency in Singapore has already been discussed by Wong (1963). Because of the length of time involved, the use of this test for screening about 100 infants' cord blood per day makes the procedure unfeasible. Then there is the quantitative method which assigns numerical values to the amount of the enzyme present. This, of course, is more involved and does not give more information than the simple screening test for the purpose needed. Obviously some other method would have to be used and Brown and Wong (1965) used a modification of the screening test of Bernstein (1962) using dichloroindophenol as an indicator. With the modification, small amounts of blood and reagent are necessary and a result is obtained in as short a time as 5 minutes. This is the test used now in the Department and about 100 blood samples can be screened in a total working time involving one technician within 1-2 hours.

Therefore infants with deficient or intermediate values were kept back for observation in the Hospital.

2. Letters to the mother

Cyclostyled letters were given to the mother under the following circumstances:

a. Addressed to the attending obstetrician for the NEXT baby informing him that a previous baby had been severely jaun-

diced as a result of G6PD deficiency, liver immaturity, ABO or Rh incompatibility, etc. and requesting him to refer subsequent babies to us for observation;

b. Addressed to the Infant Welfare Clinics to observe infants released by us after 10 days for increasing jaundice and refer back to us if this occurs for exchange transfusion. This has been necessary because the odd G6PD deficient infant has been seen by us (Wong, 1965) to suddenly become severely jaundiced at the 14th or 15th day with kernicterus while at home after discharge on the 10th day.

Such letters actually were given from 1963 to 1964 so that results were seen in 1965.

3. History-taking in KKH

All midwives have been instructed to include histories of previous jaundiced infants when interviewing mothers coming to K.K.H. for delivery, and when the infant was delivered such infants were referred to us for clearance or further observation. This procedure is highly important because:

a. In instances where letters given to mothers have been lost or mislaid;

b. In fresh instances when mothers had delivered babies prior to 1963-1964 when letters were first given.

4. Education of mothers

All mothers whose infants were held back for 10 days were instructed by the paediatrician about the dangers of jaundice in the present baby and all future infants, the danger of the use of traditional drugs for her and for her baby, the importance of contacting the nearest Infant Welfare Clinic on discharge from K.K.H. for observation till 3 weeks of age. Some explanation of brain damage due to severe jaundice with death or mental deficiency was given. The reluctance of some parents to believe what we tell them with disastrous results (i.e. giving of herbs and resultant kernicterus and death after discharge from K.K.H. or stubborn insistence and signing against medical advice (A.O.R.) and taking the baby home to return later only with kernicterus) convinces us that much in the way of education needs to be done, education not only of the lay public but also of doctors, nurses and midwives. There unfortunately still are medical and paramedical personnel who lull such parents into a false sense of security by comforting them with wrong advice, such as the following:

a. This jaundice is just physiological and it will go away with time;

b. This jaundice never harms your baby, anyway;

c. Give baby plenty of glucose and the jaundice will disappear.

The above 4-pronged attack was started in 1965 without much increase in cost or personnel:

1. The part-time services of one of our technicians already in the research project. However, he has to do the tests daily irrespective of Sundays or holidays. This involves administrative difficulties, nonetheless, and it is envisaged that we will get the services of a Government technician in 1967.

2. The maximum number of cots which had to be set aside for observation babies never exceeded the small figure of 15!

3. There was thus no fresh engagement of any extra staff or space.

4. The only real expense incurred being cost of the chemicals for the G6PD estimations, which, of course, is negligible when the number of lives that can be saved is concerned.

In actual fact, the Department is proud to state that such a project was undertaken with success without Parkinson's Law coming into operation.

RESULTS OF THE PROJECT

The real purpose of this article is to document 2 aspects of the project after it had gone on for one year, viz:

a. A study of G6PD deficient cases with reference to hyperbilirubinaemia;

b. The reduction in mortality of kernicterus cases in 1965 in Singapore.

a. G6PD Deficiency:

1. Incidence of G6PD deficiency in Singapore.

Probably the most accurate figures have been obtained here because in no other single place in the world have so many individuals been tested for G6PD deficiency. Table IV depicts the incidence in the various races in Singapore.

Table IV

Ethnic Group	No. Tested for G6PD Deficiency	% with G6PD Deficiency*		
		Overall	Males	Females
Chinese	29,013	1.6	2.7	0.5
Malays	4,126	2.0	3.4	0.6
Indians	2,289	0.22	0.4	0

* Includes deficiency and intermediate values.

There is a slight Malay preponderance compared to Chinese while in Indians, the problem is negligible by comparison. Summarising, then, it may be stated that approximately 3 out of every 100 male Chinese or Malay infants born will have G6PD deficiency; the figures for all Chinese and Malay infants being 1.6 and 2.0% respectively.

2. Incidence of intensity of jaundice.

It was realised very early on (Wong, 1961) that not all infants with G6PD deficiency developed kernicterus as many lived normally to childhood or adulthood to develop episodes of haemoglobinuria due to exogenous drugs. This has also been discovered by other workers.

There were altogether 487 G6PD deficient infants who were observed closely in the Hospital — this series being the largest single one in the whole world at present. The degree of jaundice was divided into 3 categories — mild (less than 7 mg% serum bilirubin), moderate (7-15 mg%) and severe (more than 15 mg%). Table V depicts the numbers and percentages of the different

Table V

Degree Jaundice	Mild		Moderate		Severe	
Race	No.	%	No.	%	No.	%
Chinese	239	58.5	92	22.5	77	19
Malays	45	62	15	21	12	17
Indians	4	80	1	20	0	0
Others	1	50	1	50	0	0
TOTAL	289	59.3	109	22.4	89	18.3

racial groups with the different grades of jaundice.

There does not seem to be any difference in the % among the Chinese and Malays (numbers are too small in the case of Indians). Approximately 20%, i.e. 1 in 5 of G6PD deficient infants in this country will be jaundiced to such an extent that kernicterus may develop. In fact 60% are mild — i.e. "normal". Of the 20% not all need to be exchange transfused and in fact only 41 cases had a prophylactic exchange, i.e. these patients would certainly have ended in kernicterus if nothing was done. Looked at another way, this project had saved the lives of 41 infants who would have died or terminated in mental deficiency. This, therefore, gives an exchange rate for all G6PD deficient infants of 8.4% (Smaller previous series from the Department had yielded figures of 8% (Brown and Wong, 1965) and 10% (Wong 1965). Therefore, it is fairly safe to say that 1 in 10 G6PD deficient infants may need exchange transfusion in Singapore.

3. Reasons for degrees of jaundice in G6PD deficient infants.

That G6PD deficient infants are more prone to severe jaundice compared to G6PD normal infants is proved beyond doubt by the 43% incidence in causation of kernicterus (Table III), but it is equally clear that G6PD deficiency alone does not condemn such an infant totally to severe jaundice. Therefore, there must be some other factor which together with G6PD deficiency would result in kernicterus. What this factor or factors are, still await solution but we have provided some clues as to what such factors may be.

a. Is there a sufficient degree of haemolysis in such cases to account for the kernicterus?

The answer to this is that in Singapore the

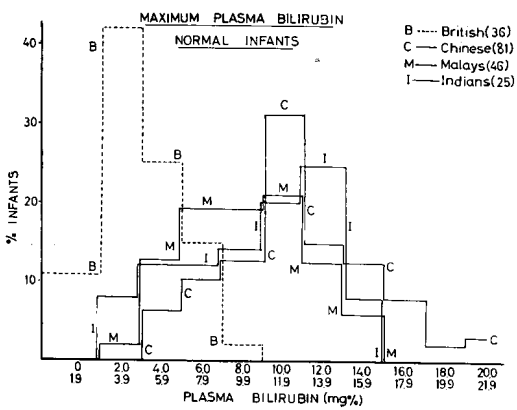
amount of haemolysis is not sufficient by itself to account for the high levels of serum bilirubin. Put in another way, the degree of anaemia for the same level of jaundice is much less in G6PD deficient cases than in Rh or ABO incompatibility. Therefore, haemolysis alone is insufficient to account for the severe jaundice, though there definitely is haemolysis, as study of the cord bloods of G6PD deficient and G6PD normal newborns have shown (Brown and Wong, 1965) Table VI:

Table VI

	Haematocrit	Hb% (14.8 G – 100%)
G6PD deficiency	45.7 ± 4.9	98.7 ± 10.7
G6PD normal	50.8 ± 6.6	105 ± 9.7
Significance of difference between means	$p < 0.001$	$p < 0.002$

b. If there is not sufficient haemolysis, then what other factor has boosted the serum bilirubin level?

The answer to this has been provided by Brown and Wong (1965) where it was shown that when *normal* full-term local and British infants born in Singapore are followed up by daily serial plasma bilirubin estimation, the levels reached by the former are 2 or 2½ times higher than the latter (Fig. 1). And since all known abnormal



factors which can cause severe jaundice have been excluded in these infants (such as G6PD deficiency, Rh or ABO incompatibility, prematurity, sepsis, instrumentation for delivery, etc.), the only logical conclusion which can be reached is that there is a diminution of liver conjugating power in our local babies, so that there is a build-up of the toxic indirect bilirubin. That such is the correct interpretation is borne out by 2 facts:

1. It explains why with insufficient haemolysis in G6PD deficient infants, severe jaundice can yet occur.
2. It accounts for the 25% (Table I) of "non-haemolytic-element" normal infants who get kernicterus, without anaemia, found in Singapore.

In other words, there is liver immaturity in many of our local infants.

c. If haemolysis can occur in G6PD deficient infants, and if liver immaturity can occur in both G6PD deficient and G6PD normal infants, then what are the causes for the haemolysis and the liver immaturity?

The answer to this question has still to be unequivocally proved. Obviously, the cause may be:

(i) Genetic, or

(ii) Environmental.

(i) **Genetic:** By this is meant that there is another genetic factor which in association with G6PD deficiency would result in severe jaundice, and those without this additional genetic factor would only be mildly jaundiced. No definite evidence of this additional genetic factor has ever been found in spite of its ardent proponents (Fessas et al, 1962).

Similarly, a genetic factor may be postulated for the liver immaturity and again there is no definite evidence. It is highly unlikely to be genetic here because all 3 racial groups, Chinese, Malays and Indians, behave similarly in contradistinction to British infants. It is difficult to imagine 3 different ethnic groups possessing the same gene.

(ii) **Environmental:** There is a better chance that the solution is probably here, because of the peculiar habits of our local population when compared to Western races. Some of these habits especially indulged in by them include:

a. Use of traditional Chinese herbs during pregnancy, especially the notorious "12B" and "13B" mixtures.

b. The feeding of newborn infants with a concoction from the bark of a tree — Coptis Chinensis, Franch — ranunculaceae, called locally "Chuan Lian" or "Hwang Lian" together with a honey preparation imported from China since the bark is extremely bitter.

c. The use of clothing which has been kept in moth balls for the newborn baby; naphthalene being well known as a possible haemolytic agent when swallowed by infants and children with G6PD deficiency.

d. The taking of Chinese wine, chicken cooked with exotic ingredients including many unidentifiable herbs, seeds and in sesame oil by pregnant women during pregnancy and in the immediate post-partum period while breast-feeding the infant.

e. The taking of a concoction from a brownish powder made from local herbs by the Malays, called "Jammu" by post-partum breast feeding infants.

It must be realised that of all the 3 "traditional" medical regimes, the Chinese one in Singapore has been better established than the other two, the herbs being sold and gathered not only privately but sold also in "Chinese medicine shops", which are therefore patronised not only by Chinese but also by Malays and Indians.

Such "unorthodox" feeding habits of drugs whose alkaloids or active principles have not been studied could conceivably lead to some of these drugs acting as:

1. External triggers for onset of haemolysis in G6PD deficient infants;
2. Depressive agents against the liver enzyme glucuronyl transferase which in newborns is already less active than adults, and a further slight lowering of such activity may be just critical in the newborn infant.

d. Is there any evidence that indeed any of the above "drugs" are environmental agents?

Unfortunately, at the present moment, no definite answer can be given because such work is hampered by the complexity of the problem as exemplified by:

a. Reluctance or ignorance of mothers in co-operating regarding history of taking "drugs." To many of them, the above are not "medicines" • but "food", "strengthening foods" and see no reason for abandoning them, or imparting such knowledge to us.

b. It is not possible to analyse *all* the concoctions used with facilities available in Singapore.

c. The deliberate feeding of such concoctions on newborns is ruled out on ethical grounds.

In spite of such difficulties, a certain amount of work has been done during the project, which included:

a. **The role of moth-balled clothes:** Approximately equal numbers of G6PD deficient infants were observed, one group clothed with "bajus" previously kept in moth balls and the other with "bajus" not so treated. Table VII shows that there is no significant difference with regard to the numbers developing severe jaundice whether they were clothed with moth-balled clothes or not.

Table VII

	No. in Trial	Jaundice		
		Mild	Moderate	Severe
G6PD deficiency *with* moth balls	100	52	19	29
G6PD deficiency *without* moth balls	113	67	26	20

b. **History of taking herbs:** A certain number of mothers with G6PD deficient infants were closely questioned as to the drugs taken during pregnancy or in the post-partum period or having admitted giving such drugs to the newborns. The

severity of jaundice of the G6PD deficient infants in those with positive drug history was compared to those with a negative drug history, and Table VIII shows the results:

Table VIII

History	Jaundice					
	Mild		Moderate		Severe	
	No.	%	No.	%	No.	%
Positive herbs	102	62	42	25	22	13
Negative herbs	34	75	6	18.8	2	6.2

Although the figures for the negative drug history are smaller, it is seen that those with a positive drug history have a two-fold increase in numbers with severe jaundice compared to those with a negative drug history. This may illustrate the importance of drugs as exogenous triggers in precipitating severe jaundice in G6PD deficient infants.

b. **Reduction in Kernicterus Mortality:**

As stated at the beginning Singapore kernicterus was the biggest killer of babies in the first week of life after excluding deaths from prematurity, and in the University Department of Paediatrics alone in General Hospital, the deaths from kernicterus had consistently averaged 30 a year and when one considers in addition, the mental deficients produced in the survivals, the tragedy of kernicterus in Singapore was in many ways a calamitous one. Therefore all the research efforts on this problem was aimed at reducing the incidence of kernicterus. The project was undertaken with the full understanding that even with all the safeguards provided for, it was not possible to totally eradicate deaths from kernicterus in Singapore for the following reasons:

1. The project dealt only with babies born in K.K.H. and therefore babies born in private clinics and at home may be missed.

2. Human errors either on the part of mothers or the medical personnel.

However, very early on, it was realised that the usually accepted teaching that kernicterus did not develop beyond the first week of life was wrong and a few cases had early kernicterus when they returned to the hospital on the 12th to the 17th day while it was definitely ascertained that jaundice was mild on discharge on 7th to 10th day without any signs of kernicterus whatsoever. To obviate this and not to increase the bed strength in KKH, the well babies were discharged still on 7th to 10th day and given letters to the nearest Infant Welfare Clinic for daily follow-up till 3 weeks of age. In this way, a few babies were referred back to us for prophylactic exchange transfusion when it was noticed that the jaundice had become more intense after going home. However, these were exceptions rather than the rule.

There were a few mothers of G6PD infants who were not at all co-operative. They insisted on taking their infants home, signing their own discharge. There was one mother to whom we reasoned and explained daily the necessity for keeping the baby for observation but we could keep her "at bay" for only 5 days after which she took her own discharge, and her parting "shot" was that she knew how to take care of jaundiced babies and that she would give him Chinese medicine to "wash" out the jaundice. True to her word, she did just that and within 2 days, the baby was brought in to General Hospital with kernicterus and subsequently died. Unfortunately, this mother felt no remorse whatsoever for her action and it is difficult not to surmise that behind such an uncompromising attitude was a psychopathic personality. Again here, fortunately, such recalcitrant cases were the exception rather than the rule, but this example gives an idea of the difficulties encountered with an unenlightened population.

Taking into consideration all the deaths from kernicterus in 1965, most of whom were babies born outside K.K.H., and comparing them with deaths from the same cause in 1963 and 1964, Table IX clearly shows the great reduction that had been achieved as a result of this worthwhile project:

Table IX

Deaths from Kernicterus		
1963	1964	1965
37	29	8

This represents a reduction of infant mortality of approximately 400%, and the number of cases of mental deficiency must have been just as much reduced by the project. This reduction in kernicterus mortality played a not considerable role in the reduction of the infant mortality rate of Singapore from 29 per thousand in 1964 to a new record low for Singapore of 26 per thousand in 1965.

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