BY INVITATION

SINGAPORE KERNICTERUS

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SYNOPSIS

Kernicterus in Singapore was the commonest cause of death in infants below the age of one week in the Department of Paediatrics in the Singapore General Hospital. In 1953, there were 146 deaths due to kernicterus, and some survivors invariably were mentally retarded, so that Singapore kernicterus was a serious health problem. The majority of the causes of neonatal jaundice in Singapore leading to kernicterus was unknown. As a result of investigational research by the Department, it was found that 43% were due to erythrocytic G6PD deficiency and 25% due to liver immaturity. A kernicterus surveillance project was initiated in 1964, and since then deaths from Singapore kernicterus fell to 5 in 1977.

Kernicterus or yellow staining of the neurones of the brain and spinal cord leading to death in the neonate, or residual neurological lesions in the survivors was known for years. However, the association between severe unconjugated hyperbilirubinaemia and kernicterus in newborns was first suggested in 1949 (1), although erthroblastosis as a basis for the hyperbilirubinaemia was known 10-20 years earlier. But the cause of the severe jaundice in erythoblastosis remained unknown until 1940 (2), when the rhesus factor was discovered. Rhesus incompatibility was then universally recognised as the cause of kernicterus, and the introduction of the Coombs test (3) resulted in the ease of diagnosis of haemolytic disease of the newborn leading to possible kernicterus. Later, ABO incompatibility was found to be as common a cause of haemolysis in the newborn though because of its lesser severity, kernicterus was less likely to supervene. However, it was later demonstrated that pathologic haemolysis itself was not necessary in the causation of kernicterus, and in 1950 (4, 5), it was shown that hyperbilirubinaemia can occur in premature infants leading to kernicterus, and this is due, of course, to the immature liver being unable to conjugate the toxic bilirubin to the non-toxic bilirubin glucuronide. In the West, these 3 states, viz. Rh and ABO haemolytic disease of the newborn and prematurity were the main causes of kernicterus. The introduction of exchange transfusion as a possible prophylactic method of lowering serum bilirubin (SB) and hence preventing kernicterus (6) provided an impetus to the further study of neonatal jaundice and kernicterus.

Kernicterus in Singapore was recognised as early as the condition was first described in the West, but because Rh incompatibility was and is rare among the local ethnic groups, doctors were reluctant to diagnose the condition as kernicterus and the alternative term, nuclear jaundice was used instead. That kernicterus or nuclear jaundice was not an insignificant factor in causing pathology in newborns in Singapore is seen in the Health Report for 1953 when there were 146 deaths due to kernicterus! This number must be seen in its proper context, for kernicterus deaths usually occur after the 4th day of life and up to about two weeks, for it takes a few days for the SB to mount up to critical levels before kernicterus can occur, and after two weeks the condition is rare. In 1978, the number of deaths of babies in Singapore from 4 days — 14 days (7) from ALL causes was only 60, so that in 1953, there were more than twice the number of deaths from kernicterus compared to all causes of death in 1978 in the particular age group. The problem of Singapore kernicterus must been in this light, i.e. it was a deadly killer of newborns and contributed to large numbers of severe mental retardates in those who survived. It was a problem which needed to be tackled vigorously.

In 1957 (8), I made a comprehensive study of cases with severe hyperbilirubinaemia culminating in kernicterus in which the babies were of good birth weight, full-term, with exclusion of Rh and ABO haemolytic disease, i.e. kernicterus not associated with the 3 causes seen in the West. This was the first time that it was pointed out that there were other causes of kernicterus affecting otherwise healthy full-term large babies. The problem was studied further for the next 5 years, when the so-called unknown causes gradually came to light.

SITUATION PRIOR TO 1964

Just as it was shown that kernicterus was a significant cause of death in newborns in Singapore, an analysis of deaths from the Department of Paediatrics, University of Singapore, showed that in the unit in Singapore General Hospital, the total deaths in 1964 from ages 1-10 were as follows:- (Table I)

TABLE I

TOTAL DEATHS (0 — 10 YEARS) : 1964

DISEASE	NO. DEATHS
Pneumonia	63
Congenital Heart Disease	45
Kernicterus	29
Gastro-enteritis	23

Kernicterus being a condition occurring only in the newborn period caused more deaths than diarrhoea from birth to 10 years. Therefore, when deaths were analysed for those under one week of age, it is seen that kernicterus was far and away the commonest cause of death: (Table II)

TABLE II

DEATHS UNDER ONE WEEK OF AGE

DISEASE	NO. DEATHS 1963	1964	TOTAL
Kernicterus	30	22	52
Pneumonia	8	5	13
Congenital Heart Disease	4	5	9
Intracranial Haemorrhage	0	8	8

Kernicterus was more common than all the other causes combined. What peculiar condition was responsible for these large numbers of deaths, the cause which was different from those seen in other parts of the world?

At this time, the metabolism of the erythocyte received the attention of workers following on the serendipitious discovery of haemoglobinuria following primaquine prophylaxis in Negro US soldiers during World War II. Gradually, this was found to be due to a deficiency of the enzyme, glucose-6-phosphate dehydrogenase (G6PD) in the hexose-monophosphate shunt of glycolysis in the erythocyte. It was also shown that haemolysis needed a trigger usually in the form of an oxidant drug which would just tip the balance in the economy of the hexose-monophosphate shunt. The relevant reactions are depicted in Fig. 1:

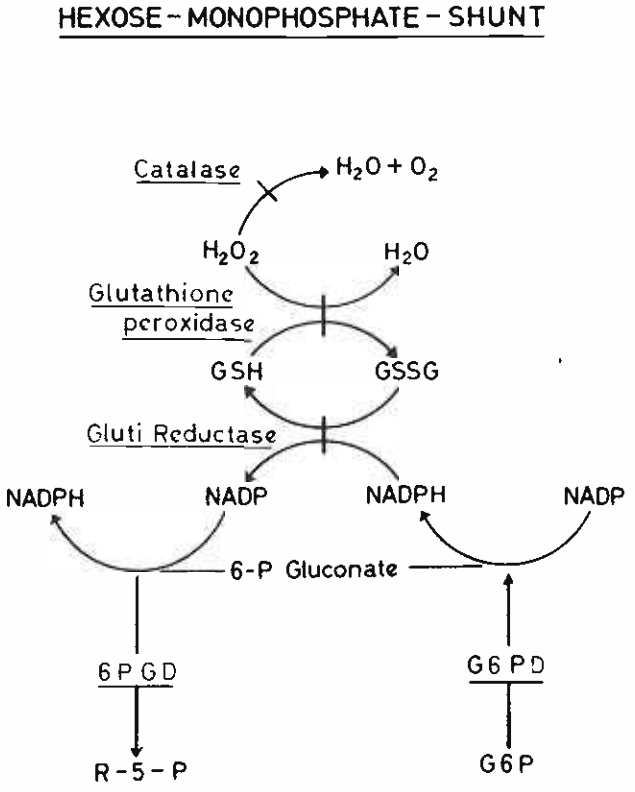


Fig. 1. Action of G6PD in hexose-monophosphate shunt of glycolysis in erythrocyte.

It is the accumulation of hydrogen peroxide together with the presence of superoxide oxygen radicals as a result of G6PD deficiency in the presence of an oxidant drug which initiates haemolysis.

It was then found that a large number of babies with kernicterus had a deficiency of G6PD (9), nearly 50%. 16% had ABO incompatibility with small numbers due to sepsis, prematurity and Rh incompatibility, the latter in Caucasians living in Singapore, as the following Table III shows:—

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

25% of the cases of kernicterus were full-term large babies without any evidence of a haemolytic cause, confirming the findings described 7 years earlier (8). This latter group must be due to an inability of the liver in conjugating bilirubin, i.e. the liver immaturity group (10).

PREDISPOSING FACTORS IN G6PD DEFICIENT BABIES

Having elucidated the G6PD deficiency and liver immaturity groups which together comprised almost 70% of the causes of Singapore Kernicterus, it remained to discover the factors which triggered off haemolysis in the G6PD deficient babies, and the factors which precapitated failure of conjugation by the liver.

Taking the G6PD deficient babies first, it was shown that even at birth, these babies had a significant though mild reduction in the life-span of their erythocytes. Table IV shows the mean haematocrit and mean haemoglobin levels (11) of a group of G6PD deficient babies compared to a control group with normal G6PD.

TABLE IV

G6PD STATUS	MEAN HAEMATOCRIT (%)	MEAN HAEMOGLOBIN (%)
G6PD deficiency	45.7±4.9	98.7±10.7
G6PD normal	50.8±6.6	105.0±9.7
Significance	$p<0.001$	$p<0.002$

However, the diminished life-span of the erythocyte is minimal though significant.

It had been suspected that some of the cultural habits of the local ethnic groups could provide triggers for G6PD deficiency haemolysis, and the widespread use of naphthalene moth balls in drawers and cupboards in which both the babies' and parents' clothes were kept, was investigated. 100 G6PD deficient newborns were given clothes previously kept in mothballed cupboards and 113 G6PD deficient babies were given clothes not so exposed. The numbers with severe jaundice (i.e. more than 20 mg/dl of SB) are shown in Table V:—

TABLE V

	NO. IN TRIAL	NO. WITH SEVERE JAUNDICE
G6PD deficiency with moth-ball exposure	100	29
G6PD deficiency without moth-ball exposure	113	20

The difference was statistically significant at $p<0.05$. Of course, other cultural habits such as the use of incense sticks or the giving of honey and other foods could well be triggers.

Similarly, two groups of G6PD deficient babies were compared with regard to the possible effects of herbs. In one group, the mothers had taken all sorts of Chinese herbs before delivery and the other group where there was no such history. The numbers with severe jaundice ($SB \geq 20$ mg/dl) were as follows (Table VI):

TABLE VI

HISTORY	NO. G6PD DEFICIENT BABIES	NO. WITH SEVERE JAUNDICE
Positive herbs	102	22
Negative herbs	34	2

The difference was statistically significant at $p<0.02$.

In CONCLUSION, G6PD deficient babies are more likely to develop kernicterus especially if triggers such as mothballs, herbs and drugs are used.

LIVER IMMATURITY

Of the 57% of cases of kernicterus not due to G6PD deficiency, 25% were not associated with blood group incompatibility, prematurity or sepsis. There were no evidence of haemolysis, and the daily haematocrit in the first week of life did not differ from other full-term infants who did not develop hyperbilirubineamia and kernicterus. This propensity to indirect hyperbilirubinaemia has been observed in local babies (12) where nearly 100% are visibly jaundiced in the first week of life compared to about 30% in Caucasian babies.

To assess the part played by liver immaturity in these babies, 188 normal full-term babies with a common regime of preparation for delivery, delivered normally, with no evidence of blood group incompatibility or G6PD deficiency had their SB estimated daily for one week. The rate of fall of haematocrit in the first week of life was comparable to that of normal babies. 36 Caucasian babies delivered in the same manner and over the same period of time were likewise investigated. All the babies were delivered in two maternity hospitals, the Kandang Kerbau Hospital (KKH) and the then British Military Hospital (BMH). Both private and public patients were included and the mean peak SB in the various ethnic groups delivered in the two hospitals is shown in Table VII:

TABLE VII

ETHNIC GROUP	HOSPITAL WARD	NO. BABIES	MEAN PEAK SB (mg/dl)	S.D.
British	BMH	36	4.4	2.8
Chinese	KKH/Teaching	57	11.5	4.2
Chinese	KKH/private	24	12.0	3.5
Chinese	Teaching and private	81	11.6	4.0
Malay	BMH	30	9.5	3.2
Malay	KKH	16	9.9	3.5
Malay	BMH and KKH	46	9.7	3.3
Indian	KKH/Teaching and private	25	9.6	3.6

Comparison of the means revealed the following:

British vs Chinese (teaching and private)	$P < 0.001$
British vs Malay (BMH and KKH)	$P < 0.001$
British vs Indian	$P < 0.001$
Chinese vs Malay	$P < 0.01$
Chinese vs Indian	$p < 0.05 > 0.02$

Hence, there is no doubt that normal full-term local babies uncomplicated by any haemolytic disease or any known disease and delivered in a normal manner are more jaundiced than British babies delivered in Singapore in a similar manner.

Fig. 2 shows the mean SB levels at different ages for Chinese, Malays and Indians compared to British babies and Fig. 3 shows the maximum SB attained by local compared to British babies.

It is difficult to envisage a genetic factor which causes liver immaturity in the local babies, whether from the lower or higher socio-economic group compared to Caucasian babies. This delay in liver conjugation of indirect bilirubin glucuronide is most likely due to cultural habits such as the taking of herbs and other drugs during pregnancy, and just before labour among the local population. The fact that such cultural practices may differ in degree among the local mothers is demonstrated in Fig. 4 which shows that among the Chinese, hyperbilirubinaemia due to liver immaturity can be roughly divided into 3 grades, mild, moderate and severe. This variation again is not likely to be due to genetic factors and reflect the fact that some mothers are more rigid and traditional in their cultural habits while others are gradually relinquishing the pernicious habits.

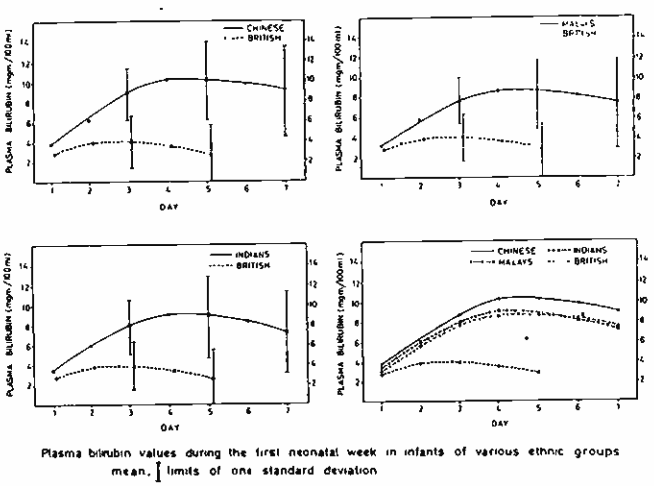


Fig. 2. S.B. levels of Chinese, Indian & Malay babies compared with those in Caucasian babies. Note the higher levels in local babies.

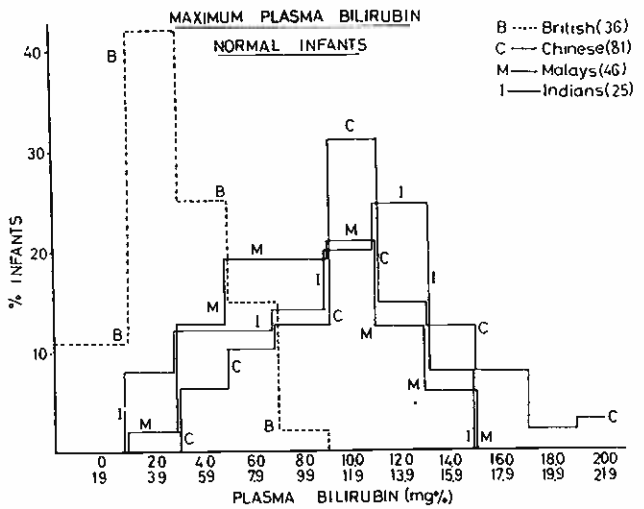


Fig. 3. Maximum SB levels attained by Chinese, Malay. Indian babies compared with those of Caucasian babies. Note the larger when of local babies with higher S.B.

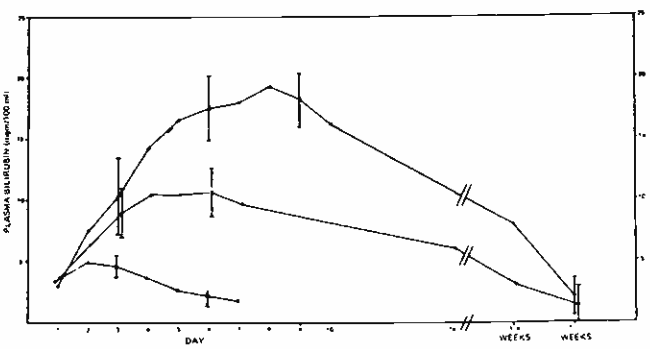


Fig. 4. Demonstrating 3 grades of severity of S.B. level in Chinese babies with liver immaturity.

In SUMMARY then, by 1964, the Department had categorised the causes of Singapore kernicterus which up to then had remained an enigma. Analysis of the causes revealed that 70% of the causes (G6PD deficiency and liver immaturity) are "family based", i.e. a genetic basis in G6PD deficiency and hence likely to run in families, the defect being inherited in a sex-linked manner (13), the triggers again being cultural and hence family-based; while liver immaturity was due to cultural habits and again tend to run in families.

KERNICTERUS PROJECT

Medical research to be meaningful must have practical applications. Research into the causes of Singapore Kernicterus was carried out with the express purpose of reducing deaths and mental retardation due to severe neonatal jaundice. In 1965, a surveillance project was started with this express purpose and the following were instituted:

a) G6PD estimations on cord blood:

At that time, the Motulsky screening method was the only one available but it took two hours for completion of the test. We used a modification of Bernstein's method (14, 11) (Appendix 1) adapting it and utilising small amounts of blood with a capability of testing 100 blood samples within 1-2 hours of a technician's time. Cord blood from all babies born in KKH were collected and transported to the Department daily and within 2-3 hours, the results were phoned to KKH, and those with G6PD deficiency were isolated and with the mother's permission were kept back in hospital for a period of 3 weeks to prevent exposure to triggers and to observe for hyperbilirubinaemia so that exchange transfusion could be carried out if necessary. The efficacy of this regime is borne out time and again in cases of non-co-operative parents who insisted on taking the babies home and within 24-48 hours after returning home, the babies were rushed to hospital with kernicterus. The screening was later extended to other hospitals, and now in Singapore, nearly all newborns are screened for G6PD deficiency. Obviously, such screening would not be totally successful unless the consumer understands what the whole surveillance project is all about.

The incidence of G6PD deficiency is about 3-4% in Chinese and Malay males and about 0.4% of Indian males, as Table VIII shows:

TABLE VIII

ETHNIC GROUP	NO. TESTED FOR G6PD DEFICIENCY	% WITH G6PD DEFICIENCY		
		MALES	FEMALES	OVERALL
Chinese	239,455	3.1	0.5	1.7
Malays	34,417	3.5	0.7	2.2
Indians	12,930	0.4	0	0.2
TOTAL	286,802			

APPENDIX I

MODIFIED BERNSTEIN'S METHOD FOR G6PD SCREENING

REAGENTS

(1) Preparation of Reagents

Dissolve 40.3 grams Tris. (hydroxymethyl) methylamine (BDH) in 700 ml. water. Filter the fine residue which will not go into solution. Adjust pH to 7.5 with HC1 (Start with Concentrated). Then add 13.5 grams Magnesium Chloride (BDH). Weigh 26.6 mgm. Dichloroindophenol (BDH) on analytical balance. Dissolve this in 50-100 c.c. water and then add to the Tris-Mag. Chloride mixture and bring volume to 1000 ml. Store in dark bottle in the refrigerator. Mixture is stable for months.

(2) Phenazine methosulphate (BDH)

Dissolve 25 mgm. in 500 ml. water. Store in brown bottle in the refrigerator. Prepare fresh each month.

(3) TPN — Triphosphopyridine Nucleotide 0.005M (Sigma)

Dissolve 250 mgm. in 65 ml. water — keep frozen.

(4) G-6-P-acid, 0.01M, GLucose-6-Phosphoric acid (Sigma)

Dissolve 1.0 gram in 322 ml. water — keep frozen.

Procedure

(1) Prepare fresh mixture of:—

DCIP	..... 7.5 parts
TPN	..... 0.5 parts
(PMS) Phenazine Methosulphate	..... 2.5 parts
G-6-P-acid	..... 2.5 parts

*(2) Add 0.01 ml. whole heparinized or oxalated blood to 0.4 ml. water — shake well.

(3) Add 1.0 ml. above mixture (1)

(4) Cover with Liquid Paraffin

(5) Note time of complete colour change:—

Normal	—	usually 5 minutes or less
Intermediate	—	10 minutes to 1 hour — (for females only)
Absent	—	more than 1 hour — usually more than 2 hours

*Note: Can use 0.005 ml. blood, 0.2 ml. water and 0.5 ml. reagent mixture.

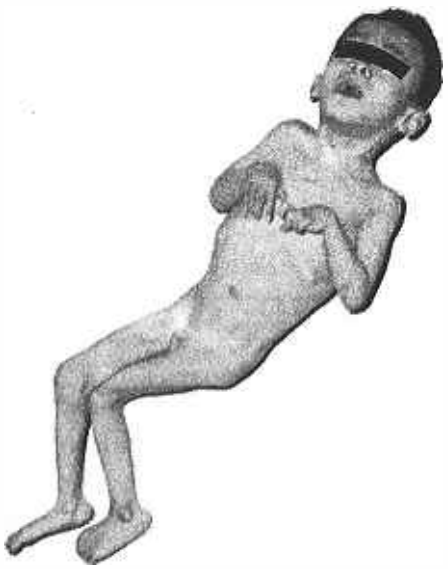
b) Education of the consumer:

Right from the beginning efforts were made to educate the public. Newspapers, radio and TV were made use of in disseminating knowledge to the public eliciting their understanding and co-operation. Talks were held and still are being held in community centres and infant welfare clinics. Pamphlets were printed by the Ministry of Health explaining in simple terms in the various languages (Appendix 2), what kernicterus is, how it is caused, what G6PD deficiency is, what the triggers are, what to avoid, and why we are isolating certain babies for close surveillance. There is no doubt that the population of Singapore is probably the most knowledgeable population in the world regarding neonatal jaundice. Yet, there are still some people who do not seem to understand, so that the education campaign should be a continuing one.

APPENDIX II

A MESSAGE TO MOTHER

YOU CAN PREVENT SEVERE JAUNDICE, BRAIN DAMAGE & EVEN DEATH . . .



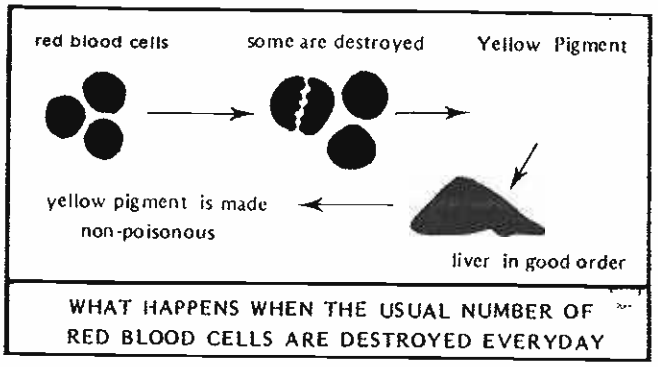
. . . in the FIRST THREE weeks of your baby's life.

WHAT IS JAUNDICE?

*Jaundice is yellowness of the skin.
*It is very common among babies during the first 3 weeks of life. In Singapore, 1,611 babies were hospitalised for observation and management of severe jaundice in 1977.
*It can cause MENTAL RETARDATION and even DEATH
*if not treated immediately.

HOW IS JAUNDICE CAUSED?

*Babies are born with red blood cells, made strong by a substance called 'enzyme'.
*A certain number of red blood cells are being destroyed and replaced everyday.
*When these red blood cells are destroyed, a yellow pigment is formed.
*If the baby's liver is in good order, it can absorb the yellow pigment and make it non-poisonous (or detoxified).



WHAT HAPPENS WHEN THE USUAL NUMBER OF RED BLOOD CELLS ARE DESTROYED EVERYDAY

*If the baby's liver cannot cope or if there are more red blood cells than usual being destroyed, the yellow pigment increases, and is carried to all parts of the body staining the skin and the eyes.

*When *too much* yellow pigment reaches the brain, the *BRAIN CELLS WILL BE DESTROYED, resulting in MENTAL RETARDATION* or even *DEATH.*

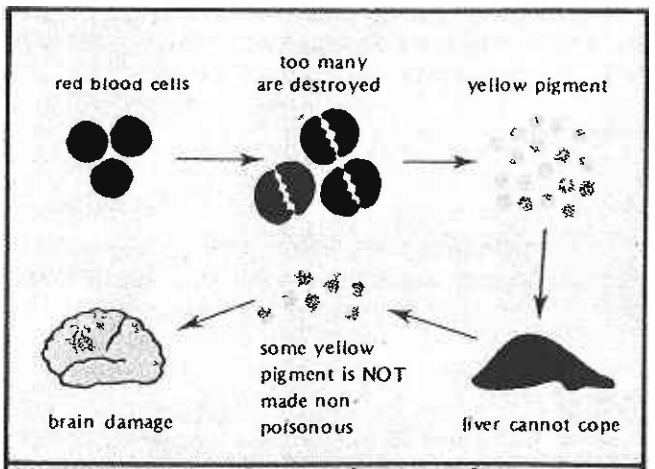
MORE RED BLOOD CELLS THAN USUAL WILL BE DESTROYED IN YOUR BABY:

*When you take certain drugs such as certain antibiotics while breastfeeding *or* when you give even a little of these drugs to your baby

or

*When you wrap your baby with clothing exposed to mothballs *or* carry your baby when you are wearing clothes exposed to mothballs

because the chemicals in these foods or in the mothballs (breathed in or absorbed through baby's skin) destroy the red blood cells ESPECIALLY THOSE LACKING IN 'ENZYME', resulting in more yellow pigment being produced.

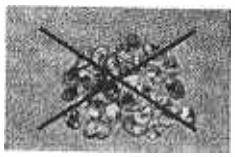


WHAT HAPPENS WHEN MORE RED BLOOD CELLS THAN USUAL ARE DESTROYED EVERYDAY

HOW CAN SEVERE JAUNDICE BE PREVENTED?
During the first 3 weeks of your baby's life . . .

*DO NOT TAKE OR GIVE TO YOUR BABY:

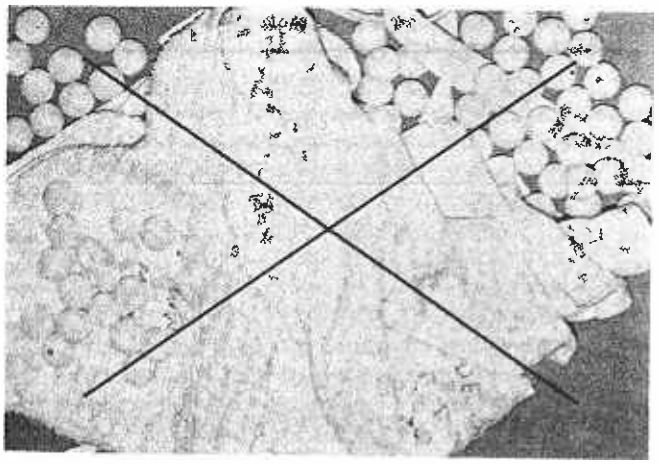
unnecessary drugs and foods like ginger and certain herbs (Chinese name — 'Chuan Lian' and 'San Tze Chze')



beans (Chinese name — 'Peetow', Malay name — 'Kacang parang')

These will cause more red blood cells than usual to be destroyed and at the same time affect the liver.

*DO NOT USE MOTHBALLS:
On your own and on your baby's clothes. Mothballs have a certain chemical which when breathed in or absorbed through the baby's skin destroys the red blood cells and affects the liver.



*DO NOT TAKE THE FOLLOWING WESTERN MEDICINES WITHOUT CONSULTING A DOCTOR:

ANTIMALARIALS
Primaquine
Pamaquine
Pentaquine
Quinine
Chloroquine

SULPHONAMIDES
Sulphanilamide
Sulphamethoxy pyridine
Sulfisozazole (Gantrisin)

ANTIPYRETICS
Acetylsalicylic acid
Acetanilid
Phenacetin
Antipyrine
Aminopyrine

NITROFURANS
Nitrofurantoin
Furazolidone
Nitrofurazone

SULPHONES
Sulfoxone (Diazone)
Diamino diphenyl Sulphone (DDS)
Sulphapyridine
Sulphapyrimidine
Sulphathiazole

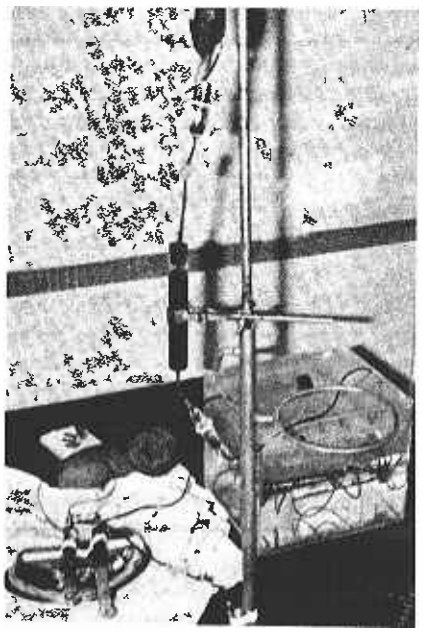
OTHER DRUGS
Dimercaprol
Methylene blue
Aminosalicylic acid
Phenylhydrazine
Vitamin K
PAS
Quinidine

THESE MAY BE A DANGER TO YOUR BABY'S LIFE!

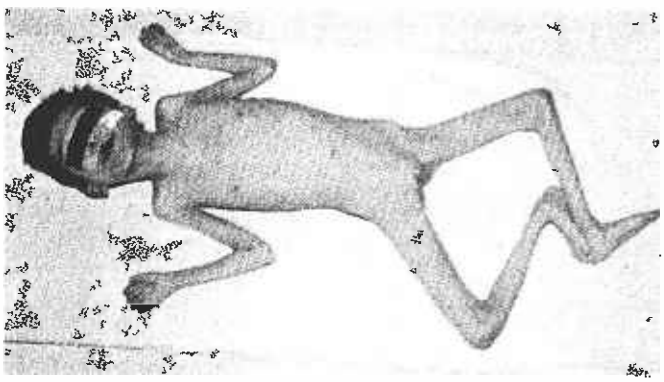
IF YOUR BABY IS JAUNDICED

BRING HIM TO A DOCTOR AT ONCE!

A severely jaundiced baby can be saved by an immediate exchange blood transfusion.



IF IT IS TOO LATE, THIS WILL RESULT:



c) HISTORY TAKING

Midwives, nurses and doctors have all been instructed to ask for newborn jaundice in previous babies. This is important for whatever the cause of Singapore Kernicterus may be, it tends to recur in the same family. Such families at risk are identified before the new baby is delivered, so that at delivery particular attention will be paid to him during the critical first few weeks of life, and all relevant tests carried out. Mothers with previous babies with severe jaundice are all given forms in which the cause of the jaundice is stated.

d) ISSUE OF FORMS

Every baby with kernicterus or severe jaundice is identified as to the cause, and a certificate or form is given to the mother, who then is instructed to produce it when she next is pregnant, so that the hospital staff and obstetrician is alerted to the possibility of the new baby being likewise affected.

If the baby is delivered, and after surveillance for a few days in hospital, and if there is no G6PD deficiency, the baby is discharged but the mother is given a letter to the nearest Infant Welfare Clinic staff to make domiciliary visits to observe the progress of the jaundice for the first 2-3 weeks, or arrangements made for the mother to bring the baby to the Clinic daily for the same period. In this way, these babies at risk released prematurely from the hospital for various reasons are observed carefully so that they can be immediately referred to hospital for SB determinations and exchange transfusions if necessary.

Any health screening procedure must prove its worth in terms of the cost-benefit ratio. The benefit of such a screening procedure is beyond doubt, viz, the high incidence of a potentially fatal disease and an almost 100% incidence of mental and physical retardation in survivors. What about the cost? The project has been implemented since 1965 and has continued for more than 15 years. Since its inception, because of the low cost of the G6PD screening procedure and the arrangements carried out and described above, no extra cost was involved. In other words, the surveillance project made use of existing staff and the actual cost of the G6PD test comes to less than 10 cents per test.

RESULTS OF SURVEILLANCE PROJECT

Initially, the main result was an increase in the exchange transfusion rates as the paramedical staff, doctors and public became more aware of the problem so that cases were sent to the Department before kernicterus set in. This increased rate continued on for about 8 years since the onset of the surveillance system, and 2-3 exchange transfusions were carried out daily and occasionally rose to six a day.

The next gratifying effect was that deaths from kernicterus gradually fell in Singapore, as the following figures show: (Table IX)

TABLE IX

YEAR	NO. DEATHS FROM KERNICTERUS	YEAR	NO. DEATHS FROM KERNICTERUS
1953	146	1965	48
1954	50	1966	43
1955	109	1967	30
1956	93	1968	18
1957	97	1969	13
1958	87	1970	24
1959	67	1971	22
1960	50	1972	19
1961	34	1973	17
1962	46	1974	10
1963	74	1975	12
1964	65	1976	8
		1977	5

Fig. 5 depicts this fall diagramatically. From 1954, there was a gradual fall of deaths from kernicterus even though causes at that time were unknown. This fall coincided with the period when I introduced exchange transfusion in Singapore for the prevention of kernicterus. By 1964, deaths had risen again and it was here that the Singapore kernicterus project was launched. The dramatic fall since then to almost less than 5 per year compared to 146 in 1953 bears testimony to the effectiveness of the surveillance programme. These are deaths due to kernicterus, and equally it may be assumed that mental retardation in kernicterus survivors has been reduced to almost neglible numbers compared to previously. This fall in deaths from kernicterus throughout Singapore is also corroborated when one considers deaths from kernicterus seen in the Department from 1963 to date. Fig 6 depicts this fall and the arrow indicates the year of institution of the surveillance programme, i.e. 1965, and deaths from kernicterus in the Department average 1 or 2 a year compared to 37 in 1963. Similarly, kernicterus which was the commonest cause of death in babies less than one week of age admitted to the Department in Singapore General Hospital and the third commonest cause of death in all admissions (up to 10 years of age), is now the least common cause of death in both age groups (Fig. 7) In conclusion, the fall in deaths from kernicterus had hence also the fall in incidence of mental retardation since the introduction of the surveillance project are real.

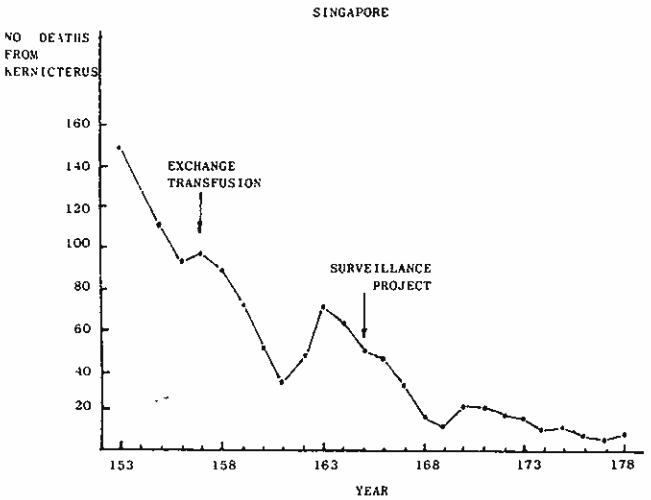


Fig. 5. Demonstrating fall in kernicterus death in Singapore with introductive of exchange transfusions & the kernicterus surveillance project.

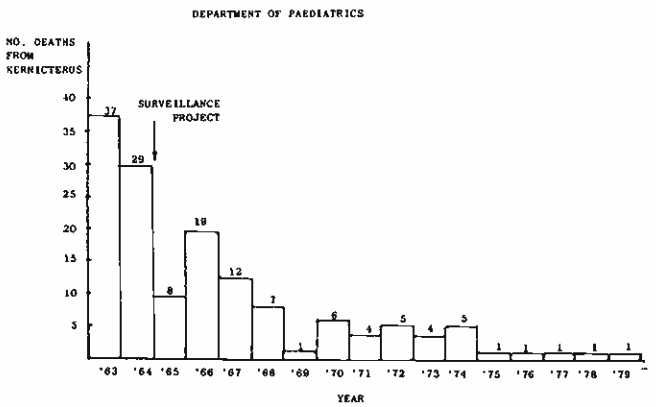


Fig. 6. Fill in deaths for kernicterus in Departure of Paediatrics after introduction of surveillance perfect.

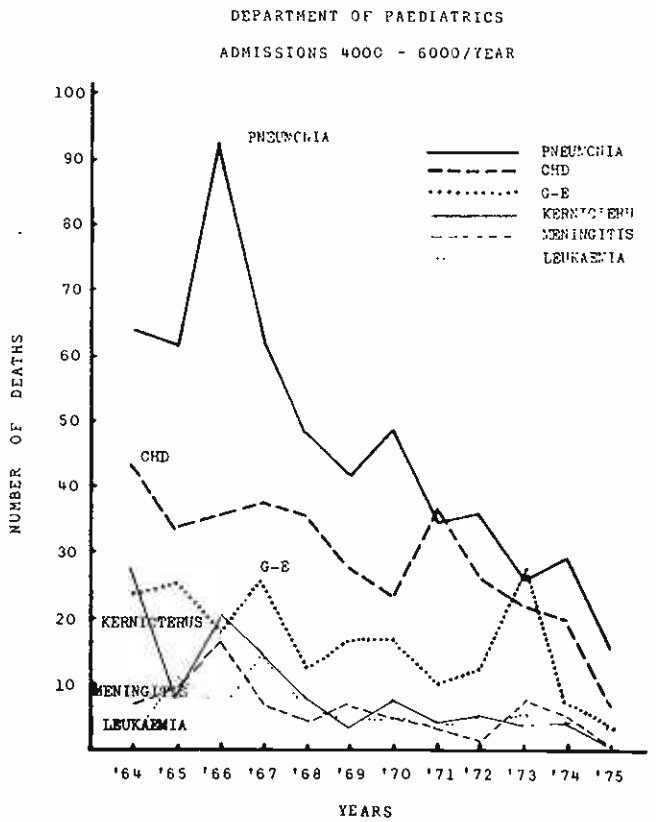


Fig. 7. Kernicterus deaths in Department composed to other cases of death.

The next effect the surveillance project has created is a change in the incidence of the various causes of neonatal hyperbilirubinaemia. As indicated above (Table III). G6PD deficiency was the commonest followed by liver immaturity. Because the project paid special attention to these 2 causes, how has the incidence of the various causes changed? A re-assessment of the incidence of the various causes of neonatal hyperbilirubinaemia in Singapore in 1973 (15) revealed the following (Table X):

The most obvious improvement has been in hyperbilirubinaemia due to G6PD deficiency, which was the commonest cause prior to 1965, and because it has been the target of the kernicterus project, it now accounts for only 9% compared to 43% before ($p<0.001$). The increase in hyperbilirubinaemia in prematures is due to better survivals in low birth weight babies as a result of establishment of more intensive care units, and also because of greater awareness of the kernicterus problem in prematures. Liver immaturity now heads the list and again confirms the peculiar situation in Singapore where local babies are less mature in their conjugation of bilirubin in the liver (8, 11). There was a 11% incidence of haemolysis due to undetermined causes because a special effort was made in this series to detect any sign of haemolysis, and tests including free pigments in the plasma and carbon monoxide levels were carried out. Pyruvate kinase and glutathine reductase estimations were done in these babies and enzyme levels were within normal limits. There was no doubt that haemolysis was present but what caused it is totally unknown, and again use of mothballs and herbs could be instigating agents. Alpha-thalassaemia, hereditary spherocytosis and haematomas as causes of newborn hyperbilirubinaemia are still uncommon, though they can be the cause of the odd patient.

The third effect of the surveillance programme has been mentioned before, viz. an increase in the exchange transfusion rate in the Department to 2-3 and up to 6 per day and this has led to efforts to reduce this. In any unit carrying out exhange transfusions for newborn hyperbilirubinaemia, certain criteria are followed as a guide to carry out the procedure or not. Factors which favour a decision to exchange transfuse the baby include a SB of 18-20 mg/dl, those who reach high levels in the first 3-4 days of life, preterm babies, those with sepsis, Rh, ABO and G6PD haemolytic disease, and those with hypoxic episodes at birth, and so on. Obviously, such a decision is never absolute, and if anything the baby is given the benefit of the doubt for fear of kernicterus supervening if an exchange is not done. The whole strategy of manage-

TABLE X

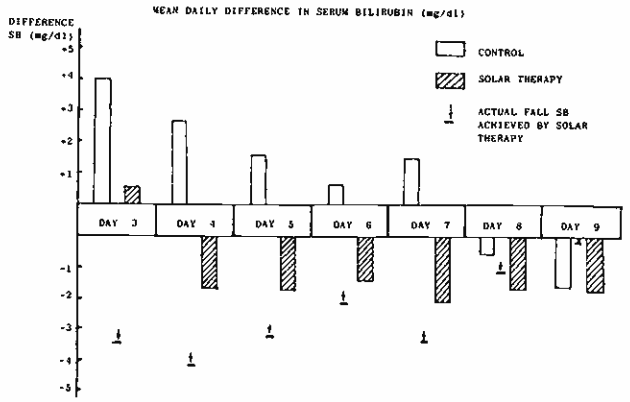
CAUSE	NO. CASES	%	SIGNIFICANCE COMPARED TO 1964 (TABLE III)
Liver Immaturity	83	38.0	$p<0.01$
ABO Incompatibility	39	13.9	Not significant (N.S.)
Prematurity	37	13.2	$p<0.001$
Haemolysis? cause	24	11.0	Significant
G6PD Deficiency	20	8.9	$p<0.001$
Sepsis	4	1.8	N.S.
Rh Incompatibility	4	1.8	N.S.
Cephalhaematoma	4	1.8	N.S.
Alpha-thalassaemia	2	0.9	N.S.
Hereditary Spherocytosis	1	0.4	N.S.
TOTAL	218		

ment of kernicterus is a preventive one because once kernicterus has set in, there is no treatment; it is too late. Coming to such a decision invariably means that many would not develop kernicterus even if no exchange transfusion is carried out. Such a decision would not have been important if exchange transfusion is a totally innocuous procedure. It is not because of possible hepatitis transmission, other transmitted infections, possible extra-hepatic portal hypertension later, and most serious of all, sudden collapse and cardiac arrest during the procedure in spite of taking all known precautions, especially in premature infants. All units carrying out the procedure report a mortality rate of about 1% or less and our experience is no different. Under the circumstances, any method which could lower the SB to levels which would not come within the ambit of a decision to be made for exchange transfusion would be extremely useful. In other words, if the SB could be lowered in those who would not have needed an exchange transfusion, it would save them from an unnecessary one.

In the 1960's we noticed that, when monitoring the SB of babies with neonatal jaundice, sometimes 6 hourly, the rise and fall was not a smooth one as depicted in Fig. 2 when the SB was estimated daily. The 9 pm level was lower than the 9 am level very often though on the same day and it was only the next day at 9 am when the SB became higher than the 9 am level of the previous day. In other words, exposure to sunlight during the day could lower the SB of the baby just as the SB of a patient with the serum kept in a bottle is lowered after exposure to sunlight. Hence, 37 babies with liver immaturity were exposed not directly to sunlight but beside the rays with eyes covered and the daily SB of these 37 babies were compared to the 81 babies with liver immaturity not so exposed. The mean daily difference in SB in mg/dl from the 3rd to the 9th day is shown in Table XI where a + indicates a rise in the mean daily difference and a — indicates a fall:

TABLE XI

DAY OF LIFE	3	4	5	6	7	8	9
CONTROL INFANTS (N = 81)	+ 4	+2.5	+1.5	+0.5	+1.5	-0.5	-1.5
INFANTS ON SOLAR THERAPY (N = 37)	+ 0.5	-1.8	-1.8	-1.6	-2.1	-1.7	-1.6
ACTUAL FALL IN SB ACHIEVED BY SOLAR THERAPY	3.5	4.3	3.3	2.1	3.6	1.2	0.1



As Fig. 8 shows, the actual fall in SB achieved by solar therapy varied from 2-4 mg/dl within the first week of life, and this is sufficient to save many a baby from an unnecessary exchange transfusion. The advantage of solar therapy is that it can be carried out by laymen in their own homes with the advice of paediatricians. However, in neonatal and paediatric units, we have installed flourescent bulbs which emit blue light, i.e. at a wavelength of 400-500 mm range which is more effective in degrading bilirubin. Its effectiveness in bringing down the SB in our hands, (16) is beyond question, but it should not be used as a replacement for exchange transfusion in those who need it acutely. Both solar therapy and phototherapy should have their use restricted to babies with neonatal jaundice where the rate of rise of SB would be gradual and not precipitous. It is a useful aid to exchange transfusion but not to supplant it. It must be realised that solar and phototherapy degrades bilirubin in the skin while exchange transufsion not only removes bilirubin from the blood but also because of the albumin the blood provides, exchange transfusion pulls out and binds bilirubin from the tissues, including the brain. In the final analysis, it is the unbound free bilirubin which is neurotoxic and not the albumin-bound bilirubin. In conclusion, solar and phototherapy obviates exchange transfusion in those not needing it but often exchange-transfused otherwise because of the difficulty in deciding on the criteria for exchange transfusion. It also may prevent exchange transfusion in those who really need it if light therapy is carried out early after birth.

There is no indication whatsoever for phenobarbitone use to bring SB down in neonatal jaundice because to be effective in actual practice, it has to be given to the mother before the baby is born, and given by injections to the baby from day one. Such an intensive use of phenobarbitone have caused developmental retardation in newborn rats.

Because of an awareness among laymen of a knowledge of kernicterus, and to refrain from certain pernicious cultural practices, the screening for G6PD deficiency and other inherited causes of haemolysis, the identification of families at risk and the institution of solar and phototherapy, not only has the incidence of kernicterus been dramatically reduced, the exchange transfusion rate has been reduced in the Department from 3 a day to less than once a week.

FUTURE PROSPECTS

In medicine, success of any regime can be permanent only if the regime is continued on with eternal vigilance. There are many examples in medicine when success has retrogressed e.g. resurgence of malaria and venereal disease due to relaxation of vigilance. Even when mosquito control has been successful, problems in malaria have cropped up as can be seen in chloroquine-resistant P. falciparum. The kernicterus surveillance system is fully accepted by the Singapore Government, the public and the doctors but reminders are still necessary. The following examples show that health education, to be effective, must be sustained and continual:—

CASE 1: A baby was born to parents in the professional class in a private hospital and received good obstetric and paediatric care. The full-term baby was screened and G6PD deficiency excluded and the baby was discharged on the 3rd day with the usual reminder to abstain from exposure to possible triggers and a final reminder by the paediatrician to the parents that in spite of all this, if jaundice should increase, the baby should be brought to hospital immediately. On the 5th day, the baby was more jaundiced but this being a Sunday, the parents did nothing about it. On the 6th day, a Monday, the father brought the baby to the private hospital in obvious kernicterus (with a SB of 34mg/dl) and was referred to our Department. Although an exchange transfusion was carried out, and the baby survived, mental and physical retardation were obvious. Discussions with the father revealed that he knew about kernicterus but did not know what intensity of jaundice means. It was their first baby and they did not have any "normal" yardstick to measure the degree of jaundice. It was a Sunday, and he did not want to bother the doctor, since the baby was feeding well. The whole point about kernicterus is that action has to be taken when the baby is still well, and when the baby is not well, it is too late. The father was ignorant about this and equated treatment with development of "unwellness", and so long as the baby was well, no treatment was necessary. Obviously, education of the public about kernicterus has to be continued and intensified.

CASE 2: This baby was born in the Government Maternal Hospital, KKH. Screening at birth revealed that he was G6PD deficient, and the parents told that the baby should be kept in hospital for 3 weeks for observation and to prevent exposure to possible haemolytic triggers. The paternal grandmother was most vehement about this, and she said that she had given birth to so many children and that nothing had happend to them and that though some were jaundiced, she knew how to deal with the problem. After a lot of explanations, it was obvious that the grandmother was the matriach of the family, the son and his wife were over-ruled, and they signed an AOR form (Discharge at own request) to absolve the hospital of any blame should anything untoward happen. In spite of this, the family were advised on things to avoid, pamphlets were given to them in English and Chinese explaining in simple language, what the disease is all about, and what to avoid, and to bring the baby to the nearest Infant Welfare Clinic for daily observation. The grandmother fed the baby "Chuan Lian", a yellow Chinese herb which contains berberine, on returning home, and within 24 hours after discharge on the 4th day, the baby was rushed to hospital by the father because the baby was severely jaundiced, refused to suck, had vomited and had a fit. On arrival in the Department, the baby was severely jaundiced with a SB of 40 mg/dl, had furrowing of the forehead, downward conjugation of the eyes, extension at the elbows, adduction at the shoulders, and pronation at the wrists with repeatable elicitation of a Moro reflex which was incomplete. The mouth was open, there was opisthotonos and fits. The baby died within one hour of admission. Nothing could have been down to save the baby. The grandmother did not come to hospital, and discussions with the father revealed that the grandmother did not believe that the jaundice had anything to do with the death of the baby, and that she would give the herb again if another grandchild was born! She was totally without remorse and totally ineducable, whether she is psychotic or not, is difficult to say. This is not the only sole example of such attitudes of the older generation, so that the kernicterus project, in spite of its many safeguards, still needs the co-operation of the consumer. The younger generation is more amenable to education, but in Singapore, there is still a hard core of the older generation who believe very strongly in cultural practices. Kernicterus cannot be *totally* eradicated until this generation disappears.

As the surveillance system continues, we are estimating bilirubin-binding by albumin as yet another method to assist in assessing "critical-ness" of a particular jaundiced baby. In neonatal jaundice, it is the free unbound bilirubin which is capable of passing the blood-brain barrier and is neurotoxic. The SB as measured is almost totally the albumin-bound bilirubin which is non-toxic and hence does not give a good indication of the free bilirubin (17-24). Direct measurement of free bilirubin is difficult, and the accuracy of the methods is questionable mainly because of the very small amounts present in serum. For example, in a normal adult, calculations reveal that he has a free bilirubin level of 0.12 m mol per litre, and in a baby with a SB of 18 mg/dl or 310 mmol/litre, and a serum albumin of 400 mmol/litre, the free bilirubin would amount only to 50 mmol/litre which may be critical in causing kernicterus. Therefore, because of the difficulty in measuring free bilirubin at present, a simple method of assessing albumin-binding of bilirubin, is to use sephadex columns, into which the serum of the jaundiced baby is passed (25). After washing the column with buffers, the albumin-bound bilirubin is eluted, and if any free bilirubin is present it remains behind in the column and can be detected (Fig. 9). Hence, the *presence* of free bilirubin detected by this method gives an indication of the severity of the condition. If free bilirubin is not detected in the column, aliquots of exogenous chemical bilirubin can be added to the serum, and the test repeated till free bilirubin is again detected. Obviously, the more bilirubin which has to be added to demonstrate the presence of free bilirubin by this method, the less saturated is the original patients albumin with bilirubin, and hence the "safer" is the patient's situation. Hence, the result can be expressed as follows: (Table XIII)

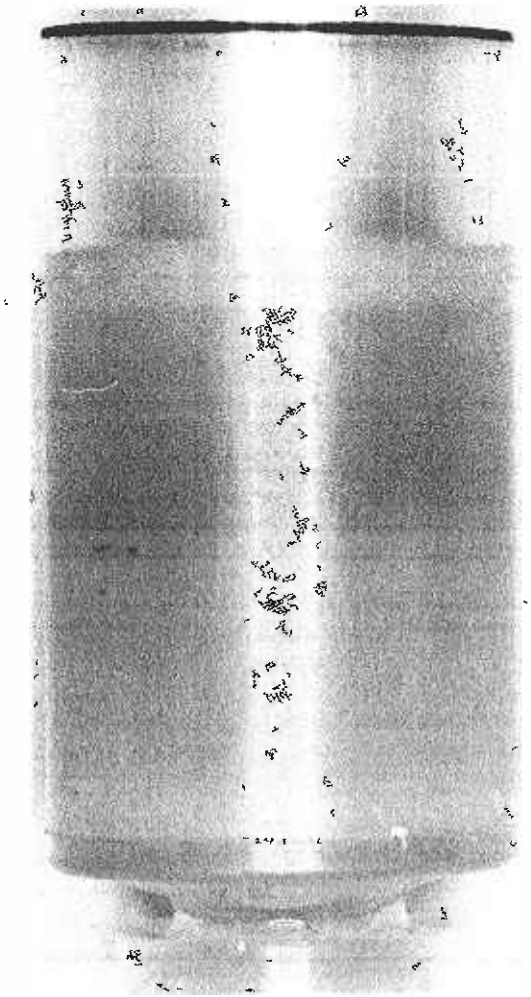


TABLE XII

BILIRUBIN ADDED TO PROVIDE FREE BILIRUBIN	SEVERITY
0 mg	+++
1 mg	+
2 mg	±
3 mg	−

The method can be made more precise by adding 0.5 mg aliquots of bilirubin. In our hands, the presence of free bilirubin in the original serum (i.e. without added bilirubin) indicates the presence of kernicterus or a situation where exchange transfusion must be carried out immediately. When it is detected with addition of 1 mg of bilirubin, we still tend to do an exchange when there are no signs of kernicterus. We do not tend to carry out exchanges if free bilirubin appears only after adding 3 or more mg. bilirubin. Using these criteria, we have not seen any babies developing kernicterus with 3 mg or more without exchange transfusions.

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