

## Ethnic group differences in bilirubinemia of Singapore Newborns

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FOR A NUMBER of years Singapore physicians have suspected that the usual criteria for "physiologic" jaundice of the newborn are not appropriate for Asian infants of this city-state. They have noted that clinical jaundice in fullterm healthy Chinese and Malay infants ordinarily is more severe, of longer duration, and more frequent in occurrence than would be expected from the descriptions of mild, transient jaundice in fullterm newborns of Western countries. In clinical observations of 700 Asian newborns at the government maternity hospital in Singapore jaundice was noted in nearly 100% of cases.<sup>1</sup>

Wong has reported that the causative factors in about 25% of severe neonatal hyperbilirubinemia cases seen at Singapore General Hospital are unknown.<sup>2</sup> In the years 1960 and 1961 he observed 61 cases of severe, apparently nonhemolytic, jaundice including 23 cases of kernicterus in fullterm otherwise healthy Chinese and Malay infants. He queried whether suboptimal nutrition or the widespread use of traditional antenatal and postnatal herbs and drugs are related causally to the apparent high incidence and severity of unexplained neonatal jaundice in Singapore Chinese and Malays.

This study was conducted in order to determine levels of plasma bilirubin in fullterm newborns in Singapore and to investigate factors that might be responsible for unusually severe hyperbilirubinemia.

### Materials and Methods

One hundred eighty-eight infants from British Military Hospital (BMH) and the University teaching service and paying class A ward of Kandang Kerbau Maternity Hospital (KKMH) were studied. BMH infants were Malay or British; KKMH infants were Indian, Chinese and Malay. All infants were healthy, term (38 to 42 weeks gestational age) products of uncomplicated vaginal deliveries who weighed 2500 g or more and were well throughout the neonatal period. The infants were kept in nursery for 5 to 7 days and whenever possible studied for longer periods as outpatients.

The following laboratory tests were performed: ABO, Rh blood grouping of mothers and babies, quantitative glucose-6-phosphate dehydrogenase (G-6-PD) estimation<sup>3</sup> on cord blood red cells, microhematocrit and total plasma bilirubin estimation daily on all infants, and reticulocyte counts.

No case of maternal-fetal difference of ABO or Rh blood groups or G-6-PD deficiency has been included in the data to be presented.

### Results

#### A. Clinical Observations

Clinical jaundice was more intense and occurred more frequently in Malay and Chinese infants than in the British infants. In the darker pigmented Indians clinical estimation was difficult. None of the infants had enlargement of

the spleen or liver or signs of neurologic damage.

## B. Laboratory Results

In TABLE I we have presented the means of maximum plasma bilirubin values attained by infants of the 4 ethnic groups. There is a 2-to 2½-fold difference between the mean values for British infants and infants of all 3 Asian groups. These differences are highly significant statistically.

Histograms in Fig. 1 illustrate frequency distribution of maximum bilirubin levels reached in the 4 ethnic groups. Only 1 British infant (3%) had a maximum bilirubin value greater than 10 mgm/100 ml; this value was exceeded by 69% of Chinese, 47% of Malay and 52% of Indian infants. Conversely, maximum plasma bilirubin was less than 4 mgm/100 ml in 52% of British infants but in only 1.2%, 2% and 8% of Chinese, Malay and Indian infants, respectively. Five of 81 (6%) Chinese and 1 of 46 (2%) Malays, but no Indian or British infants had plasma bilirubin concentration exceeding 18 mgm/100 ml.

Graphs in Fig. 2 illustrate the differences in daily bilirubin levels of the ethnic groups during the first week of life. In addition to reaching higher levels, maximum plasma bilirubin concentration was reached later in the week in Asian infants than in British infants and elevated levels were maintained for a longer time. Among British babies by day 5 mean bilirubin values had decreased to 2.7 mgm/100 ml while values in Asian infants were: Chinese, 10.1; Indians, 8.7; Malays, 8.6 mgm/100 ml.

Approximately ½ of the Asian babies could be studied after their discharge from the hospital. Normal or near-normal adult bilirubin values were eventually achieved by every infant who could be followed for an adequate time. Bilirubinemia of greater than 2 mgm/100 ml was never recorded beyond the seventh neonatal week and the duration of hyperbilirubinemia was directly related to maximum bilirubin level attained (See Fig. 3).

In TABLE II we have presented the mean packed cell volumes of the various ethnic groups during the first neonatal week. There is very little difference between values of the ethnic groups, and there is no correlation between

the average rate of packed cell volume decrease and mean peak bilirubin values.

No reticulocyte count greater than 4% was recorded.

## C. The Relationship of Plasma Bilirubin Values to Birth Weight, Gestational Age and Other Factors

The gestational age means for infants of the 4 ethnic groups were nearly identical: British, 39.9; Chinese, 39.8; Malays, 39.7; Indians, 39.9 weeks. In all groups the correlation between gestational age and maximum bilirubin values was slight (negative correlation) or nil.

Average birth weights of the infants were: British, 3551 g; Chinese, 3170 g; Malays, 3187 g; Indians, 3070 g. Within ethnic groups there was no correlation between birth weight and maximum bilirubin levels.

There was no significant difference between male and female peak bilirubin values.

Virtually all Malay and Indian infants were breast-fed; in Chinese and British infants there was no significant difference between bilirubin levels of breast-fed and formula-fed babies.

About ½ of all Chinese mothers admitted taking a mixture of 12 or 13 herbs referred to as "12B" or "13B" during their pregnancy. Occasionally other herbs were used. We found no difference between the bilirubin levels of infants whose mothers took "12B" or "13B" and those whose mothers denied taking herbs or traditional medicines of any kind.

The number of previous pregnancies varied greatly among women of various ethnic groups and KKM services. Nearly all British or Chinese private ward women were parous 2 or less, but grand multiparity was common in the teaching service Asian mothers. These differences had negligible effect on infants' bilirubin values.

Total serum bilirubin estimations in 20 unselected Asian mothers whose infants had varying degrees of bilirubinemia were all below 1 mgm/100 ml.

## Comment

It is interesting to compare our findings to the usual descriptions of "physiologic" jaundice

and hyperbilirubinemia found in Western medical literature.<sup>4,5,6</sup> Zuelzer of Wayne University in Detroit, U.S.A., has written: "In the fullterm infant physiologic icterus is clinically mild and unaccompanied by clinical symptoms. It usually disappears within 1 to 3 days and correspondingly the bilirubin level of the plasma decreases rapidly once the peak has passed, so that by the end of the first week of life values of 2 mgm per 100 ml are to be expected."<sup>4</sup> Zuelzer also suggests that bilirubin values above 10 to 12 mgm/100 ml of plasma during the first neonatal week in fullterm infants should be regarded with suspicion. It is well known that in fullterm infants hyperbilirubinemia occasionally may exceed these limits without explanation. However, our findings in Asian infants are indeed unusual, for the majority had definite hyperbilirubinemia extending well beyond the first neonatal week, and maximum bilirubin values exceeded 10 mgm/100 ml of plasma in  $\frac{1}{2}$  to nearly,  $\frac{3}{4}$  of cases. Bilirubinemia of British infants in our study, however, is quite consistent with so-called "physiologic" bilirubinemia. Our values are nearly the same as those of Davidson, et. al.,<sup>7</sup> in English infants.

In premature infants bilirubin values ordinarily are somewhat higher than in fullterm infants.<sup>8,9</sup> We conscientiously attempted to exclude all cases of prematurity. The 2500 g birth weight minimum for inclusion in the study group is probably 250 to 500 g higher than the appropriate minimum for clinical maturity in Singapore Asian newborns. That mean birth weights of our Asian newborns are lower than those of British infants undoubtedly reflects genetic differences in stature of these ethnic groups and does not indicate shorter gestational age of our Asian babies. We have shown that the ethnic group differences in bilirubin levels cannot be accounted for by their modestly lower birth weights.

Important questions evoked by our findings are: (1) what is the etiologic classification of the Malay, Chinese and Indian infants' hyperbilirubinemia; (2) can it be explained by environmental factors; and (3) what are the clinical and geographic medical implications?

"Physiologic" hyperbilirubinemia of the newborn results principally from "immaturity" of hepatic enzyme systems which are involved

in the conjugation of bilirubin with glucuronide.<sup>10</sup> Unusually elevated bilirubin levels are seen in conditions of excessive red cell destruction (hence increased bilirubin load presented to the liver), obstruction to the outflow of bile, or greater "immaturity" or inhibition of the conjugating enzymes. It is not likely that excessive red cell destruction is alone responsible for the high bilirubin levels in Asian infants. We have eliminated from our data the common causes of hemolytic hyperbilirubinemia, e.g., ABO, Rh incompatibility and erythrocytic G-6-PD deficiency. If excessive hemolysis alone were the cause of Asian infants' greater bilirubinemia we would expect some evidence of increased reticulocyte production or more rapidly falling hematocrits in the Asian babies. Obstruction to bile flow has been ruled out because we found no abnormal elevation of the direct-reacting, conjugated fraction of bilirubin. Thus it seems most likely that increased bilirubinemia of Singapore Asian newborns is a reflection of relatively less activity of hepatic enzyme systems than is present at comparable stages of development in British infants.

A great number of factors can contribute to the jaundice of newborns by influencing the activity of liver enzyme systems. None of those thus far described seem to be of importance in the infants we have reported. Hypoxia, sepsis, diabetes, hypothyroidism and the administration of vitamin K, novobiocin, erythromycin, streptomycin and sulfa drugs have been ruled out in all our cases. Pethidine, Sparine and nalorphine were used in many mothers at both hospitals as pre-delivery medication but we found no evidence that these drugs influenced neonatal bilirubin levels. We found that breast feeding is not an important factor in the hyperbilirubinemia of Chinese infants.

We cannot attribute the ethnic groups differences in bilirubin levels to differences in neonatal, obstetric or infant care at BMH and KKMH. Malay babies born at each of these hospitals had virtually identical peak bilirubin values. Malays born at BMH, however, had bilirubin levels strikingly greater than BMH British infants, even though maternal and infant care in both ethnic groups was the same.

We have tried to assess the importance of the myriad environmental factors which might

be responsible for the ethnic group differences in bilirubin levels. This is indeed a difficult task in a sociologically complex setting such as Singapore. We have no evidence that nutritional status of the Asian mothers is an important determinant of infants' bilirubin levels. Infants of private, class A mothers, who appeared to be very well nourished, were found to have maximum bilirubin levels almost identical to teaching service Chinese infants. Most intriguing is the custom among Chinese mothers of taking traditional herbs and drugs during pregnancy and the postnatal period. We have not found that any of these drugs contribute to elevation of infant bilirubin levels, but the number of agents used is so great and accurate clinical histories so difficult to obtain that it is possible we have overlooked an important agent. We can be quite sure, however, that the postnatal drugs are not important in our findings because formula-fed infants had bilirubin levels just as high as breast-fed infants. The fact that all three of the Asian ethnic groups had similarly elevated levels despite their markedly different diets, use of non-Western drugs and other cultural differences, is evidence that specific environmental agents are not responsible for the elevated bilirubin values.

It is possible that the greater hyperbilirubinemia of Singapore Asian infants reflects previously unrecognized genetic differences in neonatal bilirubin levels. There is some evidence from existing literature that this maybe true, although studies of neonatal bilirubin levels in non-Western countries are few. Our study is the only one we are aware of in which a controlled comparison is made between Oriental and European infants' bilirubinemia. In a study from Taiwan fullterm Chinese infants were found to have bilirubin values almost identical to those of our Singapore Chinese.<sup>11</sup> Pediatricians in Hong Kong<sup>12</sup> have noted that clinical icterus in Chinese neonates generally exceeds the usual criteria of "physiologic" jaundice. We have not found reports from mainland China or studies in Chinese populations in Western locations, such as San Francisco. A study from the Philippines<sup>13</sup> is difficult to interpret because of the laboratory methods used and because patients selected for study were jaundiced. Some reports from Japan,<sup>14</sup> Africa,<sup>15,16,17,18</sup> and India<sup>19</sup> suggest that severe nonhemolytic

jaundice might be common in those countries, but ranges of bilirubin for normal infants are not included in the reports. Fullterm American Negroes evidently have bilirubin levels comparable to white American infants,<sup>20</sup> although premature Negro babies may have somewhat lower values.<sup>21</sup> We were able to study a few Pakistani, Arab and Gurkha infants, Although the numbers are too few to be conclusive, average maximum bilirubinemia of the combined group is greater by 2 fold than in our British infants.

The finding of unusually elevated neonatal bilirubin levels in Asian infants has important clinical implications in Singapore and perhaps in other parts of Asia. On the one hand, neonatal jaundice, though it ordinarily exceeds the criteria of "physiologic" jaundice, is not usually the result of demonstrable pathologic conditions and can be expected to remit spontaneously. On the other hand, the finding of generalized hyperbilirubinemia in Singapore Asian newborns helps to explain why extreme jaundice and kernicterus are serious problems in Singapore.,<sup>12,22</sup> Plasma bilirubin levels in the healthy fullterm Chinese, Malay and Indian newborn without any evidence of excessive hemolysis commonly approach potentially deleterious levels (greater than 20 mgm/100 ml of plasma). It is reasonable to assume that in certain cases, in the absence of excessive red cell destruction, plasma bilirubin concentration may reach levels which are toxic to brain nuclei. Certainly the generalized hyperbilirubinemia of Asian infants contributes to the gravity of superimposed hemolytic conditions, *e.g.*, ABO isoimmunization and G-6-PD deficiency, which are commonly associated with extreme hyperbilirubinemia in Singapore newborns.

In Asian infants of this city-state plasma bilirubin levels commonly rise to high levels late in the first neonatal week or early part of the second week (see Fig. 3). This finding helps to explain an unusual problem in Singapore. At K.K. Hospital infants commonly are discharged within 24 hours after birth. At that time little or no jaundice may be visible. However, after discharge plasma bilirubin levels may steadily increase and reach toxic levels a few days later. The increasingly severe jaundice may go unrecognized until kernicterus has occurred. Thus it is important that in Singapore every

Asian baby be observed closely throughout the entire first neonatal week for the presence of unusually severe jaundice. This is necessary in order that exchange transfusion can be performed promptly and before the occurrence of brain damage.

### Summary

IN FULLTERM Chinese, Malay and Indian infants of Singapore neonatal hyperbilirubinemia generally is more severe and of longer duration than in Singapore-born British infants. The hyperbilirubinemia is non-obstructive, probably nonhemolytic and resembles an exaggeration of so-called physiologic bilirubinemia. The ethnic group differences in neonatal bilirubin levels might be the manifestation of previously unrecognized genetic differences in bilirubin metabolism, although the importance of environmental factors is not completely understood. The ordinary definitions of "physiologic" icterus, which have evolved principally from observations in Western countries, are not appropriate to Singapore-born Asian infants and may not be appropriate to infants of other parts of the world. Further geographic studies of neonatal bilirubinemia are indicated. The metabolic hyperbilirubinemia of Singapore Asian infants commonly approaches brain-damaging levels and doubtless contributes to the gravity of superimposed hemolytic conditions.

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TABLE I  
Mean and One Standard Deviation Peak Bilirubin Values during the Neonatal Period in Infants of Various Ethnic Groups.

Ethnic Group	Hospital/ Ward	Number of Infants	Mean Peak mgm/100 ml.	S.D.
British	BMH*	36	4.4	2.8
Chinese	KKMH**/Teaching	57	11.5	4.2
Chinese	KKMH/Private	24	12.0	3.5
Chinese	Combined	81	11.6	4.0
Malay	BMH	30	9.5	3.2
Malay	KKMH	16	9.9	3.5
Malay	Combined	46	9.7	3.3
Indian	KKMH/Teaching and Private	25	9.6	3.6

#### Comparison of Means (Student's Test)

British versus Chinese (combined)	-	-	-	-	p<.001
British versus Malays (combined)	-	-	-	-	p<.001
British versus Indian	-	-	-	-	p<.001
Chinese (combined) versus Malays (combined)	-	-	-	-	p<.01
Chinese (combined) versus Indians	-	-	-	-	p<.05>.20
Malays (BMH) versus Malays (KKMH)	-	-	-	-	p>.3
Chinese (Teaching service) versus Chinese (Private service)	-	-	-	-	p>.4
British versus Malays (BMH)	-	-	-	-	p<.001
British versus Chinese (Private service)	-	-	-	-	p<.001

\*British Military Hospital

\*\*Kandang Kerbau Maternity Hospital

TABLE II  
 Mean and One Standard Deviation Packed Cell Volumes for Infants of  
 Various Ethnic Groups during the First Neonatal Week.

Ethnic Group	No. of Infants	Day							Decrease in Mean values day 1 through 5
		1	2	3	4	5	6	7	
British	35	67.1±8.8	62.4±8.1	62.0±6.9	58.7±7.1	59.0±7.4			8.1
Indian	25	70.1±10.0	65.6±8.5	63.5±7.1	62.9±7.1	60.7±7.1	59.6±7.6	58.3±8.1	9.4
Malay	46	69.2±7.6	62.5±7.1	62.2±5.8	59.9±6.5	57.9±5.7	55.9±6.1	54.4±6.0	11.3
Chinese	81	66.1±8.1	63.1±7.5	61.5±6.9	59.2±10.2	58.5±7.5	57.6±6.8	56.9±6.3	7.6

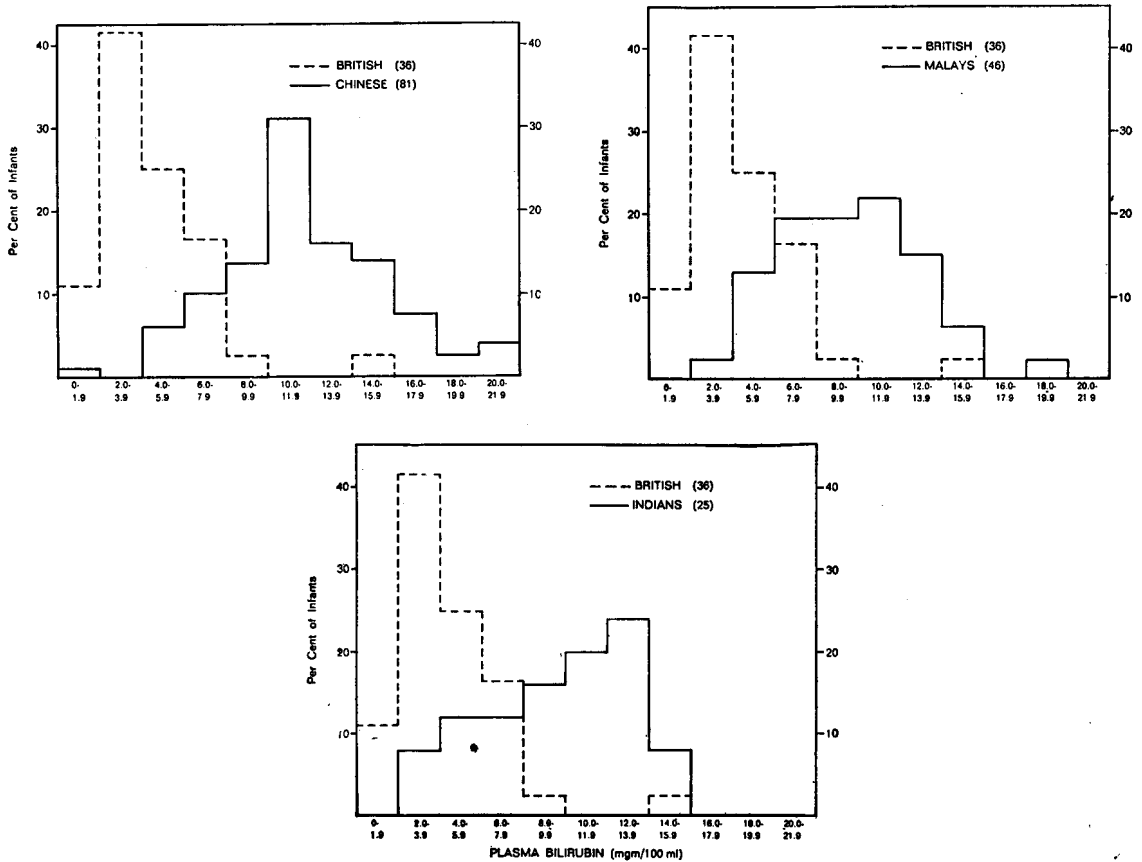


FIG. 1

Frequency distribution histograms of maximum plasma bilirubin values during the neonatal period in infants of 3 Asian groups compared to Singapore-born British infants. Number of infants studied is in parentheses.

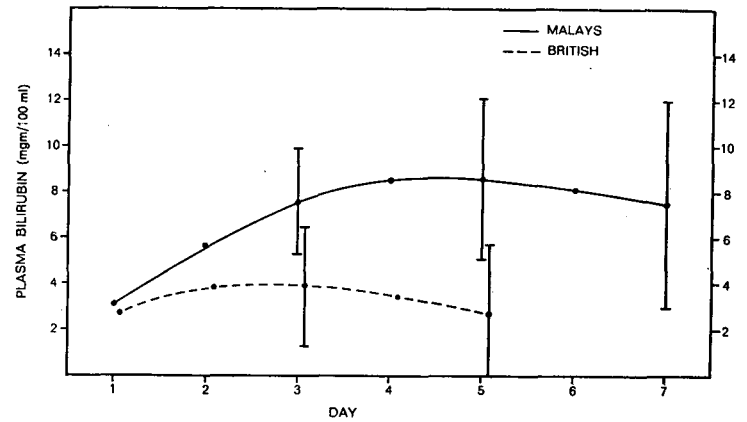
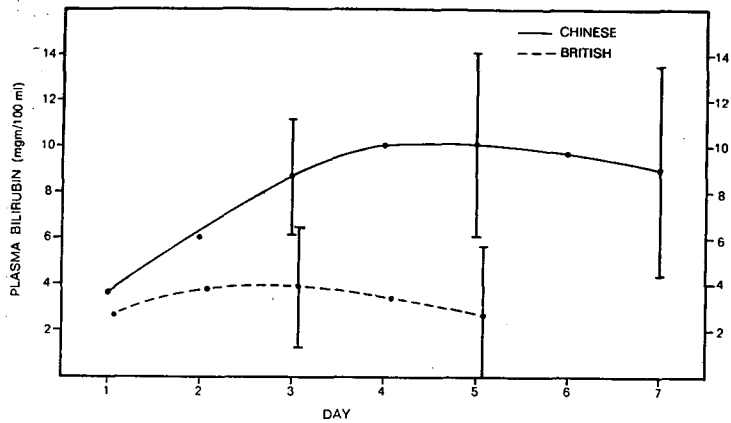


FIG. 2 (part 1)

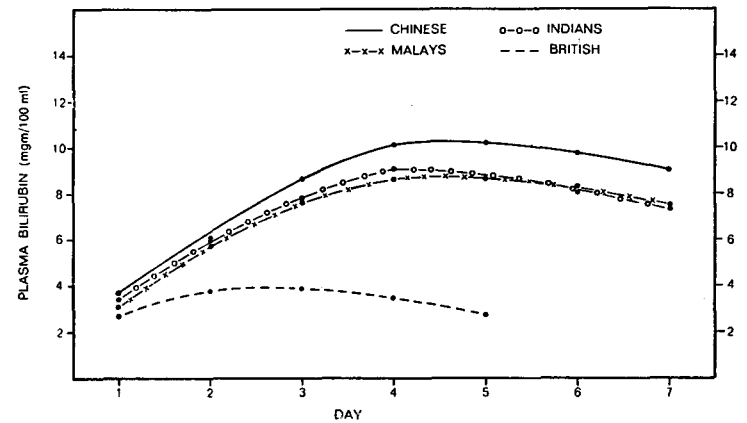
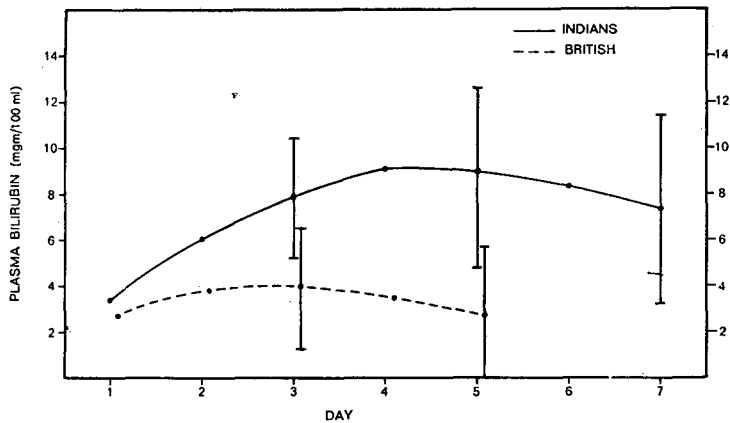


FIG. 2 (part 2)

Plasma bilirubin values during the first neonatal week in infants of various ethnic groups.

• mean; I limits of one standard deviation.



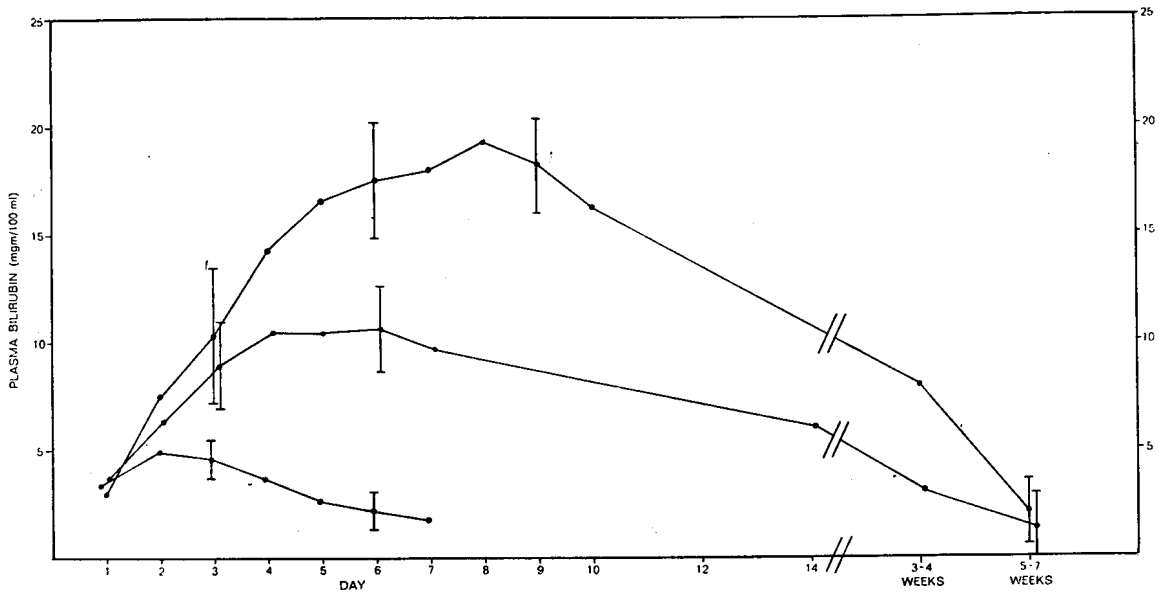


FIG. 3

Serial plasma bilirubin values in Chinese infants whose peak values fell in 3 ranges: 4.0-5.9 mgm/100 ml (5 infants), 10.0-13.9 mgm/100 ml (11), 18.0-21.9 mgm/100 ml (4).

• mean; I limits of one standard deviation.