FACTORS INFLUENCING NEONATAL JAUNDICE

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An investigation was planned to inquire into the aetiology of neonatal jaundice other than that proved to be due to haemolytic disease. The course of the work evolved on three lines: first, a two-year period of case collection at the Birmingham Maternity Hospital; second, a comparison with another hospital reputedly having a much higher incidence of jaundice and, third, a long-term follow-up to assess any residual brain damage. The first part is reported here.

The period covered two years from December 1, 1958 to November 30, 1960, excluding short periods when holidays prevented cases being recorded adequately. Babies discharged within six days of birth (home nursing) and proved cases of Rh or ABO haemolytic disease were excluded (Table 1).

TABLE 1

Total live births		3,978
Exclude: Home nursings	1,304	
Neonatal deaths	77	
Haemolytic disease	129	
Total excluded	1,510	
Number remaining in hospital over six days		2,468

All babies weighing 5 lb. 8 oz. (2·5 kg.) and under were included in the study whether jaundiced or not. All jaundiced babies weighing over 5 lb. 8 oz. (2·5 kg.) were included. Every tenth non-jaundiced mature baby was selected as a control; if the child later became jaundiced or left hospital within six days the next infant was selected. This resulted in the multiplication factor being 7·727 instead of 10 to correct the sample of controls to the total number of 1,615 non-jaundiced mature babies (see Table 2).

Incidence of Jaundice

All babies were examined daily, and clinical jaundice was noted; if more than Grade 3 was recorded on the Gossett icterometer (Culley, Waterhouse and Wood, 1960) bilirubin estimations were carried out by the method of Lathe and Ruthven (1958). Towards the end of the study the blood specimens were sent to a different laboratory using a different bilirubin standard, and duplicate specimens were analysed in both laboratories. A good correlation between the two standards was obtained and a linear regression equation was computed to transform the figures from the new laboratory to levels comparable with the original. The correspondence was such that a bilirubin of 25 mg./100 ml. 'original' method corresponded to about 20 mg./100 ml. 'new' method; around or above this level exchange transfusion was performed. A bilirubin of 15 mg./100 ml. 'original' was equivalent to 12 mg./100 ml. 'new', and this was classified as 'severe' jaundice. Present results are expressed on the new scale. As it was not possible to know how

TABLE 2

	Birth Weight		All Cases
	5½ lb. or less	5½ lb. or over	
No jaundice	131	209 × 7·727 = 1,615	1,746
Clinical jaundice	206 (61)	516 (24·2)	722
Bilirubin (mg./100 ml.):			
>12	57 (16·9)	81 (3·8)	138 (5·6)
>16	17 (5·0)	26 (1·2)	43 (1·7)
>20	3 (0·9)	2 (0·1)	5 (0·2)
Babies exchanged	4 (1·2)	4 (0·2)	8 (0·3)
Total	337	2,131	2,468

Figures in parentheses are percentages.

many of the babies leaving hospital within six days might have become jaundiced, the incidence has been calculated as a percentage of those actually remaining under observation (Table 2).

Analysis of Results

The data concerning blood groups, antenatal conditions, labour, delivery, state of baby at birth, subsequent behaviour and treatment were recorded and then punched on to an I.C.T. card. This enabled sorting to be rapidly and accurately effected.

Season. Table 3 shows the seasonal influence in clinical jaundice, and there appears to be no obvious difference apart from an apparent small rise as the study proceeded.

This was probably due to a slight change in the character of the admissions, there being relatively more cases of pre-eclamptic toxaemia admitted in the first year and more of ante-partum haemorrhage in the second.

TABLE 3

Season	Per Cent. With Clinical Jaundice		
	1958	1959	1960
First quarter	—	26·8	31·4
Second quarter ..	—	28·0	32·8
Third quarter	—	29·3	32·9
Fourth quarter ..	27·3	26·4	—

Foetal Maturity. The incidence of clinical jaundice was plotted against weight, gestational age and infant's length (Fig. 1). The relation between jaundice and weight or length appears to be approximately a straight line, while that between jaundice and gestation is an S-shaped curve. During the period of study there were 419 cases of pre-eclamptic toxaemia and 44 of maternal diabetes, both of which have a marked effect on foetal weight; we therefore used gestational age for comparing jaundice incidence.

Blood Group. Although those cases with positive Coombs' tests on cord blood or cases with severe jaundice showing an immune maternal anti-A or anti-B haemolysin were excluded, there were probably some undetected cases of mild O-A or O-B haemolytic disease as there were slightly more group 'O' mothers of jaundiced infants than would be expected.

On a statistical basis there are likely to be about 20 babies of the jaundiced group who had O-A or O-B incompatibility.

Concept of Clinical and of Severe Jaundice

Data obtained by observing clinical jaundice may be criticized on the grounds that such a subjective finding is liable to observer error even with an aid such as the icterometer. We have therefore compared the results obtained from clinical jaundice with data on severe cases where serum bilirubin estimations were performed. Where these results were in agreement confidence was felt in the implications. Fig. 2 shows the incidence of both these degrees of jaundice and how they relate to each other on a gestational basis.

The problem will now be considered under the three headings of:

1. Factors decreasing the incidence of jaundice.
2. Factors increasing the incidence of jaundice.
3. Factors having little or no significant influence on jaundice.

1. Factors Decreasing Jaundice

Maternal Age. The figures show a reduction of

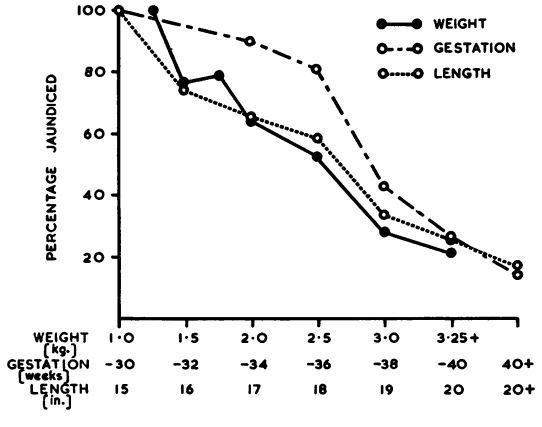

FIG. 1.—Clinical jaundice related to weight, gestation and length.

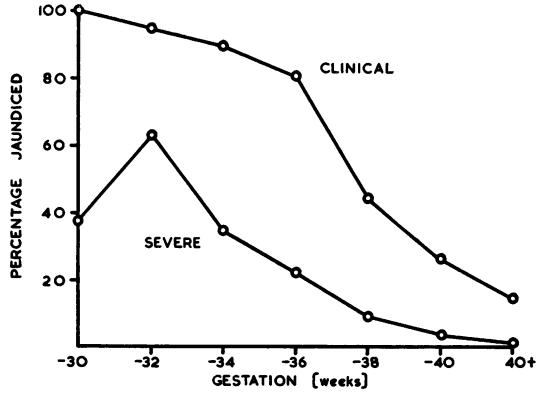

FIG. 2.—Clinical and severe jaundice related to gestation.

jaundice as maternal age advances (see Table 4).

Pre-eclamptic Toxaemia. This condition had such a marked influence in reducing jaundice, that it was thought that a false effect had arisen by neglecting the stillbirths and neonatal deaths. When, as in Table 5, allowance is made for perinatal mortality, not only is the total incidence of jaundice little affected, but also the toxaemic cases still show a marked and in several instances highly significant reduction in jaundice.

A similar effect is shown in the severe cases (see Table 6).

The number of cases of uncomplicated hypertension was small, but these also showed a reduction in the incidence of jaundice to much the same degree as in toxaemia.

Post-maturity. In order to assess this more accurately, babies over 38 weeks' gestation were put into three groups as in Table 7.

These figures show a significant fall between 40 and 42 weeks, but beyond 42 weeks this is shown in the severe cases only.

To summarize, we find that taking the total figures there is a gradual reduction of jaundice as gestation advances, but that from 36 to 38 weeks this rate is quickened quite markedly as if some definite maturation effect is occurring in the foetus. In pre-eclamptic toxaemia this effect is advanced by two weeks (Tables 5 and 6). The influence of post-maturity is less striking but definite while advancing maternal age is significant in some respects.

TABLE 4

Infant's Gestation	Mother's Age	
36 weeks and under	*30 Years and Under*	*Over 30 Years*
Clinical jaundice	90·5% ←—*—→	79·5%
Severe jaundice	33·7%	27·7%
Over 36 weeks		
Clinical jaundice	27·0% ←—**—→	21·3%
Severe jaundice	4·4% ←—**—→	2·4%

In this table and subsequently, a statistically significant difference at the 5% level is expressed by one asterisk and at the 1% level by two asterisks.

TABLE 6

Gestation (weeks)	% Severe Jaundice Within Each Two Weeks' Gestation			
	All		Toxaemia	
	No. of Cases	% Jaundiced	No. of Cases	% Jaundiced
−30	8	37·5	—	—
−32	19	63·2	—	—
−34	41	34·2	2	15·4
−36	109	22·9	2	9·5*
−38	319	8·8	3	3·9*
−40	942	3·5	1	0·6**
40+	943	1·4	1	0·9

TABLE 7

	Gestation		
	39–40 Weeks	41–42 Weeks	43 Weeks and Over
Clinical jaundice ..	27·1% ←—**—→	15·0%	11·8%
Severe jaundice ..	3·5% ←—*—→	1·72% ←—*—→	0·4%

2. Factors Increasing Jaundice. Tables 8 and 9 show the percentage of clinical and of severe jaundice at different gestational ages related to the factors which increase their frequency. As these factors differ markedly in their relation to gestation it is clearly unjustifiable to compare their incidences without regard to this fact. A 'computed average' was, therefore, obtained for each factor by applying the jaundice rates for 'all cases' (first columns of Tables 8 and 9) to the numbers observed in each gestational group for that factor.

TABLE 5

Gestation (weeks)	% Jaundice Within Each Two Weeks' Gestation					
	Excluding Perinatal Deaths				Assuming All 196 Perinatal Deaths Jaundiced	
	All		Toxaemia		All	Toxaemia
	No. of Cases	% Jaundiced	No. of Cases	% Jaundiced	% Jaundiced	% Jaundiced
−28	1	100	—	—	100	100
−30	8	100	2	100	97·5	100
−32	19	94·7	2	100	97·2	100
−34	41	90·2	13	84·6	93·3	88·2
−36	109	80·7	21	38·1**	84·2	48·0**
−38	319	44·2	77	36·4	49·3	42·4
−40	942	27·1	172	14·5**	29·8	18·8**
40+	943	14·2	117	11·1	16·7	11·9

TABLE 8

FACTORS INCREASING CLINICAL JAUNDICE

Gestation (weeks)	All		Previous Jaundiced Sib		A.P.H.		Maternal Diabetes		Asphyxia		Cyanosis		Respiratory Distress	
	Cases	% Jaundiced	Cases	% Jaundiced	Cases	% Jaundiced	Cases	% Jaundiced	Cases	% Jaundiced	Cases	% Jaundiced	Cases	% Jaundiced
−30	8	100	1	100	5	100	—	—	2	100	4	100	4	100
−32	19	95	—	—	8	87	1	100	5	100	3	100	4	100
−34	41	90	7	100	4	100	3	100	7	100	10	100	9	100
−36	109	81	17	100	22	86	19	100*	13	77	9	78	9	100
−38	319	44	25	92**	34	65*	20	60	14	86**	21	24	3	100
−40	942	27	82	58**	44	38	1	100	51	30	15	41	8	0
40+	943	14	52	52**	20	45**	—	—	94	10	4	50	1	0
Overall average ..		29		67**		61**		82*		32		56		76
Computed average ..		29		33		47		64		31		56		71

TABLE 9

FACTORS INCREASING SEVERE JAUNDICE

Gestation (weeks)	All		Previous Jaundiced Sib		A.P.H.		Maternal Diabetes		Asphyxia		Cyanosis		Respiratory Disturbance	
	Cases	% Jaundiced	Cases	% Jaundiced	Cases	% Jaundiced	Cases	% Jaundiced	Cases	% Jaundiced	Cases	% Jaundiced	Cases	% Jaundiced
−30	8	37	1	0	5	40	—	—	2	100	4	50	4	50
−32	19	63	—	—	8	62	1	0	5	60	3	100	4	75
−34	41	34	7	0	4	50	3	33	7	43	10	70	9	44
−36	109	23	17	23	22	36	19	16	13	15	9	22	9	78**
−38	319	9	25	28**	34	21**	20	20	14	21	21	5	3	33
−40	942	3	82	12**	44	4	1	100	51	6	15	20**	8	0
40+	943	1	52	10**	20	10**	—	—	94	2	4	25**	1	0
Overall average ..		5		14**		20*		20		10		29*		47**
Computed average ..		5		7		13		18		7		17		26

TABLE 10

Gestation (weeks)	All Cases % Jaundiced	Previously Jaundiced Sibling			
		Uncorrected Figures		Compatible Pairs Only	
		Cases	% Jaundiced	Cases	% Jaundiced
−34	90·2	7	100	7	100
−36	80·7	17	100	13	100
−38	44·2	25	92**	12	100**
−40	27·1	82	58**	47	63**
40+	14·2	52	52**	25	68**

Previously Jaundiced Sibling. This information was obtained from the mother; it can be seen to be significant at all gestational ages over 36 weeks in both clinical and severe jaundice. This cannot be due to ABO incompatibility for when only those mother-baby pairs of compatible group are analysed there is an even higher evidence of clinical jaundice (Table 10).

Antepartum Haemorrhage. In both clinically and severely jaundiced infants there was a higher incidence at gestations of 37 to 38 weeks, over 40 weeks and in the overall average compared with the computed average.

Maternal Diabetes. These infants were usually delivered around the 36th week and the Table shows

significance at 35 to 36 weeks and in the overall average of clinical jaundice. In the severe cases there is no significant increase of jaundice, but the numbers are small and the same trend is present.

Asphyxia, Cyanosis and Respiratory Distress. To try to evaluate these separately we took asphyxia to mean any baby needing resuscitation at birth beyond the use of a mucus catheter. Cyanosis was recorded regardless of its duration. Respiratory distress was considered to be present if after apparent resuscitation any significant dyspnoea, recession or tachypnoea occurred.

These factors show some effect at different gestations, and both cyanosis and respiratory distress have a general increasing effect in the severe cases.

3. Factors Having Little or No Effect on Jaundice

Drugs. Chlorpromazine was not given to any mothers in this group; otherwise the usual range of drugs were given to both mother and baby, but none had any significant effect apart from penicillin and streptomycin given to the baby. To evaluate this we used a group of infants who received this combination as a prophylactic for prolonged rupture of the membranes and who developed no obvious infection. A somewhat paradoxical result was obtained inasmuch that up to 38 weeks' gestation there was a nearly significant effect in increasing clinical jaundice and that beyond this gestational age a reduction of jaundice was seen.

Chlorothiazide given to the mother seemed to have a slight preventive action on jaundice in the infant, but this may well have been due to the large number of toxaemic mothers receiving this drug.

Babies having vitamin K in the dosage of 1·0 mg. to matures and 0·5 mg. to prematures had the normal incidence of jaundice at all gestational ages.

Twins. There were 212 twin babies in the series and they showed a slightly increased incidence of jaundice; this was significant at over 38 weeks' gestation only.

Use of Incubator and of Oxygen. This could only be assessed by removing from the group all those babies with respiratory distress; when this was done no difference in the jaundice incidence could be seen.

Delay in Feeding. Although there was a tendency for incidence of jaundice to increase with delay in offering the first feed, so few babies were delayed beyond 36 hours that no conclusions can be drawn.

Other Factors. Among those considered were previous births, labour, delivery, placental weight and sex of baby. None showed significant effect upon the incidence of clinical or severe jaundice.

Discussion

The infants studied were all delivered in the hospital concerned, thus differing from those reported by Brown and Zuelzer (1957) and Crosse (1961) where babies were admitted from outside hospitals sometimes at a considerable distance.

The overall incidence of jaundice, although difficult directly to compare with previous work, appears to be lower than that given by Davidson, Merritt and Weech (1941), by Findlay, Higgins and Stanier (1947), and as regards severe jaundice is lower than that of Brown and Zuelzer's (1957) cases, although at that time drugs such as vitamin K must have been confusing the picture. The recent figures of Trolle (1961) show a comparable incidence of clinical jaundice among those of 'unknown' cause, but it seems that the Danish figures for severe jaundice are higher than the present series.

In such a setting it is clear that jaundice is by no means a problem confined to the baby weighing less than 5½ lb. (2·5 kg.). There were more cases of both clinical and severe jaundice amongst the heavier babies, although the incidence was highest in the immatures (Table 2). An inclusive study in babies of all degrees of maturity is obviously more representative of the problem.

As we only performed exchange transfusion in eight infants [0·32% of all cases studied compared with Trolle's (1961) rate of 3·6% and the correctness of this awaits the judgement of time] the question arises as to the clinical relevance of such a study. During this time 71 infants had exchange transfusions performed for haemolytic disease and 24 repeat exchanges were carried out. It is generally agreed that these subsequent procedures aim mainly at removing bilirubin which has accumulated because of hepatic insufficiency. If therefore this inadequacy could be remedied we could have avoided 32 exchanges or 30% (32/103) of the total.

The factors which in our opinion decrease the incidence of jaundice are advancing maternal age, pre-eclamptic toxaemia and post-maturity. All these have been shown to be associated with decreasing placental efficiency; by Elliott and Inman (1961) in the first case, by FitzGerald and Clift (1958) in the second and by Baird, Thomson and Billewicz (1957) in the third. This protective effect of maternal toxaemia was recorded by Sacrez, Levy, Scheppler and Klein (1960) in premature babies, and they discuss whether this could be due to an acceleration of enzyme production in the liver or to reduction of

inhibitor substance shown to be present in maternal and neonatal serum by Lathe and Walker (1958). Further study on the factors which seem to protect against neonatal jaundice might be fruitful. Work based largely on cord bilirubin levels (Gottlieb and Kearns, 1931; Sjöstedt, Engelson and Rooth, 1958) has suggested an increased tendency to jaundice in the infant who is post-mature; but as is well known (Tovey, Gillespie, Guy, Valaes, Oppé and Lewis, 1959) apart from rhesus incompatibility cord blood bilirubin levels are no guide to subsequent rises. It could be argued that deficient placental clearance of bilirubin *in utero* conditions the liver to 'mature' more rapidly; attempts to do this in rats have so far failed (Schmid, Buckingham, Hammaker and Medenilla, 1959).

Turning to those factors increasing jaundice we are at once confronted with the increased familial incidence. Whether this is due to genetic enzyme defects of a temporary nature (Lucey, 1960) or to undiscovered haemolytic disease (Kauder and Mauer, 1962) remains in doubt. The present series probably includes approximately 20 cases of ABO disease, a problem recently referred to by Carrier, Usher and Shapiro (1961). Despite the views of Mores, Fargasova and Minarikova (1959) on the possible immunity of the non-haemolytic full-term baby to bilirubin encephalopathy one can never be sure that there is not some undiscovered haemolysis, and high levels of bilirubin at whatever maturity will cause concern. This of course has wider implications with increasing knowledge of red cell stability enzymes and their behaviour in the neonatal period (Doxiadis, Fessas and Valaes, 1961).

Antepartum haemorrhage might have an effect in two ways; first, the acute anoxia might disturb hepatic function and thus delay enzyme production. Second, the maternal blood might be absorbed by the baby and hence increase the bilirubin load as is well recognized in haematoma formation in the newborn (Rausen and Diamond, 1961). A similar effect of early placental separation was noted in the series of Brown and Zuelzer (1957).

The effect of maternal diabetes on the infant remains a mystery, and as a proportion of these infants develop respiratory distress the evaluation of diabetes alone is difficult because of the small numbers remaining.

Other causes of anoxia show some icterogenic effect, but this has been known for some time (Miller and Reed, 1958).

It is, however, worth noting that in the immature babies under 38 weeks' gestation penicillin and streptomycin exerted an icterogenic effect which came near to significance at the 5% level. In view of the possibility of eighth nerve involvement in prematures given streptomycin, this combination with penicillin is being viewed with increasing disfavour.

This study emphasizes that the term 'non-haemolytic jaundice' should not be used merely because haemolysis has not been proven; the baby in our present state of knowledge remains a potential case of haemolytic disease. Both this and the factor of 'hepatic insufficiency' can result in dangerously high levels of bilirubin in an infant regardless of weight or maturity. Odell (1959) showed that other factors than serum bilirubin levels may be involved in brain damage so that our decision for exchange transfusion remains an individual judgement at the time dependent upon long-term follow-up for final assessment.

Despite the fact that only 0·32% of all babies were given exchange transfusions, no evidence of kernikterus has been seen at autopsy; the neurological assessment of survivors now in progress will be reported in due course.

Summary

Over a two-year period 2,468 infants delivered in hospital were examined for jaundice, known cases of haemolytic disease being excluded.

The incidence of clinical and severe (bilirubin over 12 mg./100 ml.) jaundice was assessed according to gestation, birth weight and length. The problem was by no means confined to babies weighing 5½ lb. (2·5 kg.) or less.

Eight infants were subjected to exchange transfusion, a rate of 0·32% of all cases studied; four of these weighed over 5½ lb. (2·5 kg.).

Pre-eclamptic toxaemia, advancing maternal age and post-maturity significantly reduced the incidence of jaundice, the first being particularly effective.

Factors increasing jaundice included a history of a previously jaundiced sibling; this could not be explained on the basis of ABO incompatibility. The other factors, antepartum haemorrhage, maternal diabetes, asphyxia, cyanosis and respiratory distress, all of which cause an increased jaundice rate, are discussed.

In this series, drugs, twins, use of incubators, oxygen administration and delay in feeding showed little or no effect on the incidence of jaundice.

We wish to record the great help received from Dr. Weiner and his blood transfusion department. Dr. R. Gaddie and the late Mr. H. B. Salt were always ready to solve our biochemical problems, and Mr. W. F. Johnson willing to perform many of the estimations. The co-operation of the nursing staff at the Birmingham Maternity Hospital was much appreciated. One of

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