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EFFECT OF INTRA-PARTUM AND NEONATAL ADMINISTRATION OF SYNTHETIC VITAMIN K ANALOGUES ON THE NEWBORN

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The knowledge that persistent haemorrhage may occur spontaneously or from trivial injuries in the newborn is centuries old. No satisfactory explanation, however, was forthcoming either of this bleeding or of the observation that the coagulation time has a tendency to increase during the first five days of life and to return to normal before the tenth day (Rodda, 1920). The discovery of vitamin K in alfalfa and certain liver fats and of its relation to plasma prothrombin (Dam, 1934; Dam *et al.*, 1936), and the recognition of prothrombin deficiency as an important cause of haemorrhage in man, suggested a new approach to the problem of this haemorrhagic tendency. In five healthy and otherwise normal babies Waddell and Guerry (1939) showed that coincidentally with the prolonged coagulation time there was a variable hypoprothrombinaemia during the first five days of life. This has subsequently been confirmed, while the present work was in progress, by isolated estimations between birth and the age of 1½ years (Dam *et al.*, 1939), and by repeated estimations on the same newborn babies (Nygaard, 1939; Quick and Grossman, 1940). It has been demonstrated that persistent haemorrhage may occur during the period of prothrombin deficiency if the level falls below 30 per cent. of normal (Nygaard, 1939), and that icterus gravis neonatorum and hydrops congenitus are also characterized by hypoprothrombinaemia (Dam *et al.*, 1939).

From this association of hypoprothrombinaemia with visible haemorrhage the question must arise: Is there any relation between prothrombin deficiency and the incidence or extent of intracranial haemorrhage the result of birth injury? Recent literature and reports are very emphatic on the frequency of intracranial haemorrhage. It was stated to be the cause of death in fifty-three out of 157 stillbirths, and in fifty-two—all less than four days old and thirty-five premature—out of 142 neonatal deaths for which necropsy was performed in the Simpson Memorial Maternity Pavilion of the Royal Infirmary, Edinburgh, during 1939. In a large series of cases and with strict criteria of diagnosis Roberts (1939) establishes that 1 to 2 per cent. of all births show marked clinical manifestations of intracranial haemorrhage, that 85 per cent. of these babies

die in the first three days of life, and that 25 per cent. of the survivors show more or less severe evidence of motor or mental involvement. On the grounds that blood is found in the cerebrospinal fluid in 12 per cent. of all births he believes that subclinical haemorrhages are more frequent. Hess (1939) stresses the high incidence of symptoms of intracranial haemorrhage in premature births. The present investigation was undertaken, therefore, in an attempt to answer the following questions:

1. Is the prothrombin content of the blood lowered at birth or during the early neonatal period? Can any such deficiency be related to the occurrence of intracranial haemorrhage in the newborn?

2. Does any condition before or during labour affect the prothrombin level of the newborn?

3. If Question 1 can be answered in the affirmative does vitamin K have such an effect upon the prothrombin index as to suggest that its administration to the newborn may reduce the incidence or extent of intracranial haemorrhage? If so, is there any appreciable difference in the effect of oral and parenteral administration?

4. Can a similar effect be obtained by the administration of vitamin K to the mother ante-natally?

The structure of the active constituent of alfalfa (vitamin K₁) has recently been determined to be 2-methyl-3-phytyl-1:4-naphthoquinone (Binkley *et al.*, 1939), but of all the naphthoquinones tested for anti-haemorrhagic properties in the chicken, 2-methyl-1:4-naphthoquinone was found to be the most effective (Thayer *et al.*, 1939; Fieser *et al.*, 1939). Its synthetic preparation and the testing of its purity by physico-chemical methods (Pinder and Singer, 1940) suggested that 2-methyl-1:4-naphthoquinone was a suitable substance for clinical trial in the neonatal period. Its vitamin K activity and therapeutic value in the adult have been demonstrated by Macfie *et al.* (1939).

Method

The method used for the estimation of prothrombin (Ziffren *et al.*, 1939) is a modification of that devised by Quick *et al.* (1935), and has been shown to compare favourably in accuracy with the more elaborate quantita-

tive technique of Warner *et al.* (1936). It has the further merit of extreme simplicity.

1 c.cm. of whole blood, freshly drawn from the patient, is added to 0.1 c.cm. of a thrombokinase solution in a serological tube (measuring approximately 8×1 cm.). The tube is immediately inverted over the thumb to ensure thorough mixing, is immersed in water at $37^{\circ}\text{C}.$, and is tilted subsequently every two or three seconds. The time required for clot formation is expressed as a percentage of the coagulation time of a normal adult under the same circumstances. The resultant figure is equivalent to the "prothrombin index" (Illingworth, 1939).

The thrombokinase solution was prepared by grinding the lungs of a freshly killed rabbit in normal saline. (1 c.cm. of saline is added to each 1 gramme of lung tissue.) The mixture, allowed to stand for three or four hours, was ground periodically during this time and was then filtered through several layers of gauze. The filtrate was kept in stoppered tubes in a refrigerator and retained full activity for five to seven days. Before use, and every two or three days during use, each specimen was standardized with the blood of the same normal adult.

To minimize trauma and to make the individual results strictly comparable, blood was withdrawn through the anterior fontanelle of the babies and from the arm vein of the normal adult with a 12 S needle into an identical clean syringe. Where possible, specimens of cord and maternal blood at the end of the second stage of labour were obtained, and thereafter were taken from the infant on three occasions during the first week of life. In a few cases permission was given to take more frequent specimens. In this way it was hoped that a representative series of results would be obtained over a sufficient number of cases.

The Investigation

Estimations of the prothrombin index during the first week of life were made in fifty-four cases. Of these, fifty were vertex deliveries, forty-four spontaneous, six instrumental, and three assisted breech deliveries; one was a Caesarean section at term for a partial placenta praevia. At birth the cord blood was examined in thirty-two cases. The prothrombin index varied within a wide range, and the variation apparently bore no relation to any feature of the labour or the delivery.

In fifteen cases simultaneous specimens were taken of maternal and cord blood (Table I). It was found that the prothrombin index of the maternal blood was constantly above 75 per cent., regardless of the length of labour and the type of delivery. Of the five maternal toxæmias in which both cord and mother's blood were examined the prothrombin index lay within normal limits in three cases but showed a significant deficiency in two—a severe toxæmia and an eclampsia. Both had experienced a period of low food intake and a prolonged complicated labour during which more than one inhalation anaesthetic had been given. The prothrombin indices were respec-

TABLE I.—*Relation of Prothrombin Index of Maternal and Cord Blood in Control Series*

Series	Labour < 24 hours			Labour > 24 hours			Aggregate		
	No.	Mother	Cord	No.	Mother	Cord	No.	Mother	Cord
Spontaneous	4	78	54	4	81	69	8	79	62
Complicated labour	5	79	70	2	80	49	7	80	64
Maternal toxæmia	3	77	69	2	80	49	5	77	61
Total control	9	79	63	6	80	64	15	80	63

tively 66 and 60 per cent. There was no abnormal bleeding post partum, and the usual liver tests failed to reveal any deficiency. Nevertheless clinical recovery was considerably slower than in another case of eclampsia at the same period of gestation and with a similar history and labour, the prothrombin index of which was 90 per cent. It is possible, as Stewart and Rourke (1939) suggest, that estimation of the prothrombin index may prove a valuable indication of liver damage. In five cases of accidental haemorrhage there was no appreciable prothrombin deficiency. The prothrombin index of the cord blood varied distinctly with that of the mother, and averaged some 15 to 20 per cent. less.

In the fifty-four cases in which repeated estimations were done during the first few days of life the outstanding feature is the extreme variation in the prothrombin index both between different individuals on the same day and in the same case on different days (Fig. 1). An appreciable decrease from the cord estimation can often be

FIG. 1.—Control series (54 cases); no vitamin K analogue given. Note increase in first three days and the great variation of the prothrombin index on each side of the mean (continuous line).

demonstrated within twenty-four hours, and this fall in the prothrombin index continues, reaching its lowest value from thirty-six to eighty-four hours post partum. At this time the clot formed in the tube is soft and fluid. About the fifth day post partum the prothrombin level rises

TABLE II.—*Relation of Prothrombin Index of Cord Blood to Prothrombin Deficiency during First Week*

		Spontaneous Delivery								All Cases							
		No. of Cases	Cord	Hours Post Partum								Hours Post Partum					
				Less than 24	Less than 48	Less than 72	Less than 96	Less than 120	Less than 144	More than 144	No. of Cases	Cord	Less than 24	Less than 48	Less than 72	Less than 96	Less than 120
Control series	Cord prothrombin index > 65%	11	76	71	60	67	66	69	82	76	13	77	71	60	68	66	67
	Cord prothrombin index < 65%	8	53	49	28	42	45	58	65	78	12	49	49	30	33	36	58
Vitamin K analogue within 24 hours post partum	Cord prothrombin index > 65%										4	80	72*	78	87	87	74
	Cord prothrombin index < 65%										3	41	—	70	84	89*	77

* One reading only.

sharply, to become stabilized at about 75 per cent. From this level it gradually rises over a period of months.

The extent of the decrease in the prothrombin index is influenced by the following factors:

1. *The Prothrombin Index of the Cord Blood.*—Table II shows the relation of cord prothrombin values respectively above and below the mean, which was found to be 65 per cent. (Fig. 1), to the subsequent deficiency in the first few days of life. The comparison is especially marked in the spontaneous series, where all were otherwise healthy babies.

2. *Abnormal Delivery.*—The prothrombin index of the cord blood of cases in which labour has been uncomplicated differs little from the index of those in which operative intervention has been necessary, but the fall below normal is disproportionately greater in the latter series (Table III). That this

TABLE III.—*Relation of Prothrombin Index in Newborn to Labour and Ante-natal Conditions*

Type of Case	No. of Cases	Mother	Cord	Hours after Birth							
				<24	<48	<72	<96	<120	<144	>144	
				%	%	%	%	%	%	%	
Spontaneous delivery :		%	%	%	%	%	%	%	%	%	
healthy mother :											
Labour <24 hours :	28	78	62	58	60	57	51	65	76	81	
Labour >24 hours :	11	81	69	54	52	54	55	69	78	65	
Operative delivery ..	10	80	60	50	41	38	40	47	72	77	
Maternal toxæmia ..	11	77	59	51	51	58	49	61	65	71	
Prematurity	7	75	54	—	54	58	55	57	—	74	

increased deficiency is a consequence of trauma and is not a sequel to the method of feeding used in the babies who could not be lifted is illustrated by Fig. 2. Breast-feeding was started on the first day in thirty-five cases. To the remaining eighteen babies diluted unsterilized breast milk was given for a varying period, which was in no case less than two days.

FIG. 2.—Comparison of feeding at breast and with diluted unsterilized breast milk from a bottle. A = breast-fed from first day. B = spontaneous delivery, fed with diluted unsterilized breast milk from first day. C = assisted delivery, fed with diluted unsterilized breast milk from first day.

The curves formed by plotting the daily mean prothrombin estimations are closely comparable for the spontaneous deliveries in the two series. The curve obtained after a complicated labour, however, shows a much greater prothrombin deficiency and an appreciable lag in its spontaneous restoration. In the adult with an already deficient prothrombin a similar post-operative drop is found, some four or five times greater than that which occurs in the normal subject (Stewart and Rourke, 1939).

3. *Maternal Toxaemia.*—Severe toxæmia may cause a degree of hypoprothrombinaemia in the mother, which is reflected in the lowered prothrombin index of the cord blood. The deficiency in the first few days of life is apt to be increased by the high incidence of instrumental deliveries in such cases.

The extent of the fall in the prothrombin index does not, however, appear to be greatly influenced by the length of the labour in spontaneous deliveries or by prematurity in the infant.

Neonatal Administration of Synthetic Vitamin K Analogues

A vitamin K analogue was given in the early neonatal period to thirty-six babies—eighteen spontaneous, fourteen instrumental vertex, and two breech deliveries, and two Caesarean sections. The substances used were:

(i) 2-methyl-1:4-naphthoquinone, 5 mg. dissolved in 1 c.cm. of "alcoholized" oil and suitable for oral use or for injection. Orally, the quinone was given to fifteen babies in 2.5-mg. doses—either two or four such doses immediately before successive feeds. This latter is essential, as the substance has an unpleasant taste and exerts an irritating effect upon the mouth and throat, causing intense salivation. On only one occasion did true vomiting follow its administration in a feed. By intramuscular injection six cases were given 5 mg. and six 2.5 mg. One case showed signs of local irritation at the site of injection.

(ii) Diacetyl-2-methyl-1:4-naphthohydroquinone, which is made up in arachis oil for oral use in a concentration of

FIG. 3.—Effect of vitamin K analogue given less than twenty-four hours after delivery (20 cases). Note congregation of prothrombin index round mean (continuous line). Compare with Figs. 1 and 5.

15 mg. per c.cm., was used in nine cases. As this substance is less unpleasant to take and causes only slight salivation when followed immediately by a drink it was given in one dose of 10 mg.

The effect of the administration of these substances within twenty-four hours of birth (twenty cases) is to raise the prothrombin index to 80–90 per cent. and to stabilize it at that level during the first few days of life (Fig. 3). This effect appears to be independent of the cord prothrombin index, of the ante-natal condition, of prematurity, and of the type and duration of labour. Though the two series are not strictly comparable the quinone given orally appeared to be less potent than the same dose of quinol diacetate. In the doses given the quinol diacetate corresponded closely in activity to the quinone parenterally, and there was no difference in the effects produced by the injection of 2.5 mg. and 5 mg. of the quinone (Table IV).

TABLE IV.—*Vitamin K Analogue given less than 24 Hours after Birth*

	No.	Spontaneous	Abnormal labour	Cord	Hours after Birth						
					<24	<48	<72	<96	<120	<144	>144
					%	%	%	%	%	%	%
Oral naphthoquinone	8	2	6	56	88	74	80	82	78	89	69
Oral quinol diacetate	6	5	1	—	84	90	93	89	95	85	90*
Naphthoquinone : Injection of 5 mg.	3	1	2	67	—	85	90	89	95*	83	—
Injection of 2.5 mg.	3	—	3	—	—	90	87	87	75*	87	—
Total	20	8	12	57	86	85	86	85	83	85	75

* One estimation only.

The suggestion that 2-methyl-1:4-naphthoquinone by intramuscular injection had unusual rapidity of action (Macfie *et al.*, 1939) is amply confirmed by the effects shown in five cases so treated and specially tested for this purpose.

¹ The ethyl esters of the mixed fatty acids of arachis oil.

In one case an increase from 44 to 63 per cent. was noted in 100 minutes, and in another from 50 to 85 per cent. in 150 minutes. The effect is slight in the first two hours after oral use, but thereafter the rapidity of the increase compares favourably with that obtained by injection. The rate of this increase, expressed as a percentage of the original prothrombin index, is represented graphically in Fig. 4. To three abnormal deliveries—a forceps delivery,

FIG. 4.—Showing rapidity of action expressed as a percentage increase on the original prothrombin index. A = (X) by injection, 5 cases; B = (O) orally, 4 cases.

a forceps in an eclamptic, and a breech extraction—and to one premature baby a second dose of vitamin K analogue was given, respectively on the sixth, third, ninth, and fifth days. In each case it was again effective in raising the prothrombin index. With the dosage used there was no evidence of pathological coagulation, gastrointestinal upset, or other untoward effects in any case. No delayed effects were observed in babies who have subsequently attended the infant clinic. One baby in this series died on the third day after a trial of labour and lower segment Caesarean section. Necropsy showed the cause of death to be atelectasis.

Administration of Synthetic Vitamin K Analogues Ante-natally

Thirty-one mothers were given a vitamin K analogue ante partum. Twenty-nine—nineteen spontaneous, eight abnormal deliveries, and two Caesarean sections—were treated during or immediately before labour, and in two cases the last administration was more than twenty-four hours before delivery.

Three cases received 50 mg. of the quinol diacetate in one dose orally. 2-methyl-1:4-naphthoquinone, made up in 10-mg. tablets, was given to nineteen cases, as follows: Eleven cases, 50 mg.—30 mg. followed by 20 mg. at an hour's interval during labour; four cases, 30 mg. in a single dose during labour; one case, 80 mg. in two doses of 40 mg. at an hour's interval during labour; three cases, 100 mg. in three doses of 40, 40, and 20 mg. on three successive days before induction of labour. The quinone was given by intramuscular injection to nine mothers—four receiving 10 mg. and five 15 mg.

In these cases the effect on the prothrombin index during the first week of life was qualitatively identical with that obtained by giving the same substances directly to the baby during the first twenty-four hours after birth. The effect was independent of the length of labour, the type of delivery, prematurity (three cases), the ante-natal condition—one case of eclampsia (Table V), and the method of administration (Table VI). 15 mg. by injection, however, produces an effect closely similar to that from 50 mg. orally but slightly greater than that following 10 mg. parenterally or 30 mg. by mouth. There appears to be no advantage in a dose greater than 50 mg. by

TABLE V.—*Vitamin K Analogue to Mother in Labour. Relation of Prothrombin Index of Newborn to Duration and Type of Labour; Ante-natal State; Prematurity*

	No.	Mother	Cord	Hours after Birth						
				<24	<48	<72	<96	<120	<144	>144
Spontaneous delivery:										
Less than 24 hours' labour	14	85	78	82	77	80	83	86	88	85
More than 24 hours' labour	5	78	79	—	85	77	81	94*	85	—
Total	19	83	78	82	80	80	83	87	86	85
Operative delivery (including 2 Caesarean sections in labour)	10	82	80	80	83	79	78	83	88	—
Prematurity	3	—	—	—	80	82	79	—	89	—
Eclampsia	1	—	—	—	78	71	—	86	—	—

* One estimation only.

TABLE VI.—*Vitamin K Analogue to Mother. Relation of Prothrombin Index in Newborn to Method of Administration and Dose to Mother.*

	No.	Time of Administration (Hours before Birth)			Cord	Hours after Birth						
		Longest	Shortest	Mean		<24	<48	<72	<96	<120	<144	>144
Injection:												
10 mg.	4	20	1	8	76	—	78	72	74	80	87	—
15 mg.	5	10	1	6	91	89	79	86	88	85	89	85
Total	9	20	1	7½	83	89	79	78	81	83	88	85
Orally:												
30 mg.	4	8	1	3	78	—	75	76	74	80	89*	—
50 mg.	12	20	3	9½	75	79	80	81	84	92*	88	85
80 mg.	1	—	—	13	70	—	97	79	—	—	81	—
Quinol, 10 mg.	3	9	3	6	89*	78*	85	84	77	84	85*	93*
Total	20	20	1	6½	75	79	81	80	82	85	86	87

* One estimation only.

mouth. By both methods the optimum time for administration of vitamin K analogue appears to be between twelve and four hours ante-partum (Table VII).

TABLE VII.—*Vitamin K Analogue to Mother. Relation of Prothrombin Index in Newborn to Time of Administration before Delivery.*

Method and Time of Administration	No.	Cord	Hours after Birth						
			<24	<48	<72	<96	<120	<144	>144
Orally:									
More than 24 hours before delivery	2	70	—	62	40	55	72	—	86
24–12 hours before delivery	5	73	80	—	82	79	—	83	—
12–4 hours before delivery	11	87	82	79	83	83	88	86	84
Less than 3 hours before delivery	4	—	78	75	76	76	79	85	85
Total less than 24 hours before delivery	20	78	79	81	80	82	85	86	87
Injection:									
24–12 hours before delivery	1	60	95	—	57	—	80	—	—
12–4 hours before delivery	6	89	89	79	83	86	85	87	87
Less than 3 hours before delivery:									
(i) 50 mins. before	2	86	—	80	—	91	—	94	—
(ii) 20 " "			—	78	—	65	—	—	—
Total less than 24 hours before delivery	9	83	89	79	78	81	83	88	85

The effect of oral administration twenty-four to twelve hours before delivery closely resembles that obtained when the substance is given twelve to four hours before (Fig. 5); but in one case injected twenty hours and in two cases where the last oral doses were given respectively

twenty-six and forty-eight hours before delivery the prothrombin index fell about the second or third day to values which were approximately the same as those of the control series. It appears, therefore, that the maximal effect will be obtained in the newborn if an adequate dose is given less than twelve and more than four hours before delivery and that no advantage to the child is to be gained by prolonged ante-natal administration. Three cases were treated less than one hour before delivery—two by injection and one orally. Injection of 10 mg. twenty minutes before birth was followed by an appreciable drop on the

FIG. 5.—Effect of vitamin K analogue given less than twenty-four hours before delivery. Note raised cord prothrombin index and congregation of prothrombin index round mean (continuous line). Compare with Figs. 1 and 3.

third day, but 30 mg. orally thirty-five minutes before and 15 mg. by injection fifty minutes before appeared to be fully active in maintaining the normal prothrombin index. It is not possible, however, in these isolated examples to be certain to what extent the effect was due to the vitamin K analogue.

While ante-partum administration had little effect on the mother's blood when estimated at the end of the second stage of labour, it was found that it raised the prothrombin index of the cord blood almost to the maternal level. The value of this prothrombin increase is apparent, especially in abnormal delivery.

With the doses used there were no unpleasant reactions which could be attributed to the drug. Placental separation appeared to be entirely normal, there was no gastrointestinal upset, and no pathological thrombosis was detected clinically. No accurate measure of third-stage and post-partum bleeding was taken, but clinically in no case was the loss noted to be other than normal.

Effect on Cases of Intracranial Birth Injury

Sixteen cases showed symptoms of cerebral irritation immediately after birth, which varied from cyanosis and "murmuring" to extreme restlessness. In fourteen of these there had been abnormal pregnancy or labour:

Pre-eclamptic toxæmia ..	3	Breech delivery ..	2
Eclampsia ..	2	Prolonged labour (flat pelvis) ..	1
Prematurity ..	2	Caesarean section ..	1
Instrumental delivery ..	9		

In every case examined the cord prothrombin index was unduly low (Fig. 6). Spontaneous remission occurred with routine sedative treatment in three cases during the first two or three days. Where the vitamin K analogue had been given shortly after delivery two babies were symptom-free on the second day and another was greatly improved. Of the ten abnormal deliveries in which it had been given less than twenty-four hours before birth, in only one (a Caesarean section in labour) did the child develop any symptoms of cerebral irritation.

Exacerbation of symptoms occurred in seven cases on the second or third day. Estimations carried out at this time revealed a severe prothrombin deficiency in five of these. Symptoms were completely relieved in three cases within twenty-four hours of the addition of the

vitamin K analogue to the usual treatment by rest and sedatives. In one of the other two babies, whose mother had been given 100 mg. of the quinone more than twenty-four hours before delivery, there was a low prothrombin index on the third day, but the subsequent restoration followed a normal course. The other baby was given

FIG. 6.—Prothrombin index in cases showing signs of cerebral irritation. • = untreated with K analogue. × = 2 cases treated with K analogue (see text).

no vitamin K analogue and showed an extreme and prolonged deficiency of prothrombin, which was later associated with marked anaemia.

Fits developed for the first time on the third day in one baby to whom 10 mg. of the quinone had been given orally during the first day after birth by breech extraction. The prothrombin index was 76 per cent. Oral quinone raised the index to 89 per cent.; but the fits were not affected, and they continued intermittently for nearly two months. Another baby—an instrumental delivery from an eclamptic mother and treated with quinol diacetate at birth—had symptoms of cerebral irritation which became worse on the third day. The prothrombin index was 73 per cent. The index was raised to 100 per cent. by a second dose of quinol diacetate, and simultaneous clinical improvement was noted. Here the general condition and its rapid relief suggested an acute exacerbation of a cerebral oedema, whereas delivery and symptoms in the first case pointed to direct cerebral injury.

In no case was bile absent from the meconium or stools. Clinical icterus developed in three cases, in only one of which was there a low prothrombin index. Another had previously been treated with oral quinone; and the third, whose prothrombin index was constantly over 70 per cent., was jaundiced for six weeks. Treatment with adexolin did not have any effect upon the degree of prothrombin deficiency.

Discussion

The control series shows that in apparently normal infants the prothrombin index at birth is usually about 60 per cent. and may fall in the first three days of life to dangerously low levels. Thereafter it rises spontaneously to 70–80 per cent., and is maintained at that level for some months. This confirms the results of other workers (Waddell and Guerry, 1939; Nygaard, 1939; Quick and Grossman, 1940). Estimations done in babies born after abnormal labour or of mothers suffering from severe toxæmia suggest that the type of delivery and the ante-natal condition are factors which influence the prothrombin level in the newborn. Where 2-methyl-1:4-naphthoquinone or diacetyl-2-methyl-1:4-naphthohydroquinone is given to the baby after birth the prothrombin index rises to and remains within normal limits. A similar result has been obtained by the use of natural vitamin K (Waddell

and Guerry, 1939; Nygaard, 1939). It is held, therefore, that the reserve of prothrombin or of vitamin K is not adequate to maintain the prothrombin level in the newborn until the time when vitamin K is absorbed in sufficient quantities from the alimentary canal. In the adult intestine vitamin K is absorbed direct from the food in the presence of bile, and from the colon, where vitamin K may be synthesized by bacterial action.

Milk is a poor source of vitamin K, and in the newborn the contents of the intestine are sterile. Hence it has been assumed that enough vitamin K cannot be absorbed until bacterial invasion of the bowel occurs. Breast-feeding or the use of unsterilized breast milk on the first day should assist this synthesis by supplying numerous harmless bacteria, but does not afford any protection against the fall in plasma prothrombin. Other factors also may be involved. It is not known, for instance, whether the composition of bile in the newborn is suitable for optimal absorption of vitamin K. Jaundice and prothrombin deficiency do not necessarily coexist. The postulation, however, that icterus simplex neonatorum is due to excessive haemolysis and to functional immaturity of the liver (Rich, 1930; Ross *et al.*, 1937) inevitably suggests that deficient synthesis may also be a factor in neonatal hypoprothrombinemia.

There would seem to be no doubt that abnormal bleeding in the newborn coincides with excessive prothrombin deficiency. The association of an unduly low prothrombin index, generally where there has been maternal toxæmia or difficult labour, with the occurrence of symptoms of intracranial damage is shown in fourteen cases in this paper. Moreover, at the time when the prothrombin index is lowest and the clot formed *in vitro* most fluid there is often an increase in the signs of cerebral irritation. That a secondary oozing has occurred through this soft clot, possibly loosened from a birth injury by restlessness or a bout of crying, seems to be a reasonable conclusion. The rapidity with which symptoms were relieved after the use of vitamin K analogues and the infrequency of their occurrence when the mother has been treated suggest that the theoretical value of the naphthoquinones in suspected intracranial haemorrhage is worthy of further therapeutic trial.

It is evident that prevention of the prothrombin deficiency will decrease the incidence and severity of complications in the newborn. In most normal babies early breast-feeding will prevent abnormal or prolonged lowering of the plasma prothrombin. Adequate administration of vitamin K analogue to the mother less than twenty-four hours before delivery leads to its rapid absorption into the foetal circulation, and appears to supply a store of vitamin K sufficient not only to raise to normal limits the prothrombin content of the baby's blood at birth but also to maintain it within normal limits during the early days of life. The constancy with which a normal plasma prothrombin was found at birth and its importance in the formation of strong adherent clots in any case of difficult delivery need no emphasis. Indeed, they suggest that this is by so much the most rational method of treatment that the administration of naphthoquinone at this time may become as routine as the use of vitamins A and D earlier in pregnancy.

A similar effect after birth, with a similar absence of any untoward reactions, is obtained when the vitamin K analogue is given in the first few hours of life. Injection of the naphthoquinone gives a speed of action comparable to that of blood transfusion, and its effect seems to be more lasting.

All these facts suggest that the administration of a vitamin K analogue, either to the mother between twelve and four hours before delivery or to the newborn, would appear to be especially indicated (1) in cases of maternal toxæmia; (2) in premature labour; (3) in cases of difficult or instrumental delivery; (4) where breast-feeding is not possible; (5) when any cerebral symptoms develop during the first few days of life; (6) in cases of haemorrhagic diathesis, icterus gravis neonatorum, and anaemia; and (7) where an operation is necessary on the newborn.

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PERFORATED JEJUNAL ULCER FOLLOWING PARTIAL GASTRECTOMY

BY

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Acute perforation following partial gastrectomy is a rare condition, only two such cases being found among the records of the London Hospital for the last ten years. During the same period twenty cases of perforation following gastro-jejunostomy were recorded. I was called upon to deal with one case of perforated jejunal ulcer following partial gastrectomy, a report of which is here given, together with the record of the previous case.

Case I

In 1926 the patient, a woman aged 45, was admitted to the London Hospital, under Dr. Rowlands, with a three-years history of severe colicky epigastric pain radiating to the hypogastrium, not related to meals. Vomiting occurred about once a week, and relieved the pain. The pain and vomiting were worse for the three months prior to admission, and the vomitus was alleged to contain occasional streaks of blood. The appetite was poor and there was loss of weight. There was a history of melaena and dyspnoea on exertion.

On examination the patient had a sallow appearance, with pallor of the mucous membranes. No abnormal physical signs were found. A test meal revealed free HCl 0.28 per cent. and total acidity 80. A barium-meal radiograph showed a low hyperperistaltic stomach, an active pars pylorica and first stage of duodenum, and a defect on the inner aspect of the duodenal cap. The blood count showed erythrocytes,