Pathogenesis of intraventricular haemorrhage in newborn infants

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Cole, V. A., Durbin, G. M., Olafsson, A., Reynolds, E. O. R., Rivers, R. P. A., and Smith, J. F. (1974). *Archives of Disease in Childhood*, **49**, 722. **Pathogenesis of intraventricular haemorrhage in newborn infants.** The ventricular CSF of a group of preterm infants dying in the newborn period contained a large excess of protein which appeared to be a plasma filtrate. This excess was found whether or not an intraventricular haemorrhage (IVH) was also present. After consideration of the clinical features of the infants, their coagulation status, and the findings at necropsy, we suggest that increased cerebral venous and capillary pressure, usually caused by heart failure resulting from hypoxia and acidosis, was responsible both for the IVH, by rupturing the terminal veins, and for promoting the filtration of plasma proteins into the CSF. Abnormalities of haemostasis, though very common, did not seem to provide an adequate explanation for the initiation of intraventricular bleeding, though they may have exacerbated it.

IVH during the first few days of life accounts for the death of between 1 and 2 out of every 1000 liveborn infants (Fedrick and Butler, 1970). The incidence rises sharply with decreasing gestation and birthweight, so that more than 25% of those infants with birthweight of less than 1000 g are found to have this type of haemorrhage at necropsy (Fedrick and Butler, 1970). The site of bleeding is commonly the terminal veins, which lie beneath the ependyma in close proximity to the lateral ventricles.

The pathogenesis of IVH is poorly understood, though there appears to be an association with hypoxia, both before and after birth. For example, about 50% of infants dying from hyaline membrane disease, an illness which causes severe hypoxia, have IVH (Fedrick and Butler, 1970; Harcke *et al.*, 1972). Birth trauma, hypoxia, distortion of veins, infarction and thrombosis of the subependymal plate (germinal matrix) which surrounds the terminal veins, venous congestion, and disorders of haemostasis have all been suggested as causes for the bleeding (Gruenewald, 1951; Gröntoft, 1954; Schwartz, 1961; Larroche, 1964; Gray, Ackerman, and Fraser, 1968;

Harrison, Heese, and Klein, 1968; Towbin, 1968, 1970; Schenk *et al.*, 1968; Cade, Hirsh, and Martin, 1969; Fedrick and Butler, 1970; Harcke *et al.*, 1972).

Recently, we have found that the material issuing from the lungs of infants with the illness known as massive pulmonary haemorrhage was usually not whole blood but a filtrate of plasma containing a small proportion of whole blood; in other words, it was haemorrhagic oedema fluid (Cole *et al.*, 1973). We argued that the cause of the sudden outpouring of blood-stained fluid was increased pulmonary capillary pressure, often resulting from acute left ventricular failure arising because of the effects of hypoxia and acidosis upon the myocardium. Disorders of coagulation were found not to be importantly involved in the pathogenesis of the illness. Since infants dying from massive pulmonary haemorrhage often prove to have IVH at necropsy—17% in the large series of Fedrick and Butler (1971), 40% in our own much smaller series (Cole *et al.*, 1973)—but seldom any evidence of bleeding elsewhere, we suggested that the pathogenesis might be similar. The haematocrit and protein composition of CSF and plasma, together with the coagulation status of the blood, have therefore been investigated in a group of preterm

infants dying in the newborn period. The results have been related to the findings at necropsy.

Infants studied

During a 17-month period, 31 infants born after gestations of between 24 and 31 weeks died in the Neonatal Unit of University College Hospital. Information was available from 26 of them. Their mean gestational age was 28 weeks and mean birthweight 1077 g (range 520–1693 g). 11 were born in this hospital and 15 were admitted from other institutions: 14 were boys and 12 were girls. There were two sets of twins and 1 infant was a quadruplet. The pregnancies of 8 of the mothers had been uncomplicated until the onset of preterm labour. In the remainder, complications included threatened abortion, antepartum haemorrhage, hypertension, chronic renal disease, pre-eclamptic toxæmia, rhesus isoimmunization, diabetes, hydramnios, chemotherapy for infertility, and the insertion of Shirodkar sutures.

Twelve infants established adequate spontaneous breathing within 5 minutes of delivery. 5 infants never breathed spontaneously and were mechanically ventilated from birth. 3 of the infants weighed less than the 10th centile for their gestation (Lubchenco *et al.*, 1963). 3 had serious congenital malformations, 19 hyaline membrane disease, 3 rhesus haemolytic disease, and 2 septicaemia. Frequent measurements were made, using Radiometer equipment, of arterial oxygen tension (P_{aO_2}), carbon dioxide tension (P_{aCO_2}), pH, and base excess (BE) in samples from umbilical artery catheters or percutaneous puncture of arteries. The most abnormal recorded values for P_{aO_2} averaged 42 mmHg (range 20–84 mmHg); for P_{aCO_2} 85 mmHg (range 52–150 mmHg); for pH 7.10 (range 6.94–7.31); and for BE –10 mEq/l. (range +2 to –20 mEq/l). Since the final samples were taken at a mean time of 4 hours before death and all the infants subsequently deteriorated in condition, more extreme abnormalities of gas exchange and pH during this period can be presumed. 10 infants suffered at least one episode of bradycardia (heart rate <100/min) apparently due to hypoxia before deterioration and death. Before this deterioration, when all the infants were inert and unresponsive, abnormal movements or fits had been noted in 7. The median age at death was 40 hours (range 9 hours–33 days).

Methods

Analysis of CSF and blood for haematocrit and protein composition. Samples of CSF were obtained by needling the lateral ventricles of 11 infants within 5 minutes after the heart had stopped beating, and were placed in heparinized tubes. A similar sample had been taken 2 hours before death from another infant in an attempt to relieve raised intracranial pressure and convulsions. Specimens of lumbar CSF were obtained from 2 of the infants. The mean age at death of the whole group from whom CSF samples were taken was 44 hours (range 9–118 hours). Samples were analysed only if they had been obtained cleanly, without evidence of

contamination due to puncture of blood vessels, if the CSF had appeared uniform during sampling, and if there was no haemolysis. Heparinized samples of arterial or venous blood were also obtained, usually from indwelling catheters.

The haematocrit of CSF and blood was measured after centrifugation at 22,500 g for 10 minutes. The total protein concentration in CSF after the removal of cells, and in plasma, was measured by the method of Lowry *et al.* (1951) modified for use with an Autoanalyser (Gibbs and Bright, 1968). Samples, usually 0.2 ml, were fractionated on columns of Sephadex G-200 as previously described (Cole *et al.*, 1973).

To obtain information about the normal protein composition of CSF in preterm infants as determined by gel filtration, specimens of lumbar CSF which had been taken for the routine investigation of 9 infants suspected of infection but in whom cultures proved negative were similarly fractionated. These infants were born at gestational ages of 28 to 33 weeks (mean 30 weeks), weighing 1080 g to 1710 g (mean 1380 g), and were between 1 and 6 days (mean 4 days) old when the specimens were obtained. None of them had suffered any evident hypoxic episodes either before or after birth, and all survived.

Coagulation studies. Blood for coagulation studies (Jones, Rivers, and Taghizadeh, 1972) was collected into 1/10th volume of 3.8% (w/v) trisodium citrate solution to which ϵ -amino caproic acid had been added to inhibit *in vitro* fibrinogenolysis. The prothrombin time (PT, Quick) and kaolin activated partial thromboplastin time (PTT) were measured. Platelets were counted by light microscopy and fibrinogen levels determined by an optical density technique using thrombin, and also by a modification utilizing Reptilase-R. Fibrin monomer: fibrin degradation product complexes were detected by the serial dilution protamine sulphate titre (SDPST). Assay of factors V, VII, and X were performed as described by Biggs (1972).

Abnormalities of PT and PTT were considered to be present if the values obtained, when compared with a normal adult control sample, were prolonged by more than 2 SDs beyond the mean prolongation time determined from groups of normal infants of similar gestation. Abnormalities of other coagulation studies were defined as follows—fibrinogen <150 mg/100 ml, platelets <150,000/mm³, SDPST >1/20.

Necropsy. Full necropsies were performed on 22 infants. The brains were examined for external abnormalities and then a few weeks later by coronal slicing after fixation in formalin. Sections of a hemisphere were taken from frontal, parietal, and occipital lobes, as well as from levels in the brainstem.

Results

Haematocrit and protein composition of CSF and blood. Table I shows values for haematocrit, total protein concentration, and protein

TABLE I

Analysis of plasma and CSF. Haematocrit, total protein concentration, and protein concentration in the three protein peaks after gel filtration of 0.2 ml samples

	Haematocrit (%)	Total protein (g/100 ml)	Pk 1 (μg/ml)	Pk 2 (μg/ml)	Pk 3 (μg/ml)
<i>Normal infants (no. = 9)</i>					
Lumbar CSF	0	0.12 ± 0.01	0.05 ± 0.05	1.52 ± 0.43	9.70 ± 1.29
<i>Dead infants (no. = 11)</i>					
IVH absent (no. = 4)					
Ventricular CSF	0	0.50 ± 0.14	5.05 ± 2.94	8.37 ± 4.07	44.75 ± 15.91
Plasma	39.4 ± 6.2	2.91 ± 0.54	121.62 ± 57.37	54.02 ± 5.18	206.62 ± 25.81
IVH present (no. = 7)					
Ventricular CSF	6.91 ± 1.9	2.24 ± 0.40	26.41 ± 6.96	50.53 ± 10.69	216.61 ± 32.93
Plasma	28.9 ± 3.8	3.44 ± 0.32	64.99 ± 8.08	80.81 ± 8.94	292.90 ± 18.71

Note: Mean values ± 1 SEM are given.

composition as determined by gel filtration in the ventricular CSF and blood of 11 infants who died. The results from those who had and those who did not have IVH are given separately. None of the infants had evidence of infection or hydrocephalus at necropsy. Data available from one other infant have not been included in the analysis because the composition of ventricular CSF and peripheral blood were almost identical. Values obtained from the analysis of lumbar CSF from the control infants are also included in Table I.

From the ratio of haematocrit values in ventricular CSF and blood it was calculated that the percentage of blood present in the CSF of infants with IVH included in Table I ranged from 11 to 45% (mean 23%). The total protein concentration in ventricular CSF was significantly higher in the infants who died without intraventricular bleeding ($P < 0.002$) (as well as in those who had this type of haemorrhage, $P < 0.001$) than in lumbar CSF from the control infants. Ventricular CSF from controls was not available but would be expected to have a lower protein concentration than in lumbar samples (Davson, 1967).

The total protein concentration in lumbar CSF from two infants who died without IVH was lower than in their ventricular CSF (0.28 vs 0.65 g/100 ml and 0.27 vs 0.84 g/100 ml). The Fig. shows the results of gel filtration of plasma proteins from one of the infants who died without intraventricular bleeding. The same three protein peaks were found on gel filtration of CSF and of plasma, evidence that the protein in the CSF was derived from plasma. By calculating CSF: plasma ratios for the three protein peaks it was possible to show, in the infants who had no bleeding into the CSF, that small plasma protein molecules were present in the CSF in higher concentration, relative to plasma, than larger molecules. The CSF: plasma ratio for

FIG.—Results of gel filtration of 0.2 ml samples of plasma (pl) and ventricular CSF from an infant weighing 1380 g at 30 weeks' gestation. He developed severe hyaline membrane disease, was treated by mechanical ventilation, and died aged 41 hours after several episodes of severe hypoxia and bradycardia. The protein molecules in peak 1 have a radius of 110 Å or more, in peak 2 55 Å, and in peak 3 35 Å. The smaller molecules are present in the CSF in higher concentration, relative to plasma, than larger molecules. At necropsy, bilateral subependymal plate haemorrhages were found, but there was no intraventricular bleeding.

peak I (molecular diffusion radius 110 Å or more) was $0.085 \pm \text{SE } 0.055$, for peak 2 (molecular radius 55 Å) 0.161 ± 0.073 , and for peak 3 (molecular radius 35 Å) 0.249 ± 0.101 . Students paired 't' test shows that these peak ratios are significantly different from one another ($P < 0.05$). The protein present in the CSF of these infants has, therefore, the characteristics of a filtrate of plasma.

An attempt was made to show the presence of a

plasma filtrate, in addition to whole blood, in the CSF of the infants who died with IVH. The assumption was that an amount of undiluted plasma had been added to the CSF as a result of the haemorrhage which was proportional to the CSF haematocrit. The amount of protein added could then be subtracted from the protein values actually determined from analysis of the CSF. After performing this calculation, the total protein concentration in ventricular CSF which could not be accounted for by the presence of intraventricular bleeding was 1.47 ± 0.36 g. Similar calculations gave values of 12.1 ± 7.1 μ g/ml for peak 1, 33.0 ± 9.6 μ g/ml for peak 2, and 150.5 ± 28.5 μ g/ml for peak 3. CSF : plasma ratios were then determined for the three protein peaks and gave the following results: peak 1, $0.159 \pm SE 0.077$; peak 2, 0.391 ± 0.089 ; peak 3, 0.495 ± 0.075 . Paired 't' testing showed that the peak 1 and peak 2 ratios were significantly different from one another ($P < 0.02$). The difference between the peak 2 and peak 3 ratios was not significant ($P < 0.10$). Some tentative evidence was therefore found that the protein added to the CSF in infants with IVH was, as in the case of asphyxiated infants dying without this type of haemorrhage, a filtrate of plasma.

Coagulation studies. Coagulation studies were performed on 22 infants. All had been given 1 mg vitamin K intramuscularly shortly after birth. The first studies were done within 12 hours of delivery in 15 infants, and 18 infants had more than one study performed. In 17 infants the last values were obtained within 24 hours of death.

No systematic differences in the results were apparent between those infants who subsequently proved to have IVH and those who did not. All the infants displayed at least one abnormal value. The most striking abnormality in the first samples taken was prolongation of the prothrombin time in 15 out of the 22 infants. This abnormality often remained (6 infants) or developed later (2 infants), so that in subsequent samples it was present in 8 out of 18 infants, even though the prothrombin time had returned to normal in 3 out of 5 infants treated by partial exchange transfusion or infusion of fresh blood because of prolonged values ($> 4SD$). 2 of these 3 infants died of IVH in spite of improvement of their coagulation status, and estimation by alkali denaturation (Huehns *et al.*, 1962) of the percentage of Hb-F in intraventricular blood showed that the haemorrhage had occurred after the transfusion. The partial thromboplastin time was also commonly abnormal in early samples, prolongation being found in 11 out of 22 infants, though it almost always

resolved and was found in only 2 out of 18 infants subsequently.

In the initial samples, only 2 out of 22 infants had low fibrinogen levels, and 4 low platelet counts, but later these abnormalities became more frequent, 4 out of 18 infants showing reduced values for fibrinogen, and 8 low platelet counts. The serial dilution protamine sulphate titre (SDPST) was abnormal initially in 13 infants, and later in 7. Late developing abnormalities of fibrinogen, platelet, and SDPST levels were always in collapsed, severely ill infants. The alterations in the coagulation status of one infant in whom Factor assays were performed and who died of IVH are shown in Table II.

TABLE II

Coagulation studies from an infant weighing 980 g at 27 weeks' gestation

Sample no.	1	2	3	4
Age (hr)	00.50	09.10	35.45	38.00
Prothrombin time	30.3	24.4	38.6	42.1
Control	13.9	13.4	12.4	11.8
Factor V	72%	82%	76%	62%
Factor X	22%	20%	19%	14%
Factor VII	13%	17%	4%	2%
Fibrinogen (mg/100 ml)	116	160	150	117
Platelets	163,000	297,000	270,000	89,000
SDPST	1/20	1/20	1/10	1/10
Haematocrit (%)	47	42	43	28

Note: He had severe hyaline membrane disease requiring mechanical ventilation, developed pneumothoraces, and died with bilateral intraventricular haemorrhages at 40 hours of age. Episodes of severe hypoxia occurred between samples 2 and 3, and again between samples 3 and 4. SDPST, serial dilution protamine sulphate titre.

Necropsy. 13 out of a total of 22 infants necropsied were found to have haemorrhages in one or both subependymal plates which had originated from the anterior terminal veins and ruptured into the ventricles. These 13 included 6 out of the 7 infants with IVH from whom ventricular samples of CSF had been obtained (Table I). 5 other infants had bled from the anterior terminal veins into the subependymal plate but extension into the ventricles had not occurred. These 5 infants included 4 from whom ventricular CSF samples were available. Changes of variable degree which were regarded as due to cerebral hypoxia or ischaemia were found in 20 infants. No evidence of venous infarction of the subependymal plate of the type described by Towbin (1968, 1970) was seen. Subarachnoid haemorrhages not due to spread from the ventricular system were present in 2 infants. Conspicuous bleeding into other organs was not seen, except in 2 infants who had massive pulmonary haemorrhages.

Discussion

Most of the infants in the present investigation had suffered severe repeated episodes of hypoxia, hypercapnia, and acidosis. At necropsy 18 out of 22 of them were found to have subependymal plate haemorrhages originating from the terminal veins and in all but 5 of these 18 the haemorrhage had ruptured into the lateral ventricles.

Protein composition of CSF. Whether or not intraventricular bleeding had taken place, a large excess of protein was found in ventricular CSF obtained directly after death. This protein was shown by gel filtration to be derived from the plasma, and in the infants dying with subependymal plate haemorrhages which had not extended into the ventricles small protein molecules were present in higher concentration, relative to plasma, than larger molecules, giving evidence that it was a filtrate of plasma.

Not surprisingly, clearcut evidence could not be found that the excess protein in the CSF of the infants who did prove to have IVH was also a plasma filtrate. Two questionable assumptions are involved in trying to establish this point: that the haematocrit of the sampled CSF was representative of the whole of the ventricular CSF and that the distribution of the molecular radii of the proteins in plasma and CSF had not changed materially after the haemorrhage. Nevertheless, the same trend towards a preponderance of small plasma protein molecules in CSF was found and the results are consistent with the view that, as in the case of the infants with no intraventricular bleeding, plasma filtrate had been added to the CSF.

Mechanism of filtration of plasma proteins into the CSF and rupture of the terminal vein.

The reasons for the coexistence of damage to the terminal vein with the presence of a plasma filtrate in ventricular CSF cannot be precisely determined from our results. Nevertheless, the findings are consistent with our hypothesis that the causes of massive pulmonary haemorrhage (or haemorrhagic pulmonary oedema) and IVH are similar. During very severe asphyxia in fetal lambs, brought about by occluding the umbilical cord for 5–10 minutes, about 17% of the plasma volume is lost from the circulation (Adamson *et al.*, 1970), a finding which is attributable to the temporary, and reversible, increase in capillary filtration pressure which follows the development of bradycardia, hypertension, heart failure, and a raised central venous pressure. We suggest, therefore, that increased filtration of plasma protein into the CSF of severely asphyxiated infants

occurs because myocardial failure due to hypoxia and acidosis (Downing, Talner, and Gardner, 1965) is followed by a rise in intravascular pressures which promotes filtration through capillaries which are in close contact with the CSF.

Since G. Bucci (personal communication, 1973) has found increases of central venous pressure to as much as 20 cm H₂O during apnoeic spells in preterm infants, and since the terminal veins of infants born at less than about 34 weeks' gestation are thin-walled and poorly supported (Gruenwald, 1951), we further suggest that rupture of this vessel is also a direct result of increased venous pressure. Evidence in favour of this view comes from the demonstration by Grøntoft (1954) that the terminal veins of preterm infants dying in the immediate newborn period can be ruptured by applying an intraluminal pressure of 15–20 cm H₂O.

Because Grøntoft (1954) also showed, using perfusion techniques, that trypan blue does not penetrate the blood-brain barrier of preterm infants until at least 45 minutes after death, we doubt whether a direct effect of hypoxia (or post-mortem changes) had any influence on our results. We cannot, however, rule out some effect due to the cerebral vasodilating action of hypercapnia (Davson, 1967).

Other ways in which an acute rise in venous pressure might occur and cause intraventricular bleeding include compression of the trunk during a vertex delivery at a time when the head is exposed to atmospheric pressure, the use of excessively tight neck-seals (Vert, André, and Sibout, 1973) or high intrathoracic pressures during treatment with continuous positive airway pressure (Gregory *et al.*, 1971), and the development of a tension pneumothorax.

The influence of raised intravascular pressures and other factors on filtration of protein into the CSF and upon the incidence of IVH may prove difficult to investigate further in the human infant, but could be explored in experimental animals.

Disorders of haemostasis. The abnormalities of haemostasis found in this investigation are, as in previous studies (Gray *et al.*, 1968; Chessells and Wigglesworth, 1972), difficult to interpret. While these abnormalities were common, as in many seriously ill newborn infants, they were only thought severe enough, in the first samples obtained, to cause a real risk of bleeding in 5 infants who were then treated by transfusion. Particularly striking was prolongation of the prothrombin time, which seemed to be greatest in the infants with the worst hypoxia. The sequential changes occurring in the

one infant in whom Factor assays were performed (and which have subsequently been shown in two other preterm infants, not included in the present study) are shown in Table II. The prolongation of prothrombin time after a severe hypoxic episode was shown to be due principally to a large fall in Factor VII together with a lesser fall in Factor X. Since Factor VII is a comparatively small molecule, with a size similar to plasma albumin (peak 3), the increase in prothrombin time might possibly have been due to filtration of Factor VII out of the circulation and its extravascular utilization by complex formation with tissue thromboplastin (Nemerson and Pitlick, 1972). This complex could then activate Factor X in the extravascular space. Should activated Factor X be returned to the circulation in the presence of acidosis, poor tissue perfusion, and a deficiency of its naturally occurring inhibitor (as described in some sick newborn infants, Mahasandana and Hathaway, 1973); then the process of intravascular coagulation would be initiated and the sequence of events shown in Table II could be explained.

Probably, as in the case of massive pulmonary haemorrhage (Cole *et al.*, 1973), abnormalities of haemostasis serve to exacerbate or prolong the bleeding rather than initiate it. If a small rupture occurred in a terminal vein in the presence of defective haemostasis, then IVH would be more likely to occur than if the coagulation status was normal. Repeated asphyxial episodes appear to be likely to lead to IVH as suggested by Harrison *et al.* (1968), since they could cause progressive damage to the terminal vein together with a progressively deteriorating haemostatic mechanism.

Prevention of IVH. If our hypothesis is correct, and the main factor responsible for rupture of the terminal vein and intraventricular bleeding is an increase in venous pressure usually due to asphyxial heart failure, then measures designed to avoid pre- and postnatal asphyxial episodes should reduce the incidence of the condition. Particularly important would be intrapartum monitoring of preterm infants, rapid resuscitation at birth, and the avoidance of hypoxia subsequently due to pulmonary abnormalities or immature control of breathing ('apnoea of prematurity'). Since apnoea may occur with little or no warning in small preterm infants when no member of the medical staff is present, we regard it as extremely important that all such infants should be monitored and that nurses should be able to resuscitate them rapidly, if necessary by endotracheal intubation.

Trials of the administration of clotting factors to preterm infants in an attempt to prevent IVH have

given conflicting results (Dietrich and Krebs, 1965; Gray *et al.*, 1968; Cade *et al.*, 1969; Hambleton and Appleyard, 1973; Thomas and Burnard, 1973; Waltl *et al.*, 1973). Recently, one such trial (Waltl *et al.*, 1973) showed an increased incidence of haemorrhage after treatment, but a significant improvement in coagulation status appeared not to have been achieved in the treated group. In the present study, 2 out of 3 infants in whom transfusions had returned severely abnormal prothrombin times to within normal limits for preterm infants died later from IVH. Nevertheless, since serious bleeding after damage to the terminal veins will be more likely in the presence of deficient haemostasis, it seems that a trial of therapy aimed at achieving higher Factor VII and X levels than has been the case in the past might be worth while.

Haemodynamic factors as a cause of bleeding and loss of protein from the circulation in newborn infants. We conclude that the most important factor in the pathogenesis of both massive pulmonary haemorrhage (or haemorrhagic pulmonary oedema) and IVH is probably raised venous and capillary pressure following myocardial failure due to asphyxia. Because we have observed, in severely asphyxiated infants (unpublished data), the presence of plasma filtrates in the pleural, pericardial, and peritoneal spaces as well as in the urine, which sometimes also contains red blood cells, we suggest that a variety of disorders in the newborn period may result from raised intravascular pressures.

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Addendum

Since the preparation of this article, Simmons *et al.* (*New England Journal of Medicine*, 1974, **291**, 6) have suggested that intraventricular haemorrhage can be caused by the excessive administration of sodium bicarbonate solution, with or without hypernatraemia. We have therefore calculated the sodium intakes of the 18 infants in the present study who bled into their sub-ependymal plates or ventricles. Our attitude to fluid therapy was much as described by Simmons *et al.* for their second study period, 1970–71. Most of the infants were fed human milk through a nasogastric tube and given a supportive intravascular infusion of sodium bicarbonate solution (100 mEq Na/l.) for the first hours of life followed by a sodium chloride solution (30 mEq Na/l.), both made up in 10% dextrose. Some of the infants were totally parenterally fed with a mixture containing 27 mEq Na/l. A 5% sodium bicarbonate solution (600 mEq Na/l.) was given by injection only if a very severe asphyxial episode occurred, or to correct partially a severe metabolic acidosis. The total amount of sodium administered exceeded 8 mEq/kg per 24 hr—the level regarded as safe by Simmons *et al.*—in only 2 of the 18 infants. In one of these infants, and one other (who was undergoing peritoneal dialysis for hydrops fetalis) plasma sodium levels above 150 mEq/l. were found. Plasma sodium levels in the other 8 infants in whom measurements were made were always below 147 mEq/l. These findings make us doubt whether excessive administration of sodium, or hypernatraemia played any important part in causing bleeding from the terminal veins of the infants in our study.