

Disseminated Fibrin Thromboembolism among Neonates Dying within 48 Hours of Birth

J. F. BOYD

From Brownlee Laboratory, Department of Infectious Diseases, University and Ruchill Hospital, Glasgow, and University Department of Pathology, Western Infirmary, Glasgow

The cause of death within 7 days of birth remains uncertain in about 14% of neonates (Butler and Bonham, 1963). Many authors have commented on the presence of thrombosis in neonatal deaths, for example, Cruickshank (1930) noted thrombosis in 30 of 800 deaths. Zuschlag (1947) reported a study of lung infarction in 38 children, one of whom was less than a month old. These infarctions were frequently associated with thrombi and often related to infection. More recently, Emery (1953) made a similar observation, two of his cases being 5½ days and 9 days old, respectively; no aetiology was apparent in the younger case. Groniowski (1963) reported 15 more cases and while at least half of them had obvious infections (mainly otitis media), the pulmonary thrombi were not obviously infected. Lately, Scott (1965) and Sanerkin, Edwards, and Jacobs (1966) have reported thrombosis with and without embolism as a consequence of prolonged umbilical vein catheterization.

Dieckmann (1936) established that cases of abruptio placentae and concealed accidental haemorrhage showed hypofibrinogenemia, and that the fatal cases showed widespread pulmonary thrombosis and embolism. This view received support from Schneider (1950, 1951), McKay, Merrill, Weiner, Hertig, and Reid (1953), and Johnstone and McCallum (1956). The lesions were localized at capillary level and the circulating blood became depleted of fibrinogen. Schneider showed that placenta and uterine decidua were very rich in tissue thromboplastin, and suggested that this substance was released into the circulation during one of these catastrophes to lead to the pathological and histological findings described above. Further studies have shown the syndrome of hypofibrinogenemia of pregnancy to be a complex state involving at times the fibrinolytic system (Stefanini, 1958; Phillips, 1959; Schneider, 1959; Sherry, Fletcher, and Alkjaersig, 1959; Stefanini and Turpini, 1959;

Flute, 1964; Merskey, Johnson, Pert, and Wohl, 1964). In pursuing the original argument, Boyd (1957) reported fibrin deposits on the villi of many placentae, and suggested that these minor deposits, which could become major and result in 'infarctions', could represent another manifestation of this process of intravascular thrombosis. The next step was to determine if placental thromboplastin could enter the foetal circulation to cause effects there similar to those in fatal maternal hypofibrinogenemia. Two possible examples were reported in 1958 (Boyd), and both are incorporated in greater detail in the present article. A larger series of stillbirths and neonatal deaths was reported recently (Boyd, 1965), and a complete series of stillbirths showing the syndrome has also been reported (Boyd, 1966). In the present article the findings among neonates dying within 48 hours of birth are recorded.

Material and Methods

These have been detailed elsewhere (Boyd, 1965). Of 755 perinatal deaths studied, nearly 66% was a prospective series, and blocks of tissue were taken from all major organs regardless of whether or not distinct pathological features were visible. In addition to H. and E. sections, a duplicate set of sections was stained by Lieb's (1948) phosphotungstic acid haematoxylin (PTAH), by which method fibrin is stained blue-black. Rarely, results were confirmed by employing other stains for fibrin.

Antemortem fibrin thromboemboli. In this survey of 226 neonates dying within 48 hours of birth, intravascular fibrin deposits were noted in one or more organs in 58 cases (26%). The fibrin deposits were considered to be postmortem, agonal, or antemortem in type from the morphological disposition of the fibrin strands. In the case of antemortem fibrin thromboemboli, the fibrin strands tend to be parallel to one another and to the vessel wall, to lie along the direction of blood flow, and to be long. They may be packed tightly together, they stain deeply, and they show a saddle embolus effect at bifurcations. Such thromboemboli may acquire a varying component of platelets, or

Findings in Eight Neonates Living for Less than 48 Hours

Case No.	Maternal State			Length of Gestation (wk.)	State of Placenta		
	Age (yr.)	Parity	Antepartum			Intrapartum	Postpartum
1	?	?	Pre-eclamptic toxæmia; twins	—	—	28	Monovular
2	?	2	Rh neg. with antibodies	—	Mild postpartum hæmorrhage	40	—
3	46	13	Mild antepartum hæmorrhage	—	Pyrexia	36	Old infarction
4	28	5	Mixed accidental hæmorrhage	—	—	34	Retroplacental hæmatoma
5	31	4	Chronic bronchitic, hypertension	—	Pyrexia due to exac. of chronic bronchitis	38	—
6	38	3	Premature rupture of membranes	—	Mod. postpartum hæmorrhage	39	—
7	?	?	—	—	puerperal pyrexia	40	—
8	31	3	Disproportion	Lower segment caesarian section	—	40 +	—

* + and - indicate presence or absence of thromboemboli; a blank indicates that no histological examination was made.

of white or red corpuscles, but these elements must be in the minority so that the essential fibrin nature of the thromboemboli remains clear, thus suggesting that the lesions have formed selectively from the circulating plasma. Other evidence of antemortem formation is the finding of ischaemic changes in the organs, tissues, and cells in the vicinity of the lesions. Older thromboemboli show adhesion to the vessel wall, retraction, and lining of the exposed faces by vascular endothelium, and even older lesions show gradual loss of their customary staining properties.

This series revealed eight cases with fibrin thromboemboli to match the description given above, one of which (Case 6 below) also had streptococcal septicaemia, but the fibrin thromboemboli showed no evidence of being infected. (A ninth case showed antemortem mixed thrombosis which was considered to be infected. This last case is not reported.)

Case Reports

The eight cases are reported in order of increasing survival after birth.

Case 1. Mother admitted when 26 weeks' pregnant, draining blood-stained liquor, showing mild pre-eclamptic toxæmia, and x-ray examination confirmed twins. Premature labour started 2 weeks later, and monochorionic male twins were delivered. The puerperium was satisfactory. The first twin died when less than 12 hours old, and the second twin died some time later.

Necropsy of twin I showed patchy atelectasis and a blood-stained right pleural effusion. Four blocks of lung showed patchy expansion of atria and alveoli, without infection. Sections stained by PTAH showed widespread intravascular thromboembolism in three blocks. The lesions were composed entirely of fibrin, and were located in the arterioles, in the capillaries (Fig. 1) to the extent that capillary beds of whole lung lobules had become functionless, and in pulmonary venules. The affected parenchyma showed ischaemic changes though frank infarction was absent. It was estimated that three-quarters of the vascular bed of three of the four blocks was obstructed by thromboemboli.

Necropsy of twin II showed immaturity and atelectasis.

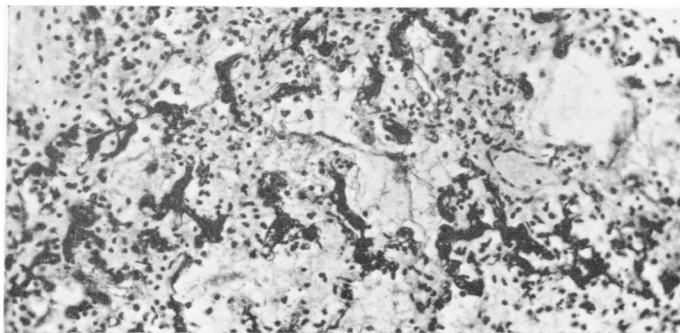


FIG. 1.—Case 1. Lung. Extensive capillary fibrin thromboembolism; alveolar oedema shows delicate network of fibrin. (PTAH $\times 170$.)

I
and Showing Disseminated Fibrin Thromboembolism

Length of Infant's Survival (hr.)	Organs Showing Fibrin Thromboembolism*									
	Adrenal	Lung	Liver	Brain	Heart	Kidney	Thymus	Thyroid	Pancreas	Pituitary
< 12		++								
12	-	++	+	++	+	-	+	+	+	
12	++	-	++	-	-	-			-	
13½	++	-	-			-		-	-	
21	-	++	++	-	++	++			-	-
25	+ [+]	-	-	-		-		-		
31	++	-	-	-	-	-		+		+
32	+	-	-	++	-	-			-	

Histological examination of the lungs failed to reveal any additional finding.

Case 2. Mother para-2, blood group O rhesus negative, and anti-D titre of 1/128 at term, though the titre had been low on previous tests. At birth, the baby was grey and limp. There was a mild post-partum haemorrhage. The cord blood tests revealed a 'moderately affected rhesus infant', whose condition improved during replacement transfusion, but the child collapsed suddenly at the end of this procedure, and died when less than 12 hours old. Necropsy showed the features of erythroblastosis foetalis, and this was confirmed on histological examination.

Lieb's PTAH showed fibrin thromboemboli in several pulmonary arteries (Fig. 2). The lesions were dense and the individual fibrin strands difficult to identify because of tight packing and a heavy overcoating by platelets. In the liver, scanty agonal thrombi were present, and, rarely, venules carried a coating of almost pure platelet thrombus. This appearance is similar to

that recorded by Scott (1965) as an iatrogenic lesion following prolonged umbilical vein catheterization. This finding is very uncommon among neonatal deaths in my investigation which was completed before prolonged umbilical vein catheterization was a common practice. Mixed platelet and fibrin thromboemboli, in small numbers and of small size, were found in the thyroid gland, thymus, myocardium, and in the pancreas (Fig. 3). Similar lesions occurred in the cerebral cortex, in cerebral white matter, and in the cerebellum. They appeared to be most dense, however, in the brain-stem close to the nuclei of the glossopharyngeal and vagus nerves. No secondary effects were identified. Fibrin thromboemboli were not present in the kidneys or in the spleen.

Case 3. Mother, 46 years, para-13, admitted with vaginal bleeding and passing several clots. The membranes ruptured spontaneously on the following day and labour started one week later, the 36th week of pregnancy. A male infant of 1930 g. was cyanotic

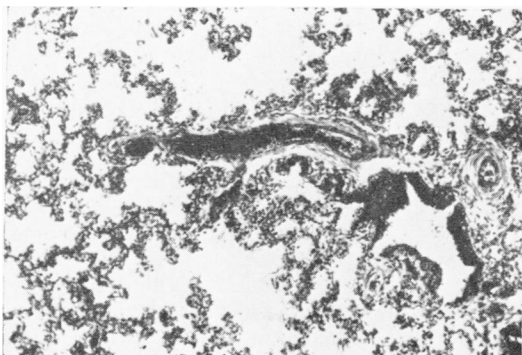


FIG. 2.—Case 2. Lung. Dense fibrin/platelet thromboembolus in arteriole. (PTAH × 95.)

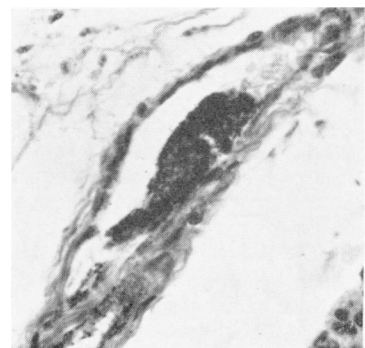


FIG. 3.—Case 2. Pancreas. Fibrin/platelet thrombus in arteriole. (PTAH × 310.)

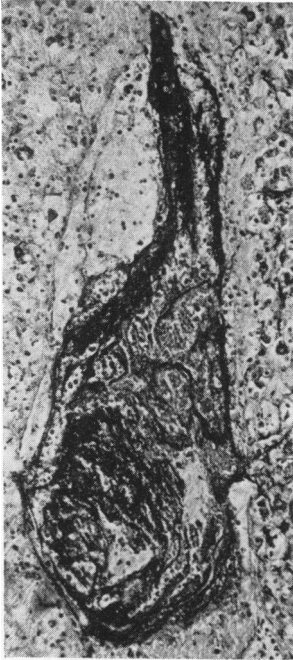


FIG. 4.—Case 3. Adrenal. Fibrin thromboemboli emanating from medullary sinusoids to form mixed thrombus in vein. (PTAH $\times 95$.)

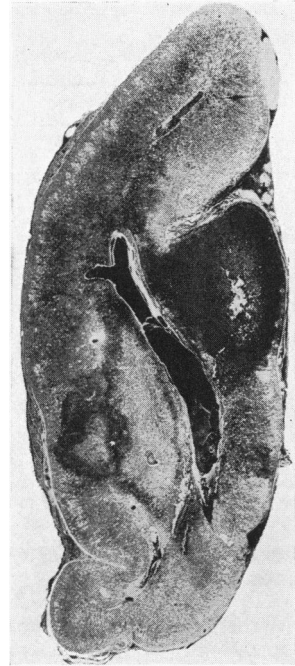


FIG. 5.—Case 4. Adrenal. Two spherical haemorrhagic cortical infarctions with much sinusoidal fibrin, and thrombus in vein. (PTAH $\times 3.5$.)

and limp. The placenta showed a large, old infarction. The mother developed pyrexia which responded well to penicillin. The cord blood fibrinogen level by the micro-Kjeldahl method was 458 mg./100 ml., being greater than the normal mean + 2 SE (unpublished results).

The infant responded slowly to resuscitative measures. Breathing became established and intramuscular oxytetracycline was given. Later, cyanotic attacks occurred while aeration remained good. Following the appearance of haematuria, 1 mg. vitamin K was given. The child lived 12 hours.

Necropsy showed mild cyanosis. Only the right middle lobe of the lungs showed aeration. The heart was normal. The liver (109 g.) and both kidneys showed severe congestion. Both adrenal glands showed medullary haemorrhages which did not distort the shapes of the glands. The brain (275 g.) showed severe congestion, and bilateral intraventricular haemorrhages. Histological examination confirmed these findings. There was no evidence of respiratory infection.

Lieb's PTAH showed antemortem sinusoidal pure fibrin thromboemboli in one adrenal gland and in the liver. There was none elsewhere. In the adrenal gland, the sinusoidal fibrin was situated in relation to the haemorrhagic infarctions. The fibrin strands were long, deeply stained, and in many areas lay in the axial stream parallel to the sinusoid walls. In areas where the fibrin

was dense the sinusoids were collapsed, and the sinusoids of neighbouring areas showed attempted compensatory dilatation even though some of these also contained fibrin deposits. In some areas the fibrin deposits no longer occupied the central portion of the sinusoid, but lay on the endothelial lining. The deposits involved a tributary of the adrenal vein, where laminated mixed thrombus was present (Fig. 4). The liver showed widespread sinusoidal fibrin thromboemboli scattered evenly throughout the organ.

Case 4. Mother, 28 years, para-5, admitted with mixed accidental haemorrhage and shock. Next day, membranes were ruptured artificially. Blood-stained liquor was obtained. On the following day a female infant of 2380 g. was delivered. There was a 240 ml. retroplacental clot. The puerperium was satisfactory.

The infant's breathing was laboured at first, its colour becoming satisfactory later. Respirations became sighing in character, and it died at 13½ hours after a nasal haemorrhage. Necropsy showed extensive petechiae over both pleurae and the pericardium. Numerous pulmonary haemorrhages were present, and congestion of the liver and brain was marked. The kidneys were pale and there was apoplexy of both adrenal glands. Histological examination confirmed these findings and showed no evidence of infection.

Sections stained by PTAH showed intravascular fibrin thromboemboli only in the adrenal glands and most

concentrated in the foci of haemorrhage (Fig. 5). Nearly all lay centrally in the sinusoids. Adrenal vein thrombosis was well developed (Fig. 5) and was very rich in fibrin at its origins, but assumed a more mixed character at its head.

Case 5. Mother, 31 years, para-4, had chronic bronchitis and high blood pressure and gave birth to a female infant of 2550 g. after a normal pregnancy of 38 weeks. In the puerperium the mother had an exacerbation of chronic bronchitis and showed early heart failure, both of which responded well to treatment.

The infant was well for 3 hours. Then she became cyanotic, and the respirations were grunting. Air entry was good and fine râles were audible. With oxygen the colour improved. Oxytetracycline was given. A systolic murmur became audible 10 hours later. The infant's condition began to deteriorate and she died at 21 hours.

Necropsy showed mild jaundice, well-aerated lungs, and dilatation of the right side of the heart. Dissection showed two firm pale vegetations on the posterior cusp of the tricuspid valve. There was no evidence of fibroelastosis. The pulmonary artery, aorta, and ductus arteriosus were normal. The lungs histologically showed moderate hyaline membrane. Intravascular fibrin thromboemboli were present in several organs. In the liver there was laminated mixed thrombus in the

portal vein of the left lobe (Fig. 6), with widespread pure fibrin thromboembolism in the small radicles and with smaller seedlings in some central and subhepatic veins, while the branches in the right lobe were free from involvement. One vegetation on the tricuspid valve was composed mainly of platelets, but there was a basic network of fibrin strands which were most dense at the base of the lesion. There were no polymorphs, red blood corpuscles, or clumps of bacteria, and the valve stroma showed no reaction to the mass. These features suggested that the mass had no infective basis, and to lend support to this, aerobic and anaerobic culture of the second vegetation gave no growth of organisms. Similar thrombus of mixed fibrin-platelet composition was found in a myocardial venule, having possibly entered the coronary sinus during diastole. All lobes of both lungs showed scanty pure fibrin thromboemboli in the pulmonary arterioles, but there were very numerous thromboemboli of mixed fibrin-platelet composition, and one or two of these were retracted to one side of the vessel wall. Extensive pure fibrin thromboemboli were found in the straight vessels of the renal medullary pyramids (Fig. 7).

Case 6. Mother, 38 years, para-3, gave birth to a female infant of 4110 g. after a normal pregnancy of 39 weeks. The membranes ruptured spontaneously two days before labour started. A true knot was present in



FIG. 6.—Case 5. Liver. Fibrin thromboemboli in several portal veins, and mixed laminated thrombus in a large portal vein. (PTAH \times 25.)

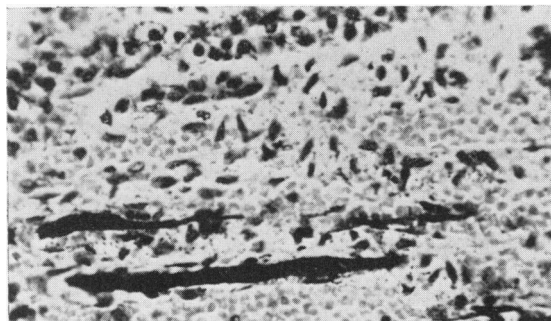


FIG. 7.—Case 5. Kidney. Antemortem fibrin thromboemboli in the straight vessels of a medullary pyramid. (PTAH \times 310.)

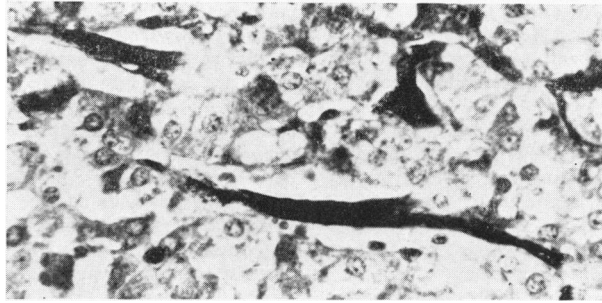


FIG. 8.—Case 7. Adrenal. Fibrin thromboemboli in axial stream in sinusoids of cortex. (PTAH \times 310.)

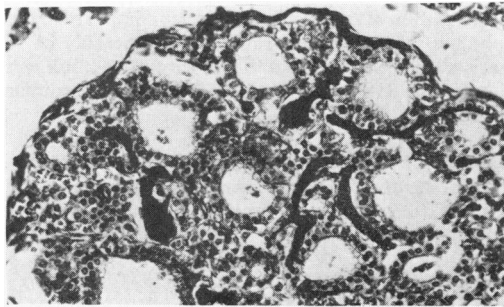


FIG. 9.—Case 7. Thyroid. Fibrin thromboemboli in capillaries around vesicles. (PTAH \times 170.)

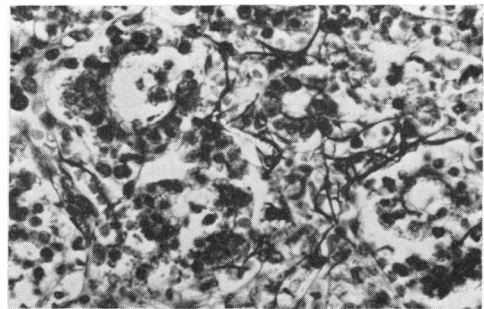


FIG. 10.—Case 7. Thyroid. Delicate capillary fibrin strands elsewhere in the gland. These may be agonal. (PTAH \times 310.)

the cord, and a brisk moderate post-partum haemorrhage followed expulsion of the placenta. The mother developed fever of 40° C.; haemolytic streptococci were cultured from a high vaginal swab. Response to treatment was satisfactory.

The infant was well for 6 hours when cyanosis developed, and later peripheral circulatory failure appeared; death occurred at 25 hours. Necropsy showed bilateral haemorrhagic bronchopneumonia, blood-stained pleural effusions, marked fatty change in the liver, haemorrhages in the splenic pulp, bilateral enlargement of the adrenal glands with central medullary softening, and petechial subcapsular haemorrhages over both kidneys. Histological examination showed a suppurative haemorrhagic pneumonia and septicaemia. Gram-positive cocci in chains were seen in many organs. Fibrin thromboembolism was minimal, being found only in one portion of one adrenal gland.

Case 7. The infant, a full-term male weighing 2950 g. was born in hospital after a normal pregnancy. He was transferred because of a large exomphalos which was repaired satisfactorily. Small feeds were started on the following day, but he became cyanotic with laboured respirations, and died after 31 hours.

Necropsy showed dilatation of all cardiac chambers associated with marked elevation of the diaphragm and an extremely tense abdominal wall, the surgical wound being perfectly healthy. Histological examination showed no other abnormality and scanty fibrin thromboemboli were found at two points in one adrenal gland (Fig. 8) and at one point in the thyroid gland (Fig. 9). The thyroid gland also showed a more delicate intravascular fibrin deposition (Fig. 10), the significance of which is uncertain but which I consider to be a variety of agonal thrombosis. The pituitary showed several short blunt fibrin thromboemboli, capable of being interpreted as either antemortem or agonal.

Case 8. Mother, 31 years and para-3, had been well throughout pregnancy and was admitted with delayed labour at term. Disproportion was confirmed and a lower uterine segment caesarean section was performed, with delivery of a male infant of 4680 g. At birth, the baby was pale. Later, cyanotic attacks appeared, the limbs were spastic and death occurred at 32 hours. Necropsy showed severe congestion of all thoracic and abdominal organs and of the brain, where there were also multiple confluent haemorrhages in the left frontal lobe with early cerebral softening.

Fibrin thromboemboli were present only in the brain and adrenal glands. In the brain, most haemorrhages were devoid of stainable fibrin, but intravascular fibrin was found only in the left frontal lobe (Fig. 11). Fibrin was not present elsewhere in the brain. Occasionally wisps of fibrin were found in haemorrhages, but their configuration suggested that they had lain originally in vessels. In the adrenal glands, scanty loosely-formed fibrin deposits were present deep in the 'foetal zone' of the adrenal cortex. These may be agonal, though the disposition of the major strands suggests that there could be an antemortem element to the deposits.

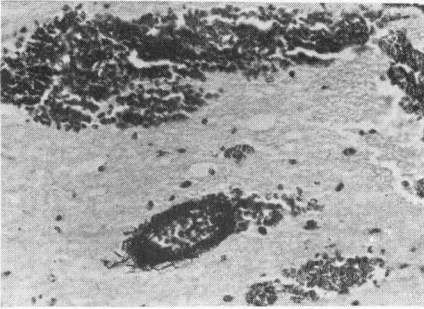


FIG. 11.—Case 8. Brain. Antemortem annular laminated fibrin thromboembolus in cerebral vessel below. Vessel disrupting with loosening of fibrin network peripherally. Petechial haemorrhages elsewhere, mostly devoid of fibrin. (PTAH \times 310.)

Discussion

There is no consistent background maternal state to the eight cases recorded in this article. More of the mothers had antepartum complications in this series than occurred in a comparable number of mothers whose stillborn infants showed this condition (Boyd, 1966). Four mothers had no abnormality during pregnancy and one of the others had a twin pregnancy with mild pre-eclampsia. Another had a mild antepartum haemorrhage and one had a mixed accidental haemorrhage. The other case had chronic bronchitis and hypertension. (In the stillbirth series, five, and possibly six, mothers of the eight 'positive' cases showed no maternal upset.) During the intrapartum period, only one mother showed any upset, which was delay due to disproportion. In the post-partum period two had small and moderate haemorrhages, and one of these also had pyrexia associated with puerperal sepsis. There was no clinical evidence that these haemorrhagic episodes were related to the hypofibrinogaemic state, though haematological tests were not carried out in either case since they arose in 1952 and 1953 before simple methods for estimating the plasma fibrinogen were in regular use. Two other patients had pyrexia which was due in one to

an exacerbation of chronic bronchitis. It appears, therefore, that there is no correlation between the occurrence of the syndrome in the infant dying within 48 hours of birth and the presence of any particular upset in the mother. Nor was there any common placental abnormality on inspection, or histologically.

The question is raised of platelets from the fresh blood transfused to Case 2 being responsible for the mixed thrombotic picture noted histologically, a situation recently described by Scott (1965) and by Sanerkin *et al.* (1966). But since a similar picture of fibrin/platelet thromboemboli was noted in Case 5 which received no transfusion of any kind, it is possible that the platelets are the infant's own platelets. In Case 5, it may be valid to suggest that the thromboplastin responsible for initiating the fibrin thromboembolic process was not of platelet origin. Scott's cases were subjected to *prolonged* umbilical vein catheterization, a situation that did not take place at the time when the present series was being collected, and catheterization of the umbilical vein was not carried out in any other case in this report.

By analogy with infarctions in other organs, it is improbable that the lesions of the adrenal glands of Case 3 are only 12 hours old (the length of the infant's extrauterine survival), and the haemorrhagic infarctions are more likely to be about 7 days old. If these assumptions are correct, they take us back in time to the mother's admission with a mild antepartum haemorrhage. The thromboembolic process in the liver is thought to be of more recent origin, and may have so depleted the infant's blood of fibrinogen after birth that extensive haemorrhages occurred, in the ventricles of the brain, in the adrenal glands, and as an episode of haematuria.

In contrast to Case 3, the fibrin thromboemboli of Case 4 are situated axially in the adrenal sinusoids. Since this infant had an extrauterine survival of 13 hours and survived *in utero* for 32 hours after a mixed accidental haemorrhage, a total of 45 hours, there is support for accepting the histological findings as being compatible with the shorter history.

Case 6 is an early example of the question to be encountered among the later neonatal deaths (i.e. those occurring after 48 hours), when other factors enter, which become increasingly difficult to segregate from the possible role of disseminated fibrin thromboembolism. Death in this case resulted from severe suppurative bronchopneumonia and septicaemia, probably due to the haemolytic streptococci responsible for puerperal pyrexia in the mother. Very little fibrin thromboembolism was encountered histologically and the questions which

are raised include: was there never very much, or was there some in the lungs which has now been digested by α -fibrinolysin? Further, were the widespread haemorrhagic manifestations part of a septicæmic state, the result of action by the streptococci, or were they part of the secondary haemorrhagic state following defibrination?

The lesions noted in Case 7 are minor and do not appear to be due to cardiac embarrassment.

Death in Case 8 was due to cerebral and pulmonary haemorrhage. This would normally be attributed to asphyxia associated with prolonged labour. The site of the cerebral haemorrhage is unusual, however, and it was not associated with fracture of the skull or with a tear of one of the dural sinuses. Special staining reveals features which could be attributed to fibrin thromboembolism and the secondary bleeding tendency could be responsible for bleeding into the damaged part of the brain and also into the lung substance.

Comparison of the distribution of fibrin thromboembolism in these 8 neonatal deaths, with the earlier series of 9 stillbirths (Boyd, 1966), shows that fewer neonates had involvement of the liver (3 cases only, compared with 7 stillbirths), but 3 neonates showed lesions in the lungs compared with the stillbirths which failed to show any lesions there. The high incidence of involvement (63%) of the adrenal glands compares strikingly with the stillbirth series where only one example was encountered. The foetal heart had ceased for at least 1 hour before delivery in the case of 4 of the 9 stillbirths.

The part played by the process of disseminated fibrin thromboembolism in causing death is important: it was considered to have been entirely responsible for the deaths of Cases 1, 2, 4, 5, and 8; to have been partly responsible for death in Cases 3 and 7; and to have been an incidental finding in Case 6. In theory, therefore, half of this series might have been saved, had the condition been known to exist and if it had been recognized clinically. There are no recognizable symptoms and clinical signs, and once the haemorrhagic state ensues, the condition is liable to be mistaken for hypoprothrombinaemia of the newborn, as Case 5 was. Even by invoking laboratory tests for prothrombin, the clinician is liable to be confused because the result will likely confirm his clinical suspicion. The difference between this syndrome and that due to pure hypoprothrombinaemia is that disseminated fibrin thromboembolism causes depletion of all clotting factors whereas only prothrombin ought to be reduced in hypoprothrombinaemia. However, when dealing with neonates of confirmed or doubtful maturity, the clinician can never accept the above

statement fully (Roberts, Davies, and Bloom, 1966).

This series of infants apparently either did not possess a fibrinolytic system, or death occurred before the system had been mobilized to a sufficient degree. This situation was more convincingly illustrated in the series of stillbirths, because some foetuses had died *in utero* and had remained there for up to four weeks before delivery, and still exhibited lesions. It is known that fibrinolysis can occur in the cadaver, and especially if the body is retained in a warm environment (Mole, 1948).

An association between hepatic sinusoidal fibrin thrombi and pulmonary hyaline membrane formation has been considered by Wade-Evans (1961, 1962). My own, partly comparable, series (Boyd, 1966) fails to yield similar results, but they do not invalidate one of his conclusions, namely that anoxia may play some part in the initiation of these thrombi. Anoxia may be responsible for the release of placental thromboplastin in the first instance. In the present series, 10 neonates showed both hepatic sinusoidal fibrin thrombi as well as hyaline membranes and I have observed that the more fibrin that was present in the hepatic sinusoids, the less deeply blue-black did pulmonary hyaline membranes stain with Lieb's PTAH. The explanation may be that when most of the circulating fibrinogen is precipitated in the hepatic sinusoids, less remains in circulation to precipitate as an integral part of the pulmonary hyaline membranes.

Study of the eight reported cases as well as of the negative cases of the series suggests that newborn infants may have a varying amount of circulating fibrinogen, and that the infants who exhibit the most severe state of disseminated fibrin thromboembolism are those who, besides other criteria, have had a reasonably high plasma fibrinogen level before the episode of thromboembolism occurs. This high fibrinogen level does not appear to be a function of foetal maturity or immaturity.

Summary

Eight neonates, dying within 48 hours of birth, showed disseminated fibrin thromboembolism, a histological condition that is very similar to one form of maternal hypofibrinogenaemia.

The mothers had had more antepartum and postpartum complications than would be expected in a series of normal neonates, and more than was encountered in a series of stillbirths showing the same condition and reported elsewhere.

The condition is not confined to any particular period of gestation, and one twin can show the condition while the other does not. The incidence

was 8 in 226 neonates dying within 48 hours of birth (3.5%).

Haemorrhagic manifestations may appear about 12 hours after birth and may be confused with hypoprothrombinaemia of the newborn. The infant usually shows some difficulty in establishing respiration at birth.

I am grateful to Professor D. F. Cappell, Dr. A. D. T. Govan, Dr. A. D. MacDonald, and Dr. R. A. Rankin for giving me many facilities for carrying out this work; and to the obstetricians and paediatricians for permission to extract the relevant case records. Mr. N. L. Russell, Mr. D. Johnstone, and Miss M. Malcolm (Mrs. Hamilton) carried out the technical work. The photographs were made by Mr. G. Kerr.

REFERENCES

Boyd, J. F. (1957). The possible role of the placenta in hypofibrinogenemia. *Surg. Gynec. Obstet.*, **105**, 741.
 — (1958). Two possible cases of acquired hypofibrinogenemia in the newborn. *ibid.*, **106**, 176.
 — (1965). Disseminated fibrin thrombo-embolism among stillbirths and neonatal deaths. *J. Path. Bact.*, **90**, 53.
 — (1966). Disseminated fibrin thrombo-embolism in stillbirths: a histological picture similar to one form of maternal hypofibrinogenemia. *J. Obstet. Gynaec. Brit. Cwlth.*, **73**, 629.
 Butler, N. R., and Bonham, D. G. (1963). *Perinatal Mortality. The First Report of the 1958 British Perinatal Mortality Survey.* Livingstone, Edinburgh and London.
 Cruickshank, J. N. (1930). Child life investigations. The causes of neonatal death. *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 145.
 Dieckmann, W. J. (1936). Blood chemistry and renal function in abruptio placentae. *Amer. J. Obstet. Gynec.*, **31**, 734.
 Emery, J. L. (1953). Pulmonary thrombosis and its association with unexpected death in childhood. *Arch. Dis. Childh.*, **28**, 187.
 Flute, P. T. (1964). Haemorrhage and fibrinolysis. *Proc. roy. Soc. Med.*, **57**, 603.
 Groniowski, J. (1963). Thrombotic arteriolar lesions in lungs of newborn. *Arch. Path.*, **75**, 144.

Johnstone, J. M., and McCallum, H. M. (1956). Hypofibrinogenemia in pregnancy: report of a case. *Scot. med. J.*, **1**, 360.
 Lieb, E. (1948). Modified phosphotungstic acid-hematoxylin stain. *Arch. Path.*, **45**, 559.
 McKay, D. G., Merrill, S. J., Weiner, A. E., Hertig, A. T., and Reid, D. E. (1953). The pathologic anatomy of eclampsia, bilateral renal cortical necrosis, pituitary necrosis, and other acute fatal complications of pregnancy, and its possible relationship to the generalized Shwartzman phenomenon. *Amer. J. Obstet. Gynec.*, **66**, 507.
 Merskey, C., Johnson, A. J., Pert, J. H., and Wohl, H. (1964). Pathogenesis of fibrinolysis in defibrination syndrome: effect of heparin administration. *Blood*, **24**, 701.
 Mole, R. H. (1948). Fibrinolysis and the fluidity of the blood *post mortem*. *J. Path. Bact.*, **60**, 413.
 Phillips, L. L. (1959). Etiology of afibrinogenemia; fibrinolytic and fibrinolytic phenomena. *Ann. N.Y. Acad. Sci.*, **75**, 676.
 Roberts, J. T., Davies, A. J., and Bloom A. L. (1966). Coagulation studies in massive pulmonary haemorrhage of the newborn. *J. clin. Path.*, **19**, 334.
 Sanerkin, N. G., Edwards, P., and Jacobs, J. (1966). Pulmonary thromboembolic phenomena in the newborn. *J. Path. Bact.*, **91**, 569.
 Schneider, C. L. (1950). Complications of late pregnancy in rabbits induced by experimental placental trauma. *Surg. Gynec. Obstet.*, **90**, 613.
 — (1951). 'Fibrin embolism' (disseminated intravascular coagulation) with defibrination as one of the end results during placenta abruptio. *ibid.*, **92**, 27.
 — (1959). Etiology of fibrinopenia: fibrination defibrination. *Ann. N.Y. Acad. Sci.*, **75**, 634.
 Scott, J. M. (1965). Iatrogenic lesions in babies following umbilical vein catheterization. *Arch. Dis. Childh.*, **40**, 426.
 Sherry, S., Fletcher, A. P., and Alkjaersig, N. (1959). Fibrinolysis and fibrinolytic activity in man. *Physiol. Rev.*, **39**, 343.
 Stefanini, M. (1958). Fibrinolysis as a mechanism of hemorrhagic tendency. *Acta haemat. (Basel)*, **20**, 85.
 —, and Turpini, R. A. (1959). Fibrinogenopenic accident of pregnancy and delivery: a syndrome with multiple etiological mechanisms. *Ann. N.Y. Acad. Sci.*, **75**, 601.
 Wade-Evans, T. (1961). Thrombi in the hepatic sinusoids of the newborn and their relation to pulmonary hyaline membrane formation. *Arch. Dis. Childh.*, **36**, 286.
 — (1962). The formation of pulmonary hyaline membranes in the newborn baby. *ibid.*, **37**, 470.
 Zuschlag, E. (1947). Infarction of the lung in children. *Amer. J. Dis. Child.*, **74**, 399.