HÆMORRHAGIC DISEASE OF THE NEWBORN.

BY

RUBY S. BEVERIDGE, L.R.C.P., M.R.C.S.

(From the Medical Department, Royal Hospital for Sick Children, Glasgow.)

In recent years there has been an increasing amount of literature on the subject of the forms of hæmorrhage occurring in the newly born. One of the rarest of these is the group known as "hæmorrhagica neonatorum," and consequently it may be of interest to record some facts ascertained during a survey of the case histories of 24 examples of this condition which have been under observation in the Royal Hospital for Sick Children, Glasgow.

Holt¹ applies the term "hæmorrhagica neonatorum" to "those cases in which the hæmorrhages are not associated with any other known processes, and in which the escape of blood from the smaller blood vessels is the chief or essential symptom." This definition excludes such varieties of neonatal hæmorrhage as are due to birth traumatism, asphyxia, syphilis, gastric or duodenal ulcer, and hæmophilia.

A curious characteristic of the disease lies in the spontaneous commencement and termination of the bleeding. It is noteworthy, too, that although present-day treatment will normally stop the bleeding, this result very often occurs naturally. Another interesting feature of the malady is constituted by the region or regions of the body that may be the seat of hæmorrhage. It would appear that the mucosa of the alimentary tract, the umbilicus, or the subcutaneous tissues, are the sites most frequently affected. The bleeding may be internal, external, or both combined. Post-mortem examination will, of course, reveal the presence of internal bleeding. It is an interesting fact too, that gross lesions, e.g., ulcers, are rarely found in cases exhibiting bleeding from the alimentary tract. Holt found post mortem in 24 cases of bleeding from the stomach and intestines ulceration of the gastric mucosa in 9 and of the intestinal mucosa in only 4 cases.

AETIOLOGICAL FACTORS.

"Hæmorrhagica Neonatorum" is a disease of obscure ætiology. Well nourished infants are apparently just as liable to be attacked as the feeble or ill nourished.

It has been clearly established that it is not a manifestation of hæmophilia: the frequency with which females are attacked and the absence of any tendency for bleeding to recur, being quite sufficient to differentiate it from hæmophilia. The latter has been observed to occur rarely in infants under one year. Grandidier² in 1871 stated that in 185 bleeder families comprising 576 bleeders, only 12 infants were affected with hæmorrhage at the separation of the umbilicus.

Capon³ regards it as unlikely that birth traumatism plays a part in the causation of this disease. Formally sepsis was noted to be often associated, and this gave rise to a theory of a possible infective origin, a view favoured by Townsend⁴. Nowadays, however, sepsis neonatorum is rare and is not considered to play any part in the causation.

Syphilis has been recorded as an associated factor in a relatively small proportion of cases. Hess⁵ collected some instances relating to this point with a view to determining the question "are we dealing with syphilis hæmorrhagica or a secondary infection of a syphilitic infant?" Hess's own case was that of a female infant with the onset of hæmatemesis and melæna on the 6th day, subcutaneous hæmorrhages and death on the 7th day. At the post-mortem examination the child was jaundiced, with exfoliation of the skin of the hands and feet: hæmorrhages were found in the stomach and bladder, and histological examination revealed interstitial changes between the lung alveoli, and also cirrhosis of the liver. In one of a series of 13 cases of spontaneous hæmorrhage of the new-born recorded by Abt⁶ there was a history of the mother having contracted syphilis during pregnancy. The child weighed 3½ lbs. at birth and lived one hour only. Autopsy revealed hæmorrhages into the peritoneal and pleural cavities. In another case in Abt's series there was no history of syphilis, but it was suspected on account of the premature birth of the infant and the presence of pulmonary atelectasis and pneumonia. Hæmorrhages were found in the lungs, skin, thymus, thyroid, liver, stomach, intestine, suprarenals, spleen and pericardium. Hess, summing up these cases with several others from the literature, concluded that "syphilis is undoubtedly an important factor, in some acting as a direct cause due to changes in the vascular system, not alone on the blood-vessel walls but on the blood as well."

Modern research has been concentrated on the examination of the blood in these cases in order to ascertain if the essential cause of the disease lies in some defect in the blood constituents. Rodda⁷, in an extensive study of the coagulation and bleeding times in the newly born, shows that in cases of idiopathic hæmorrhage these times are invariably prolonged beyond the normal. According to his method of determination the normal coagulation time ranged from 5 to 9 minutes, with an average of 7 minutes, whereas in cases of hæmorrhagica neonatorum there was a prolongation to 20, 30 or even 90 minutes, with a corresponding prolongation of the bleeding time. Rodda further demonstrated that in the normal infant "the coagulation time varied on different days of the infant's life, showing a tendency to prolongation over the 2nd, 3rd and 4th days, with a maximum on the 5th day, and a return to the time obtained during the first 24 hours before the 10th day." The average bleeding time was 3½ minutes, with a range of 2 to 5 minutes.

Through the kindness of Dr. G. B. Fleming I have been enabled to test the coagulation and bleeding times of newly born infants at the Glasgow Maternity Hospital, and thus to investigate this question for myself. None of these infants presented during the time of study any evidence of hæmorrhage. The apparatus used was that devised by Gibb⁸, and employed as he recommends. For obtaining blood the skin was punctured by a spring lance as used by Rodda. Gibb found that in adults the average coagulation time was 97 seconds. The figures obtained by this method in the newly born are shown in Table I.

TABLE I.
OBSERVATIONS ON BLOOD COAGULATION IN THE NEW BORN.

Age in Days ..	1	2	3	4	5	6	7	8	9	10
Average coagulation time (seconds) ..	118.2	139.6	137.0	134.5	123.5	115.9	119.4	108.3	104.7	103.4

Average bleeding time, 2½ minutes.

The individual results as seen in the Chart below show a fairly wide variation but the averages show a definite rise in the coagulation time on the 2nd, 3rd and 4th days, and thereafter a fall to below that of the level of the 1st day.

Fig. 1. Chart showing Distribution of Coagulation Time in Normal Infants from 1 to 10 Days.

It is interesting that in hæmorrhagic disease of the newly born the onset of the bleeding is most frequent during the first week in life, and its greatest incidence is from the 2nd to the 5th day, thus corresponding with the period in which there is normally prolongation of the coagulation time. Capon has in consequence suggested that the pathogenesis may in part be dependent on a delay in reaching the normal level.

The exact nature of the element here lacking, which is essential to normal coagulation, is still under dispute, being variously ascribed to some deficiency in prothrombin, thrombin, thrombokinase, fibrinogen, or the blood platelets. Gelston⁹ favours the view that it is due to lack of prothrombin. Pearce¹⁰ discussing this question, remarks that "whatever the cause, the results of treatment show that the introduction of whole adult blood will in all cases materially inhibit, and in nearly all cases control, the bleeding, causing a coincident return to normal of the coagulation and bleeding times."

SYMPTOMS.

The predominant feature is hæmorrhage, which may be copious and alarming and thus ensure prompt attention, or slight in amount, when it may be permitted to continue for days before advice is sought. Anorexia of varying degree is usual, and has been observed in some cases before the onset of bleeding. The temperature is variable; it may remain normal, but is more frequently subnormal, though on occasion, especially at the onset, slight fever is present. Pallor, cyanosis, coldness of the extremities, weakness or collapse may follow, the degree of collapse being proportionate to the amount of blood-loss.

The diagnosis is usually obvious. Difficulty may arise when internal bleeding alone occurs, but this is extremely rare. In cases of hæmatemesis or melæna due to swallowed blood, the bleeding is invariably small in amount and there are no signs of constitutional disturbance.

The course of the disease is limited by recovery or death; in fatal cases death usually occurs within 1 to 3 days of the onset.

ANALYSIS OF CASE HISTORIES OF PRESENT SERIES.

24 cases of "hæmorrhagica neonatorum" were admitted to the Royal Hospital for Sick Children, Glasgow, during the period August, 1915, to November, 1926, inclusive. Examination of the histories indicates that the sex incidence is practically equal, 54 per cent. being males and 46 per cent. females. This is in agreement with the findings of most writers.

Only a few instances are recorded in the literature of any familial tendency to the disease. Gelston quotes a case of Reichard's, a ninth child, whose brother died at the age of 4 days of gastro-intestinal hæmorrhage. There is a similar case in the present series.

CASE 1. M., boy, aged two days. The mother, aged 40, had had 4 previous pregnancies: (1) girl, aged 6 years, alive and well; (2) boy, melæna at 2 days, responded to treatment, but died, *æt.* 10 weeks, of debility; (3) abortion at 2 months; (4) abortion at 2 months; (5) patient.

The patient was well developed at birth, but pale. Six hours after birth hæmatemesis and melæna occurred. 20 c.cm. of human blood were injected subcutaneously, but melæna continued.

26.4.26. Admitted to Hospital. 10 c.cm. of human blood injected subcutaneously.

27.4.26 Child very pale, lips cyanosed, melæna still present. Blood:—Hb., 40% ; Red B.C., 1,760,000 ; White B.C., 5,600.

28.4.26. Bleeding stopped but general condition of child not improved. Blood transfusion performed because of anæmia. 100 c.cm. of an uncle's blood given intranevously.

29.4.26. Hb., 72% ; Red B.C., 4,070,000 ; White B.C., 14,800. No further bleeding occurred. Child's colour was good. Made good recovery.

In no case was a source of sepsis found nor any lesion suggestive of syphilis.

In 18 of the 24 cases under consideration pregnancy and labour were normal, with the birth of full-time, apparently normal, infants. In the 6 remaining cases labour was abnormal, being premature in 3 cases, instrumental in 2 cases, and in the 6th (a breech presentation) trauma must be admitted as a possible factor, though delivery was spontaneous.

The site of bleeding is various, and for comparison the relative frequency of different sources, as detected later by clinical and post-mortem observation in the present series and in that of Townsend, are placed in parallel columns. (Table II.)

TABLE II.
SITES OF HÆMORRHAGE.

Site of Hæmorrhage.	Present Series. (24 Cases)	Townsend's Series. (50 Cases)
Intestine	17	20
Stomach	15	14
Mouth	5	14
Nose	4	12
Umbilicus	7	18
Skin	11	21
Meninges	1	4
Brain	3	1
Cephalhæmatoma	2	2
Abdomen	2	1
Pleura	1	1
Lungs	5	1
Thymus	1	1
Pericardium	2	0
Kidneys	1	0

Most authorities agree that the average time of onset of the bleeding is from the 2nd to the 4th day after birth. In Fall's¹¹ series of 14 cases it ranged from the 1st to the 14th day. In Townsend's series of 50 cases, in all but three, the onset was during the first week of life, the exceptions being one on the 8th, 9th and 14th days respectively. The details regarding time of onset in the present series are given in Table III. compared with the findings of Townsend.

TABLE III.

TIME OF ONSET OF BLEEDING.

Time of Onset.	Present Series.	Townsend's Series.
At birth	2	0
During 1st day	6	2
„ 2nd day	11	13
„ 3rd day	2	16
„ 4th day	0	8
„ 5th day	6	0
„ 8th day	0	1
„ 9th day	0	1
„ 14th day	1	1
„ 21st day	1	0

In two instances in the present series an unusually delayed onset of bleeding was observed. It is remarkable that on both occasions it was in the case of children born 8 and 6 weeks prematurely, which may in some way have been responsible for the delay in its appearance. Details of these cases are:—

CASE 2. M. D., male child, aged 14 days. The mother, aged 41, had had 15 previous pregnancies of which seven terminated in stillbirths and one in a miscarriage. In the case of the patient the pregnancy was normal, labour 8 weeks premature, but delivery spontaneous. The infant was said to be jaundiced at birth. There was no history of rash, snuffles, conjunctivitis or convulsions. The child was breast fed, thrived, and was apparently healthy. The cord separated on the 9th day, and the umbilicus seemed quite normal until the 14th day, when constant oozing of blood was noted therefrom. The child came under observation that night (aged 14 days). On examination he was small and jaundiced, with oozing of venous blood from the umbilicus. Nothing further abnormal was detected with the exception of a palpable spleen. Local pressure was applied to the umbilicus by gauze pads steeped in adrenalin but 9 hours later the child died.

An autopsy revealed marked jaundice of the skin and liver (the bile ducts, however, were patent). The spleen was larger and softer than normal. Several large hæmorrhages over the base of the brain and also meningeal hæmorrhages were seen. No gross lesion was found in the other organs.

CASE 3. M., female child, six weeks premature, aged 21 days. The mother had had three previous pregnancies and the children are alive and well. While pregnant with patient the mother had during the last 5 weeks recurrent uterine hæmorrhages. The infant, 6 weeks premature, seemed healthy at birth, and moved and cried readily. She was breast fed and sucked well for 3 days and was then artificially fed with cow's milk. Increasing anorexia was noted after the 3rd day. On the 21st day hæmatemesis occurred and the child was brought to hospital in a moribund condition, the tissues were depleted, the eyelids discoloured and the pulse feeble and running. Blood: Hb., 61%; Red B.C., 2,780,000; White B.C., 3,200. On admission 10 c.cm. maternal blood were injected subcutaneously, but no improvement followed, and the child died soon after. The post-mortem examination revealed distention of the pericardial sac with fresh blood, also hæmorrhages in both lungs and blood in the pleural sacs. The stomach contained altered blood, and the brain showed numerous petechial hæmorrhages on its surface. The C.S.F. was blood-stained. Hæmorrhages were also found in the thymus and in the peritoneal sac.

Fatal Cases. In the present series of 24 cases 8 infants died and autopsies were held on 7 of these. The situation of the bleeding was as follows :—

Abdominal Cavity, 1; Stomach 1; Intestines 3; Thymus 1; Lungs 5; Pleura 1; Pericardium 2; Kidneys 1; Bladder 1; Meninges 1; Brain 3.

It is interesting to note that in three cases intracranial hæmorrhage occurred, and that in all birth was premature. Two of these cases are reported in detail above (Cases 2 and 3). The history of the other case is as follows :—

CASE 4. A male child, aged 5 days. The mother was healthy during pregnancy but the labour was difficult, instruments being used. The child was 1 month premature, and breathed well at birth but did not cry for 15 minutes after birth. The child was spoon fed and did fairly well for 2 days and then bleeding from the mouth and nose was noted, continuing for 2 days. Child came under observation on the 5th day when slight bleeding from the mouth was observed, also a large hæmatoma over the right parietal bone. The child was small and poorly nourished, with generalised cyanosis, and also sclerema of the body. There was generalised spasticity affecting principally the legs. The child died 3½ hours after admission. A post-mortem examination showed multiple hæmorrhages into the lungs, and congestion of the liver, spleen and kidneys, but no gross lesion in the peritoneum or bowel. There was a large cephalhæmatoma on the right side of the skull posteriorly, and around this were numerous hæmorrhages into the scalp tissues. A large hæmorrhage was found over the vertex of the brain chiefly on the right side where it extended some distance into the cortical layers.

Warwick¹² in a series of 200 necropsies on the newly born, including 41 cases of hæmorrhagic disease showing multiple hæmorrhages, found cerebral hæmorrhages in 20 cases. Rodda had already shown that “ hæmorrhagica neonatorum ” may be an important factor in the causation of intra-cranial hæmorrhage. He differentiates between hæmorrhage due to trauma and that due to hæmorrhagic disease by the fact that in the former the coagulation and bleeding times fall within normal limits. Foote¹³ also expresses the opinion that intracranial hæmorrhage may be a manifestation of “ hæmorrhagica neonatorum.” He advises early lumbar puncture and the injection of substances to increase blood coagulability in all cases of suspected intracranial hæmorrhage in the newly born. Sharpe¹⁴ on the other hand, maintains that “ hæmorrhagica neonatorum ” is a rare cause of intracranial hæmorrhage in the new born, and in this connection the predisposition of the premature to cerebral hæmorrhage must be borne in mind.

TREATMENT.

The first notable advance in the treatment of this disease was in 1910 when Welch¹⁵ advocated the use of injections of normal horse serum. The more recent adoption of whole human blood therapy, either by subcutaneous, intramuscular or intravenous injections, has further considerably decreased the mortality (Table IV.) Thursfield¹⁶ in 1913 remarked that the condition is serious and generally fatal. Holt, however, in 1922, stated that “ no case should be looked upon as hopeless, for recovery has repeatedly taken place after transfusion of blood when the infant was moribund.”

TABLE IV.

MORTALITY.

Author.	No. of Cases.	Treated by Transfusion.	Number Died.	Mortality, %
Townsend (1894)	50	None	31	62.0
Robertson, Brown and Simpson (1921)	43	All	1	2.3
Fall (1923)	14	All	0	0.0
Present Series (1926)	24	2	8	33.3

The treatment adopted in the present series varied in different cases as follows :—

TABLE V.

RESULTS IN PRESENT SERIES.

Method of Treatment.	No. of Cases.	Recovered.	Died.
Subcutaneous injections of normal horse serum ..	8	5	3
Subcutaneous injections of human blood (alone) ..	10	7	3
Subcutaneous injections of human blood and horse serum	2	2	0
No treatment, death immediately after admission ..	2	0	2
Subcutaneous injections and intravenous transfusions of human blood	2	2	0

Details of one of the cases treated by transfusion has already been given (Case 3). The details of the second are as follows :—

CASE 5. Male, aged 3 days. The mother had had ten previous pregnancies. All the children are living and well. Labour in this case was prolonged, but non-instrumental. The patient was apparently normal at birth, but 2 days later commenced to bleed from the cord. This was ligatured: the bleeding was controlled temporarily, but recurred.

29/9/26. Admitted to Hospital, aged 3 days. Physical examination showed the child to be in good condition, but there was considerable oozing of venous blood from the cord to which pressure was applied with gauze soaked in adrenalin, and at 5 p.m., 20 c.cm. of an uncle's blood were injected subcutaneously. Copious oozing from the cord continued: 6 hours later (11 p.m.) blood transfusion was performed, 80 c.cm. of Dr. S. G's. blood being given.

3/10/26. No further bleeding occurred after transfusion.

Having regard to the short course and the urgency of the symptoms in "hæmorrhagica neonatorum," it is now generally accepted that the ideal method of treatment is by blood transfusion. It is acknowledged, however, that in the

less severe examples subcutaneous or intramuscular injections of whole human blood, or failing this, of normal horse serum, may control the bleeding; but it must be remembered that such injections do not relieve any consequent anæmia. In all severe cases, and especially where anæmia is profound, blood transfusion is indicated, and in fact may be essential to recovery. In the opinion of such observers as Cherry and Langrock¹⁸, de Biasi¹⁹, Falls and Pearce, either parent, but preferably the mother, is the most suitable donor and obviates preliminary compatibility tests. On the other hand, Jones²⁰, Happ²¹ and Learmouth²², consider that preliminary cross agglutination tests are necessary in all cases because of the fact that occasionally iso-agglutinins and iso-hæmolysins are present in the blood of the new born infant. Doan²³ in a recent comprehensive review of the problem also advises such preliminary cross testing of bloods as being the safer course in the light of present day knowledge. On account of its comparative simplicity the transfusion of citrated blood, the so-called indirect method, is usually performed nowadays. The route selected depends on the choice of the operator and may be the internal saphenous vein at the ankle, the external jugular vein, the longitudinal sinus, etc. The amount of blood transfused is generally estimated at 30 c.cm. per kilogramm. of body weight of the infant.

The results of treatment by transfusion are distinctly encouraging. In Fall's series of 14 cases, many of which had had previous unsuccessful treatment by injections of whole blood or horse serum, recovery followed in every case after transfusion. In all of these cases the mother was used as donor, preliminary cross agglutination tests were not performed, and no reaction occurred. Robertson, Brown and Simpson, in their 43 cases similarly treated, had only one death; these writers carried out cross agglutination tests before selecting a donor. In the present series only 2 cases were treated by transfusion and both recovered; both children had been previously treated by subcutaneous injections of human blood without apparent benefit.

In view of the fact that transfusion gives the best result in these cases, it would be advisable, in the event of either parent proving unavailable or unsuitable as donor, to have on hand suitable donors whose presence could be insured with a minimum loss of time. Properly controlled, a band of voluntary donors as suggested by the Red Cross Society would undoubtedly perform valuable service in such an emergency. The condition is one of urgency and necessitates prompt and efficient treatment, as any delay renders the chances of recovery more remote.

CONCLUSIONS.

1. It would appear that the sex incidence of the children affected is practically equal.
2. Infants in the first week of life, especially within the first four days, most frequently exhibit the condition.
3. The question of natal trauma as a factor in the present series only arises in three cases (two instrumental deliveries and one breech presentation).

4. It is suggested that the determination of the coagulation and bleeding times would assist in the diagnosis between hæmorrhage due to trauma and the true hæmorrhagic disease.

5. Examination of the blood is helpful for estimating the gravity of the condition from the amount of blood lost.

6. From the facts and figures available it is apparent that the most efficient and satisfactory treatment is the injection of whole human blood. Transfusion is essential in all cases where the constitutional symptoms are severe.

REFERENCES.

1. Holt, L. E., *Diseases of Infancy and Childhood*, N.Y., 1922, 98.
2. Grandidier, Quoted by Townsend, *Arch. Pediat.*, N.Y., 1894, XI, 559.
3. Capon, N. B., *Lancet*, Lond., 1924, i, 1203.
4. Townsend, *Boston Med. & Surg. J.*, Boston, 1891, CXXV, 218.
5. Hess, A. F., *Arch. Pediat.*, N.Y., 1904, XXI, 598.
6. Abt, I. A., *J. Amer. Med. Ass.*, Chic., 1903, XL, 204.
7. Rodda, F. C., *Amer. J. Dis. Child.*, Chic., 1920, XIX, 268.
8. Gibbs, O. S., *Quart. J. Med.*, Oxf., 1924, XVII, 31.
9. Gelston, C. F., *Amer. J. Dis. Child.*, Chic., 1921, XXII, 351.
10. Pearce, N. O., *Abt's Pædiatrics*, Philad., 1923, II, 354.
11. Falls, F. H., *J. Amer. Med. Ass.*, Chic., 1923, LXXX, 678.
12. Warwick, M., *Amer. J. Dis. Child.*, Chic., 1921, XX, 492.
13. Foote, J. A., *Ibid*, 1920, XX, 18.
14. Sharpe, W., *J. Amer. Med. Ass.*, Chic., 1923, LXXXI, 620.
15. Welch, *Amer. J. Med. Sc.*, Philad., 1910, CXXXIX, 800.
16. Garrod, A. E., Batten, F. E., & Thursfield, H., *Dis. of Children*, Lond., 1913, 92.
17. Robertson, B., Brown, A., & Simpson, R., *Northwest Med.*, Toronto, 1921, XX, 233.
18. Cherry, T. H., & Langrock, E. G., *J. Amer. Med. Ass.*, Chic., 1916, LXVI, 216.
19. De Biasi, B., *Ibid.*, 1923, LXXXI, 1776.
20. Jones, B. B., *Amer. J. Dis. Child.*, Chic., 1921, XXII, 586.
21. Happ, W. M., *J. Exp. Med.*, N.Y., 1920, XXXI, 313.
22. Learmonth, J. R., *Glasgow Med. J.*, Glasgow, 1924, CI, 116.
23. Sharpe, W., *J. Amer. Med. Ass.*, Chic., 1923, LXXX, 620.