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Hemorrhagic disease of the newborn

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HEMORRHAGIC DISEASE OF THE NEWBORN

MARJORIE EVERETT

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INTRODUCTION

Hemorrhagic disease of the newborn is an idiopathic, spontaneous bleeding, occurring during the first week of life in otherwise healthy infants. It is now a relatively rare disease.

An important factor in the disease at present, and one considered in this paper, is the consideration of its relationship to cerebral hemorrhage, especially in explaining cerebral hemorrhage in infants which were delivered with apparently the least amount of trauma possible.

The vitamin factors--especially B, D and K have come into the picture, and bring forth some interesting speculation.

In this paper, I am considering the hemorrhagic disease of the newborn as a specific disease entity, but following the work of the past few years, the elimination of most cases of sepsis of the newborn, the diagnosis of various blood dyscrasias, of syphilis, etc., which were previously erroneously classified as hemorrhagic disease, I am wondering how much longer this disease will remain as a distinct entity?
HISTORY

About the earliest report of hemorrhage of the newborn is that of Maureceau in 1682, in which he mentions the hemorrhage but offers no suggestion as to etiology. (28) Dr. Watts in England in 1752 published in the Gentleman's Magazine a description of a case of umbilical hemorrhage in which "the blood drilled in a uniform equable stream down the belly"

He remarked that he had heard of several similar cases, and asked for reports from other men.

Underwood (49) in 1786 published the first systematic treatise in the English language on diseases of children. He mentions this hemorrhage as one 'attendant upon infants who are in a bad state of health during the month', but remarks that it is not critical and should be controlled with styptics and compresses.

In 1822, Mr Pout reported of a family in which three infants had died of umbilical hemorrhage. (Med. Chir. Trans.) In 1824--Elissaesser (49) reported a case, in the Hufeland's Journal, which had occurred in a family of marked hemorrhagic predisposition. In 1832, Radford reported two cases, in the Edinburgh Medical and Surgical Journal, one of which was not fatal, being stopped by compression, and the other one was fatal. He thought the disease was due to an arterial bleeding, in the case which was not fatal, and since in the fatal case, at autopsy, the vein appeared uncontracted, he concluded that venous bleeding was less amenable to treat-
ment than arterial, which he thought could usually be checked by compression. He recommended cutting down on and tying the vein, as treatment.

Dr Tiemann of Bielefield (49) in 1837 reported an instance in which the umbilical hemorrhage was associated with jaundice, bleeding from nose, mouth and bowels. Previous to this, most reports had been merely of umbilical hemorrhage.

Homans, in 1849 reported seven cases, four of which died. All had umbilical bleeding with some ecchymoses of the skin. The three which lived were treated mainly with caustics, locally.

From Professor Burn's Principles of Midwifery (85) in 1820 we find that 'sometimes, a day or two after the cord separates, or at that time, hemorrhage takes place around the naval. This may yield to astringents, etc., or may prove fatal.'

Ray (1849) reports of a woman with several children, of which four males died of hemorrhagic disease and three females remained healthy. He concluded that it was a familial disease to which the male sex was especially liable. He reported an autopsy on one case which had a malformation of the umbilical arteries and veins. As treatment, he recommended maintaining the mother's health during pregnancy, local use of collodion, on the funis at separation, controlling the hemorrhage mechanically by pressure—cotton wool with collodion, plaster of paris cast, eschar or tying
the bleeding vessels. Dr Churchill (49) in 1841 in reporting two fatal cases related to him by a friend had proposed the idea of the plaster of paris cast.

Anderson (3) in 1850 reported a case which was deeply jaundiced at birth, and died at about the eleventh day. Autopsy showed the common duct not patent. The meconium was dark, apparently because of hemorrhage. His idea of hemorrhagic disease was that it was probably due to direct communication between the interlobularies and radicles of the hepatic duct. He thought that the hemorrhagic diathesis was due to faulty secretion of bile and he was probably the first to publish an observation of the connection between reabsorption or non-elimination of bile and the hemorrhagic tendency.

Bowditch (10) in 1850 reported the case of a woman who had four children, all normal deliveries, two of which hemorrhaged from the cord. One female child on the third day began to ooze at the umbilicus and was treated locally with astringents, then operation—cutting down on and tying the cord. Death occurred on the seventh day. The other, a male, began to ooze at the cord, on the tenth day, and was treated with actual cautery. Purpuric spots appeared on the scapula, elbow, and the skin was icteric. It died on the fourteenth day. Autopsy revealed an enlarged, yellow liver. The other organs appeared pale but normal. The mouth appeared red during life, but there was no actual hemorrhage. He noted a lack of coagulation of blood for many hours after death. He
remarks that these cases were of both sexes, although literature gives a predisposition to the male sex, also that local treatment seemed to excite rather than check the disease, and in these cases, even violent surgical procedures were of no avail. He suggested that transfusion would be indicated, but it seemed that the older doctors of the time thought that it was no good, and the younger ones were too skeptical to try it.

Coale (17) in 1852 reported a case of a child which was normal at birth, vomited blood on the second day, and blood appeared in the stools, which ceased after the third day. He treated it with aromatic sulphuric, internally, one drop every two hours, substituting iron sulphate, grains one sixth every three hours on the third day.

Minot (73) in the same year read a paper before the Boston Society for Medical Improvement--an essay giving a complete description of the disease, based on an analysis of forty six cases. He remarks of a description of a well marked cases in Cheynes essays on the Diseases of Children, Edinburgh, 1801, in which 'bleeding proceeded from an unhealth- y change produced in the blood by the reception of bile into the mass of fluids, an original and incurable malformation of the liver, and impermeable thickening of the beginnings of the hepatic ducts.' Minot described the disease as an oozing, occurring a few days after birth, at the separation of the umbilical stump, which could not be controlled by styptics,
associated often with well marked jaundice, infrequent, light-colored stools, no pain, a greater incidence in males, and rather of a familial occurrence. Of the nineteen cases which he had observed, the average time of onset was five and one half days. It occurred mostly in infants which were stout and healthy at birth. Ecchymoses appeared in many cases. A few exhibited pain, especially upon extension of the legs. Occasionally there were cerebral symptoms. The morbid anatomy was not constant nor distinct. As to etiology, he enumerated; hereditary--the mother showing epistaxis in some cases; sex--more male; liver disfunction and imperfect closure of the umbilical vessels. He found that of the forty-six cases, 68% were males. Jaundice appeared in a number of cases, yet many jaundiced infants were not bleeders. Of this series, 84% were fatal. As to treatment, he recommended caustics to the naval--lunar caustic, lead acetate, tannic acid, alum, matico, actual cautery, and pressure--plaster of paris casts. Ligature might be effective, or cutting down on and tying the vessels, or ligature enmasse.

Dr Gage (49) in 1853 reported arresting umbilical hemorrhage by binding down a ladies thimble to the abdomen. Jenkins in this article summarizes all of the available literature on umbilical hemorrhage, to date, with case reports. He collected one hundred and seventy eight cases from German, French and English literature. From these he concluded that there are two varieties of umbilical hemorrhage--the first
and most common depending on a 'depraved' condition of the blood, possibly resulting from jaundice—a result of malformed or deranged function of the liver, or an inherited scrofulous or syphilitic taint, or due to deprivation and despondency of the mother during gestation, or during the same period an excessive use of alkalies or diluent fluids. Secondly—umbilical hemorrhage arising by unusual patency of the umbilical vessels, in otherwise apparently healthy children.

In four of the series, one or both parents were scrofulous or phthisical and in five were syphilitic. He noted that 'a diseased condition of the umbilical vessels, the result of their inflammation' is undoubtedly a cause of hemorrhage from the newborn navel. We would probably now classify this disease as an infection of the newborn, rather than hemorrhagic disease.

In nine of the cases—there was a history of profuse hemorrhage, excess bleeding at labor or injuries of the mother or hemorrhagic tendency in the family (seventeen other cases). He does note that there was scarcely any history of infants with umbilical hemorrhage in families known as 'bleeders'.

Of this series, 73% were males, of the cases in which sex was recorded. Difficult labor is recorded in only two instances. Jaundice was present in more than 43 1/2%, purpura accompanied 20% and bleeding from the gastrointestinal tract, 9.6%.
The hemorrhage commenced on an average at about the eighth day. The hemorrhage was described in most cases as an oozing, though a 'continual dribbling' or 'hemorrhage very free' occurred in some cases. It appeared to be either arterial or venous. The blood was described as pale, and non-coagulable in many cases. It was seldom observed to have exuded from a distinct orifice, but rather oozed from the walls of the cord. The average duration of the hemorrhage was three and one-half days.

Of this series, 22 cases were recorded in which examinations after death were done. The results were not particularly constant. The condition of the liver was often noted as congested or impatency of the ducts. Occasionally ecchymoses of the abdominal viscera or lungs was noted. The umbilical vessels were patent in several cases. There was an 83.7% fatality.

Larrabee (62) in a report of a case gives reference to the reports of Grandidier (1871). He had a series of 220 cases, 64 with jaundice, 7.6% females, many showed symptoms of inherited syphilis, and 6% were of hemophilic families, indicating strongly, he thought, a hereditary tendency.

Larrabee reports 37 cases, with a 60% mortality, 17% of which were females, and he observed hemorrhage from the umbilicus, skin, bowel, joints, gastro-intestinal tract, wounds, gums and stomach.
Thayer (105) gives the case history of a child which died at seven days of age of umbilical hemorrhage, autopsy showing the common duct not patent. From a study of reported cases, he finds that the etiological factors are: acute fatty degeneration of the heart, lungs, liver and kidney, near close of fetal life, or obliteration of the common or hepatic ducts by mucous plug or by cicirtization, that hemorrhage begins on an average at the eighth day, with epistaxis, hematemesis, emaciation or purpuric manifestations, the duration of the hemorrhage averaging about three and one half days. The infants were usually jaundiced several days before the hemorrhage began. Constipation was frequent. As treatment, he recommended fixing the integument at the base of the cord with needles and carrying a figure of eight ligature under them. He thought styptics and compression were of no value. Possible internal remedies to relieve the liver, such as nitro-hydrochloric acid, and tincture of iron, with aathartics, especially calomel were of value.

Jacobi (46) in 1878 published an article concerning acute fatty degeneration of the newborn. She reported the case of a child, the fifth in a family of which one male had previously died of umbilical hemorrhage. Bleeding began on the first day of life, the umbilical vessels were ligated, hare-lip pins placed cross-wise and the whole sutured, but the child died. Autopsy showed free blood in the abdomen, and hemorrhagic spots over the surface of the lung. There
was fatty degeneration of liver, kidney, and heart. Microscopic examination showed blood cells free in the lungs. (undoubtedly another case of infection of the newborn)

Heckner von Buhl (1861) had described a hemorrhagic condition of the newborn, with lesions of the viscera and fatty degeneration, which was later known as a disease entity --Buhl's disease, but which we would now probably consider as merely a pyogenic infection of the umbilicus. He identified it with malignant icterus of adults, when preceded by icterus. He considered that possibly the blood was poisoned by bile absorption.

Cohnheim believes that stagnation allows the red blood cells to penetrate the capillaries, the theory is that stagnation produced fatty degeneration of the tissue--possibly occurring before birth due to lesions of the placenta.

Townsend (107)(108) in 1891 and 1894 reported a series of fifty cases at the Boston-Lying-In Hospital and gives a different idea of etiology. Of these cases, forty-five were in the hospital and the remainder observed in the outpatient department. The hospital incidence was .67%, and the outpatient .1%. The bleeding appeared in the first seven days of life in all but 13 cases, most of the cases had a slight temperature--101 to 103 degrees--these factors suggesting to him an infectious etiology. Of his series, 60% were males, the mortality was 62%. He identified melena by finding whole corpuscles or hemine crystals in the stools.
Of the 609 cases which he found reported to date, there were 127 recoveries, a 79% mortality, 210 were males, 150 females and in 249 instances, the sex was not reported. Of eighty-one autopsy reports on these cases, syphilis, enlarged spleen, enlarged liver, inflammation of umbilical and portal veins, acute fatty degeneration were reported.

The various etiological factors thus far reported were --deficiencies of nutrition, changes of elasticity of capillaries, acute fatty degeneration of the newborn (Buhl's disease), feeble coagulability, jaundice, exanthemata, birth injury, true hemophilia, early ligature of the cord, plethorism, debility, retention of meconium, difficulty in establishing the pulmonary circulation--and a host of different organisms--including Klebs and Eppingers Monas Hemorrhagica (which they thought specific).

He found that the prognosis was better in bleeding from the gastrointestinal tract, than in other type of hemorrhage. He recommended as treatment --quiet, careful feeding, alcoholic stimulants and warmth. Internal astringents seemed of little value, though external pressure might be helpful.

Kilhan and Merelis (53) in 1899 reported ten cases! Bacteriologic examination from two cases showed pathogenic non-motile, facultative, anaerobic organisms, suggesting the diplococcus of pneumonia.
Von Preuschen and Pomorski (1892) proposed the theory that the hemorrhagic tendency was due to injury of the vasomotor center of the brain, from head injuries at the time of delivery—causing a hyperemia of the gastrointestinal tract mucosa and lungs, and they substantiated their work with rabbit and dog experiments. Further work along this line was never reported.

We will note, that up to this time, hemorrhage of the newborn has been considered as mostly umbilical hemorrhage. Following the papers of Townsend, more reports began to appear in the literature of hemorrhage from other sites.

Following Townsends report on hemorrhagic disease, for the next few years, little was reported of the disease in the literature, until Lambert (6) in 1908 reported a case cured by transfusion. His case was of a girl child, with subcutaneous hemorrhage and melena. Lambert did a direct transfusion, an end to end anastomoses of the radial artery of the father with the popliteal of the child. The bleeding of the child cease d immediately. He concluded that the rapid change in the course of the disease was due to the effect of the blood transfused on the blood of the infant, not on the blood vessels.

During this period, preceding Lamberts report, the common trend was to explain the disease on an infectious basis, and treat it accordingly. Hamil (34) in 1903, grouped under infections of the newborn—melena neonatorum, hemorrhagic disease of the newborn, Buhl's disease, Winkel's
disease, and hemophilia of the newborn. He reported 15 cases—with the following bacteria isolated from them: Bacillus pyocyaneus, B. lactus aerogenes, colon bacilla, Staph aureus, B. Coli mobilis, and a streptococcus. He added that from the literature: pneumococcae, Pfeiffer's bacillus, Bacillus of Babe's, B. Hemorrhagica of Kolb, B. of Gaertner, and encapsulated bacillus of Dungeri are reported. The institutional and almost epidemic character of the disease precluded a bacteriological etiology to him. Fever, as a common symptom, also indicated an infectious etiology. He found diarrhea, often, icterus, all sorts of skin eruptions, apathy, emaciation, disinclination to nurse and nervous phenomena among the symptoms. The most common autopsy findings were congestion and hemorrhage. He suggested profound cleanliness in the hospital as a prophylactic measure, from this standpoint, and isolation, sunny room, withdrawal of 15 to 20 cc. of blood, then injection subcutaneously of 20 to 30 cc. of artificial serum as treatment. He suggested that the source of the organism might be the mother's milk, cows milk, bath water, or air borne.

Of course, we realize now that he had a series of diseases here, rather than one entity.

Abt (1) in 1903 similarly reported 13 cases—considering infection strongly as an etiological factor, though he thought syphilis could be a factor in some cases. He
found no blood chemistry changes. He considered the deaths as due to a general toxemia, rather than to blood loss. The fact that there was no tendency to recurrent bleeding also seemed to substantiate the theory of an infectious etiology. Of his series—he found bleeding from the umbilicus in 3, skin in 6, nose in 6, mouth 6, stomach 2, vagina 2, bowel 5 and ear 1. The temperature was increased in all but one case. Some of them were icteric. His incidence was one in 500 to 700 births. For treatment, he recommended subcutaneous gelatin as possibly of some value, but it seemed to have the possibility of toxic effects. Oral and local gelatin, he thought might be effective.

To this time, the hemorrhagic tendency of the congenital syphilis was not differentiated from hemorrhagic disease. Wilson (118) in 1905 reported hemorrhage in 1.4% of 3,364 cases of the Philadelphia Lying In Charity Hospital, 22% of which were luetic. He found hemorrhage from the skin, mucousa, serous membranes, meninges, brain, glands, conjunctiva, ears and umbilicus, and especially from the skin of the lower abdominal wall, scrotum, vulva and umbilicus after ligation of the cord. The hemorrhages of the skin seemed to follow the trabeculae into the subcutaneous tissue. In the lungs, small apoplectic areas were present on the upper lobes. Icterus in some degree appeared in every case. The hemorrhage seemed to be predisposed by prematurity and subdevelopment. Probably the constitutional effects of syph-
ilia underly the degenerative changes in the blood vessels which lead to hemorrhage. He considered a bacterial infection as etiological in most cases. For treatment, he recommended oil baths alternating with mercurial inunction, keeping in an incubator, ice-cap for fever, and internally--suprarenal extract in half grain doses, adrenalin, one to one thousand, one drop, gelatin water or fluid extract of ergot.

Schwarz and Ottenburg (98) in 1910 write that multiple hemorrhage, though often of an infective basis may rarely be due to congenital stenosis of the bile ducts, cirrhosis of the liver, leukemia, pseudo-leukemia and congenital syphilis. (Finkelstein thinks true syphilis hemorrhagic neonatorum does not exist, that it is always due to a secondary infection.) They find that nasal hemorrhage is most often syphilitic rhinitis, that vaginal hemorrhage is rare.

To date (1900) little attention has been paid to the condition of the blood in this disease. Most of the work has been directed toward the supposedly infectious etiology, and toward finding the specific organism or organisms. Now the idea of correcting the blood deficiencies begins to come into the picture.

Schwarz and Ottenberg (98) reported two cases, the first of which was definitely septic. Calcium was used in one, horse serum in the other and neither found of much val-
ue. They believe that the injection of fibrin ferment (i.e. transfusion of defibrinated blood) will cause intravenous clotting and often death, also that intravenous injection of small amounts of thrombokinase, is liable to cause death because of the formation of multiple thrombi. Possibly the fibrin ferment injected is neutralized by antifibrin ferment, if too large amounts are not injected, and no clotting results. They concluded that transfusion replaces the lost blood and stops the hemorrhage by supplying new material for the production of ferments. Serum injection seemed of doubtful value. They thought that there was a deficiency of thrombokinase.

Schloss and Comisky (70) in 1912, after studying the blood of a series of cases, found that the clotting time was prolonged, and that experimentally it was not due to calcium or fibrinin deficiency. They also found poor retraction of the clot in some cases, with normal clotting time. They classified hemorrhage etiologically as:

I. Traumatic.

II. Accidental--inadequate ligature of the cord and vaginal hemorrhage.

III. Spontaneous--
Classified as to site--Melena (symptomatic of some disease, spurious and vera or idiopathica), purpura, cerebral, umbilical, hepatic, and adrenal.
They found an incidence of about .15% as reported in several series of cases. In considering syphilis as an etiological factor, they think of it only as causing an enfeebled resisting power to infections by other organisms. Ulcers of the stomach, duodenum and lower esophagus were considered as possible local causes. The possibility of a deficiency of thrombokinase, as indicated by experiment, might cause the hemorrhage, yet this would not initiate the hemorrhage, so they reasoned, there must be some additional changes—in the blood vessels.

Graham (29) in 1912 postulated five possible etiological factors in hemorrhage of the newborn—syphilis, infection, mechanical factors, heredity, and chemical agents. Substantiating these are: Other syphilitic manifestations in syphilis; the close similarity of the blood picture to that of naval sepsis, epidemicity of Winkels and other infections, microscopic findings at autopsy and also other lesions suggesting infection and the experimental production of hemorrhage in animals by injection of bacteria. (they are considering the hemorrhagic diseases of the newborn as all similar—Buhl's disease, Winkels disease, melena, icterus gravis, etc.); Pomorski and von Preuschens work suggests a traumatic etiology; heredity is repeatedly suggested in earlier reports of several cases in a family, of successive children, or possibly of a tendency of the mother to bleed; chem-
ical agents are suggested by the possible relationship to toxemia in the mother, to the seeming relationship to drug poisoning in adults (especially of Winkels and Buhls diseases) with fatty degeneration of the liver and other organs. Possibly the chloroform given to the mother during labor, as proven experimentally in animals to cause fatty degeneration of the liver of the young—with cyanosis, hemorrhage and acute parenchymatous degeneration of the liver. Ulcerations of the gastric and duodenal mucosa have appeared after the use of chloroform experimentally in some cases, also asphyxia seems to produce essentially the same changes.

Whipple (114) in 1911 suggests a reclassification of hemorrhagic diseases according to the clotting factors deficient and as he had studied the different clotting factors described by Howell and Morowitz.

Summarizing the history of the reports of hemorrhagic disease, we find that—early little attempt was made to determine the etiology and that treatment was confined mostly to local measures of hemostasis. We find that true idiopathic hemorrhagica neonatorum was badly confused with syphilis, infections (which were common at this time), trauma, and careless ligature of the cord, but that eventually attention was directed toward the blood—its deficiencies as etiological factors and its use therapeutically to supplement clotting factors and combat anemia. Since this attitude has become popularized, the disease has been fairly well under control.
INCIDENCE

The incidence of Hemorrhagic disease of the newborn is considerably less at present than it was 50 years ago, probably due to modern diet, obstetrical methods, control of systemic diseases, asepsis and of course, it must also be remembered that several other diseases were included under the heading of hemorrhagic disease, which are now differentiated and recognized as definite disease entities.

Schloss (96) in 1912 gives statistical reports of; 37 cases out of 29,333 deliveries (Silverman), 17 of 12,500 (Kling) and 2 out of 3,000 (Hergott). Rodda (90) in 1921 reports an incidence of one percent in the Minnesota hospital in which he worked. Kaiser (30) in 1922 reported .8% of 3000 deliveries in the Rochester general hospital.

McCullum (69) finds that it occurs in about one percent of births, and seems to increase in frequency when there is an epidemic of sepsis in the hospital.

Hefferman in 1932 reports that 3% of infants die during the first ten days of life, of which approximately 65% of deaths are due to intracranial hemorrhage. He thinks that a number of these are due to birth trauma in combination with hemorrhagic disease.

Capon (14) in 1932 in studying 28 cases at the Liverpool Maternity Hospital found an incidence of one in three to five hundred births, occurring equally in the sexes,
often the first or second child, and having little relationship to the type of labor. Griffith (31) in 1937, statistically finds an incidence of .15 to 1.3%, (varying with exclusion of cerebral hemorrhage). Brinkhaus in 1937 reports an occurrence of about one case in 200 births. Capon (15) adds that the average time of onset is 41.5 hours after birth in his series (60 cases), with variations up to 120 hours. Sanford (90) in 1938 reports only two cases out of 5,500 births in 8 years at Rush, in Chicago. Javert (48) reports .7% and .3% in the Woman's Clinic and Berwind Premature Clinic.

Morse finds that it occurs equally in the sexes, does not recur in later life, is self-limited, and does not occur after the second week.(76) Beveridge, in a study of 24 cases at the Royal Hospital for Sick Children, Glasgow, found that it occurred in 54% males, with no history of familial tendency, no luetic lesions, no sepsis.

At present, the incidence seems to be less than one percent, and it seems to occur equally in the sexes.
ETIOLOGY

The etiology of the disease is unknown, though numerous theories of it have been advanced, and many factors which are accessory but not fundamental brought to light.

In looking back over the history of this disease, we find many apparently definite etiological factors, but these are mostly eliminated, when we discover that other diseases were being confused with this one. In considering the etiology, we must of course understand the blood conditions found and view it from that angle.

Schloss (96) in 1912 classifies hemorrhage of the newborn as 1) Traumatic--injuries received during delivery, 2) Accidental--inadequate ligation of the cord, or vaginal hemorrhage, 3) Spontaneous--which we are considering here. He classifies spontaneous hemorrhage according to origin--as melena (subclassfied as symptomatic of some disease, spurious, or melena vera), purpura, cerebral, umbilical, hepatic, and adrenal. The old idea of the cause of hemorrhage is too early ligation of the cord, --but at this time, the most frequently attributed etiologic factors were prolonged labor, general plethora, congestion of the mesenteric arteries, respiratory embarrassment, vascular thromboses, rupture of the bloodvessels, irritation due to swallowed amniotic fluid, ulcers of the gastro-intestinal tract, bacterial infection, hemophilia or congenital lues. Schloss thinks that there is possibly a deficiency of throm-
bokinase, but that this would not initiate the hemorrhage, and it must be based on some bloodvessel changes.

Graham (29) in 1912 enumerates five etiological factors--syphilis, infection, mechanical factors, heredity, and chemical agents, and questions the relationship to toxemia of the mother, to drug poisoning in adults, asphyxia and chloroform poisoning--concluding that there is often a chloroform effect and deficient oxidation.

The infectious theory came into the 'limelight' with the work of Townsend in 1894, in which he found a rather epidemic character to the disease, in his series, the majority occurring in institutions, with very few in the homes.

Various causitive organisms have been reported. Nicholson (49) in 1903 reported a case of melena neonatorum apparently due to infection by Bacillus pyocyaneus. Klebs (11) isolated the Monas Hemorrhagica. Gartner (1) in 1903 claimed to have isolated the specific organism. Turk experimentally produced hemorrhage in the newborn, and premature birth by feeding pregnant animals bacillus coli, but closer clinical examination revealed that these cases, though due to infection were some other disease entity. However, modern asepsis has nearly out-ruled infection as an etiological factor.

Torland (106) suggests quinine, used with castor oil in the induction of labor as an etiological factor, reports a case of a child, stillborn, which had intrapleural, peri-
toneal, pericardial hemorrhage and hemorrhage into the kidney, found at autopsy.

Whipple reports a case of hemorrhage in an infant in which chloroform was used for the mother during delivery. At autopsy there was central lobular necrosis of the liver of the child, and hemorrhagic findings. Sanford (93) reporting a series of 600 cases, of which nitrous oxide, ethylene, and no anaesthetics were used at delivery, in a series of 200 each. He found that the bleeding and coagulation times were prolonged one minute with nitrous oxide, and two minutes with ethylene, over that of the normal. He explains it as possibly due to a slight liver damage, with a disturbance of the antithrombin and heparin production. Probably the type of anaesthesia used has but slight effect on the hemorrhagic tendency of the infant.

The type of labor seems to have little effect on the hemorrhagic tendency--Javert finds that in cases of hemorrhagic disease, there has been a slightly longer labor, a higher incidence of abnormal pelvis, of complications, of operative procedures and of post-partum hemorrhage.

Kugelmass (56) believes that the most common hemorrhage is due to the physiologic hyperemia of the first few days of life, and that birth trauma and mechanical manipulation when attempting resuscitation are predisposing factors. Signovelli (102) adds that in the newborn, if there is a slight hemorrhagic tendency, manipulation may
add slight trauma to the viscera, which causes a clot to form, adding more trauma, producing more hemorrhage, that in breech delivery, there is more injury to the abdominal viscera, more hyperemia, and congestion to the later coming parts, and trauma to the viscera in the frantic attempts at resuscitation in these cases. The liver, adrenal, pancreas and bladder are the most common sites of hemorrhage. Possibly the hemorrhage is so trivial in most cases, that it goes undiagnosed.

Beveridge (7) in 1938 from a history of 24 cases found that 3 were premature, 2 instrumental, and one breech, indicating these as etiological factors. Kaiser (50) differs. He finds it as often in normal deliveries as in complications of any sort. Carr (61) in studying a series of 200 cases, with and without instrumentation, found that there were no changes or variations in the blood--i.e. clotting, fragility, or bleeding time, with prolonged labors, forceps, version, or manipulation.

Hefferman (36) thinks that toxemias of pregnancy and prematurity predispose to hemorrhage. Lossee (67) believes that the hemorrhage occurs because the hemopoetic system is not complete at birth, in some cases, and especially in the premature.

In the past few years, as in many other diseases, the vitamin factor has appeared in relation to this disease.
Moore (75) found that a vitamin B deficiency in the maternal diet of rats, produced a hemorrhagic tendency in the young, especially while nursing. He also reports a case of a mother with a vitamin deficiency having lived mostly on starches during gestation. The child was hemorrhagic and at autopsy bore more or less the beriberi picture. The mother also had profuse hemorrhage after delivery.

Hemorrhagic disease has been produced experimentally in chicks, associated with a low prothrombin concentration in the blood, by feeding them on a diet deficient in vitamin K (high concentration of it in green leaves). The clotting time and prothrombin concentration rapidly returns to normal, after feeding vitamin K concentrates. (84)(21)(4)(22)(81).

Snell (104) finds in studying Clover disease of animals, a hemorrhagic disease resulting from their eating spoiled clover hay, resulting in a prothrombin deficiency and explained on a toxic basis. It seems to be relieved by K concentrates (as found in alfalfa hay) suggesting K as a stimulant in the production of prothrombin. I was unable to find any work on this subject, in relation to hemorrhagic disease of the newborn, but it could very likely be a factor in that disease. Most of the work at present concerning the K factor is in relationship to the bleeding of jaundiced patients with liver disease.
Sanford (94) in studying the effects of ultraviolet radiations and the administration of vitamin D on the newborn finds that it tends to increase the fibrinogen, and decrease the antithrombin slightly, thereby increasing the tendency for the blood to clot. Hemorrhagic disease has been found by Belknap to occur more in the months when the mothers tend to stay indoors, and do not get the effects of the sun rays --all of which may suggest a vitamin D deficiency.

Sanford also finds that withdrawal of fat and protein from the diet of the newborn tends to decrease the fibrinogen, and of course decrease the clotting.

Which--briefly brings us to the conclusion that the etiology of the disease is unknown, but may be influenced to some degree by dietary factors, especially the vitamins --B, D, and K, birth trauma, prematurity and anaesthetics used during delivery.
PATHOLOGY

The pathology of this disease lies in the condition of the blood, or rather in the clotting process of the same. In order to understand this thoroughly, we must consider the mechanism of blood coagulation.

The most acceptable explanation of the clotting process is that advanced by Howell, in 1914 (42). Blood, as it coagulates, changes from a sol to a gel, after it escapes from the vessels (normally). This jelly-like mass continues to contract, expressing a clear fluid—serum. The essential part of the clot is fibrin, an insoluble protein formed from the soluble fibrinogen. The exact process here involved is unknown—i.e. whether it is a hydrolytic cleavage, changing the fibrinogen to an insoluble fibrin and a soluble fibrin globulin, or a denaturation of fibrinogen, similar to the process of heating. However, this transition occurs only in the presence of thrombin (fibrin ferment). Thrombin action has often been looked upon as an enzyme action, yet it cannot be a true enzyme, because a small part of it is used up in the reaction (one part thrombin to 215 times its weight in fibrinogen)(41). Possibly it is a chemical union.

Since intravascular clotting does not occur normally, thrombin cannot exist as such in the circulating blood. Its precursor, or inactivated form, prothrombin is present there, however. Howell contends that its origin is in the
the blood platelets, though others maintain that it is formed in the bone marrow, possibly in the megakaryocytes. Thrombin is a protein substance, possibly a protein compound--protein with cephalin or some other lipid. It loses its power on long standing (not active after two weeks). In old serum it probably exists as metathrombin, an inactive form, the result of having been acted upon by antithrombin.

Bancroft, et.al. (5) find that prothrombin is a protein, identical with albumen, and globulin, electro-negative in the blood which acts as a nucleus of electricity.

Clotting in the circulating blood is prevented by an inhibitory substance which affects the prothrombin, called antiprothrombin (or heparin, because relatively large quantities of it have been extracted from the livers of dogs, suggesting that organ as a source). It is a polysaccharide compound, containing a glucuronic acid group and sulphuric acid and calcium in its molecule. When this substance is neutralized, clotting occurs.

Tissue extracts, and possibly the platelets contain thromboplastic substances, the active factor of which is cephalin (Howell). When, following injury, and possibly in some pathologic conditions, this substance is liberated, it neutralizes the antiprothrombin, and clotting occurs by the action of calcium on the prothrombin, converting it to thrombin, which in turn activates or unites with
fibrinogen, forming fibrin.

Howell also postulates an extra-protective mechanism in the blood—the presence of an antithrombin, which neutralizes small amounts of thrombin which may be formed and initiate coagulation. This substance, he thinks is similar to hirudin, a substance secreted by leeches and other blood sucking animals, a protein albuminose.

Later workers find that antithrombin is a heat stable substance, albumen, or a substance closely associated with it (83), apparently produced in the liver, produced experimentally in animals by peptone injection and similar to the substances produced in the body by antiphalactic shock (115). Quick (83) finds that fibrinogen has a greater affinity for thrombin than antithrombin, and so it does not act until all of the fibrinogen is used up—but when heparin is added, its affinity for thrombin is increased, producing an anticoagulant effect.

Summarizing Howells theory—we have soluble fibrinogen converted to insoluble fibrin by the action of thrombin, which in turn has been activated by calcium from its inactive form, prothrombin. This action in the circulating blood is prevented by antiprothrombin, which at the time of clotting is neutralized by a substance in the tissue extracts. Small amounts of antithrombin in the circulation act as an accessory clot preventing factor.

Another theory commonly accepted of coagulation is
of Morowitz (42). According to him, the prothrombin is changed to thrombin by the combined action of calcium and tissue extract (thrombokinase).

The blood picture in the newborn varies slightly from that of the adult. Haden and Neff (33) found the red blood cell count to be 112% of that of adult life, and the hemoglobin 113%, with high volume and color indices, in the first ten days of life. Hurwitz, et al (44) found an average red count of 5.41 million at birth, which dropped to 4.89 million by the eleventh day, the hemoglobin at the same time changing from 124% to 99.5%. Merritt (71) reports a drop of about one million red cells the first month and a drop of hemoglobin from 23.4 to 16.4 mg.%, with birth variations from 17 to 27.5 mg. percent. Lucas (68) gives eight million maximum, five and one half million minimum and an average of six million red cells, with a drop to four and one half by the fourteenth day. Rosenbloom (91) reports about 6.4 million red cells and 108 to 120 percent hemoglobin in the first two days of life. It seems granted, then that there is a decrease in red cells and hemoglobin during the newborn period.

The white cell count also shows a drop during this period. According to McCollum (67) he finds a drop from twenty to ten thousand in the first ten days. Rosenbloom reports average counts of nineteen to twenty-three thousand during the first two days of life.
Hurwitz finds that sedimentation time at birth is about 100 hours, which is reduced to about 10 hours by 10 days.

The blood platelet count varies from 280,000 to 471,000 during the first few days of life, according to Rosenbloom. Merritt in studying a series of authors, reports findings of from 100,00 to 600,000 with little change from the newborn period to older infants. Leslie and Sanford (65) after studying the platelets of forty normal infants, find that the disintegration of the platelets in the plasma is less in the first 10 days of life, and that this lack increases for the first four days of life, then the platelets become more likely to disintegrate. (this parallels the prolongation of the coagulation time of the first four days of life.)

Rebauld (47) found the platelet count to be increased during pregnancy, possibly as high as 950,000 and that after delivery there was a sudden fall, then a gradual return to a high level again, which count was paralleled in the blood of the infant. Morse (76) found no increase during pregnancy and that the count of the infant at birth varied, tending to rise if low, or drop if high--leveling out by seven days. Jarcho (47) found in a series of 100 cases, that in the majority of them the count was 150,000 to 200,000 and the coagulation and bleeding times within normal, that the infant
with the longest bleeding and coagulation times had a platelet count of 450,000—thereby showing no relationship of platelet counts to hemorrhagic tendency.

Downey (23) considers the platelets as cellular particles, passive cells, probably originating in the megakaryocytes of the bone marrow. In clotting, they seem to function as the nucleus of the clot, that is, masses of fibrinous threads first appear from the agglutinated platelets (indicating them as a source of thrombokinase!). Trauma to the lumen of a vessel causes agglutination of the platelets to the site of injury, thereby obstructing the flow of blood and preventing bleeding. Platelets also have an adhesive action, to foreign bodies, especially to the site of the wound. Clot retraction is hastened by the presence of platelets, and experimentally their injection has shown some hypotensive effects, possibly suggesting the presence of some substance in them which causes vasodilitation—lessening the blood pressure, and reducing hemorrhage.

Since, in hemorrhage disease the platelet count is essentially normal, their role in deficient coagulability can only be on the basis of their qualitative rather than quantitative changes. There is probably a delayed disintegration and qualitative lack (of thrombokinase). (47)(68).

The calcium content of the newborn's blood has been found to be normal or slightly increased, especially in males. Therefore this cannot be a factor in the hemorrhage.
The fibrinogen level of the blood in normal infants is found to be about the same as that in adults, except in cases of severe liver damage. It is normally 0.8 to 0.2 grams per 100 cc. of blood. (115) Crane (81) found an average fibrinogen value of 0.389 with a variation of 0.22 to 0.67 for the first ten days of life. He found a constant, though slight rise from the third to fifth days, with no consistent change thereafter. There appears to be no record of change of fibrinogen content in cases of hemorrhagic disease.

The prothrombin content of human blood has been found to be about one fifth of that of animals—rabbits, cats and dogs. In man, when it is decreased to 20% of normal, there is some hemorrhagic tendency and when it is decreased to 10% of normal there is serious hemorrhage. Quick finds that there is a prothrombin deficiency only in a) Kavitaminoses, b) toxins produced (sweet clover hay, in animals), and c) liver injury.

Brinkhaus, Gelston, Hurwitz, and Kugelmass (12)(28)(43) (57) find a marked decrease in prothrombin in hemorrhagic disease of the newborn. Brinkhaus found prothrombin levels in normal infants to be about one fourth of that of adults, gradually rising to the adult level, by one year. The found levels of 14 to 39% of the adult level for the first month of life. Lucas (68) found prothrombin levels to be diminished for the first four or five days of life, normally. In one case reported, of a child bleeding on the fifth day
from the umbilical stump, the prothrombin level was 5% of normal. Gelston found a low prothrombin level in his case study of hemorrhagic disease, which came up shortly after transfusion. Whipple (116) in 1911 found in a series of experimental studies that although the calcium and fibrin were normal—there was a deficiency in prothrombin.

Rodda (89) studied the coagulation time of the blood in 126 normal newborn infants. His method, that used in many later studies, the shot and watch glass method, tilting the watch glass, until the drop of blood clotted, preventing the shot from rolling. He found an average coagulation time of 7 minutes, with a variation of one and one-half minutes. He also found that there was normally a prolongation of the coagulation time, on the second, third and fourth days of life, the maximum on the fifth day, and returning to normal by the tenth day. The bleeding time as studied by Dukes method (24) showed a similar increase. (Dukes method--using a blotter, taking a drop of blood every 30 seconds). The average bleeding time by this method was three minutes, with a normal variation of from two to five minutes. In those infants in which the bleeding time and coagulation time were both prolonged, there some hemorrhagic tendency, whereas with normal bleeding time and prolonged coagulation time, there was no hemorrhagic tendency. Lee and White (64) in studying the coagulation time (withdrawing blood into a syringe, placing it in a Widal
tube 8 mm. in diameter, tipping the tube every 30 seconds, until coagulation occurs) found the normal coagulation time to be six and one half minutes, varying from five to eight. Shaw and Williams (99) find a slightly shorter coagulation time of infants than of adults. They report an average coagulation time of one and one half minutes, with a variation of only fifteen seconds, in either direction. They used a method similar to that of Rodda. Lucas found coagulation time to be about 15 minutes, Sanford—four and one half, while Merritt (71) in a study of 73 full term, healthy infants on a normal diet, found a bleeding time of one and one half, to two and one half minutes, with coagulation time of two to four minutes.

From these studies we find that in normal infancy, there is a physiologic hyperemia at birth (slight increase in red and white cells and hemoglobin), which levels off by the end of ten days, that calcium is normally slightly increased, fibrinogen about the same as in the adult, and prothrombin low, not reaching the adult level until the end of the first year, but especially low during the first five days. In hemorrhagic disease, it may be extremely low.

The platelet count is neither increased nor decreased, either normally or in hemorrhagic disease, but there seems to be a slightly increased resistance to disintegration, both normally and in hemorrhagic disease, and probably a qualatative defect (of thrombokinase).
The coagulation and bleeding times are normally prolonged the second, third and fourth days of life (time of appearance of hemorrhagic disease, and are greatly prolonged in that disease). Aside from these changes, the blood is normal in hemorrhagic disease, excepting for the anemia produced by that disease.

As to gross pathology, most cases at autopsy show only paleness and anemia of the viscera, with ecchomotic spots over the various organs. Signovelli (102) reported cases quoted from literature (1000 by Hedren) in which were found subcapsular hemorrhage with rupture of the liver, rupture of the spleen, hemorrhage into the pancreas, adrenals, uterus and testicles. These cases were associated with sudden death.

Javert (48) in his series of cases found at autopsy only multiple hemorrhages of the internal organs, no ulcers of the gastro-intestinal tract, and no luetic manifestations. McCollum reported hemorrhages in the mucous membrane of the stomach, intestine, ecchymoses of the skin, possibly signs of bleeding in the pericardium, peritoneum, serosa of the lungs, in fact, any internal organ. In some cases, he also found intracranial hemorrhages—subdural of any part of the brain, extending to the spinal cord. Kaiser (50) reports no constant autopsy findings, only congestion, and ecchymoses of the mucous membranes.
Welsh (112) reports post mortem finding of hemorrhage into brain, liver, ecchomoses into other organs and into the spinal canal. The first appearance of hemorrhage is at the juncture of the cord and skin. Capon (13) thinks there may be ulcers in the first part of the duodenum, though in not more than 50% of cases. Kennedy (51) reports a case of melena neonatorum, in which necropsy found a duodenal ulcer (which he thinks is not associated with hemorrhagic disease) although it may appear simultaneously with that disease.

Warrick (110) in reporting 208 necropsies on newborn infants, finds evidence of hemorrhagic disease in 20%, only 13 of which showed clinical signs of prolonged bleeding or hemorrhage from mucous membranes. Fifty percent of this forty one showed intracranial hemorrhage, while only 7 showed evidence of congenital syphilis, and four were associated with developmental defects. One ulcer of the hard palate was found, and two ulcers of the duodenum, associated with multiple hemorrhage of the viscera. Five showed hemorrhage into the lung, two into the liver, one thymus and one suprarenal. Acute infection was rare in this series, bronchopneumonia being most common.

Summarizing the gross findings, we have usually merely a pale appearance of the viscera with ecchomotic spots over the mucous and serous surfaces, and in some cases, gross hemorrhage of the adrenal, liver or brain, or ecchomoses of brain or cord, and the question of presence of ulceration of the gastro-intestinal tract.
RELATIONSHIP TO CEREBRAL HEMORRHAGE

Green (30) in 1914 first suggested some possible relationship between hemorrhagic disease and cerebral hemorrhage of the newborn. He reported two cases, observed at the Boston Lying-in, of two infants--normal, easy deliveries, following which the child nursed and appeared normal. After several hours, symptoms of intracranial hemorrhage appeared. They were treated with transfusion, but with poor results. Autopsy showed blood clots beneath the dura, with no demonstrable point of bleeding, and there was also oozing from other parts.

Foote (27) remarks that there are many cases where there is little or no trauma during delivery, but an oozing of the meninges follows, which does not produce classical early symptoms of hemorrhage. He reports that Kundrat believes many intracranial hemorrhages are without clinical symptoms. He also mentions a report of Wehe in 1889, in which he finds that 12% of 959 infants at necropsy show intracranial hemorrhage.

Warrick (109) thinks that cerebral hemorrhage may occur before birth, and is often associated with hemorrhage in other organs. She found in a series of 36 necropsies on newborn infants--hemorrhage into the dura over the brain surface in 50% of the cases. Two were stillborn, 4 premature, one forceps delivery, 4 showed signs of asphyxia, and 8 hemorrhage into other organs--pericardium and skin, and
one into the adrenal. There were no signs of congenital syphilis. (110)

The cranial hemorrhage was predominantly over the cerebrum, usually unilateral. She finds that prematures often have cerebral hemorrhage and thinks that they are predisposed to hemorrhage by an underdevelopment of the bloodvessels. She finds manifestation of hemorrhagic disease of the newborn in about 44% of a series of deaths of cerebral hemorrhage. She recommends routine coagulation and bleeding times on the third, fifth, and ninth days and also routine Wassermans, as diagnostic procedures.

Kaiser (50) thinks that cerebral hemorrhage in some cases is but a localized manifestation of a generalized disease, hemorrhagic disease of the newborn.

Ehrenfest (25) believes that a slightly prolonged coagulation time may make a slight hemorrhage of the cerebrum into one of importance.

There seems definitely to be a relationship between cerebral hemorrhage and hemorrhagic disease, which is quite important in view of treatment of cases in which symptoms of cerebral hemorrhage appear following an easy delivery, wherein hemorrhage would not usually be suspected.
RELATIONSHIP TO ULCER OF THE GASTRO-INTESTINAL TRACT

Ulcer of the stomach or duodenum may produce melena and hematemesis. It is rare, very few cases having been reported, rare in the first year of life, and more rare in the newborn. In the newborn it occurs more frequently in the duodenum than in the stomach. There have been a few cases of it occurring with hemorrhagic disease, and some authors think of it as a possible etiologic factor, or at least an associated condition. Many cases may go undiagnosed, may be mild or indicated only by occult blood in the stools.

Bonar (9) found occult blood in the stools of 23 to 44% of a series of 109 cases, during the first four days of life. He attributed this to irritation of the gastro-intestinal tract, unused to food, and also possibly to bacteria entering a previously sterile tract. It could be due to ulcer, hemorrhagic disease, general sepsis, hemorrhoids, fissures, or blood from extramamn sources.

Mills reports a case of a normal infant, which on the fourth day of life, began to bleed from the umbilical stump and died on the sixth day. At autopsy, many ulcerations of the stomach wall, one half centimeter in diameter were found. He suggests passive congestion of the gastric vessels as an etiologic factor.

Kennedy and also Kunstader (51)(59) report cases of ulcer. Kennedy thinks that although it is reported as occurring with hemorrhagic symptoms, it is probably coincident
with that disease, rather than being connected with it in any way, which is the general consensus of opinion.
SYMPTOMATOLOGY AND FINDINGS

Hemorrhagic disease of the newborn is a self-limited disease of the first week of life, often the second or third day and clearing up spontaneously if not fatal within three to four days.

The outstanding feature of the disease is of course, hemorrhage--slight or severe. The hemorrhages are usually multiple. They may be manifested by blood-tinged emesis, melena, skin and mucous membrane ptechae, subcutaneous hemorrhage and cord hemorrhages, most commonly.

Melena or bleeding from the gastro-intestinal tract is often difficult to differentiate from meconium, but a bloody stain is usually noticed on the napkin. The blood is usually well mixed with the stool. Vomited blood is of small amount and dark.

Subcutaneous hemorrhage occurs more frequently over the points of pressure and may be quite extensive. When they occur as the only lesion, the prognosis is quite favorable. Alexander (2) reported one unusual case with swelling over the maxillary bone (sub-periosteal), right eye, protrusion of the eyeball and hemorrhage of the conjunctiva.

Bleeding may also occur, more rarely from: conjunctiva, as a drop of blood squeezed from the palpebral fissure; bladder, as slight blood tinged urine or clots; nose and mouth --mucous membrane of mouth, pharynx, esophagus, stomach or bronchi; female genitalia; or ear. These hemorrhages are usually not severe.
The bleeding may not be obvious--due to intra-cranial hemorrhage. The infant appears drowsy on the second or third day, finds nursing difficult, has a rapid weight loss, dry skin, poor color, possibly twitchings and symptoms of meningitis.\(^{(50)}\)

The symptoms may appear as a cephalohematoma, dyspnea, from hemorrhage into the lungs, pericardial or pleural spaces or collapse from hemorrhage into liver, adrenals, or abdominal cavity.\(^{(6)}\)

The symptoms may occur in the first day of life, or skin ptechae be present at birth, and it may occur as late as the twelfth or fourteenth day. The infant is often premature. In 50\% of the cases, there is bleeding from two or more sites.\(^{(48)}\)

The temperature may be elevated or depressed. Icterus occurs in about 20\% of the cases, but probably not more commonly than in normal infants. After some hemorrhage has occurred, the infant appears pale and listless due to anemia.

The bleeding and clotting times are markedly prolonged, the clot retraction poor and the prothrombin concentration of the blood definitely decreased. Other blood findings are normal, excepting those resulting from hemorrhage.
DIAGNOSIS

Abnormal bleeding occurring in otherwise healthy infants, during the first week of life, especially the third to fifth day, should be looked upon as hemorrhagic disease of the newborn, if other diseases are ruled out. Prolongation of coagulation time, bleeding time and poor retraction of the clot, with low blood prothrombin and spontaneous recovery or prompt cessation of bleeding following transfusion or intramuscular blood confirm the diagnosis. Internal hemorrhage may be a little difficult to diagnose, immediately, but should be established eventually by symptoms of anemia, if nothing else.
DIFFERENTIAL DIAGNOSIS

True hemorrhagic disease of the newborn must be differentiated from other hemorrhagic diseases of infancy. It is most often confused with syphilis, sepsis, and hemorrhage of traumatic or spurious origin, although there are a number of other diseases which may be confusing.

Traumatic hemorrhage may be manifested by hematoma of the sternocleidomastoid muscle, caput succidenum, cephalo-hematoma, or possibly vaginal hemorrhage, or hemorrhage from other sites. It is usually slight in amount, the bleeding does not continue, there is only one site of hemorrhage and it is gradually absorbed. Visceral hemorrhage from birth injury of the brain, and more rarely lungs and abdominal viscera due to difficult labors, may simulate hemorrhagic disease, or be associated with it, but usually there are no changes in the clotting power of the blood.

Spurious bleeding melena or hematemesis, may be due to fissures in the mothers nipples, blood swallowed from the birth canal, or trauma from the use of a rectal thermometer. Blood on the napkin may be due to exorations of the buttocks. (41) Of course it is very slight in amount, and there are no other symptoms.

Genital bleeding of the female occurs in 2 to \(2\frac{1}{2}\%\) of the cases, probably due to the effects of the mothers hormones. It occurs about the 6th to 7th day, lasts two to
three days, is rarely severe, and rarely goes on as precocious menstruation. (11)(39)

Bleeding from the umbilicus may be due to careless tying of the cord or to slipping of the ligature, but is usually controlled by retying the cord.

Hemophilia does not occur in the newborn period, usually does not appear until the end of the first year of life, and is predominantly in males. There is a history of 'bleeders' in the family.

Congenital syphilis may be manifested by a hemorrhagic tendency. The child is usually in a poor state of nutrition, the liver and spleen enlarged, there may also be pemphigus, bone changes, snuffles or anemia. The bleeding may not occur until about the 10th day. The bleeding rather than the coagulation time is prolonged. Positive seriology of the mother would substantiate the diagnosis. (11)

Infections of the newborn often show hemorrhagic features. Sepsis neonatorum may appear the second or third day, with fever, jaundice, (often severe), splenomegaly, hot and dry skin. There is parenchymatous degeneration of the viscera and may be multiple abscesses. It is rapidly progressive, and the prognosis is poor.

Buhl's disease, acute fatty degeneration of the viscera, is thought to be merely a severe type of sepsis. The infant is often asphyxiated at birth and may die immediately
or survive for 4 to 5 days. There is an associated severe hemorrhage from the alimentary tract, ecchymoses, generalized icterus and cyanosis. Hematuria is common. The temperature may be slightly elevated or depressed, the child prostrated or restless and have vomiting, diarrhea and frequent urination. Again, this disease can be differentiated from hemorrhagic disease by its severity and toxicity.

Icterus gravis may be a severe form of physiologic icterus, and may have hemorrhagic manifestations. It is, however, more often thought of as being due to sepsis, syphilis, toxicosis of pregnancy, globular anemia, or alterations of the reticulo-endothelial system of parent or child.(Naegli) The syndrome is of severe icterus, occasionally congenital, swelling of the spleen, liver, bile pigments in the urine, sometimes convulsions and hemorrhagic diathesis. Hemorrhagic disease rarely or never shows so severe an icterus, and has no toxic symptoms.

In recent years, cases have been reported of a disease of infants which—shortly after birth had spells of cyanosis, petechial hemorrhages, enlargement of liver, spleen, hypertrophy of the heart. Anemia or edema with or without jaundice might be present at birth or occur in 12 to 24 hours. There may be a history of neonatal deaths of previous siblings, possibly a golden yellow color to the vernix caseosa, an unusually large placenta. The blood shows a high
percent of nucleated red blood cells (5% may be normal) and there may be an increase of erythrocytes in the next few days. This disease is known as erythroblastosis fetalis. It would be readily differentiated from hemorrhagic disease by the blood picture.\textsuperscript{(119)}

There are several other more rare blood diseases which may present hemorrhagic manifestations, but little is known about them at present.

**PROGNOSIS**

Although Townsend reported a mortality of 79% in this disease in 1894, at present, if proper treatment is instituted, it is practically negligible.
The early methods of treatment were very ineffective. It was not until 1908, when Lambert (60) first successfully used transfusion for treatment of this disease, that the present conception of therapy for controlling the hemorrhage, i.e. that of using whole blood, came into general use. Bowditch (10) in 1850 suggested using transfusion, but did not have the self-conviction to do so.

As considered in the history of this disease, we found that most of the therapeutic attempts up to about 1908 had been directed to local treatment—that is styptics, cauterization and compression for umbilical hemorrhage, and internal styptics for hemorrhage of the gastrointestinal tract. This type of treatment met with little success and probably the reported cures by it were because the disease had run its course and the patient spontaneously recovered.

Of course, local attempts at stasis should be made, especially with umbilical hemorrhage. Prophylactic careful ligation of the cord is most important, although retying the cord, adrenalin, tannic acid, or viper venum may be helpful. (15) Thromboplastic substances, such as cephalin coagulin, coagulose are often valuable. (61)

Calcium (used internally) although intricately concerned in the mechanism of blood clotting, has no value here therapeutically because the blood calcium of these infants is not reduced, in fact, it is often above the normal ad-
ult level.

Gelatin, intravenously, subcutaneously, or orally has been used (97) but is not very effective, and may have some dangerous side effects.

Serum therapy seemed to be the next thing to be considered, to supply the deficient clotting factors—mainly prothrombin.

Animal sera was first used to reduce bleeding by Welch (112) in 1910. He found most sera effective, but that beef sera was too toxic. He had successful results with rabbit sera, which was less toxic and less likely to contain disease than sera of other animals. (especially than horse sera which occasionally contained tetanus) Rabbit sera was easily procured, also. Leary (63) prescribed subcutaneous sera with intravenous sera for cases of quite severe bleeding. However since serum of different species often carries the danger of serum sickness, it is not often used.

Moss (77) suggested the use of defibrinated blood, not only to supply the clotting factors but the cells being necessary to combat the anemia. This is really reasonable, considering that the loss of one ounce of blood in an eight pound infant is equal to the loss of one pint in an adult. (13)

Whole blood is now used, more or less as a specific for the disease. The result of the treatment being nearly instantaneous cessation of the bleeding.
Hefferman (36) reports a series of 800 cases, in which 10 cc. of mother's whole blood was injected subcutaneously into the infra-scapular region of newborns, routinely, as a prophylactic measure. The blood was absorbed in twenty-four to thirty-six hours. In this series, he had a very low incidence of intracranial hemorrhage and only one very mild case of hemorrhagic disease, which recovered spontaneously.

Blood is usually given subcutaneously or intramuscularly. If given intramuscularly--20 cc., 10 cc. into either buttock is the usual procedure, and repeated in two hours if the bleeding does not stop. Intravenous blood must be typed and grouped, but intramuscular need not. Usually sixty to one hundred cc. are given intravenously. (15)

The blood may be taken from any donor, providing it is compatible blood, and disease free, but it is usually more convenient to use that of either the mother or father. Either of the parents is more likely to have the same blood group as the child, as shown by Robertson (87) in which 56% show the father, 57%, the mother and 25% of both parents to be of the same blood group as the child.

Sanford (95) reporting studies of blood injections of 20 normal infants, ten with 10 cc. of mother's blood and ten with the same amount of father's blood, that the coagulation was slightly aggravated in all cases and probably more in
in those injected with mothers blood than fathers, indicating the father as the better donor.

I believe that fathers blood usually would be indicated anyway, because the mothers is too much like the infants, that is, it may contain the same etiologic-hemorrhagic factors, and she may have already suffered the loss of a relatively large amount of blood during childbirth.

Although the blood group is established in few infants at birth (one fifteenth, according to Happ(35)), 32 to 50% of infants in the first ten days of life do contain cell receptor (67), and cause agglutination of the donors blood, so blood matching is essential in all cases of transfusion.

Transfusion may be given either by the direct or indirect method. Since indirect transfusion of citrated blood requires fewer assistants, less elaborate technique and apparatus, it is most often used. About 15 cc. of blood per pound of body weight of the infant (or 10% of its body weight)(101) is usually considered sufficient.

The point of injection in transfusion of so young an infant often presents a problem. Sidbury (101) found that the umbilial cord vessels remained open for at least the first four days of life and are a good point for the injection of blood.
Shoemaker (100) found the superior sagittal sinus an easily accessible point for injection. Of course, there is some danger attached to going into the sinus, the danger of injecting into the brain tissue, and the psychic effect on the mother may not be so good.

Fockner (26) injects through the superficial scalp veins, which may be quite prominent at this age. Injection through the ligated end of the internal jugular is possible, but not advisable. The internal saphenous, over the internal malleolus on the antecubital veins are probably the most commonly used, though they often require cutting down on the vein.

In cases associated with cerebral hemorrhage, additional treatment may be indicated, to reduce the cerebral pressure. Often spinal puncture is necessary.

Additional treatment of the child should include quiet, move the child as little as possible, heat, or at least warmth, sunshine, --infact merely good nursing care.

Prophylactic prenatal diets high in vitamins B, K, and D, may be very important.
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