The article describes the main historical periods of the study of hemorrhagic disease of newborns. Clinical observations, describing bleeding of newborns, which occurs without visible damage, known since the seventeenth century and are found in the works of Francois Mauriceau and Georg Wolfgang Wedel. The role of the liver injury in the development of bleeding of infants noticed English physicians John Huxham (1672-1768) and John Cheyne (1777-1836). In 1871 Ludwig Grandidier conducted differential diagnosis between umbilical bleeding of neonates and the hemophilia clinic. Later I.P. Pavlov showed, that the clotting time of dog’s blood significantly prolongs when you turn off the liver from the blood circulation. In that way, partly began to understand the etiology of hemorrhagic syndrome, but the pathogenesis of this suffering, in diseases of the liver remained unknown. Charles Wendell Townsend in 1894, describing 50 cases of coagulopathy of newborns, at the first time paid attention to the connection between breastfeeding and development of bleeding and offered to call this nosological form as “hemorrhagic disease of newborns”. In the late 20s of the last century Henrik Dam have identified the unknown substances from green lucerne leaves and described them as the fat-soluble vitamin K (coagulation). In 1943 H. Dam and E. Doisy received the Nobel prize for the discovery and establishment of the chemical structure of vitamin K. In 1943, a group of Soviet biochemists have synthesized a water-soluble analogue of vitamin K (K₃, vicasolum), quickly introduced into clinical practice and showed their high efficiency in patients with hypovitaminosis K. In 1945 Yu.F. Dombrovskaya suggested that haemorrhagic disease of newborns caused by deficit of vitamin K. Further researching of the development of haemorrhagic disease of newborns is associated with the study of the biochemistry of the pathogenesis of the disease, identify its various forms and development of treatment techniques and prevention, depending on the identified features.

Keywords: hemorrhagic disease; vitamin K deficit; newborns; intracranial hemorrhage; liver damages.

ИСТОРИЯ ИЗУЧЕНИЯ ГЕМОРРАГИЧЕСКОЙ БОЛЕЗНИ НОВОРОЖДЕННЫХ

© Д.О. Иванов

ОГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России

В статье отражены основные исторические периоды изучения геморрагической болезни новорожденных. Клинические наблюдения, описывающие кровотечения у новорожденных, возникающие без видимого повреждения, известны с XVII века и встречаются в работах Франсуа Морисо и Георг Вольфганга Веделя. Роль поражения печени при развития кровотечения у младенцев отмечали английские врачи Джон Хуксхам (1672–1768) и Джон Чейн (1777–1836). В 1871 году Людвиг Гранди дерье провел дифференциальную диагностику между пупочными кровотечениями у новорожденных и клиникой гемофилии. Позднее И.П. Павлов показал, что у собак значительно удлиняется время свертывания крови при выключении печени из кровообращения. Таким образом, отчасти стала понятна этиология геморрагического синдрома, но патогенез этого страдания при заболеваниях печени оставался неизвестен. Чарльз Таунсенд в 1894 году, описывая 50 случаев коагулопатии у новорожденных, впервые обратил внимание на взаимосвязь между объемом грудного вскармливания и развитием кровоточивости, а также предложил называть эту нозологическую форму «геморрагическая болезнь новорожденных». В конце 20-х годов прошлого века Хенрик Дам выделил неизвестные вещества из зеленых листьев люцерны и описал их как жирорастворимый витамин K (от слова коагуляция). В 1943 году Х. Дам и Э. Доиси получили Нобелевскую премию за открытие и установление химической структуры витамина K. В 1943 году группа советских биохимиков синтезировала водорастворимый аналог витамина K (K₃, викасол), быстро внедренный в клиническую практику и показавший свою высокую эффективность у больных с гиповитаминозом K. В 1945 году Ю.Ф. Домбровская предположила, что геморрагическая болезнь новорожденных обусловлена дефицитом витамина K. Дальнейшее изучение...
Clinical observations of bleeding without visible damage in newborns have been documented since the 17th century [15]. In 1694, François Mauriceau described a child who vomited blood during his first day of life and continued to do so, albeit less profusely, on the second and third days [16].

In 1683, A.M. Abégauz (1970) drew attention to the monograph entitled “De haemorrhia universalis ex ictero nigro lethali” published by the famous German physician and alchemist Georg Wolfgang Wedel (1645-1721) (Figure 1), a versatile scientist engaged very productively in chemistry, who invented new medicines and published a German translation of the Greek Bible. In the mentioned monograph, Wedel first described patients with “black jaundice” dying from hemorrhage. The next known monograph on the frequent co-existence of hemorrhage and jaundice was published in 1773, after the death of its author, the famous English physician John Huxham (1672-1768) (Figure 2).

Probably, the first account of the association between umbilical hemorrhage and obstruction of the bile ducts was given by John Cheyne (Figure 3) [16] in his 1801 monograph titled “Essays of Diseases of Children.”

Today, the physician is remembered not for this discovery but for describing a respiratory disturbance in patients with stroke; this respiratory disturbance was named Cheyne after him. Later, the Edinburgh professor William Stokes described a similar symptom occurring in patients with heart failure. The breathing pattern (now known to be normal in young children) is known as Cheyne-Stokes respiration in honor of both discoverers. In addition, in the English-language literature, John Cheyne is considered one of the founders of scientific neurology [17-20]. In particular, he proposed a new pathogenesis and classification for acute hydrocephaly.

In 1683, A.M. Abégauz (1970) drew attention to the monograph entitled “De haemorrhia universalis ex ictero nigro lethali” published by the famous German physician and alchemist Georg Wolfgang Wedel (1645-1721) (Figure 1), a versatile scientist engaged very productively in chemistry, who invented new medicines and published a German translation of the Greek Bible. In the mentioned monograph, Wedel first described patients with “black jaundice” dying from hemorrhage. The next known monograph on the frequent co-existence of hemorrhage and jaundice was published in 1773, after the death of its author, the famous English physician John Huxham (1672-1768) (Figure 2).

Probably, the first account of the association between umbilical hemorrhage and obstruction of the bile ducts was given by John Cheyne (Figure 3) [16] in his 1801 monograph titled “Essays of Diseases of Children.”

Today, the physician is remembered not for this discovery but for describing a respiratory disturbance in patients with stroke; this respiratory disturbance was named Cheyne after him. Later, the Edinburgh professor William Stokes described a similar symptom occurring in patients with heart failure. The breathing pattern (now known to be normal in young children) is known as Cheyne-Stokes respiration in honor of both discoverers. In addition, in the English-language literature, John Cheyne is considered one of the founders of scientific neurology [17-20]. In particular, he proposed a new pathogenesis and classification for acute hydrocephaly.
In 1871, the famous German physician Ludwig Grandidier (1810-1878), who had studied hemophilia for 40 years, published a monograph on this disease. In it, he described diagnostic differences in clinical pictures between umbilical bleeding and hemophilia in newborns [21].

Next, in the 19th century, many researchers became aware that hemorrhagic syndromes frequently develop often in the context of liver diseases. In 1885, I.P. Pavlov (Figure 4) established, with a number of experimental studies, that in dogs, the blood clotting time is significantly prolonged when the liver is excluded from the circulation. Thus, some unclear pathogenesis in the liver was suspected of causing hemorrhagic syndromes.

In 1894, Charles Wendell Townsend (Figure 5) was the first one to describe a coagulopathy with symptoms of severe vitamin K deficiency [15]. He based his reported on the study of 50 children who shared clinical manifestations [22]. He also found differences between the clinical presentations of the hemorrhagic syndrome and hemophilia in infants. According to his texts, the hemorrhagic syndrome develops much earlier (2-3 days after birth) than hemophilia, familiar “predisposition” is absent, and the disease is limited to the neonatal period. However, the physician went further, citing the medical history of a 9-day-old infant with a presumed diagnosis of hemophilia, intracranial hemorrhage, and a hopeless prognosis and noted that “the child’s hemorrhage developed as a result of breast milk deficiency in the mother, and feeding him by a foster nurse in sufficient amount saved his life.” Thus, it was C. Townsend who first noted the association between the volume of breast-feeding and the possible development of hemorrhage. He also proposed to call this condition as hemorrhagic disease of newborns (HDN). It is worth pointing to the reader that C. Townsend is best known to the world as an ornithologist and writer. However, in his homeland, in Boston, he was an experienced obstetrician and a pediatrician.

However, even after all these useful clinical observations, HDN pathogenesis eluded physicians. A breakthrough happened later in a somewhat unexpected manner. In the late 1920s, a Danish biochemist and lecturer at the University of Copenhagen, Carl Peter Henrik Dam (1895-1976) (Figure 6) was studying the effects of a cholesterol-free diet on chicken when he noticed that after several weeks, some birds had developed multiple internal hemorrhages throughout the body (see Figure 7) and had prolonged clotting times. However, feeding the chicken with purified cholesterol did not alleviate the symptoms, but they disappeared once the chickens were fed with cereal grains [23, 24]. Later, in 1939, H. Dam, together with P. Carrer (Swiss biochemist, Nobel Prize winner in chemistry in 1937) isolated an unknown substance from the green leaves of the alfalfa plant and described it as a fat-soluble vitamin. The new vitamin (now known to be a phylloquinone) increased the rate of blood clotting. H. Dam named it vitamin K (from the German word for coagulation).

Furthermore, H. Dam revealed that intestinal bacteria of animals and humans form vitamin K, which is necessary for the synthesis of prothrombin (coagulation factor II), and suggested using the vitamin in the clinical practice (for arresting hemorrhage, including during surgical interventions and liver disease). H. Dam is also known for other studies on the metabolism of vitamins. For example, during the 1940s and 50s he found that muscular dystrophy occurs due to vitamin E deficiency.

In 1935, A. Quick discovered vitamin K deficiency in patients suffering from obstructive jaundice [25, 26].
Further, in 1939, at the University of St. Louis (USA), Edward Adelbert Doisy extracted a vitamin with anti-hemorrhagic properties from rotting fishmeal, with a chemical structure different from that of the vitamin obtained from alfalfa leaves. This vitamin was called K2 (menaquinone) [27]. It was later discovered that the structural and functional differences between the two substances are extremely insignificant. Structurally, phyloquinone differs from menaquinone by the presence of only one double bond in the isoprene fragment closest to the ring (Figure 8).

In 1943, H. Dam and E. Doisy were awarded the Nobel Prize for the discovery and establishment of the chemical structure of vitamin K.

| Chick No. | Age in days | Weight g. | Haemorrhagic clotting time of blood (sib) | Haemorrhagic clotting time of blood of guinea pig | K 100 |
|-----------|-------------|-----------|------------------------------------------|-----------------------------------------------|-------|
| 807       | 23          | 92        | 48                                       | >30                                           | +     |
| 808       | 23          | 81        | 20                                       | >30                                           | +     |
| 809       | 23          | 81        | 30                                       | >30                                           | +     |
| 810       | 23          | 71        | 12                                       | >30                                           | +     |

Fig. 6. Carl Peter Henrik Dam (1895–1976)
Рис. 6. Хенрик Дам (Carl Peter Henrik Dam) (1895–1976)

In that same year, a group of Soviet biochemists led by the academician A.V. Palladin synthesized a water-soluble analog of vitamin K (K, Vicasol). The compound was quickly introduced into clinical practice as it proved its efficacy in treating vitamin K deficiency, for example, in patients with underlying liver diseases. Although the current criticisms against Vicasol are warranted given its pronounced side effects, we must not forget that the historic use of this preparation saved thousands of lives. In addition, merit should be granted for this achievement to the group of Soviet biochemists.

Fig. 7. From the work of H. Dam "The antihaemorrhagic vitamin of the chick." Chickens with a hemorrhagic syndrome were studied, and their blood coagulation time was measured
Рис. 7. Из работы Х. Дама «The antihaemorrhagic vitamin of the chick». Оценили цыплят, имеющие геморрагический синдром, у каждого цыпленка измерено время свертывания крови и т. д.

Fig. 8. Forms of vitamin K (Shearer M.J., Newman P., 2014) [50]
Рис. 8. Формы витамина K (Shearer M.J., Newman P., 2014) [50]
headed by Alexander Vladimirovich Palladin, a gradu-
ate of St. Petersburg University and President of the
Academy of Sciences of the Ukrainian Soviet Socialist
Republic (Figure 9).

Any mention of vitamins in a historical context
would not be complete without mentioning Nikolai
Ivanovich Lunin (Figure 10). He was a young student
at the Dorpat University who defended his doctorate
in medicine with a thesis titled “On the Importance of
Inorganic Salts for Animal Nutrition.” Lunin had been
experimenting with diets on mice and concluded that
“if, as it is derived from the above experiments, it is im-
possible to provide life with proteins, fats, sugar, salts
and water, it follows that milk, in addition to casein,
fat, milk sugar and salts, contains other substances that
are indispensable for nutrition. It is of great interest
to investigate these substances and to study their sig-
nificance for nutrition” [28]. Lupin was conferred the
desired title for his work, but it took 30 years before
his conclusions could be explained. In 1929 F.G. Hop-
kins and C. Eijkman received the Nobel Prize for dis-
covering vitamins. During his lifetime, Nikolai Ivano-
vich was the chairman of the Society of Pediatricians
(from 1914 to 1920); he was buried in St. Petersburg
at the Volkov Lutheran Cemetery, near his teacher
K.A. Rauchfuss (Figure 11).

Returning to the history of HDN, according to the
account of M.S. Machabeli [29], I.M. Rtskhiladze had
identified vitamin K deficiency in newborns during the
first hours of their life in as early as 1945. In the same
year, Julia Fominichna Dombrovskaya (Figure 12), an
academician of the Academy of Medical Sciences of the
USSR suggested that HDN is due to vitamin K defi-
ciency.

The reader is directed to the memories of Dombrovskaya’s pupil D.V. Kolesov, which contain interesting
details about her life [30], but a few circumstances
are worth mentioning. Julia Fominichna Dombrovskaya
graduated from the Women’s Medical Institute
in St. Petersburg in 1913. She was the chairman of the
presidiums of the All-Union and Moscow societies of
pediatricians. In 1970, she, together with A.F. Tur and
G.N. Speransky, was awarded the Lenin Prize “for a se-
ries of works on the physiology and pathology of young
children, contributing to a rapid decline in morbidity
and mortality among them.”

The main works of Yu.F. Dombrovskaya are devoted
to the role of vitamins in normal and sick children with
pathologies, such as infectious and allergic diseases and
pneumonia. The manual “Propedeutics of Childhood
Illnesses” written in collaboration with V.I. Molchanov
and D.D. Lebedev is very well-known. It was repub-
lished five times.

In addition, in 1970 in Leningrad, the famous pe-
diatric hematologist A.M. Abezgauz released a mono-
graph titled “Hemorrhagic diseases in children” while
working at the Leningrad Pediatric Medical Institute.
In this text, the author described in detail the etiology,
pathogenesis, and clinical picture of HDN. Although he
did not provide a classification for the disease (which is
important for disease prevention), he provided detailed
clinical observations and drew attention to the toxic ef-
facts of increased doses of synthetic preparations of vi-
tamin K (Vicasol).
Further, in as early as 1961, experts of the American Academy of Pediatrics recommended the administration of vitamin K1 (phylloquinone) to all newborns immediately after birth. Since then, the prevention of HDN has been discussed many times, on the basis of numerous studies.

Until the 1980s, two forms of HDN, early and classical, were distinguished. It should be noted that in as early as 1966, a late form of hemorrhagic disease was described in Thailand [31], but this fact did not get importance in the West. However, in 1983 in Great Britain, an article appeared with the symbolic title “Hemorrhagic disease of newborns returns” [32]. The authors of the article suggested that an increase in the frequency of hemorrhagic syndrome in children in the postnatal period was associated with the rejection of artificial food and the large number of infants being exclusively breastfed.

This leads to a decrease in the vitamin K supply with all the expected clinical consequences. Therefore, the late form of HDN was described once more.

In 1985 P.A. Lane and W.E. Hathaway [33] proposed a new classification (Table 1) approved by the pediatric subcommission of the International Society for Thrombosis and Hemostasis. Currently, the picture is more complex with the recognition of idiopathic and secondary forms of the disease (children with atresia of bile ducts, deficiency of α1-antitrypsin, hepatitis, etc. can develop HDN). However, the classification, although requiring modifications, has remained the same.

Present studies on the development of HDN are focusing on molecular pathogenesis, identification of its various forms, and methods for its treatment and prevention.

REFERENCES
1. Sutor AH, von Kries R, Cornelissen EA, et al. Vitamin K deficiency bleeding (VKDB) in infancy. ISTH pediatric/perinatal subcommittee. International society on thrombosis and haemostasis. Thromb Haemost. 1999;81:456-61.
2. Woods CW, Woods AG, Cederholm CK. Vitamin K deficiency bleeding: a case study. Adv Neonatal Care. 2013;13(6):402-407. doi: 10.1097/ANC.0000000000000026.
3. Seguna R, Maw KZ, Lyall HD, Bowles KM. Haemorrhagic disease of the newborn” 89 years later than expected: vitamin K deficiency bleeding. Lancet. 2014;384(9942):556. doi: 10.1016/S0140-6736(14)60999-5.
4. Шабалов Н.П. Неонатология. Учебное пособие для студентов: в 2 т. — 7-е изд., испр. и доп. — М.: МЕДпресс-информ, 2015. — Т. 1. [Shabalov NP. Neonatology. Study guide for students in 2 vol. 7th ed. Moscow: Medpress-inform; 2015. Vol. 1. (In Russ.]]
5. Shearer MJ. Vitamin K deficiency bleeding (VKDB) in early infancy. Blood Rev. 2009;23(2):49-59. doi: 10.1016/j.bler.2008.06.001.
6. Salomonsen L. On the prevention of hemorrhagic disease of the new-born by the administration of cow’s milk during the first two days of life. Acta Paediatr. 1940;28:1-7. doi: 10.1111/j.1651-2227.1940.tb15999.x.
Classification of the hemorrhagic disease of newborns [32]

| Form | Time | Manifestation of the hemorrhagic syndrome | Etiological factors |
|------|------|------------------------------------------|--------------------|
| Early | First 24 h of life | Skin, intracranial, pulmonary, and gastrointestinal hemorrhages | Medications used by the mother (such as warfarin and anticonvulsants) |
| Classical | Days 1–7 | Gastrointestinal and umbilical hemorrhages, epistaxis, and ecchymosis | More often idiopathic, as a rule, children are breastfed |
| Late | Eight days after birth (the maximum time for manifestation of clinical symptoms is 3–8 weeks after birth) | Intracranial, dermal, and gastrointestinal hemorrhages | Idiopathic and secondary. Risk factors include breastfeeding, often cholestasis. Secondary cases caused by malabsorption due to certain diseases (such as biliary atresia, deficiency of alpha-1-antitrypsin, and cystic fibrosis) or chronic diarrhea. Long-term antibiotic therapy is considered as an additional risk factor |

7. Centers for Disease Control and Prevention (CDC). Notes from the field: late vitamin K deficiency bleeding in infants whose parents declined vitamin K prophylaxis. Tennessee, 2013. MMWR Morb Mortal Wkly Rep. 2013;62(45):901-902.
8. American Academy of Pediatrics, Committee on Nutrition. Vitamin K compounds and the water-soluble analogues: use in therapy and prophylaxis in pediatrics. Pediatrics. 1961;28:501-507.
9. McNinch AW, Tripp JH. Haemorrhagic disease of the newborn in the British Isles: two year prospective study. BMJ. 1991;303:1105-1109. doi: 10.1136/bmj.303.6810.1105.
10. Takahashi D, Shirahata A, Itoh S, et al. Vitamin K prophylaxis and late vitamin K deficiency bleeding in infants: fifth nationwide survey in Japan. Pediatr Int. 2011;53(6):897-901. doi: 10.1111/j.1442-200X.2011.03392.x.
11. Darlow BA, Phillips AA, Dickson NP. New Zealand surveillance of neonatal vitamin K deficiency bleeding (VKDB): 1998-2008. J Paediatr Child Health. 2011;47:460-464. doi: 10.1111/j.1440-1754.2010.01995.x.
12. McNinch A. Vitamin K deficiency bleeding: early history and recent trends in the United Kingdom. Early Hum Dev. 2010;86(Suppl.1):63-65. doi: 10.1016/j.earhumdev.2010.01.017.
13. McNinch A, Busfield A, Tripp J. Vitamin K deficiency bleeding in Great Britain and Ireland: British Paediatric Surveillance Unit Surveys, 1993-94 and 2001-02. Arch Dis Child. 2007;92(9):759-66. doi: 10.1136/adc.2006.104752.
14. Stokowski LA. Reemergence of vitamin K deficiency bleeding. Adv Neonatal Care. 2014;14(2):75.
15. Obladen M. Innocent blood: a history of hemorrhagic disease of the new-born. Neonatology. 2015;107(3):206-212. doi: 10.1159/000369523.
16.ABELGAUZ A.M. Геморрагические заболевания у детей. — М.: Медицина, 1970. — 324 с. [ABELGAUZ AM. Hemorrhagic disease in children. Moscow: Medicine; 1970. 324 p. (In Russ.)]
17. TOLLIS D. Who were... Cheyne and Stokes? Nurs Times. 1995;91(14):40.
18. Lyons JB. John Cheyne's classic monographs. J Hist Neurosci. 1995;4(1):27-35. doi: 10.1080/09647049509525624.
19. Sternbach GL. John Cheyne and William Stokes: periodic respiration. J Emerg Med. 1985;3(3):233-236. doi: 10.1016/0736-4679(85)90078-2.
20. Bendiner E. The Dublin school: from poverty, a rich legacy. Hosp Pract (Off Ed). 1984;19(6):221-247. doi: 10.1080/21548331.1984.11702853.
21. Grandidier L. Die Haemophilie oder die Bluterkrankheit. Wigand; 1855. 158 p.
22. TOWNSEND CW. The haemorrhagic disease of the newborn. Arch Pediatr. 1894;11:559-565.
23. Dam H. The antihaemorrhagic vitamin of the chick. Biochem J. 1935;29(6):1273-85. doi: 10.1042/bj0291273.
24. Dam H, Lewis L. The chemical concentration of vitamin K. Biochem J. 1937;31(1):17-21.
25. Quick AJ. The thromboplastic reagent for the determination of prothrombin. Science. 1940;92(2379):113-4. doi: 10.1126/science.92.2379.113-a.
26. Quick AJ. Effect of synthetic vitamin K and of quinine sulfate on the pro-thrombin level. J Lab Clin Med. 1946;31:79-84.
27. Thayer SA, Maccorquodale DW, Binkley SB, Doisy EA. The isolation of a crystalline compound with vitamin k activity. Science. 1938;88(2280):243. doi: 10.1126/science.88.2280.243.

28. Lunin N. Über die Bedeutung der anorganischen Salze für die Ernährung des Thieres. Zeitschrift für Physiologische Chemie. 1881:5:31-39.

29. Machabeli MS. Koagulopaticheskie sindromy. – M.: Meditsina, 1970. – 303 s. [Machabeli MS. Coagulopathies syndromes. Moscow: Medicine; 1970. 303 p. (In Russ.)]

30. Kolesov DV. Устойчивая доминанта моего внутреннего мира (к 110-летию со дня рождения Ю.Ф. Домбровской). [Kolesov DV. Stable dominant of my inner world (to the 110 anniversary since the birth of the U.F. Dombrowskaya). (In Russ.)]. Доступно по: http://rl-online.ru/info/authors/35.html.

31. Chuansumrit A, Isarangkura P, Hathirat P. Vitamin K Study Group. Vitamin K deficiency bleeding in Thailand: a 32-year history. Southeast Asian J Trop Med Public Health. 1998;29:649-654.

32. McNinch AW, Orme RLE, Tripp JH. Haemorrhagic disease of the newborn returns. Lancet. 1983;1:1089-90. doi: 10.1016/S0140-6736(83)91921-9.

33. Lane PA, Hathaway WE. Vitamin K in infancy. J Pediatr. 1985;106:351-9. doi: 10.1016/S0022-3476(85)80656-9.