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HISTORY OF THE STUDY OF HEMORRHAGIC DISEASE OF NEWBORNS

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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 (K_3, 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

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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 Георга Вольфганга Веделя. Роль поражения печени при развитии кровотечения у младенцев отмечали английские врачи Джон Хуксхам (1672–1768) и Джон Чейн (1777–1836). В 1871 году Людвиг Грандидье 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 К (от слова коагуляция). В 1943 году Х. Дам и Э. Дойзи получили Нобелевскую премию за открытие и установление химической структуры витамина К. В 1943 году группа советских биохимиков синтезировала водорастворимый аналог витамина К (K_3, викасол), быстро внедренный в клиническую практику и показавший свою высокую эффективность у больных с гиповитаминозом К. В 1945 году Ю.Ф. Домбровская предположила, что геморрагическая болезнь новорожденных обусловлена дефицитом витамина К. Дальнейшее изуче-

ние развития геморрагической болезни новорожденных связано с изучением биохимии патогенеза заболевания, выявлением его различных форм и разработкой методик лечения и профилактики в зависимости от выявленных особенностей.

Ключевые слова: геморрагическая болезнь; дефицит витамина К; новорожденные; внутричерепные кровоизлияния; поражения печени.

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].

Fig. 1. Georg Wolfgang Wedel (11.12.1645–09.06.1721)
Рис. 1. Георг Вольфганг Ведель (Wedel G.W.) (12.11.1645–06.09.1721)

Fig. 2. Front page of the monograph by John Huxham
Рис. 2. Титульный лист монографии Джона Хуксхама (John Huxham)

In 1683, A.M. Abezgauz (1970) drew attention to the monograph entitled "De haemorragia universali 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.

Fig. 3. John Cheyne (1777–1836)
Рис. 3. Джон Чейн (John Cheyne) (1777–1836)

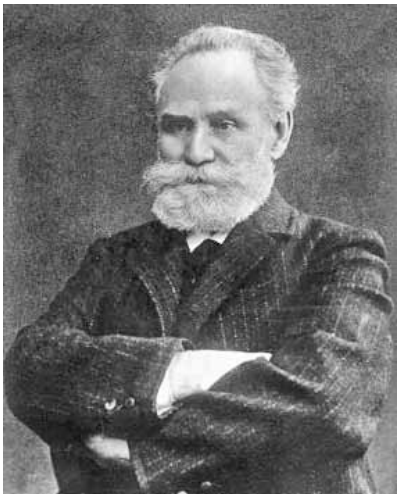

Fig. 4. Ivan Petrovich Pavlov (1849–1936)
Рис. 4. Иван Петрович Павлов (1849–1936)

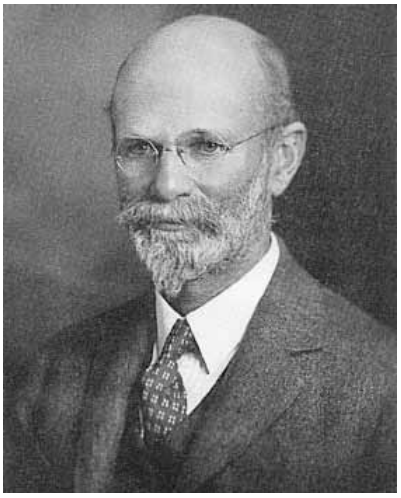

Fig. 5. Charles Wendell Townsend (1859–1934)
Рис. 5. Чарльз Таунсенд (Charles Wendell Townsend) (1859–1934)

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 pathognesis 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 breastfeeding 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 philloquinone) 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 antihemorrhagic 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, phylloquinone 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.

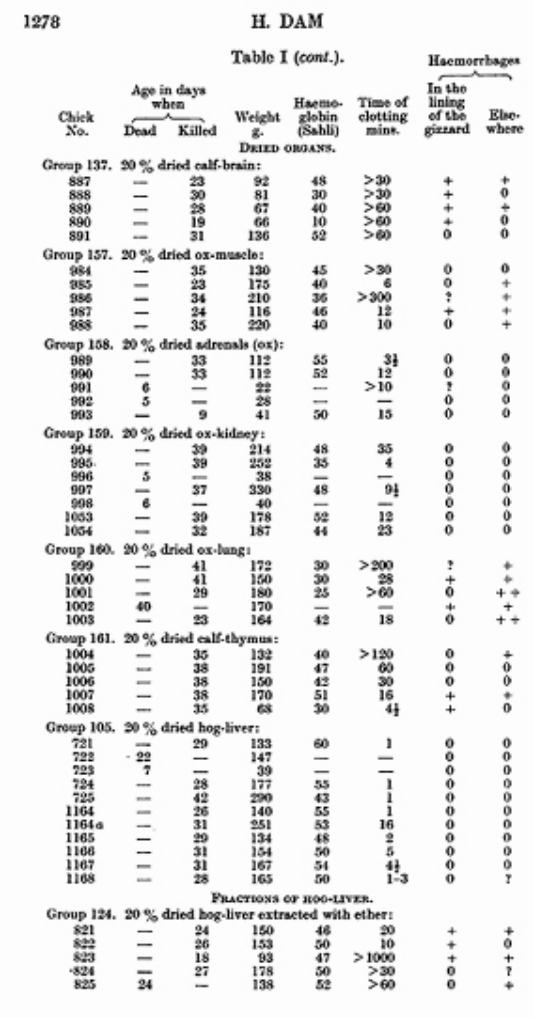

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Table I (*cont.*).

Chick No.	Age in days when Dead	Age in days when Killed	Weight g.	Haemoglobin (Sahli)	Time of clotting mins.	Haemorrhages In the lining of the gizzard	Haemorrhages Elsewhere
Dried organs.							
Group 137. 20 % dried calf-brain:							
887	—	23	92	48	>30	+	+
888	—	30	81	30	>30	+	0
889	—	28	67	40	>60	+	+
890	—	19	66	10	>60	+	0
891	—	31	136	52	>60	0	0
Group 157. 20 % dried ox-muscle:							
984	—	35	130	45	>30	0	0
985	—	23	175	40	6	0	+
986	—	34	210	36	>300	?	+
987	—	24	116	46	12	+	+
988	—	35	220	40	10	0	+
Group 158. 20 % dried adrenals (ox):							
989	—	33	112	55	3½	0	0
990	—	33	112	52	12	0	0
991	6	—	22	—	>10	?	0
992	5	—	28	—	—	0	0
993	—	9	41	50	15	0	0
Group 159. 20 % dried ox-kidney:							
994	—	39	214	48	35	0	0
995	—	39	252	35	4	0	0
996	5	—	38	—	—	0	0
997	—	37	330	48	9½	0	0
998	6	—	40	—	—	0	0
1053	—	39	178	52	12	0	0
1054	—	32	187	44	23	0	0
Group 160. 20 % dried ox-lung:							
999	—	41	172	30	>200	?	+
1000	—	41	150	30	28	+	+
1001	—	29	180	25	>60	0	+ +
1002	40	—	170	—	—	+	+
1003	—	23	164	42	18	0	+ +
Group 161. 20 % dried calf-thymus:							
1004	—	35	132	40	>120	0	+
1005	—	38	191	47	60	0	0
1006	—	38	150	42	30	0	0
1007	—	38	170	51	16	+	+
1008	—	35	68	30	4½	+	0
Group 105. 20 % dried hog-liver:							
721	—	29	133	60	1	0	0
722	22	—	147	—	—	0	0
723	7	—	39	—	—	0	0
724	—	28	177	55	1	0	0
725	—	42	290	43	1	0	0
1164	—	26	140	55	1	0	0
1164a	—	31	251	53	16	0	0
1165	—	29	134	48	2	0	0
1166	—	31	154	50	5	0	0
1167	—	31	167	54	4½	0	0
1168	—	28	165	50	1-3	0	?
Fractions of hog-liver.							
Group 124. 20 % dried hog-liver extracted with ether:							
821	—	24	150	46	20	+	+
822	—	26	153	50	10	+	0
823	—	18	93	47	>1000	+	+
824	—	27	178	50	>30	0	?
825	24	—	138	52	>60	0	+

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». Отмечены цыплята, имеющие геморрагический синдром, у каждого цыпленка измерено время свертывания крови и т. д.

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, that 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

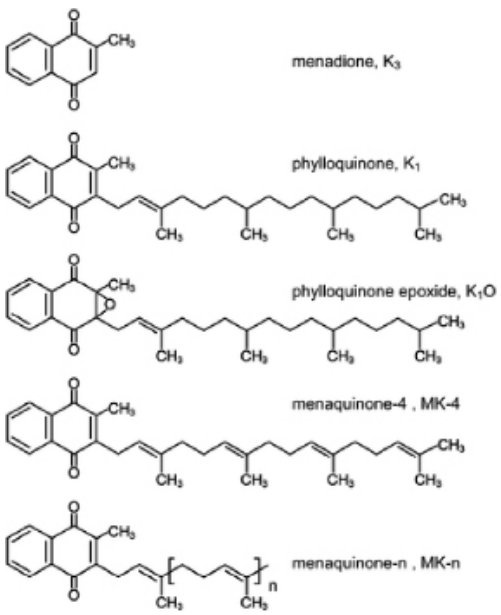

Fig. 8. Forms of vitamin K (Shearer M.J., Newman P., 2014) [50]

Рис. 8. Формы витамина К (Shearer M.J., Newman P., 2014) [50]

Fig. 9. A.V. Palladin [August 29 (or September 10), 1885 (Moscow)–December 6, 1972 (Kiev)]
Рис. 9. А.В. Палладин (29 августа (10 сентября) 1885, Москва – 6 декабря 1972, Киев)

Fig. 10. Nikolai Ivanovich Lunin (1854–1937)
Рис. 10. Николай Иванович Лунин (1854–1937)

headed by Alexander Vladimirovich Palladin, a graduate 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 impossible 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 significance 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. Hopkins and C. Eijkman received the Nobel Prize for discovering vitamins. During his lifetime, Nikolai Ivanovich 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 deficiency.

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 series 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 republished five times.

In addition, in 1970 in Leningrad, the famous pediatric hematologist A.M. Abezgauz released a monograph 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 effects of increased doses of synthetic preparations of vitamin K (Vicasol).

Fig. 11. The grave of N.I. Lunin. On the right, there is a plate on the grave of K.A. Rauchfuss
Рис. 11. Могила Н.И. Лунина. Справа плита на могиле К.А. Раухфуса

Fig. 12. Yu.F. Dombrovskaya (1890–1976)
Рис. 12. Домбровская Ю.Ф. (1890–1976)

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.

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Table 1

Classification of the hemorrhagic disease of newborns [32]

Таблица 1

Классификация геморрагической болезни новорожденных [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

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