Haemophilia
The Official Journal of the World Federation of Hemophilia,
European Association for Haemophilia and Allied Disorders and
the Hemostasis & Thrombosis Research Society

*Haemophilia* (2013), **19**, 643–647 DOI: 10.1111/hae.12243

COMMEMORATIVE ARTICLE

# Erik von Willebrand

R. LASSILA and O. LINDBERG*
*Helsinki University Central Hospital and Doctagon, Helsinki, Finland*
*O. L., a geriatric physician, is the great grandson of Erik von Willebrand

## The Biography of Erik Adolf von Willebrand

Erik Adolf von Willebrand (VW) was born in 1870 in the city of Vaasa in Finland (Figs. 1 and 2). Although the family was socially active and class conscious, VW's upbringing was austere by modern standards. He attended Vaasa Lyceum especially excelling in chemistry, botany and zoology. In the summers, he trekked widely collecting botanical, lepidopterological and ornithological specimen and in the winters he toured the frozen Gulf of Bothnia. After gaining his baccalaureate in 1890, VW enrolled at the University of Helsinki and before gaining his license in 1896, he spent the summers of 1894 and 1895 on the Åland islands (Fig. 2) as a junior spa physician. However, at this time, there is no evidence that he would have encountered the disease he later was to describe.

After graduation, in 1897, VW was attached as assistant physician to the Department of Medicine at the Deaconess Hospital in Helsinki where Professor

**Fig. 1.** Photograph of Erik von Willebrand at the age of 45.


**Fig. 2.** Map of the Gulf of Bothnia showing the Åland Islands.

Ossian Schauman, an eminent haematologist, supervised VW's dissertational work on changes in blood cell count following venesection. Other early haematological studies of VW included regeneration of blood in anaemia and a novel method for staining of blood smears using eosin and methylene blue. After completing his dissertation in 1899, VW took up the position as chief physician at the Heinola Spa, and the focus of his work changed to applied physiology. Between 1900 and 1906 VW also held positions at the Departments of Anatomy and Physiology at the University of Helsinki. His publications included studies on hot air therapy, phototherapy and the description of an apparatus for measurement of dermal excretion of carbon dioxide and water with the results from studies with this contraption (Fig. 3).

The calling of internal medicine however, was stronger than that of physical therapy and balneology, and thus VW in 1907 took on the position as physician in chief at a municipal hospital for internal Medicine in Helsinki. Concomitant with his appointment as senior

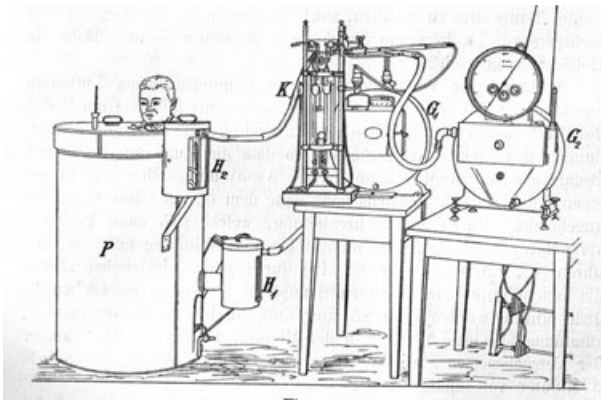


Fig. 3. $H_2O$ and $CO_2$ excretion monitor.

lecturer in internal medicine in 1908 VW succeeded professor Ossian Schauman, as the head of the department of medicine and of the laboratory at the Deaconess Hospital in Helsinki. This laboratory was well known for the good quality of its haematological service which continued under the leadership of VW. From 1922 until 1931, VW was physician-in-chief of the Deaconess Hospital and remained department head until his retirement in 1933.

As head of the department of medicine, VW published on metabolism and therapies for diabetes, obesity and gout (Table 1). He also published an exceptionally large clinical-statistical study on heart valve conditions based on data from more than 10 000 autopsies performed in Helsinki 1867–1916. It was not until 1918, after a gap of almost 20 years, that VW resumed publishing haematological papers on aplastic anaemia, pernicious anaemia and the health status of previously chlorotic subjects.

During the first decades of the 20th century Finland was torn by a linguistic conflict between the Finnish-speaking majority and the Swedish-speaking minority who included VW. Schauman, who was VW's mentor, was one of the founders of an organization striving insure the successful survival of the Swedish-speaking minority. In common with many other academic Swedish-speaking Finns, VW gave his wholehearted support to this cause involving the pursuit of eugenics. These activities were very common in the Western world at that time.

## Observations of a new bleeding disorder

The most transformative period in VWs career was probably in early 1924. In February, VW succeeded in reversing the moribund state of a patient in diabetic coma making use of the first batch of insulin delivered to Finland. Only 2 months later, the 5-year old girl Hjördis, who had a history of recurrent severe mucosal bleeding, presented at VW's clinic in Helsinki. Three of her older sisters had previously died from mucosal bleeds and according to the parents several female and some male relatives were bleeders. The girl was healthy, bright and in a good nutritional state. Her examination was normal apart from scattered small haematomas. Apart from slight anaemia (Hgb 108 g $L^{-1}$) and slight thrombocytopaenia ($140 \times 10^9$ $L^{-1}$) her blood count was normal. Whereas her clotting time and clot retraction were both normal, her bleeding time (Duke) lasted more than 2 h, and a tourniquet test was highly positive.

VW considered that the disorder was due to platelet dysfunction coupled with a defect of the vessel walls. If the disease could be proven to be hereditary it would constitute a new entity. Moreover, in line with the endeavours to promote the Swedish-speaking minority, a hereditary disease affecting this population, was of greater than medical interest.

Further investigations of the hereditary nature of Hjördis' bleeding disorder were undertaken. VW did not go to Hjördis' native Föglö in the Åland islands for fieldwork, but he obtained the cooperation of a local schoolteacher for drafting of the pedigree. In February 1926, almost 2 years after first encountering Hjördis, VW published the first paper on the disease which later would bear his name. The paper, which includes a brief review of haemorrhagic diathesis distinct from 'genuine' haemophilia, describes 58 individuals in a pedigree of two interrelated families spanning four generations, and an analysis of the heredity involved, suggesting dominant sex linkage (Fig. 4).

## Early observations in von Willebrand disease

In 1926, the 'Pseudohemophilia' description differed from haemophilia in that the cases were at least as often female patients as male patients [1]. The maternal grandmother had died during labour due to continuous bleeding. The mother of the index case, Hjördis, had 11 children of whom, only three were devoid of bleeding symptoms (Fig. 4). The diagnostic findings included a normal or modestly decreased platelet count, but the size and morphology of the platelets appeared normal. The clot retraction was also normal, unlike in Glanzman thrombasthenia, which had been described 8 years earlier, in 1918, in Bern. The Duke bleeding time was very prolonged, more than 2 h in some instances, the response to applied stasis (the Rumpel-Leeder test) was abnormal, suggestive of early fibrinolysis. The coagulation time of 20 drops of blood on a watch glass lasted for 30 min (Table 2).

The early observations of Erik von Willebrand were added to by the fieldwork of Dr von Juergens on the island of Föglö, and Åland islands. These two scientists co-authored three articles about VWD in 1933–1934 (both in German and in Swedish) together with

 

**Table 1.** Publications of Erik von Willebrand

| | |
|---|---|
| 1. | Ossian Schauman and EAvW: Einige bemerkungen über die blutregeneration bei der Chlorose. Ber.Klin.Wshr. 1899; No 1. Diak |
| 2. | *Th Tallqvist & EAvW*. Zur Morhologie der weissen Blutkörperchen des Hundes und des Kaninchens. ScandArchPhys. 1899;Vol X;/ |
| 3. | EAvW. Zur Kentniss der Blutverenderungen nach Aderlässen. Dissertation 1899. Diak |
| 4. | EavW: Eine Methode für gleichzeitige Combinationsfärbung von Bluttrockenprepataten mit Eosin und Methylenblau. Dtsch.Med. Wschr. 1901;No 4 |
| 5. | EAvW: En universal färgningsmetod med eosion och metylenblått. FLS Hand. 1902;543–552 |
| 6. | EAvW: Über die Kohlensäuren- und Wasserascheidung durch die haut des Mänchens. Scand Arch.Phys.1902;Vol XIII:337–358.Physiol |
| 7. | EAvW:Om hetluftbehandlingens fysiologi. FLS Handl. 1902;435–456. Physiol |
| 8. | EAvW: Om den lokala hetluftsbehandlingen enligt Biers metod. FLS Handl. 1903;197–218. Heinola |
| 9. | EAvW:Om den moderna ljusbehandlingen. FLS Handl. 1903;435–456 |
| 10. | EAvW: Morbus Addison med atrofi av binjurarna. FLS handl. 1905;536–592. Diak |
| 11. | EAvW: Zur Physiologie und Klinik der Heissluftbehandlung. Scand Arch hysiol. 1906;Vol 19:123–161. Physiol |
| 12. | EAvW: Om fettsotens orsaker och dess behandling. Kliniska föredrag Nord Tidsk Ther 1906/07;Vol 5:129–37, 161–170, 199–212/ |
| 13. | EAvW: Ett fall av cerebral hemianopsi. FLS Handl. 1907:__–__ |
| 14. | EAvW: Om giktens behandling. Kliniska föredrag Nord Tidsk Ther. 1907/08;Vol 6:353–358/ |
| 15. | EAvW: Bidrag till kännedomen om meralgia paresthetica. FLS Handl. 1910; Vol LII:No 12;491–505/ |
| 16. | EAvW: Om den konstitutionella fettsotens patogenes och behandling. Nord Tidsk Ther. 1911/12;Vol 10:132–143/ |
| 17. | EAvW: Om sockersjukans patogenes enligt nyare teorier. FLS Handl. 1911;Vol LIII:363–370EAvW:En metod för approximativ uppskattning af acetonkroppsmängden i urinen. FLS handl. 1912;Vol LIV:515–524/Diak |
| 18. | EAvW:Om behandlingen av diabetes med sockerlavemang. FLS handl. 1913;Vol LV:412–423/Diak |
| 19. | EAvW:Kolhydratkurer och alkalibehandling vid diabetes mellitus. FLS handl. 1914;Vol LVI:1277–1334/Diak |
| 20. | EAvW&Axel Cedercreutz: Book review Lärebog i intern medicin. FLS handl. 1954;Vol LVII:210–219 |
| 21. | EAvW:Till kännedom om den aplastiska anemien. FLS handl. 1918;Vol LX:859–922/Diak |
| 22. | EAvW:Klinisk-staistiska studier öfver hjärtvalvelfelen. FLS handl. 1918;Vol LX:1107–1143/InstPathAnat |
| 23. | EAvW:Perniziöse Anemie mit ungewönlichem Remissionsstadium.Acta Med Scand. 1922;Vol LVI:419–431/Diak |
| 24. | EAvW: Die gesundheitszustand bei Personen, die früher an Chlorose gelitten haben. Acta Med Scand. 1923;Suppl III/Diak |
| 25. | EAvW: Coma diabeticum- Insulinbehandling. FLS handl. 1924;Vol LXVI:266–273/Diak |
| 26. | EAvW: Hereditär pseudohemofili. FLS handl. 1926;Vol LXVIII:87–112/Diak |
| 27. | EAvW: Über hereditare psedohaemphile. Acta Med Scand. 1931;Vol 76:521 |
| 28. | EAvW: Om naturskyddet i Finland. Östnyländsk ungdom. 1942 |
| 29. | EAvW: En ärftlig blodsjukdom bland skärgårdsbefolkningen på Åland. Nordensköldsamfundets tidskr. 1945;5:44–55 |
| 30. | EAvW: Hepatogen hemorrhagisk diates. FLS handl. 1933;Vol LXXV:829–846/Diak |
| 31. | EAvW& R.Jürgens:Über ein neues vererbbares Blutungsübel:Die konstitutionelle Thrombopatie. DtschArch.klin.Med. 1933;175:453-/diak |
| 32. | EAvW&R.Jürgens: Über eine neueBluterkrankheit, die konstitutionelle thrombopathie: Kl.Wo.Schr. 1933;12:11,414./Diak |
| 33. | EAvW&R.Jürgens& U Dahlberg. Konstitutionell thrombopati, en ny ärftlig blödarsjukdom. FLS handl. 1934;Vol LXXVI:194–232 |
| 34. | EAvW: Rasfågor i modern belysning. Östnyländsk ungdom. 1938:5 |
| 35. | EAvW: Rasfågor i modern belysning II. Östn yländsk ungdom. 1939:3 |
| 36. | EAvW& J Olin: Nyare erfarenheter om de hemorrhagiska diateserna. Nord Med. 1939;Vol 2: 1743 |
| 37. | EAvW: De hereditära trombopatierna. Nord Med. 1941;Vol 12:3317 |
| 38. | EAvW: Svenskbygdens befolkningsfråga.Östnyländsk ungdom. 194 |
| 39. | Bertel Lemberg &EAvW: Naturstudier och naturskydd i Pernå skärgård. Finlands natur. 1943;1:9 |
| 40. | EAvW: En ärftlig blodsjukdom bland skärgårdsbefolkningen på Åland. Nordensköldsamfundets tidskr. 1945;5:44–55 |

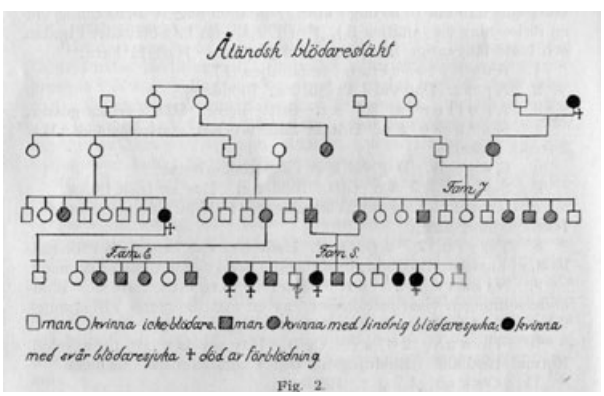


**Fig. 4.** Pedigree of the Sundblom family of Hjördis.

**Table 2.** Methods used by Juergens and VW to study the bleeder families (Ref. [2])

| | |
|---|---|
| 1. | Counting and differentiation of red and white blood cells. Determination of haemoglobin |
| 2. | Counting platelets according to Thomsen or Fonio, and assessing their morphology |
| 3. | Platelet agglutination by Juergens and Nauman |
| 4. | Bleeding time by Duke method |
| 5. | Determination of coagulation time on a watch glass according to Morawitz, Bierich, Sahli-Fonio |
| 6. | Clot retraction on watch glass |
| 7. | Thrombosis time determination by Morawitz and Juergens by capillary thrombometer |
| 8. | Rumpel Leede experiment; subjection to stasis |
| 9. | Capillary microscopy |
| 10. | Determination of the plasma proteins and their distribution |
| 11. | Analysis of blood group |

Ulf Dahlberg in the Finnish Medical Society's Practical Journal, *Finska Läkaresällskapet Handlingar,* under the title 'Constitutive thrombopathy–a new inherited bleeding disorder' [2]. In 1930, Juergens and Morawitz had developed a 'capillary thrombometer', which can be considered as the predecessor of flow-mediated studies (Fig. 5). Blood was drawn to a double capillary system in paraffin-treated glass tubes and pumped back and forth until it started to build up a thrombus, which eventually occluded the whole capillary system.

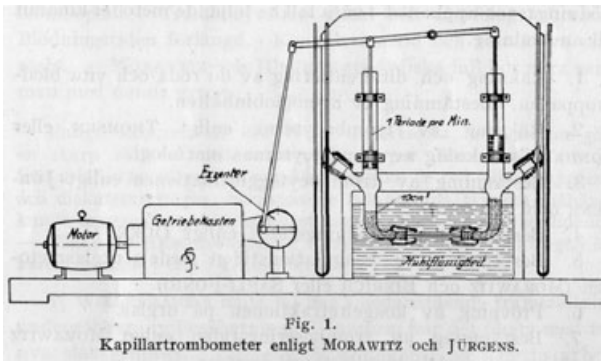


Fig. 1.
Kapillartrombometer enligt MORAWITZ och JÜRGENS.

**Fig. 5.** Capillary thrombometer by Morawitz and Juergens.

Manometers captured the event and the time to occlusion, thus the thrombosis time was normally 3–4 min. The thrombosis time was prolonged by 10-fold the normal in the patients studied by Juergens and VW, suggesting a platelet abnormality. The abnormal Rumpel-Leeder test suggested a vascular defect, and the combination of the inherited platelet and vascular defect led to a diagnosis of 'constitutional thrombopathy'. The innovative armamentarium of coagulation assays is depicted in Table 2.

In recognition of the extensive work by VW in the Åland island family, the name of VW was assigned to the disease between the late 1930s and early 1940s. Similar observations were reported from the US in 1928–29 and later by Fowler 1937, Geiger and Evans 1938, Drukker 1941 and Revol 1950 [3].

## Historical context

As early as 1852, Lange had described similar families with bleeders, up to 140 in number, from both US and Europe and both female and male bleeders, but the disorder was labelled haemophilia [3]. The bleeding started in early childhood, consisted of epistaxis, petechiae, ecchymoses and haematemesis. In 1920, Minot and Lee had described a familial bleeding tendency resembling thrombocytopaenia, but having normal platelet count. Armand Quick in 1957 called the condition Minot-von Willebrand disease or pseudopathic purpura. Many other patient descriptions and publications were later recognized as possible VWD. In fact, in the paper published by VW and Juergens it was suggested that the familial bleeding disorder in female patients, previously thought to represent haemophilia, was 'pseudohemophilia' or 'constitutional thrombopathy'. In Germany, the disease carried the name VW-Juergens for two decades, but later the name VWD became established throughout the world.

In 1953, a puzzling observation was made by scientists in three laboratories that some patients with VWD also lacked FVIII, as well as the distinct clinical symptoms, mode of inheritance and laboratory findings of haemophilia. Twenty years later in 1972, Owen and Wagner could identify that the antihemophilic globulin constituted of two proteins, FVIII and the larger multimeric protein. They called this protein VWF and its importance in carrying FVIII, platelet plug formation and haemostasis and autosomal inheritance was confirmed. The characteristics of VWD were further detailed by the two remarkable pioneering Swedish female scientists, Inga-Marie Nilsson and Margareta Blombäck.

**Fig. 6.** The country house and study of Erik von Willebrand in Finland. After his retirement VW devoted his time to gardening, nature conservation and hosting family gatherings.

## Other studies of Erik von Willebrand

It is really intriguing how the biomedical commitment of Erik von Willebrand was interwoven with other

disease entities, which have later revealed associations with VWD. These include an interest in blood smears and platelets. Later it has been recognized that thrombocytopaenia is a specific feature of one subtype of VWD (VWD 2B). The main passion of Dr. von Willebrand was to study blood in laboratory. With his equipment in 1926 he was able to reach the remarkable and exact conclusions of the defect involving vasculature, platelet contribution and a plasma factor (later VWF), the lack of which prolonged the bleeding time, but failed to impair coagulation times and clot retraction. Also, highly relevantly, he pursued, together with Dr Juergens, the study of blood under flow conditions to understand the mechanisms underlying bleeding disorders [2]. VW also studied aortic valvular disease by collecting an extensive retrospective autopsy registry over 70 years. Today, it is understood that VWF multimers undergo proteolysis in association with aortic stenosis, resulting in acquired VWD and bleeding tendency.

von Willebrand was among the first doctors in Finland to inject the first dose of insulin to a patient with diabetes in 1924. Diabetes is complicated by vascular disease there is an increased risk of thrombosis, where the role of VWF has been established by many scientists. VW also wrote a significant review on Addison's disease. It is now understood that high cortisol and thyroid hormone levels increase FVIII levels and hypothyroidism is a cause of acquired VWD.

During his life Erik von Willebrand became interested in clinical physiology and balneology and studied exercise and stress. Under these conditions VWF is released to support haemostasis, a normal physiological response, but high adrenaline levels may lead to arterial thrombosis in vulnerable patients via this mechanism. VW vas involved in new rehabilitation techniques and designed new physiotherapy equipment (Fig. 3). Rehabilitation, to improve the quality of life among patients with bleeding disorder, is the corner stone in modern management among patients who have not received prophylactic treatment. In addition to haemophilia, patients with severe VWD may develop disability due to joint bleeds, and such bleeds were occasionally described among the initial observations by VW, usually in the form of ankle bleeds.

## Links to modern era

Nowadays the genetics and structure-function relationship studies of VWF have revealed highly complex mechanisms. As this multimeric VWF protein resides in plasma, platelets and endothelial cells and its function is influenced by blood flow, the clinical and 'correct' diagnosis of VWD depends on multiple laboratory tests, which are difficult to perform and interpret. Bleeding assessment tools, unravelling genetic backgrounds and applying the diagnostic tests to better define and target specific therapies have been at the forefront of continuing international research. Specific plasma-derived concentrates (with and without FVIII) and the recently developed first recombinant form of VWF replacement therapy are the latest therapeutic advances.

The availability of the right diagnosis and therapy in remote districts, far from treatment centres (including islands such as Åland), and increasing costs of the modern care remain challenges for patient care of this bleeding disorder. Erik von Willebrand certainly provides a role model for the modern thrombosis and haemostasis community to meet these challenges (Fig. 6).

## Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

## References

1 von Willebrand EA. Pseudohaemophilia. *Finska Läkaresällskapet Handlingar (FLS Handl)* 1926; **LXVII**: 87–112.

2 von Willebrand EA, Juergens R, Dahlberg U. Konstitutionell thrombopati, en ny ärftlig blödarsjukdom. *FLS Handl* 1934; **LXXVI**: 194–232.

3 Nichols WL, Bowie EJW eds. Inherited coagulation factor deficiencies. In: *A History of Blood Coagulation*, Rochester, MN: Mayo Foundation for Medical Education and Research, 2002: 126–8.