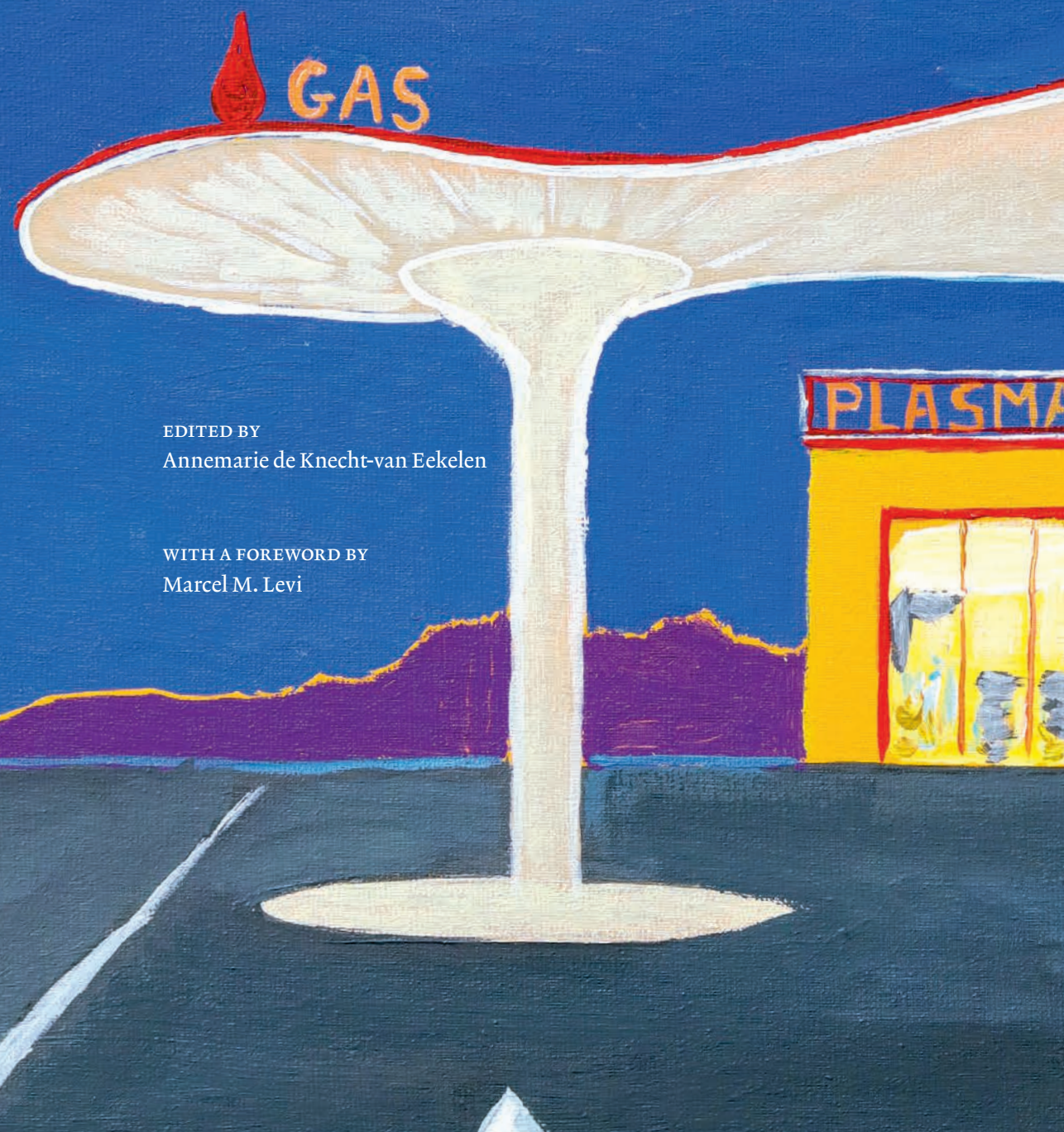
Surviving hemophilia

A road trip through the world of healthcare

IN MEMORY OF THOSE
WHO DID NOT GET THE TIME
TO WRITE A BOOK LIKE THIS



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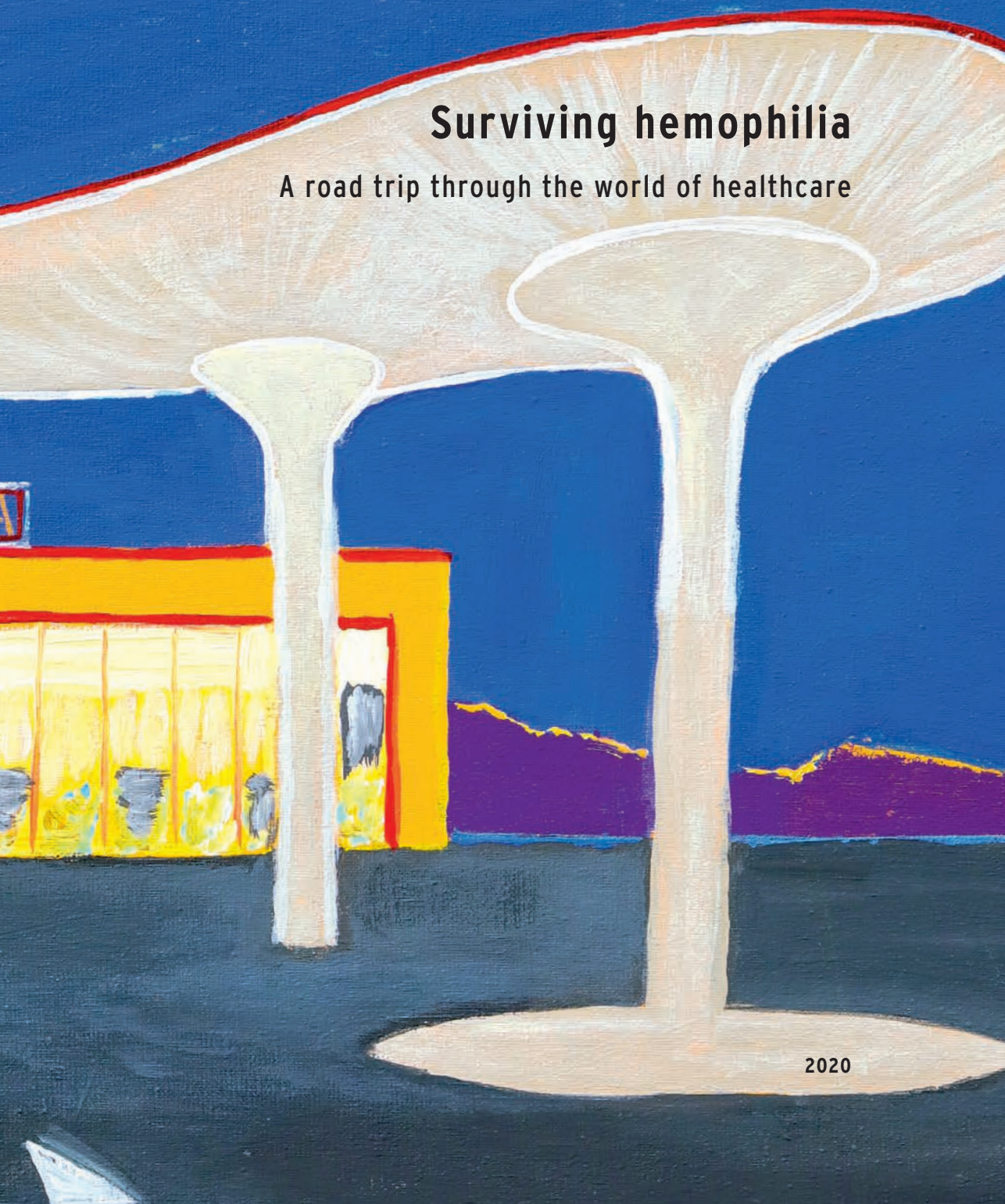

2020

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DISCLAIMER

To parents of young children, adolescents with hemophilia, and carriers of hemophilia:
Your future will be totally different from my history described in this book. Nowadays, in countries like the Netherlands, with a proper health care insurance system, a choice of treatment options for people with hemophilia is available. I advise you to talk with an experienced hematologist in hemophilia care.
This book reflects my personal experiences and my views on difficult periods in the history of hemophilia care. Although this is a personal account of a life with hemophilia, we have given utmost attention to check the facts described in this book. See our references and illustration credits.
For correspondence: info@smitvisch.nl.

FOOTNOTES

No footnote numbers are used in the main text. Footnotes are to be found at the end of the book and are recognized by the page number and the first words of the sentence. This will contribute to the readability of the book.

Content


ZWART

A carefree childhood!

Being born with hemophilia

During a stormy night, while the neighbors rescued the thatched roof of our farmhouse, I was being born under that same roof on New Year's Night 1951 in Nieuwe Niedorp. This is a small village in West-Friesland, in the north-west of the Netherlands, some sixty kilometers north of Amsterdam. My parents – Jan Smit and Marie Kroon – were married in 1943 during the Second World War and started a bakery for bread and pastries in this village. My sister Wil was born shortly afterwards in 1944. The house is situated on the Laagzijde, the lower part of the Dorpsstraat. The front part of the house where we lived, still exists (Figure 1a). It is a picturesque place with a lovely painting to show for it (Figure 1c). Figure 1b shows the houses opposite ours.

It sounds rather ridiculous to say that I had a carefree childhood, while I stayed a larger part of the first sixteen years of my life in hospital. And the more ridiculous it is, when one realizes in hindsight that my medical problems caused my parents and my sister a lot of stress. It was not that my parents kept the troubles of hemophilia away from me. For sure, I was just too young to realize the severity. Figure 2 shows images of my childhood.

A timely diagnosis

It was not long after my birth that my mother saw some bruises on my back. She went to our general practitioner and showed him the discolorations. His answer was sympathetic, but also quite patronizing: she should handle me with more care. My mother was rather upset with him for saying so, as she knew how careful she lifted me in and out of my crib. As the bruises continued appearing and I also displayed pain while crawling, a referral to a pediatrician followed. She, it was a female doctor, had her practice in Alkmaar, a city about 25 kilometers away from our bakery.

Figure 1. My birthplace: a. The house where I was born still exists (2019); b. The houses opposite ours on a sunny morning in spring (1940s); c. The painting of my birthplace by Jannie Kuiper, a Dutch painter from Nieuwe Niedorp

Luckily enough, this pediatrician – Dr Anna G. Schoo – had been trained in Amsterdam by Prof. Cornelia C. de Lange, Professor in Pediatrics and the first female professor in a medical faculty in the Netherlands. Hemophilia was one of the topics studied in Amsterdam and Anna Schoo had a basic knowledge of hemophilia. I understood much later how lucky my parents had been in finding this pediatrician. Dr Schoo immediately diagnosed me with a severe form of hemophilia.

It was known that hemophilia is a genetic disease occurring in males. A person with hemophilia misses the genetic information to produce one of the proteins that is needed for the blood clotting. The protein I am missing, is called Factor VIII. However, no one in our family seems to have had hemophilia before me. This happens regularly and is caused by a mutation. More than 30 percent of the boys with hemo-

Figure 2. Images of my childhood: a. In the arms of my mother; b. My birth announcement card; c. On the arm of my father; d. With my sister Wil; e. Outside the hospital with my parents, recovering from a bleeding

philia are born in a family without a history of hemophilia. Later, my mother, my sister and one of my nieces were diagnosed as carriers. For those who want to know more about the genetics of hemophilia, I have made an overview in the following text box.

How I inherited the hemophilia gene

Hemophilia is a recessive sex-linked genetic disease. Sex-linked means that the gene is located on one of the X-chromosomes. Humans have 23 pairs of chromosomes, one of those pairs consists either of two X-chromosomes or one X- and one Y-chromosome. If you have two X-chromosomes you are a female, with one X- and one Y-chromosome you are a male. A recessive gene is a gene whose effects are masked in the presence of a dominant gene. When a woman has a genetic defect on one of her X-chromosomes, we call her carrier. A carrier does not have the disorder herself when the gene is recessive. There is a 50% chance that a carrier passes the X-chromosome with the defect to her son. Her daughter has a 50% chance of being a carrier. This is shown in Figure 3a. My father had no hemophilia. Men with hemophilia generally get no sons with hemophilia. However, their daughters will be carriers. The father with hemophilia transfers his defected X-chromosome to his daughters. This situation is shown in Figure 3b. I use the figures from a booklet that I published in 1996, explaining hemophilia for laypeople.[1)]

Unfortunately, I got hemophilia and my sister became a carrier, chance was not on our side. Carriers can experience bleeding problems during menstruation and after medical interventions.[2)] Mothers who carry the hemophilia gene, are at risk for serious bleeding after delivery.[3)]

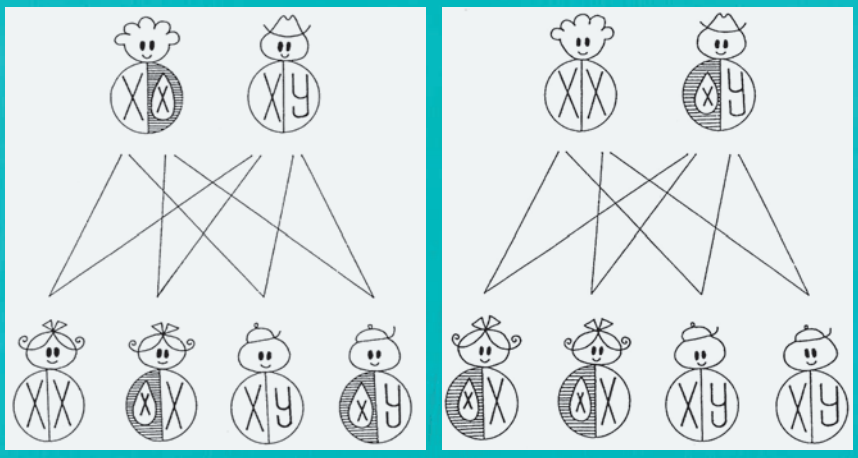

Figure 3. Genetics of hemophilia: a. Mother is carrier; b. Father with hemophilia

1) Smit C, Rosendaal FR. Hemofilie. AO reeks nr 2587. April 19, 1996.
2) Plug I, Mauser-Bunschoten EP, Bröcker-Vriends AHJT, et al. Bleeding in carriers of hemophilia. Blood. 2006;108(1):52-6.
3) Information on hemophilia for women. Retrieved 02/17/2020 from https://www.cdc.gov/ncbddd/hemophilia/women.html.

When I was born, there was only one type of hemophilia identified, now called hemophilia A. The missing plasma factor, which was named the "anti-hemophilic factor" (AHF), had only been discovered in 1950. AHF was later named Factor VIII. Subsequent research showed that one can have mild, moderate, or severe hemophilia depending on the level of clotting factor in the blood. The clotting factor level is shown as a percentage: mild = 6% to 50% factor level; moderate = 1% to 5% factor level; severe = less than 1% factor level. I have severe hemophilia A.

Without Factor VIII, a bleeding hardly stops. The greatest risk is not an external cut that continues to bleed – although it can be dangerous –, but an internal bleeding. This often occurs in a joint – knees, ankles, elbows –, or in a muscle when you bump into something. The most dangerous is a bleeding in the skull when you hurt your head. Bleedings can take place after an injury but also spontaneously. You can imagine how anxious my parents were to prevent me from getting a bleed.

Living the innocent life of a kid

As far as I can remember, I had a nice youth together with the neighborhood kids in the countryside. One of the neighbors had a farm with cows. My father had some pigs in our back yard that were fed with the leftovers of our bakery, especially old bread. My father worked in the baker's tradition as is shown in Figure 4. To his nearby customers, he delivered the bread door-to-door using a special basket, named the "Kriel". It had become a particularity that was described in an historical journal, together with my father's picture.

The farm, the garden, and the grounds surrounding the house were our playgrounds, where we gradually discovered the world around. It resembles the life of the twin brothers Sietse and Hielke Klinkhamer in a famous Dutch children's book series titled *De Kameleon* [= The Chameleon]. In about seventy books, you can read about the adventures of the twins with a boat. We only lacked the boat. Sometimes, I could not play because I had a bleed. When not, I played just like the other kids. One day, I fell off a hay wagon but without consequences. Brushing teeth was forbidden in those days as it could cause gums bleeds.

I was not allowed to swim and to cycle, so I had no bicycle. In Holland, everyone owns a bicycle, and it is the major means of transport. Having no bicycle is like having no shoes. To solve this problem, I just took the bicycle from one of the other kids. This made my parents buy me a bike too, even though it was against the formal advice. With our bikes, we cycled down our street, around the corner into another street and then to a high bridge over a canal with a typical Dutch windmill by its side.

To compensate for not participating in sports, I joined a choir, but that was not a success. I took part in all kind of activities: there was the yearly flower show, the Floralia, in our village. It still is a big event in Nieuwe Niedorp where beautiful

Figure 4. My father delivering bread to our neighbor Atie Vonk (1951)

Figure 5. I am the "injured cyclist" at the Floralia

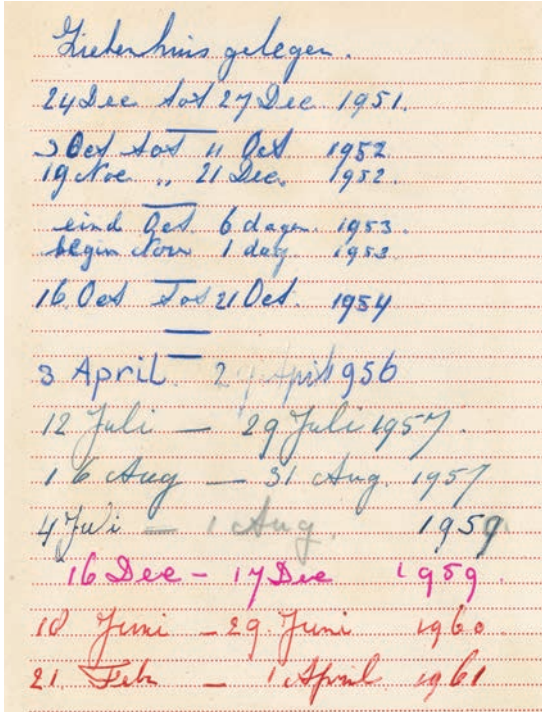

Figure 6. My stays in hospital recorded by my mother

flower mosaics are shown. Figure 5 shows me at the Floralia as the injured cyclist. Together with the neighbor kids we performed a "First aid" act. In my younger years, I enjoyed living a full life, at least that is how I felt.

The only thing I remember from my visits to Dr Schoo was the house at the Emmastraat 3 in Alkmaar opposite the hospital, where she had her doctor's practice. After every visit, my mother gave me an ice-cream. We had to take the bus from our village to Alkmaar, which was for us the "big city". In fact, a bus ride was an attraction too in the mid-fifties. After some years, another pediatrician, Johan Hofstra, joined Dr Schoo. He knew a few other children with hemophilia. He took care of me until I was old enough to see an internist. I often had bleeds in my knees and joints for which I was hospitalized in the Centraal Ziekenhuis [= Central Hospital] in Alkmaar. My mother kept a record of my hospital admittances (Figure 6). In my memory, I was many more times in hospital; it shows what impact the hospital had on my childhood.

Side effects of treatment, the DES hormone

There was no effective treatment for hemophilia during the first sixteen years of my life. Because of that, I hardly survived some critical incidents in my youth. After a couple of these events, my pediatrician Hofstra told my parents that he used diethylstilbestrol (DES hormone) to treat his other two patients with hemophilia. DES was used as a medication for a variety of female reproductive problems and to stop growth in adolescent girls who were growing very tall.

The use of DES in hemophilia had been presented by a French pediatrician, Raymond A. Turpin, at a conference in Paris in the late 1940s. The idea that ovarian extract would have positive effects on hemophilia, had already been suggested in 1904. This was because hemophilia was not seen in women, which was interpreted as being due to a protective influence of the ovaries. In the 1930s, the newly found female sex hormones were thought to stimulate blood clotting. Turpin was not specialized in hemophilia, most of his work is devoted to Down syndrome.

Be that as it may, a Dutch pediatrician, who heard Turpin's lecture, started using DES for three of his patients. From mid-1949 on, these boys, aged 7, 9 and 13, were treated with DES during one-and-a-half years. Their condition improved, they had less pain; however, their clotting time did not change. The physicians considered the positive effects of DES treatment prevailing over what they mentioned as "a little handicap". This was the swelling of the breasts of the boys that asked for "measures when swimming". I think that they had to wear a bathing suit covering the breasts. It is astonishing how these adverse effects were downplayed at the time. For me, the effects were even worse. The use of DES had a devastating impact on my growth. I gradually stopped growing. Its effect is still visible as my length is only 1.45 meters.

Unfortunately, some ideas are hard to kill. Around 1970, there were again doctors who promoted the use of female hormones, this time Lyndiol (The Pill), to treat hemophilia. It was based on the observed increased chance of clotting in women using Lyndiol. I know people who have been treated with hormones in these days, of course without any effect. In a few years' time, this treatment was refuted.

Later in my life, I became involved in a DES lawsuit, when it became clear how catastrophic its use had been. DES caused a rare vaginal tumor in girls and young women who had been exposed to this drug *in utero*. Also, prenatally DES-exposed males had an increased risk of testicular cancer, infertility and urogenital abnormalities; it is considered an established human carcinogen. DES and thalidomide brought about a reinforcement of the regulations for medical research. Thalidomide is the drug that was marketed between 1957 and 1961 as a sedative, and for morning sickness in pregnancy. Thalidomide caused major impairment of the development of the limbs of the fetus. In 1964, the World Medical Association (WMA) developed the Declaration of Helsinki as "a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data". It has since undergone seven revisions, the last one in 2013 when the need to disseminate research results, including negative and inconclusive studies, was highlighted. For me, the lawsuit did not result in a settlement, because hemophilia treatment was not mentioned as an indication for DES on the package leaflet of the medicine.

The impact of my severe hemophilia on my family

As I was hospitalized frequently and for longer periods of time, my parents had to bring me to the hospital and visit me there. That was quite a burden for my mother, as she also took care of the household and the bakery shop. When I was just about ten, my parents decided to close the bakery and move to another village, Oudorp, a few kilometers from the hospital in Alkmaar. My father found a new job as a traveling salesman of rye bread, rusks and all kind of cookies. So, he often visited his former colleagues in West-Friesland.

Only later, I realized that this must have been a life changing event for them. Unfortunately, more in-depth questioning for this book is impossible, as my mother and father died respectively in 1987 and 1993. I always felt grateful that they both died before my other hemophilia-related issues became a big problem. Thankfully, they lived to see me grow up.

My sister was around seventeen when we moved. It had a great impact on her life. She lost most of her friends and it took her quite some time to get used to the new situation. In those days, she got to know her future husband Rinze Dragstra. He often mentioned to her and to his family that I would not grow very old. That is what

the physicians had told my parents. Before 1940, the average life expectancy of a Dutch hemophilia patient was 16 years of age and in the early 1960s it was still only 23 years.

Although I was often absent at primary school, I did well and was advised to go the Rijks HBS in Alkmaar. The HBS was a type of secondary education with a five years course that focused on modern languages, mathematics and sciences. The HBS had been established in 1863 as an alternative for the gymnasium where the classical languages Latin and Greek were taught. Since 1917, an HBS diploma gave access to most university studies. My parents thought that – if I would grow older, which was not that sure by then – I would have to earn my living using my intellectual abilities, and not with hand labor. My family encouraged my education. From my grandparents, I got a special present: a large round globe, as I was so much interested in geography. It was only one of my many interests at that time. The globe is still present in my study. My grandparents were proud that their grandson was attending a school at such a high level. They themselves had only basic education. They owned a grocery store in Oudkarspel, not far from Nieuwe Niedorp.

Hemophilia research till the early 1960s

To understand why there was no proper treatment for my hemophilia, I have added a little history about the discovery of the clotting factors. Just remember that blood clotting or coagulation is a biological process that stops bleeding. The question was of course: "What happens in this process"? The Dutch pioneer in hemophilia research, the physician Simon van Creveld, wrote as early as 1925: "There is still a variety of opinions about the cause of the delayed clotting in hemophilia. Most researchers agree that platelets, fibrinogen and thrombin values are normal. Some suppose that there is an inhibiting substance in the plasma that prevents clotting." Together with the chemical engineer Willem M. Bendien, Sc.D., Van Creveld showed that there was no inhibiting substance. They discovered that human blood plasma contains a substance that accelerates coagulation. However, Van Creveld's publications between 1935 and 1941 were disregarded abroad.

Cohn fraction I

Van Creveld was nominated as Professor of Pediatrics at the University of Amsterdam in 1938 as the successor of Cornelia de Lange. In World War II, Van Creveld had to step down, because he was a Jew. After the war, he was reinstated and continued with his investigations on blood plasma. He had read about the breakthrough that was achieved by the Harvard biochemist Edwin J. Cohn, head of the Department of Physical Chemistry. Cohn succeeded in fractionating plasma, which is a biochemical processing technique separating plasma into its functional

Fractionation: separation in components

After a donor has donated blood, the unit of blood is spun in a centrifuge to separate it in three components: red blood cells, platelets and plasma. The separation of plasma in its proteins can be compared with the refining of crude oil. The oil is transformed and refined into several useful products. That is like what happens with a donation of blood. Blood plasma is the source of products that are further separated, freeze-dried and have a long-shelf life. These are different proteins like albumin, immunoglobulins, clotting factor concentrates (FVIII and FIX) and others (Figure 7).

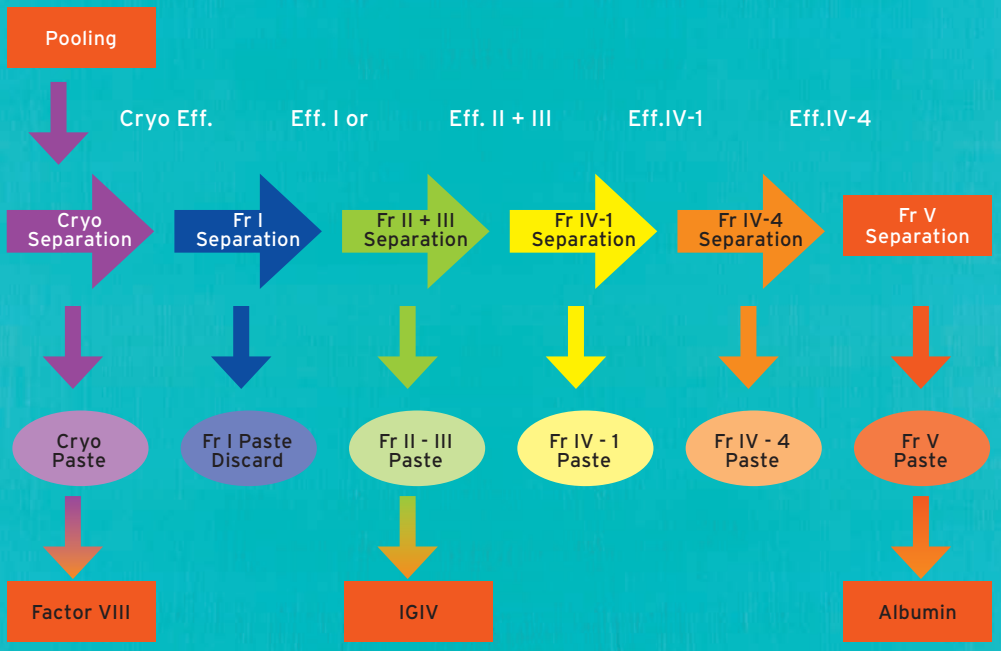

Figure 7. The plasma fractionation process

components. He got five main fractions, which were named Cohn fraction I-V. Cohn fraction I is rich in fibrinogen and other serum proteins that facilitate clotting. The significance of plasma fractionation for hemophilia research was clear.

In the 1950s, several research groups developed production methods to concentrate the anti-hemophilic factor AHF. Van Creveld mentioned that these products were not used regularly. He himself used transfusions with whole blood or with plasma to treat his patients. By the end of the 1950s, the required quantity for transfusion and the transfusion time could be monitored by the determination of AHF in the patient's blood. Van Creveld stated that in serious bleedings a continuous infu-