A walk to answer TTP together

For several years now, Answering T.T.P. Foundation held an International TTP Day in September to raise awareness of this rare disease. Money is collected for research, but attention is also drawn to the stories of those affected or their family members, combined with training events and the provision of information material. The Answering T.T.P. Foundation was set up in 2009 by Sydney Kodatsky, who had TTP herself. ([https://www.answeringttp.org/patient-stories](https://www.answeringttp.org/patient-stories)).

We have already organized three TTP days in Switzerland: a hike on the Gurten, a walk along the renatured Aare between Bern and Belp, and a flea market stand in Bern.

Unfortunately, due to corona pandemic, we could not organize a patient event this year. During advent time, we would like to start shaping “TTP in Switzerland” publishing every day little stories until Christmas - hopefully we will also receive some reports from those affected. We will also continue this project next year as a monthly calendar.

On behalf of the Bern TTP team from research and clinic, I wish you a peaceful and informative advent season.

**Johanna Kremer Hovinga and her Bern TTP Team**
HYALINE THROMBOSIS OF THE TERMINAL ARTERIOLES AND CAPILLARIES: A HITHERTO UNDESCRIBED DISEASE

Eli Moschcowitz, M.D.

In the clinical pathological conference of January 10, 1924, Dr. Eli Moschcowitz, pathologist and internal consultant at Mount Sinai / Beth Israel Hospital in New York, presented the case of a deceased 16-year-old girl. She became seriously ill after spending Labor Day in Rockaway Beach, Queens, New York, on the Atlantic Ocean. She was admitted to the Mount Sinai / Beth Israel Hospital with a high fever of up to 40 °C, poor general condition and body aches. On physical examination, she was pallid with some petechiae on the arms. The laboratory confirmed severe anemia (40g /L). The blood smear showed numerous normoblasts (red blood cells that left the bone marrow so early that they still have a nucleus. They are an expression of a massively increased production of red blood cells), but no sign of fragmentocytes, which are what we are mainly searching nowadays, and nothing was reported about the number of platelets. The urine test also showed a certain involvement of the kidneys. The blood cultures obtained remained negative, so the hypothesis of an infection was rejected.

The hospitalization was dramatic. After a few days, the patient complained of weakness in her left arm and leg, went into a coma and died a day later, a week after being admitted to the Mount Sinai / Beth Israel Hospital. During her hospitalization, the young patient was looked after or seen by various doctors, including by Dr. Emanuel Libman (who later gave his name to a disease, Libman-Sachs endocarditis), who was convinced that they were dealing with a new disease. He was right!

Dr. Moschcowitz, the pathologist in charge of the Mount Sinai / Beth Israel Hospital, performed the autopsy. In his report, he described for the first time thrombotic occlusions of arterioles and capillaries (small vessels) in the heart (where he found most of the thrombotic occlusions), in the spleen, in the kidneys and a few in the liver. These are what we consider now the classic findings of TTP.

Even though he had not examined the brain and given the clinical picture of the patient (probable stroke with weakness of the arm and leg on the left side and then a coma), the brain may have been affected too.

Moschcowitz suspected that the cause of death was a potent poison or toxin, which is both agglutinative and haemolytic, i.e. it had the ability to decompose red blood cells.

Today we know the disease as Thrombotic Thrombocytopenic Purpura (TTP) or as it was first described as Moschcowitz syndrome.
1924 – A new disease

Referenzen:


Eli Moschcowitz lived in New York for most of his life. He was born on August 2, 1879 in Girált in the Kingdom of Hungary, which was part of the Austrian and Hungarian Monarchy. He was the ninth and last child of Moritz and Rosa Moschcowitz-Friedländer after 5 girls and 3 boys, including their 14-year-old brother Alexis, who later became a respected surgeon at the Mount Sinai Hospital in New York. In 1881 the family emigrated from Hamburg to the USA, the crossing took place by ship. Moschcowitz studied medicine at Columbia University College of Physicians and Surgeons in New York. After graduating in 1900, he followed an obligatory practical semester at Mount Sinai Hospital and then in 1903/1904 he went to Berlin, where he trained as a pathologist with Prof. Ludwig Pick. Back in New York, he became a pathologist at Beth Israel Hospital and continued his education in clinical medicine. In 1920 he moved to Mount Sinai Hospital, which soon merged with Beth Israel Hospital and became one of its directors, as well as professor of clinical medicine at his alma mater at Columbia University in New York. He held both positions until he retired in 1945. During his career, he wrote more than 80 scientific papers, many with groundbreaking observations, such as the first description of TTP, changes in the blood count (eosinophilia) as a result of allergic reactions, on pulmonary hypertension or on the cause of arteriosclerosis. He was one of the first to see connections between the psyche and organic diseases (e.g. stress and high blood pressure or stomach ulcers, etc.). He was a valued internist, scholar, and scientist. His colleagues admired his diagnostic skills in solving unusual cases. He liked to travel - before the Second World War he was in Europe almost every year, as the numerous preserved ship passenger lists of the New York port authorities have shown. Later he went by steamship to South Africa, South America and Hawaii. He was a lover of music and art, books and good food, a long-time member of the Manhattan Chess Club, and apparently a magician. He was active well into old age, writing scientific articles and practicing until his death on February 23, 1964 at the age of 82.
Sources:
2. Baehr G. Foreword. Journal of the Mount Sinai Hospital 1945; XII (No 1, May-June)
3. Lilienthal H. Eli Moschowitz – on the doorstep of the hospital. Journal of the Mount Sinai Hospital 1945; XII (No 1, May-June):1-4
The Mount Sinai Hospital in New York – for almost 100 years a TTP working place

The Mount Sinai / Beth Israel Hospital in New York plays an important role in the history of the TTP. Not only the world's first TTP patient was hospitalized, but also Dr. Eli Moschowitz’s and Dr. HM. Tsai worked here. He described the Von Willebrand factor-splitting protease, the “scissors” or the Swiss Army Knife, at the same time as our team in Bern under the direction of Prof. Miha Furlan. But we come to Dr. HM. Tsai and to Prof. Furlan another day.

The Mount Sinai Hospital was founded in 1852 to provide medical care to the rapidly growing Jewish immigrant community in Manhattan. A suitable piece of land on New York's rural periphery was quickly located and acquired, just south of the Empire State Building built in the 1930s. At that time, sheep were still grazing here, as well as the residents of New York were picking tomatoes or roasting potatoes on campfires in this area. The foundation stone was laid on Thanksgiving in 1853 and the 45-bed hospital opened its doors to patients on June 5, 1855. In the first year, 216 patients were treated, but only 16 of them could pay for their treatment. The hospital was soon bursting at the seams and the need of a new building arised. As the population continued to grow rapidly, the Mount Sinai Hospital moved to a larger area on the east side of Central Park in East Harlem, Manhattan, where is still located today.

Since the establishment of the Mount Sinai / Beth Israel Hospital, many pioneers have worked in its premises. To name an example, prof. Abraham Jacobi as founder of paediatrics and later president of the American Medical Association, was so popular and respected that envious dodgy general practitioners and quacks employed a doppelgänger to lure patients into their clinics. Further examples are Prof. Jonas Salk, the inventor of the polio vaccination and the gastrointestinal specialist B.B. Crohn to name a few.
The Mount Sinai Hospital in New York – for almost 100 years a TTP working place

Sources:
At Murtenstrasse 40 (Bern, Switzerland), we, the TTP research group, share a big laboratory space with 9 other groups, and we consist of a total of 40 people coming from 13 different nations. We have different cultural traditions around Saint Nicholas and Christmas. Let’s discover what our colleagues told us:

In Italy we don’t have Saint Nicholas, but we have “la Befana”. La Befana is a very friendly and amiable Italian witch who rides around on a broomstick. She brings candies and gifts to the good children and coal to the bad children on the morning of Epiphany, January 6.

In Morocco we usually do not celebrate Christmas, but you can find Christmas trees and decorations around. We prefer to celebrate New Year’s Eve.

In Belgium we celebrate Saint Claus and Saint Nicolaus. We have been told that he comes from Spain because he brings tangerines and nuts.

In Spain we mainly celebrate January 6, the three kings day.

In France we only celebrate Christmas.

In Lebanon it depends on the families. Some celebrate Santa Claus and Christmas, other not.

In India we do not celebrate Christmas because it is not part of our culture, but because we learned in school we celebrate anyway.

In China we don’t celebrate Santa Claus, but me and my family live for so long in Switzerland that we celebrate it anyway with family and friends.

In Macedonia we do not celebrate Santa Claus, it is not fully part of our culture.

In Nepal we do not celebrate Christmas, it is not fully part of our culture.

In Germany, Switzerland and The Netherlands we celebrate Saint Nicholas. To discover more about this festivity, open the door tomorrow!
Sinterklaas is the name of St. Nicholas in the Netherlands.

On the Saturday after Martini, in the middle of November, Sinterklaas arrives with his assistants in the Netherlands. They are warmly welcomed by many people, young and old, old and young. He brings tangerines, oranges, pepper nuts and other delicacies from Spain. While Sinterklaas wears a white beard, a red cape, a bishop's miter and a crook, his assistants (Zwarte Piet = Black Peter) are dressed in splendid, oriental robes and their faces blackened with shoe polish. The latter has given rise to heated debates on racism in recent years, and there have even been calls for Sinterklaas to be abolished. Since then, in addition to the typical Zwarte Piet, you can also see helpers with green, blue or red makeup. On his white horse, Sinterklaas rides across the land and the roofs, and comes into the houses through the chimney with his assistants. The children put their shoes or winter boots with an apple or a carrot for the horse, or a drawing or something handicraft for Sinterklaas in front of the fireplace or the front door. If Sinterklaas and Zwarte Piet are in the area, the children gifts are replaced by small gifts or treats, otherwise you may try again in the next evening. The actual festival is celebrated on the evening of December 5th. It's Pakjesavond (gift evening). On this evening Sinterklaas brings gifts, toys for children. The recipient usually gets the first letter of his name made of chocolate. Adults often have to guess the content of their gifts, funny rhymes or short poems serve as a hint.

Samichlaus in der Schweiz

Santa is living in a dark forest where he documents the good and bad behavior of all the children. He writes everything down in his book. Once a year on December 6th, Santa travels with his donkey and Schmutzli to the children’s homes. While Santa is dressed in a nice red robe, Schmutzli is clothed in brown rags, his face blackened by grime. The donkey is carrying the heavy bag with all the gifts for the well-behaved children, while Schmutzli carries the rod for the bad behaving children. The children will tell Santa rhymes or poems and as a reward will get nuts, tangerines, gingerbread and chocolate from Santa. Schmutzli will stuff the bad behaving children into the now empty bag, carrying them back to the forest where they become Santa’s helper for one year.
Saint Nicholas in Germany

St. Nicholas Day or Nikolaus sometimes also spelled Nikolas is the Patron Saint of Children and on December 6th children throughout Germany wake up to find small gifts and goodies in their shoes. On the evening of December 5th, children not only place a boot or shoes outside their bedroom doors, but they also have to clean them first, hoping that St. Nicholas will fill them with presents overnight. The German Nikolaus tradition is still very strong in Germany and to this day children look forward to cleaning their shoes and receiving small gifts.
Thrombotic thrombocytopenic Purpura – a concept was born

Already long before the platelets (thrombocytes) were identified as component of the blood, the German doctor and poet Paul Gottlieb Werholf, described in detail the first case of thrombocytopenia purpura. He was really famous in Hannover as it was the royal physician.

He called this clinical picture morbus maculocosis hemorrhagica, because the patient presented petechiae (the purpura) and a bleeding tendency in particular in the area around the mucosae.

The rise of high microscopy resolution in the middle of 19 century helped in finding the connection between the discovery of platelets and so called Werholf syndrome. Today we know this disease as idiopathic thrombocytopenic purpura (ITP), causing 50-100 cases per million per year. ITP occurs 50 times more frequently than TTP. It comes often after infections and it affects children more than adults. In many cases, thrombocytopenic purpura has presented a benign course. In children it resolve spontaneously, as it is not happening for TTP.

In 1947 the physician Karl Singer treated in Chicago a 11-years old girl with thrombocytopenic purpura, she died after a week of hospitalization. She had a similar disease course as the girl treated some years before by Dr. Eli Moschocowitz (Story Advent calendar Day 1). In his report, Singer stressed the difference of his case to the well known and more frequent ITP. He described all the histopathological findings he could observed. He also reported together with this case 11 other additional cases including Dr. Eli Moschocowitz’s case and linked together the clinical findings with laboratory results. This new disease was, indeed, quite rare, but highlighted the continuous occurrence of certain distinct signs present in all 12 cases.

Singer recognized that the thrombocytopenic purpura was caused by platelet consuption in small vessels. He was the first one calling this new disease thrombotic thrombocytopenic purpura, to mark the clear difference with ITP. The name remained.

Sources:
Today, we look at TTP in Switzerland, from the research team prospective. Isabella, our fantastic lab-technician and coordinator of the Hereditary TTP Registry, told us about her research:

“I’m working for the TTP Registry since January 2015 as a coordinator and also supporting Erika Tarasco our Registry manager. From the beginning on, when I was getting to know all the theory about TTP, I realized how strongly patients are suffering when diagnosed with TTP. We also enroll family members and therefore whole families are affected by one patient’s diagnosis. I am also working in the lab doing research. This is also a good way to find out more about TTP and hopefully to contribute to a relief or even cure. It motivates me to go on and I’m still excited to learn more about TTP every day”.
Karl Singer and his team carefully noted all clinical symptoms, including those that preceded the acute illness, and remarked the laboratory changes in the first 12 TTP cases. All of them were pale, including the low platelet counts, had fever; eleven patients had purpura or at least bruises, and half complained of nausea or vomiting.

It took another twenty years until, in 1966, Edward L. Amorosi and John E. Ultman set down again, screened through the literature and summarized the already published cases (they were now at least 271) with their own 16 cases.

Amorosi was in his training as a haemato-oncologist. Ultman was an oncologist already known for his careful elaboration of diagnostic criteria, e.g. to differentiate among different lymphatic cancer diseases and their stages.

The TTP was an interesting clinical picture for them, part of the "benign hematology" and they could - as I assume - go to work with ease. The most common signs, the fundamental symptoms of TTP, are summarized in the now famous TTP pentad. The pentad includes fever (38-40 ° C); severe thrombocytopenia and / or purpura; hemolytic anemia; neurological symptoms; as well as kidney involvement (see table below). In addition, Amorosi and Ultman reported again on the reserved prognosis that of their 16 cases, only one patient survived.

As treatment options increase and improve, survival has improved and today we no longer wait for a patient to have the full pentad; therapy has to be started as earlier as possible. Hence, the proportion of patients with the full pentad has now become small.

<table>
<thead>
<tr>
<th></th>
<th>1925-1964²</th>
<th>1964-1980³</th>
<th>1995-2008⁴ ADAMST13 &lt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Fever</td>
<td>98%</td>
<td>59%</td>
<td>15%</td>
</tr>
<tr>
<td>2 Thrombocytopenia</td>
<td>96%</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>3 Microangiopathic hemolytic Anemia («Schistocytes»)</td>
<td>96%</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>4 Neurologic symptoms</td>
<td>92%</td>
<td>84%</td>
<td>76%</td>
</tr>
<tr>
<td>5 Renal involvement</td>
<td>88%</td>
<td>76%</td>
<td>65%</td>
</tr>
<tr>
<td><strong>PENTADE (all 5 signs)</strong></td>
<td>88%</td>
<td>40%</td>
<td>~4%</td>
</tr>
<tr>
<td><strong>Survival rate</strong></td>
<td>~6%</td>
<td>46%</td>
<td>78%</td>
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The pentad - a clinical picture emerges from individual cases

Sources:
Plasma therapy - exchange and infusion, finally the first TTP survivor

Given the dramatic clinical course, the doctors tried everything to save their patients. Unaware of the pathophysiology, the TTP patients received treatments such as those used for similar or overlapping clinical pictures. High dose steroids and splenectomy (removal of the spleen) were successful in idiopathic thrombocytopenic purpura (Werlhof’s disease), they were used in TTP patients, and have sometimes been successful. High fever, thrombocytopenia and the presence of fragmentocytes often suggested a severe infection with blood poisoning (sepsis) and disseminated intravascular coagulation, so heparin (a drug used to thin the blood) was used. Due to the large number of platelets in the thrombotic occlusions, anti-platelet drugs (e.g. aspirin) were given. In addition, attempts were made to dissolve the thrombotic occlusions with special enzymes (urokinase), as in the case of "normal" heart attacks, large pulmonary embolisms or other thrombotic vascular occlusions.

Another approach, that has been used, was the exchange of whole blood for fresh whole blood (“exchange transfusion”). Moschcowitz had suspected that a powerful poison or toxin with «agglutination properties» and red blood cell decomposing abilities was the cause of TTP. This poison therefore had to be removed. By 1976 circa 20 patients were treated, a little more than half of them survived and gone into remission. A first ray of hope.

Bukowski’s team in Cleveland, Ohio, who had a lot of experience with exchange transfusions, assumed that the effect of exchange transfusions was based on the removal of a soluble poison. They successfully replaced the very complex exchange transfusion with plasmapheresis in two patients. Bukowski correctly suspected that antibodies against a still unknown factor (antigen) were to blame for the TTP. If the antibody production were to stop, the pathogenic immune complexes between the antibody and the antigen could be removed by plasmapheresis and the TTP could be cured. He dismissed the idea that there may be some factor missing in TTP in the blood or plasma. He wasn't right about that.

John J. Byrnes and Mohan Khurana suspected a missing plasma factor and this was the motivation to treat their patients - also successfully - with plasmapheresis. Jefferson D. Upshaw found the missing plasma factor through the care of a patient with the hereditary form of TTP. In a wonderful and very readable analysis of the course of her illness, her hemoglobin and platelet levels over 11 years, he found that whenever she received plasma-containing blood products or plasma, her illness got better. Therefore, he concluded that his patient was congenitally deficient in plasma factors and treated her with plasma infusions for many years.
Plasma therapy - exchange and infusion, finally the first TTP survivor

Sources:
At the beginning of the 20th century, researchers in Paris discovered that, after large blood donations in the serum, a soluble factor, resp. a hormone, is present and is able to stimulate the production of red blood cells. In 1948 the Finnish doctors Eva Bonsdorff and Eeva Jalavisto gave this hormone the Greek name erythropoietin (erythros = red, poiein = to make). Soon the observations increased that erythropoietin, or EPO, is formed by the kidneys - if these are not supplied with enough oxygen, e.g. in the case of anemia. Kidneys increase the EPO level in order to stimulate the production of oxygen carriers, i.e. red blood cells. Today, EPO has become an indispensable part of medicine and is also used in sport, here as a doping agent.

Irving Schulman, a pediatrician in Chicago and later at Stanford University in California (https://news.stanford.edu/news/2009/june17/med-obitschulman-061709.html), speculated that EPO was the hormone responsible for the stimulation of erythropoiesis, which could also stimulate the production of other blood cells, especially platelets (thrombopoietin).

He looked after an 8-year-old girl who had hematomas shortly after she was born in Germany. At 20 months of age, the diagnosis of idiopathic thrombocytopenic purpura (ITP) was made. A splenectomy did not help. Repeated transfusions were necessary because of severe thrombocytopenia and bleeding. The girl, who emigrated to America with her parents, received whole blood, plasma and freshly frozen plasma. After each administration of plasma, fresh or frozen plasma, the platelets rose rapidly, peaked after 9-11 days, but then decreased again and after 20-23 days reached initial values of 20x10^9/L. Schulman documented this process over 50 times. Occasionally, in addition to the thrombocytopenia, there was also mild jaundice, hemolysis and anemia; sometimes these responded to the plasma administration, other times not. He saw evidence in the bone marrow that the platelet's mother cells, the megakaryocytes, only produced large quantities of platelets after plasma was given. He concluded that chronic thrombocytopenia is the result of the lack of a factor in the girl's plasma, that this factor occurs in the plasma of healthy blood donors. This factor can be frozen and is required by megakaryocytes in the bone marrow for platelet production. Later on, in addition to thrombocytopenia, the girl often had attacks of hemolytic anemia.
Jefferson D. Upshaw, a doctor from the south of the Mississippi Delta, who later practiced in Memphis, the city of Elvis Presley and rock and roll, treated a similar case a few years later (see Advent story 10). He recognized the parallels to the TTP, even if his patient never developed the full picture with Pentad. He concluded that his and Schulman's patients had the same disease, which he attributed to a congenital deficiency of a plasma factor. However, this factor does not work like thrombopoietin. Both Schulman and Upshaw realized that the cases they observed suffered from something far rarer than ITP.

Just one year after Upshaw's report, the new clinical picture was called Upshaw-Schulman Syndrome. Today we know that this is the hereditary form of TTP, the result of a congenital deficiency in ADAMTS13. Ultimately, however, Schulman was also right in his hypothesis that there is a thrombopoietin, only this is not ADAMTS13.

Sources:
Today, we look at TTP in Switzerland, from the research team prospective. Erika, our Project Manager of the Hereditary TTP Registry, told us about her:

“After graduating in Biology, I moved to Switzerland to pursue a career in medical sciences. During my PhD at the University of Zürich I studied glucose and lipid metabolism in the context of metabolic syndromes (obesity, diabetes, hypercholesterolemia) and the effect of bariatric surgery. The final goal of this project was to create a model to improve the understanding of the underlying mechanisms of metabolic syndromes and to prevent them in a patient setting. The close interplay between research and clinical applications always fascinated me and I knew this is where I saw my future. This is why I was very excited to start working for the Registry almost 2 years ago. Collecting and analyzing data from the Registry taught me how serious TTP is and how important it is to keep doing research for the better health of all patients. Even if the process is long, I hope that my contribution will help in reaching the final goal in slowing down the disease and find a final cure to stop the disease.

As Thomas Edison said “Many of life’s failures are people who did not realize how close they were to success when they gave up.”
On the trail of Jefferson D. Upshaw into the Mississippi Delta

“The Mississippi Delta begins in the lobby of The Peabody Hotel and ends on Catfish Row in Vicksburg.”

David L. Cohn (in God Shakes Creation, 1935)

The Peabody Hotel is situated in downtown Memphis, Tennessee. It was in Memphis where J.D. Upshaw, after having studied medicine at Johns Hopkins University in Baltimore, completed his internship and residency. He was on the medical staff at Baptist Hospital in Memphis for over 40 years and on the faculty at University of Tennessee Health Sciences Center. He was a son of the Mississippi Delta.

The Mississippi Delta, or simply The Delta (not to be mistaken for the Mississippi River Delta south of New Orleans) is a distinctive northwest section of the U.S. state of Mississippi. It extends from the south of Memphis, between the riverbanks of the Mississippi and those of the Yazoo River, encompassing nearly 18,000 km². The rich alluvial soil allows intense farming of soybeans, corn, rice and cotton that for nearly 150 years dominated economically. The population is predominately African-American.

The Delta is the cradle of many modern music styles, such as the Blues (and the Delta Blues), Jazz of Rock’n’Roll. But, the Mississippi Delta saw also important battles of the American civil war (1861-1865; Vicksburg) and had an important role in the civil-rights movement in the 1960ies.

After completing a visiting professorship at the University of Oklahoma Health Sciences Center in May of 2018, Cristie Upshaw Travis and her husband Pat took me on a whirlwind weekend trip to their Delta.

I had got to know the Upshaw’s in 2014, and Cristie had attended as special guest the 2nd Meeting of the Hereditary TTP Registry 2014 in Bern, and the 61st Annual meeting of the Society of Thrombosis and Haemostasis Research (GTH) 2017 in Basel, Switzerland (read more in this here: Cristie goes to Bern and here: Falling for Switzerland).

We left Memphis southbound on U.S. Highway 61, also known as the Blues Highway and stopped in Tunica for a traditional Delta breakfast in the Blue & White. After my first Fried Green Tomatoes, we went on to Clarksdale (Shack Up Inn, its bar and tavern, a must for Blues addicts. Associated is an open-air museum of old farming equipment and old Shacks, today rooms for rent, which had served slaves and later itinerant laborers who tried to earn their living as cotton pickers) and Indianola, where the great Blues guitarist and singer B.B. King grew up as a child. And yes, we had time to visit his museum, which provides interesting information and insights in to living in the Mississippi Delta in the 1940-1970ies, as well as in the civil rights movement.

Ever further southbound, with a visit to an old plantation home, white and with monumental Doric columns near Betonia, we finally reached Louise, Mississippi, J.D. Upshaw birthplace and the town where his family had lived for generations. The small town still has an Upshaw Street, and family pews in the nearby church.
Dinner was offered by Cristie’s friends who live on a farm in the next small town. Upshaw relatives and friends, from near and far, came to say hello and welcome me, the special guest form Switzerland. The dinner was superb with many traditional dishes and I experienced the famous Southern hospitality. The next day, we met Louise’s mayor and visited Yazoo City, where Dr. Upshaw found his final resting place in 2008 on Glenwood Cemetery. Then it was time to head north, back to Memphis to meet more Upshaws and have a marvelous dinner at Cristie and Pat’s. A wonderful and memorable weekend, which gave me a good impression on who Dr. Upshaw was.
A real Southerly Gentleman, as Dr. James George of Oklahoma described him. Thank you, Cristie!

Johanna Kremer

Quellen:
1. Karte:
   https://de.wikipedia.org/wiki/Lower_Mississippi_Delta_Region#/media/Datei:Mississippi_Delta_SVG_Map.svg
Today, we look once more at TTP in Switzerland, from the research team prospective. Monica, our Senior Scientist, told us about her:

“My motivation to do basic research is best expressed in a quote from Marie Curie quote start “Nothing in life has to be feared, it only has to be understood” ...Ever since getting my PhD from the Faculty of Science of the University of Bern (1999), I dedicated my research efforts to study different autoimmune diseases. Since 2009 I am part of the Bernese TTP research with my main focus on studying the acquired form of TTP. A misguided immune response is at the origin of this autoimmune response. Thus in acquired TTP patients, a vital self-protein, named ADAMTS13 ("scissor") is attacked by auto-antibodies, produced by one’s own white blood cells. Those antibodies will bind the "scissor" in the blood and block it, so that the vonWillebrand protein chains cannot be cut anymore and will accumulate in the blood vessel and cause the blood to clot, the key feature of TTP. To develop a therapy targeting the autoantibodies, we need to understand first the genetic composition and the mechanism how these autoantibodies confer the disease. We could isolate from the spleen or blood from these autoantibodies and used them as tools to find proteins, that could bind and specifically block them, instead of the binding the „scissor“, resulting in a normal blood coagulation. We have found 22 potential candidates. The next step is now to test these blocking proteins, whether they are efficient, safe, and how long they can prevail in the blood circulation. We are still very far to be able to administer these proteins as a new therapy. Nevertheless, clearly it is our long-term goal to develop such a therapy to slow down the disease or even prevent relapses.

This perspective is for me the biggest incentive to make my small contribution to potentially increase the quality of life of acquired TTP patients, so that quote continuation “Now it is the time to understood more, that we may fear less” quote end, Marie Curie”.
In the past years, our TTP Bern Team organized some events with TTP patients to raise money for the “Answering TTP Foundation” founded by Sidney Kodatsky in 2009. We went for a hike on the Gurten, we walked along the renatured Aare between Bern and Belp and we had a flea market in Bern. Here you are some memories of these events:

Hoping more events will come... for now

**SAVE THE DATE ...**

TTP Patients Day in Switzerland, Zoom – meeting on January 12, 2021 h 17:00-19:00 CET
Von Willebrand Factor: the platelet-aggregation factor in TTP

Until late the end of the 1970ies, the pathophysiology of TTP was still elusive. Platelets were somehow involved, this was evident. The microvascular occlusions consisted of platelets, while platelets were lacking in CBCs and on the blood smear. The first therapeutic success in TTP through plasma therapy was initiated by Eric C. Lian at the University of Miami School of Medicine. He was a colleague of John J. Byrnes, who had performed the first plasma therapy for TTP (see advent calendar, day 10) to study the plasma of TTP patients in more detail.

Incubation of plasma of three TTP patients with platelets of healthy donors and platelets of the three TTP patients withdrawn during remission resulted in the aggregation of the platelets. Platelet inhibitors, such as Aspirin, or anticoagulants such as heparin or hirudin, were unable to prevent this platelet aggregation; however, plasma of healthy donors reversed the process induced by TTP plasma.

Joel L. Moake, who had been studying platelet adhesion and aggregation under conditions of shear stress since a number of years, recognized similarities of the process described by Lian and colleagues, to that of platelet agglutination induced by large multimeric von Willebrand factor. Consequently, he investigated the von Willebrand factor multimers in plasma of TTP patients, some of them with a chronic relapsing course. Indeed, in plasma of four TTP patients (A-D, two with acquired TTP A and C; and two with hereditary TTP B and D) he observed unusually large von Willebrand factor multimers. Their size was that of newly synthesized von Willebrand factor multimers of endothelial cells. During acute episodes of TTP, these unusually large von Willebrand factor multimers were not present, because – as Moake speculated - they were consumed in the platelet thrombi in the microvasculature. He concluded that patients suffering from TTP lacked a plasma protein, a so called depolymerase, that functions as a von Willebrand factor size regulator. Later, Moake coined the term «The Clumping Plague» to describe TTP.

Of the four patients, who provided plasma for Joel Moake’s studies, three had participated in landmark studies before. Patient B was described by Schulman in 1960, and patient D by Upshaw in 1978 (see advent calendar, day 11), while patient C had participated in the first study by Eric Lian in 1979.

References:
Nowadays randomized controlled studies are the gold standard in medicine to obtain a clear statement in the case of a clear question and to prove the causality, i.e. cause and effect. The individual reports on plasma treatment in TTP have been promising, but what better way to exchange plasma with removal of toxic substances and supply of large amounts of plasma, or would the infusion of a few plasma bags be sufficient?

An ideal question for a randomized controlled trial. One of them was started by the Canadian Apheresis Group in 1982 at sixteen Canadian centers and hospitals. The TTP patients should either exchange plasma with fresh plasma (1.5 times their plasma volume should be exchanged on the first three days, then only one plasma volume at a time), or plasma infusions (30 ml plasma / kg in the first 24 hours, then 15 ml / kg body weight). All patients with a diagnosis of acute TTP based on platelet counts <100x10⁹ / L and micronagiopathic hemolytic anemia should be included. To diagnosed TTP these two factors were not explained by any other cause or disease.

An ADAMTS13 measurement was not yet possible, the Von Willebrand factor-splitting protease, ADAMTS13, had yet to be discovered. 100 patients should be recruited. Since large volumes of fluid would be given with the plasma infusions (without taking anything away at the same time), the patients had to have relatively good cardiac and kidney function.

Because of the rarity of TTP, it took a full 7 years to recruit 102 patients, 51 for each study. The response rate and mortality on day 9 and after 6 months were examined:

<table>
<thead>
<tr>
<th></th>
<th>Plasma exchange</th>
<th>Plasma infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>After 1 cycle (day 9)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responsive</td>
<td>24/51 (47%)</td>
<td>13/51 (25.5%)</td>
</tr>
<tr>
<td>Deceased</td>
<td>2/51 (4%)</td>
<td>8/51 (15.7%)</td>
</tr>
<tr>
<td><strong>After 6 months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responsive</td>
<td>40/51 (78.4%)</td>
<td>25/51 (49%)</td>
</tr>
<tr>
<td>Deceased</td>
<td>11/51 (21.6%)</td>
<td>19/51 (37.3%)</td>
</tr>
</tbody>
</table>

The mortality for the entire study (all patients treated with plasma exchange or plasma infusion) was 29.4%, which was much lower than in all previous observations. Treatment with plasma exchange was more effective and mortality was lower in this group than in the group treated with plasma infusion only. As a result, plasma exchange with fresh plasma became the gold standard of TTP therapy. Gail A Rock, who led the study for the Canadian Apheresis Group, is still president of this medical society today.

Sources:
Today, we look at TTP in Switzerland, from the research team prospective. Silvan, our amazing PhD student, told us about him:

Given the opportunity to do research in the lab of Professor Kremer Hovinga, I gained access to the world of hematology. The different roles of the blood, the supply, the defense mechanisms as well as positive and negative effects are always affecting the whole body; that is what is so interesting about investigating blood and its diseases. This fact becomes also clearly visible when observing the rare disease TTP, where single components of the blood have an influence on several organs and ultimately the whole body.

The research of a rare disease brings many challenges, that is what we are reminded of every day during our lab work. However, which huge burden such a rare disease brings for patients, I realized during the impressive discussions with affected persons during one of our TTP-walks. Their stories and their gratitude let us go on every day and hopefully we will be able to contribute to the solution of yet unsolved riddles.
The von Willebrand factor-cleaving protease

The Von Willebrand Factor (VWF) was purified from plasma by gel electrophoresis for the first time in the early 1970s. The complete sequence (amino acid sequence) has been known since 1986, when various research groups published their results. In the 1980s the purification technique for the VWF Multimer Analysis got better and better and the examination on patients helped again. The multimer analysis showed that the VWF was strongly degraded in the plasma of patients with type IIA Von Willebrand disease (VWD). Only small multimers were shown, they were flanked by clear satellite bands, while in the plasma of healthy individuals whole ladders with small ones up to large VWF multimers were shown (Figure 1). Even in healthy people, the main band was surrounded by satellite bands, but these were less pronounced. Analysis of the satellite bands suggested that they were degradation products of larger VWF multimers. There were various hypotheses as to which enzyme could be responsible for the breakdown of the large VWF multimers. Possible candidates appeared to be cathepsin G, produced by white blood cells, a platelet-aggregating cysteine protease, or calpain from platelets. Judy Dent and colleagues then characterized the cleavage site at which VWF multimers were cut into smaller fragments; the cleavage took place between the tyrosine at position 842 (according to the new nomenclature Tyr 1605) and methionine 843 (Met 1606). None of the known proteases degraded proteins by cleaving a Tyr-Met bond, so the Von Willebrand factor-cleaving protease had to be a new, as yet unknown protease that had to be found.

The further, very exciting but also arduous path to the VWF-cleaving protease, ADAMTS13, was long. The knowledge of the cleavage site in the VWF made it possible to develop laboratory tests to measure the VWF-cleaving protease in plasma, a key requirement to purify it from plasma. First findings on VWF-cleaving protease, a metalloprotease (bivalent metal ions are necessary for functioning), were found in various ways and in 1996 by H.M. Tsai, who works at the Mount Sinai Hospital in New York (see Advent calendar day 4) and the Bern group around Miha Furlan publishes in Blood. It took another 5 years until the amino acid sequence and the gene (located on chromosome 9q34) of the VWF-cleaving protease, ADAMTS13, were published in 2001.

A very interesting review of the discovery and characterization of the Von Willebrand factor-splitting protease, ADAMTS13 - wonderfully told by Miha Furlan, who also drew the picture with the Swiss Army Knife that cuts the sticky VWF decorated with platelets (Figure 2) - was published in 2004 in the Journal of Thrombosis and Haemostasis.
The von Willebrand factor-cleaving protease

Sources:
3. Tsai HM. Physiologic cleavage of von Willebrand factor by a plasma protease is dependent on its conformation and requires calcium ion. Blood 1996;87:4235–44.
In TTP, the von Willebrand factor-cleaving protease is absent

What was now the physiological importance of the Von Willebrand factor-cleaving protease. Why should it be necessary to split the large Von Willebrand factor (VWF) multimers, which are important for hemostasis, into small multimers that are not very effective for hemostasis?

A few years earlier, Moake et al. observed that in patients with chronically relapsing TTP, the VWF in the multimer analysis was unusually large (cf. Advent calendar, day 16). This work was known also to Miha Furlan and Bernhard Lämmle. In the plasma of two brothers who lived near Bern and suffered from chronically recurrent TTP, they documented the complete absence of the VWF-cleaving protease, which was also absent over time. The brothers' sister had a highly normal activity of the VWF-cleaving protease, the parents about a semi-normal activity. The hereditary form of TTP (or chronically relapsing TTP) was thus due to the complete lack of VWF-cleaving protease. The cause of the acquired TTP was clarified a year later by Furlan and Lämmle. A severe deficiency of the VWF-cleaving protease was also documented in this almost 34-year-old patient who had to be treated repeatedly for TTP for almost a year and only came into sustained remission through a splenectomy 24 years ago. In this case, however, the severe deficiency was due to an inhibitor against the VWF-cleaving protease.

The New England Journal of Medicine still rejected these two manuscripts, but in 1998 a larger patient series from the Bern laboratory was accepted for publication by this most important medical journal. In the same issue of the New England Journal of Medicine, a parallel work with similar results from Mount Sinai Hospital was published. A severe deficiency of VWF-cleaving protease in TTP patients was thus also found in another laboratory. The skeptics were finally convinced. A few years later, with the help of some of the patients studied at Mount Sinai Hospital, the gene for the VWF-cleaving protease, ADAMTS13, was found on the long arm of chromosome 9.
In TTP, the von Willebrand factor-cleaving protease is absent

Sources:
The severe ADAMTS13 deficiency (<10% of the value in healthy people) allows a special form of thrombotic microangiopathies (TMA) to filter out and prove the TTP. If, in addition to the ADAMTS13 activity measurement, the ADAMTS13 inhibitor or ADAMTS13 antibody determination is added, a further distinction is made between innate TTP and acquired TTP, where antibodies against ADAMTS13 are detected.

Among the TMAs severe ADAMTS13 deficiency is the one prone to recurrence. Thanks to the famous Oklahoma TTP Registry, the team led by James N. George (Oklahoma, USA) was able to show that after an initial episode of an acquired TTP, almost half of the patients suffer a relapse in the course of time, and almost a quarter of them relapse within the first 12 months. In patients with TMAs without ADAMTS13 deficiency at diagnosis, relapses are rare.

A year later, Marie Scully’s team (London, UK) showed that the recurrences of TTP (mostly) occur later when the monoclonal CD20 antibody rituximab is used in addition to cortisone derivatives to suppress the immune reaction against ADAMTS13. For this reason, patients at many centers today receive therapy with rituximab as soon as the first TTP attack (but this also treats patients who might never suffer a TTP relapse). Rituximab is used practically everywhere at the latest with the first relapse.

Patients are now usually followed up to prevent recurrence. In the first 2 years after a relapse, the check with blood count and determination of the ADAMTS13 activity is usually carried out every three months for the first two years. Then the check-up interval is partly adapted to the request of the patient, in most cases to every 6 months. The aim of follow-up care is to detect a dangerous decrease in ADAMTS13 activity (below 15-20%) at an early stage and to initiate prophylactic therapy with rituximab before a full TTP relapse occurs (every TTP flare-up carries a risk of long-term damage and mortality). Such prophylactic therapies were launched on a large scale by the French TMA Reference Center and are now being used with great success worldwide, even though there may also be patients among the patients who would have spontaneously normalized ADAMTS13 activity. Perhaps in the future it will be possible to better identify the patients with an immediate risk of recurrence and thus only treat those who need rituximab treatment through the detection of an ADAMTS13 circulating in an open conformation. Whether the open ADAMTS13 conformation is suitable as an important additional marker for the follow-up of TTP patients in addition to the severe ADAMTS13 deficiency has yet to be further investigated in studies.
The ADAMTS13 Deficiency - Evidence and Marker for Follow-up Care and Therapy Planning

Quellen:
The prospective of new TTP therapies

In 2002 Joel Moake published a review entitled “Thrombotic thrombocyto-penic purpura - The clumping plague”. The title combined perfectly most clinical problems of TTP and this lump formation. New TTP therapies aim to prevent them.

On the one hand, drug Cablivi® (caplacizumab) has market authorization in the USA, Europe and Switzerland. Caplacizumab is so-called nanobody, a small molecule originally derived from a one-armed antibody found in lamas, camels and sharks, which binds to the platelet binding site in the Von Willebrand factor (VWF) A1 domain. The platelets can no longer bind to the “blocked” VWF, and the clumping that characterizes acute TTP ceases almost instantaneously. The platelet counts normalize quickly, the ischemia-related organ damage decreases, as does the mortality. The plasma exchange treatment can usually be rapid, i.e. be stopped within a few days (typically 3-5). Therapy with caplacizumab is already part of the standard therapy in many places. The first selected patients with acute acquired TTP have already been successfully treated with only caplacizumab and immunosuppression - further studies must follow before the current gold standard (plasma exchange) can be dispensed with. Since caplacizumab does not treat the cause of the acquired TTP, the autoimmune reaction with the formation of antibodies against ADAMTS13, immunosuppressive therapy will become more important in the future, so that rituximab must be used as early as the first attack.

We also have great hopes and expectations of the recombinant ADAMTS13, i.e. genetically engineered ADAMTS13. Patients with the hereditary form of TTP will benefit first. Currently, they only have regular plasma infusions, which they receive every 1-3 weeks in transfusion centers or hospitals, as causal therapy. With this genetically engineered ADAMTS13, home self-treatment is finally possible for patients with Upshaw-Schulman syndrome, very similar to how patients with hemophilia (hemophilia A and B) have been treated with factor substitutes (factor VIII or IX) since 20 or 30 years.

It will also be possible to administer larger amounts of ADAMTS13 than what is currently possible with plasma infusions. As a result, patients with Upshaw-Schulman syndrome can be better protected against organ damage (e.g. stroke) as a result of vascular blockages caused by clumping. Perhaps recombinant ADAMTS13 will one day also be available for the treatment of acquired TTP. Appropriate studies are currently underway for at least both indications - congenital and acquired TTP.

It still a long way before we could have plasma-free TTP treatment with caplacizumab and recombinant ADAMTS13, but it is a dream that is worth working on.

There is still a lot to do, let’s get started ...
The prospect of new TTP therapies

Sources:
Quellen:
Christmas eve

Wishing you a delightful and magical holiday season ahead!
Have a Merry Christmas and a prosperous New Year!
Our best wishes to you!

Your TTP Bern Team

Johanna   Monica   Silvan   Erika   Isabella   Irmela