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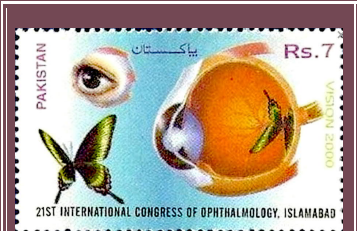


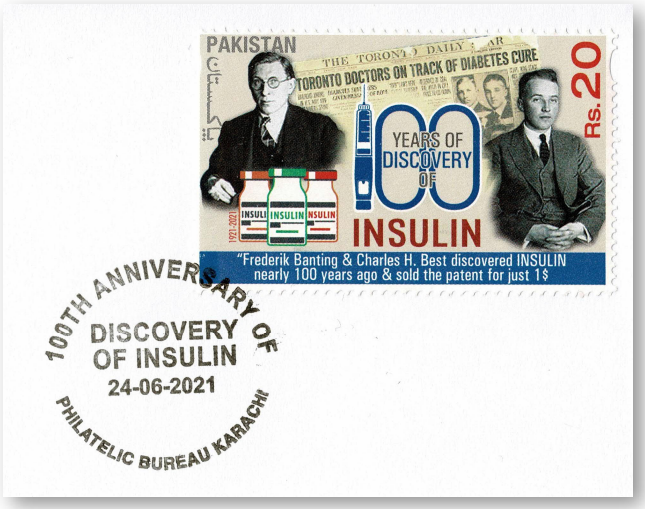
Ein Schimmer von Licht, ein Hauch von Glanz,
die Schmetterlingsflügel, ein faszinierender Tanz.
Der Flug in der Luft, so leicht und frei,
das Auge verfolgt jede Bewegung, wie Zauberei.

REDAKTIONSSCHLUSS HEFT 210: 15. August 2023

Insulin, a more than 100-year journey of discovery

Johan Diesveld

Foreword



Last year was marked medically by the 100-year discovery of insulin - a milestone in medical history. Insulin is an important hormone (chemical messenger) in the human body. This substance, which is produced in the pancreas, influences the blood sugar level, which, when elevated, is called diabetes (= sugar disease).

In the following story I will tell a little about the connection between the hormone insulin and diabetes and what you can do about it. Wim Hogendoorn has reported on this in a stamp blog: https://www.postzegelblog.nl/2021/07/10/100-jaar-insuline-deel/, and https://www.postzegelblog.nl/2021/07/13/100-jaar-insuline-deel-2/. This article borrows heavily from my article in NVFT - February 2023.

My main focus is the search for the molecule insulin and its chemical structure.

Introduction

Fig. 1

Diabetes is not a "modern" disease. The ancient Egyptians had already described diabetes (Fig. 1, Ebers Papyrus from about 1550 BC). The Greek Aretaeus of Cappadocia (130-200) also described the disease diabetes quite accurately (Fig. 2).

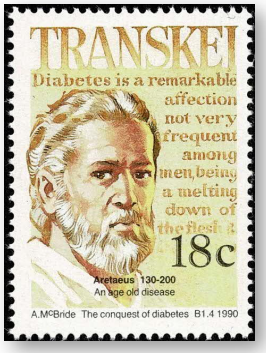


Fig. 2

In the Middle Ages, people depended on all kinds of more or less good "experts" for their health. One of their examination methods was uroscopy, the so-called urine examination. Observed were: Quantity, viscosity, colour, odour, transparency, precipitation/flocculation and foaming of the urine. Evidence of some diseases could be found in the vial of very personal fluid. There were also other ongoing research, er .... studies. After all, as a doctor you do everything for your patients, but this is going a bit too far for me. All right, urine tastes sweet in diabetics. So the urine observer (Fig.3) pitched his tent at the market, people queued up and one by one they got a consultation. In public, no problem at all!

Fig. 3

The next person to start analysing things further was the Frenchman Claude Bernard (1813-1878) (Fig. 4, Rue Claude Bernard in Paris is named after him). He was able to show that the pancreas has a decisive influence on digestion. The pancreas produces all kinds of digestive enzymes that are discharged into the duodenum to begin their work in digesting food. These are

called exocrine secretions. The pancreas also has endocrine secretions, including insulin, which is secreted directly into the blood.

The German pathologist Paul Langerhans (1847-1888; Fig. 5) discovered cell clusters in the pancreas in 1869. In these, the β-cells that produce insulin were identified. These cell collections are

Fig. 4

Abb. 5

known as Langerhans' islets (you will look in vain for their location in a Bos atlas (Fig.6)).

The next step was taken by the German-Lithuanian doctor Oskar Minkowski (1858-1931) and the German doctor Josef von Mering (1849-1908). In 1889, they removed the abdominal salivary gland from a dog, which then developed diabetes (Fig. 7).

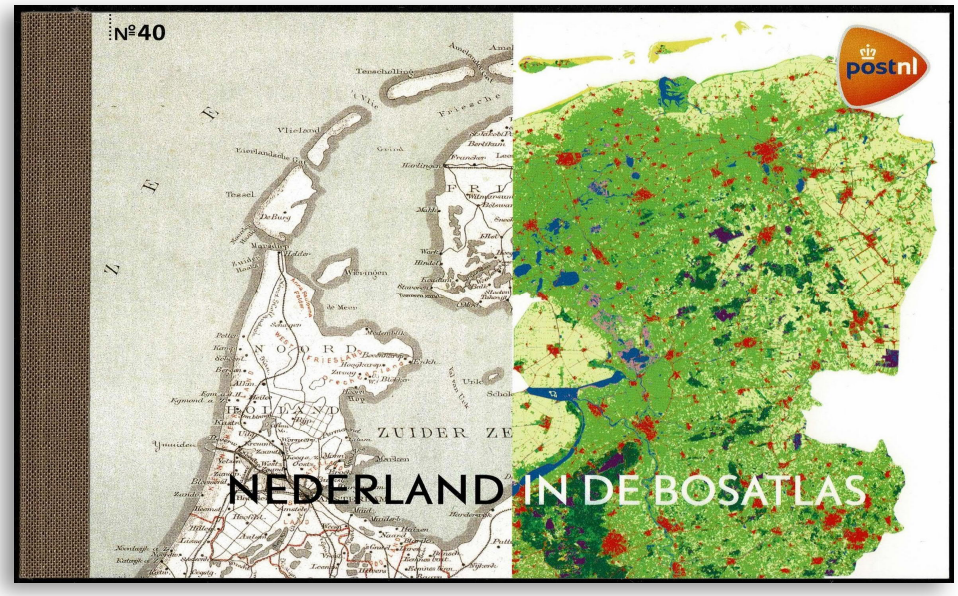


Fig. 6

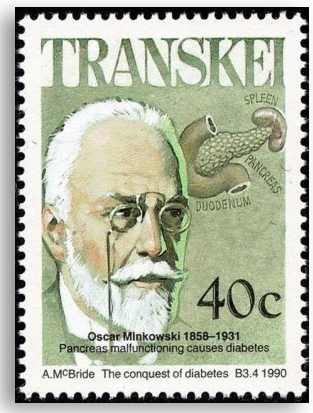


Fig. 7

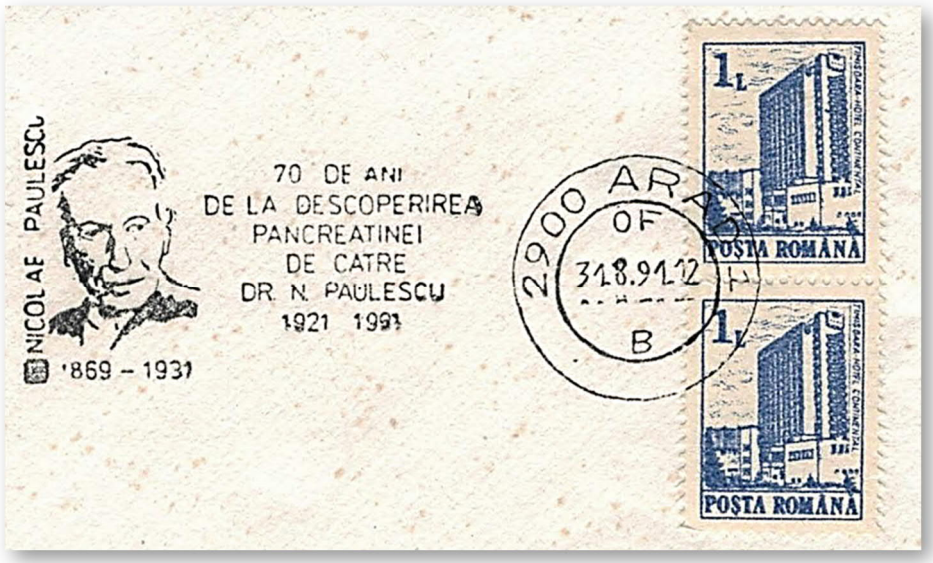


Fig. 8: der Stempel erinnert an die Forschung mit Pankreatin

Fig. 9: die Entdeckung des Insulins ist vielleicht zu viel des Guten

Discovery of insulin

With the transition to the new century, a big step was taken in diabetes research. In the first years of the First World War, the Romanian Nicolae Paulescu (1869-1931) worked on this topic. After feeding an aqueous extract from the pancreas (in which insulin was dissolved = pancreatin) to a dog suffering from diabetes, he observed a favourable effect on the blood sugar level (Fig. 8). He had come this far in 1916 when he was drafted into the army. After the war, he continued his research and published extensively on the subject in 1921. His "purification" of the pancreas for insulin production gave a direction, but the resulting "brew" was not readily applicable in humans. However, a positive effect in humans could be demonstrated (Fig.9). For this work, however, he did not receive the recognition he deserved.

Fig. 10

The next group of people to venture into this research were Canadians. Frederick Banting (1891-1941) (Fig. 10) certainly saw possibilities; he sought help from John Macleod (1876-1935), the head of a laboratory who had the spatial and technical resources for these experiments. With his experienced assistant Charles Best (1899-1978, Fig.11), the decisive experiments were carried out on dogs. It was possible to cause the exocrine part of the pancreas to die by surgery, but the islets of Langerhans remained intact. This proved advantageous for the purification of an insulin extract. Injecting this extract into diabetic dogs gave hopeful results, i.e. blood glucose levels were lowered.

After consultation with Macleod, the research was intensified. Another collaborator was brought in for the research: James Collip (1892-1965).

Fig. 11: *a Croatian obligatory stamp on the occasion of 75 years of insulin. The stamp was obligatory on all letters from 10 to 17 October 1996, a practice that was very well known in the former Yugoslavia, whose successor states include Croatia.*

Fig. 12

At the end of 1921 the researchers had built up that much knowledge and experience, that it was regarded tob e justified to move on to make the first experiments in humans (Fig. 12). In January 1922, 14-year-old Leonard Thompson, who had diabetes, was treated with an injection of the (impure) insulin extract. Unfortunately, the extract was so impure that Thompson suffered a severe allergic reaction. However, Collip succeeded in obtaining a completely pure extract from the bovine pancreas within two weeks. The extract had a very positive effect on blood sugar levels and did not cause any health problems (Fig. 13). And what follows is, as they say, history.

Collip had already shown that bovine insulin also works well in the human body. Later, it was shown that insulin from pigs is also effective in the human body. According to today's knowledge, this is not surprising, because the composition of human, bovine and porcine insulin hardly differs from each other. Another fortunate circumstance was that the pancreas of cattle and pigs was always and almost everywhere available in slaughterhouses.

Purification was also improved even further, so that allergic reactions occurred less and less frequently.

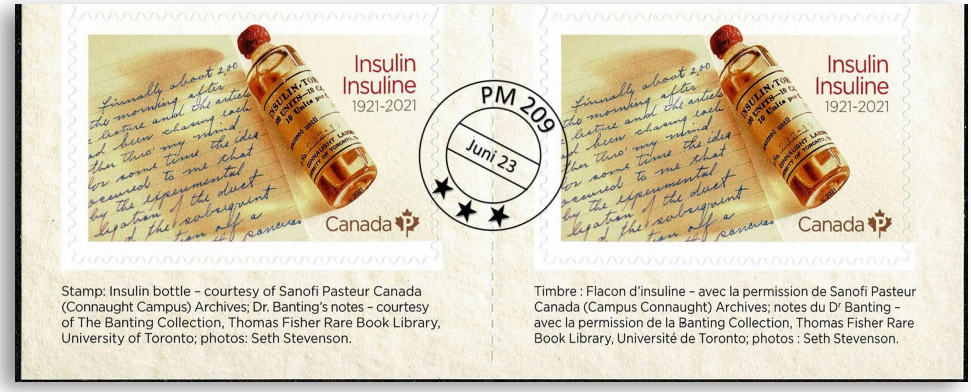


Fig. 13: Part of Banting's notes on the stamp of a stamp booklet

Such an important research result, whose benefit to humanity is undeniable, is worthy of a Nobel Prize. Indeed, the Nobel Prize in Physiology and Medicine was awarded in 1923 for the discovery of insulin. The Nobel Prize is awarded to a maximum of three (still living) persons. So problems are inevitable! It was eventually awarded to Banting (Fig.14, as one of the most famous Canadians of the twentieth century) and Macleod (he was never depicted on a Canadian stamp; after some time he returned to his native Scotland). This caused some surprise. Banting was so upset that his collaborator Best was not nominated that he shared half his prize money with him. Similarly, Macleod went ahead and shared his prize money with Collip. It was often noted with surprise that the Romanian Paulsecu was not nominated or at least mentioned. But it was not the first (and certainly will not be the last) time that there was or will be a controversy about a Nobel Prize.

Fig. 14

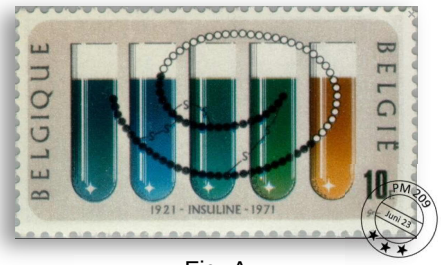


Fig. A

Much more could be told about the history of insulin, such as the determination of its primary structure (amino acid sequence; Fig. A) by Frederick Sanger (1918-2013), or the elucidation of the molecular structure of insulin by means of X-ray crystallography by Dorothy Crowfoot Hodgkin (1910-1984; Fig. B), or the beginning of the production of insulin by genetic engineering, or, o-the..... But this will be told another time.....

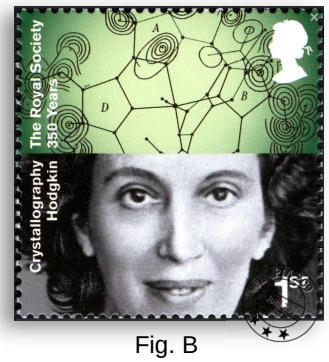


Fig. B

New therapies for degenerative eye diseases

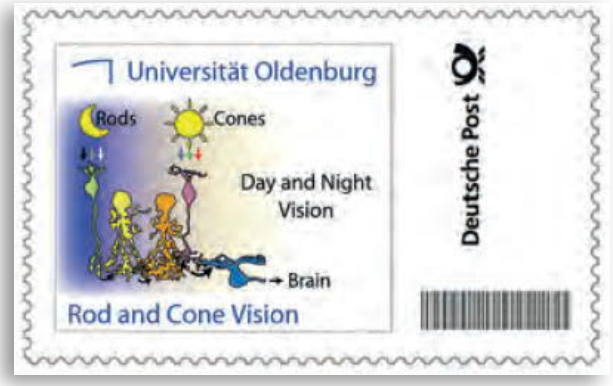
D.M. Vogt Weisenhorn

Belgium 2021: a healthy eye is a miracle of nature - not only in humans (Liechtenstein 2018)

Retinitis pigmentosa, a group of rare eye diseases, alters the retina's response to light as photoreceptor cells slowly die over time. The most common early symptom of this chronic disease is nyctalopia, or loss of night vision, which often begins at a young age. Retinitis pigmentosa affects about one in 4000 people in the United States and one in 5000 worldwide.

In the retina, rod and cone photoreceptors convert light into electrical signals, which the brain then interprets as vision via the ganglion cells. In most forms of retinitis pigmentosa, the rods in the outer part of the retina are affected first. The rods are mainly activated by weak light. Their degeneration thus impairs peripheral vision and night vision.

As the disease progresses and the cones are affected, visual acuity, colour perception and central vision are also affected. Daytime vision is initially unaffected, but the loss of night vision can lead to impairment in everyday activities, such as driving in the dark. Over time, the gradual narrowing of visual fields and loss of peripheral vision can cause patients to bump into objects in the periphery and notice missing aspects of their vision. In later stages of the disease, the visual field narrows until only part of the central vision remains. In severe cases, the disease can lead to total blindness by the age of 20.



Personalised stamp 2017 with representation of the rod and cone receptors

Djibouti 2020 (Agency Issue): The Nobel Prize in Chemistry was awarded in 2020 for the use of Crispr/Cas - a gene scissor. With these scissors, gene therapies have moved further into the realm of the possible.

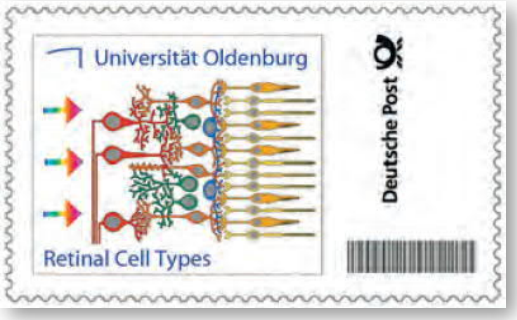
Retinitis pigmentosa is a hereditary disease caused by mutations in genes. More than 100 mutations on 50 different genes with different patterns of inheritance and expression of retinitis pigmentosa are now known. Due to this clear genetic cause, this disease is excellently suited for gene therapy.

In a gene therapy approach, a specific mutation in a particular gene is corrected using viral vectors or genome editing using gene scissors, or a healthy gene is introduced into the genome. Knowing the mutated gene - through genetic testing - can help people qualify for clinical trials and inform them about what future therapies might be of benefit. Because the first therapies are already on their way.

The 2018 FDA and EMA approval of Voretigene neparvovecrzyl (Luxturna) for the treatment of Leber's congenital amaurosis was a major breakthrough in this regard, as it is the first gene therapy at the severe end of the retinitis pigmentosa spectrum. Here, children were treated who had a mutation in the gene RPE65, which affects 5-16% of patients. RPE65 produces an enzyme that maintains the function of the visual pigment rhodopsin. In the case of Luxturna, a virus that is unable to replicate and carries the correct RPE65 is injected into the eye. This gets the correct gene into the cells and ideally restores receptor function. Most of the participants' vision in the dark improved significantly, and they were also better able to orient themselves in low light conditions. However, the treatment had no effect on visual acuity in bright light. Overall, the quality of life of most patients improved noticeably. Whether the effect of the treatment lasts over a longer period of time (> 3 years) is not yet known.

Canada 2020: Till and McCulloch were medical pioneers who demonstrated the existence of multipotent stem cells in 1961. These stem cells exist in almost every tissue and can regenerate destroyed tissue.

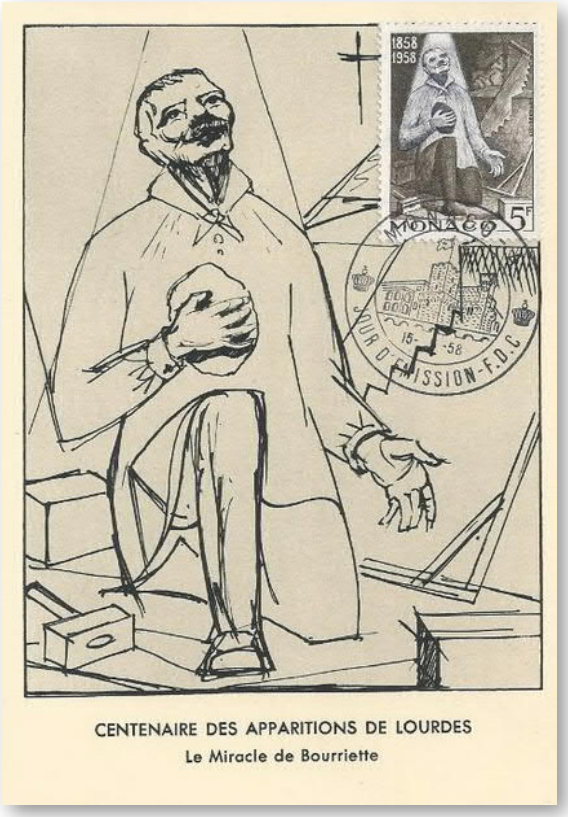
Another avenue is the application of the substance EA-2353, which is also already being tested in clinical phases. This product was developed on the basis of an artificial intelligence-driven drug discovery platform. It is administered intravitreally and is thought to be able to selectively activate the body's own retinal stem and progenitor cells that differentiate into photoreceptors, potentially preserving or restoring visual function. The advantage of this therapy would be a broad application, which is not possible in highly specific gene therapy.



Personalised Stamp 2017: Representation of the retina. The light-sensitive protein is introduced into the ganglion cells (left in red)

But how can we help patients whose receptor cells (rods and cones) have already died? Here, too, there is a future - optogenetics. Optogenetics is a form of gene therapy in which a light-sensitive protein is introduced into the remaining retinal cells (ganglion cells). These can then react to light even without the receptor cells that have already died. The first patient treated in this way was able to identify objects again after treatment, but could see neither colours nor fine details. There is still room for improvement here, similar to the implantation of a "mini-camera connected to a retinal chip", which made pixelated vision possible again.

In summary, we are facing an exciting time in the treatment of degenerative diseases of the eye, and in the future there may be ways to preserve or partially restore vision to these patients and no longer have to hope for a miracle.



Maximum card 1958 Monaco: Healing of a blind man in Lourdes

Literature:
https://www.hcplive.com/view/shot-in-the-dark-searching-therapies-treat-retinitis-pigmentosa; Sahel, J-A. et al., Partial recovery of visual function in a blind patient after optogenetic therapy Nat Med . 2021 Jul;27(7):1223-1229.

The blind receive their sight - "their eyes were opened" (Luke 24:30)

Ulrich Treutlein

Fig. 1: The Disciples of Emmaus (Equatorial Guinea 1973)

At the end of the pre-Easter period or at the beginning of a new time of seeing, we hear several times in the Gospels, with different accentuation, where theologically interpreted blind people gain sight or where their eyes open (the women at the tomb, Thomas-Didymus, the doubter, Bartimaeus, the formerly blind man, the disciples at Emmaus (Fig. 1)), but here we are dealing with a person who helped people to see or brought them relief.

"It is the light, sweet and lovely, to behold the sun". This is the inscription on the grave of **Albrecht von Graefe** (Fig. 2) in Cemetery II of the Jerusalems- und Neue Kirche in front of the Halleschen Tor in Berlin. The inscription on the monument on the Charité grounds in Berlin expresses it similarly: "*O, a noble gift from heaven is the light of the eye, all beings live by light*".

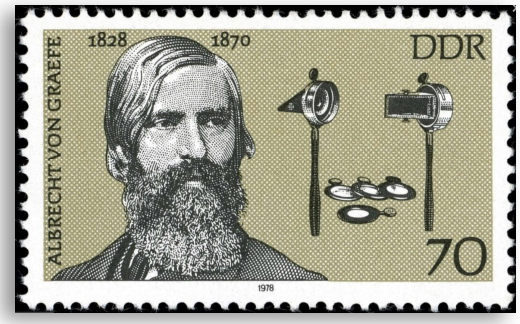


Fig. 2: Albecht von Graefe (GDR 1978)

Fig. 3: Free as per obverse stamp of the Friedrich Willhelms University Berlin - year???

Born on 22 May 1828 in Berlin, died on 20 July 1870 in Berlin, Friedrich Wilhelm Ernst Albrecht von Graefe first worked as an ophthalmologist, later as a Royal Prussian Privy Councillor of Medicine and Full Professor of Ophthalmology, which he reformed, at the Friedrich Wilhelm University in Berlin (Fig. 3). He is regarded as the founder of ophthalmology as an independent subject, which until then had belonged to surgery.

Excursus: He should not be confused with his father, Carl Ferdinand von Graefe, born on 8 March 1787 in Warsaw (at that time part of Prussia), who spent the first years of his life at Dolsk Castle. He first studied in Halle and Leipzig. After receiving his doctorate in 1807, he worked in Ballenstedt, where he built up a hospital. After briefly working as a surgeon in Königsberg and Halle, he was appointed to the University of Berlin in 1810, where he took over the founding chair of surgery and ophthalmology. He is a Royal Prussian civil servant and holder of high state offices (Privy Councillor of Medicine and at the same time Surgeon General of the Prussian Army). It is also thanks to his fame that members of the Prussian royal family were godparents to his son - Albrecht von Graefe. The godparents were the Prussian King Frederick William III and his youngest son, Prince Albrecht of Prussia (Fig.4). Albrecht von Graefe's first name refers to him.

Fig. 4: Seal of the Court Marshal's Office of Prince Albrecht of Prussia, the "namesake" of Albrecht von Graefe.

Fig. 5: A doctoral thesis on a grass does not necessarily indicate a career as an ophthalmologist (Germany 2018)

Fig. 6: Special postmarks 1993 and 1996, honouring the two doctors Lukas Schönlein (6a) and Emil du Bois-Reymond (6b) respectively. Right: F. von Arlt Austria 1937 (6c)

Carl Ferdinand von Graefe died in 1840 in Hanover, where he was to cure the Crown Prince of his blindness by an operation.

Some milestones in the astonishing life of A. von Graefe: After graduating from the French Gymnasium (both French and English are part of the language canon [curriculum]), A. v. Graefe studied medicine, mathematics, physics and chemistry in his native city from 1843. One year later, after his dissertation ("De bromo eiusque praesipuis praeparatis"- On the trespe, a genus of sweet grass (Fig. 5) and its preparation), published in 1847, he passed the examination to become a doctor, surgeon and obstetrician in 1848 at the age of barely 20. In the same year he embarked on a scientific study trip, similar to the journeys of journeymen craftsmen, which took him from Prague to Paris, Vienna and London. He met famous teachers and fellow doctors who introduced him to new surgical methods and optical aids and with whom he exchanged ideas throughout his life. The following names read like a Who's Who of the medical, physiological and pathological world of the time: Lukas Schönlein (Zurich, Berlin; Fig. 6a), Emil du Bois-Reymond (Berlin; Fig. 6b), Rudolf Virchow (Berlin), Johann Christian Jungken (Vienna), Ferdinand von Arlt (Vienna; Fig. 6c). Other teachers and colleagues are: Sichel (Paris), Desmarres (Paris), Friedrich Jäger von Jaxttal (Vienna), Wil-liam Bowman (London), George Critchett (London).

Fig. 7: Donders was co-founder of the "Archiv für Ophthalmologie" (Netherlands 1935).

At the end of this study trip, he qualified as a university lecturer with a thesis "On the effect of the eye muscles" and opened an ophthalmological practice in Berlin on 1 November 1851, which he expanded in the following years into a world-renowned eye clinic with 120 beds. As a further achievement, the journal "Archiv für Ophthalmologie" (Archive for Ophthalmology), founded in 1854 together with his Austrian colleagues Ferdinand von Arlt and Frans Cornelis Donders (Utrecht; Fig. 7), must be mentioned as the first ophthalmological journal.

Fig. 8: The Ophthamological Society of Italy was founded 12 years after the German Society founded by A. v. Graefe (Italy 2019).

In 1857, he founded the DOG, the German Ophthalmological Society (Fig. 8), which still exists today. It is therefore not surprising that in 2017 the DOG is focusing on the special achievements of Albrecht von Graefe in the development of ophthalmology under the theme of "German Ophthalmology internationally"..

Decisive for the establishment and development of ophthalmology in Switzerland is his role as a teacher to his pupil Johann Friedrich Horners. Other students are: Karl Schweigger, who worked for several years in Berlin with A. von Graefe as an assistant physician before being appointed in 1871 as Albrecht von Graefe's successor at the Department of Ophthalmology at the Berlin Charité; another student, Alfred von Graefe (cousin of Albrecht von Grafe), also habilitated under his famous uncle. It seems as if the choice as well as the inclination for

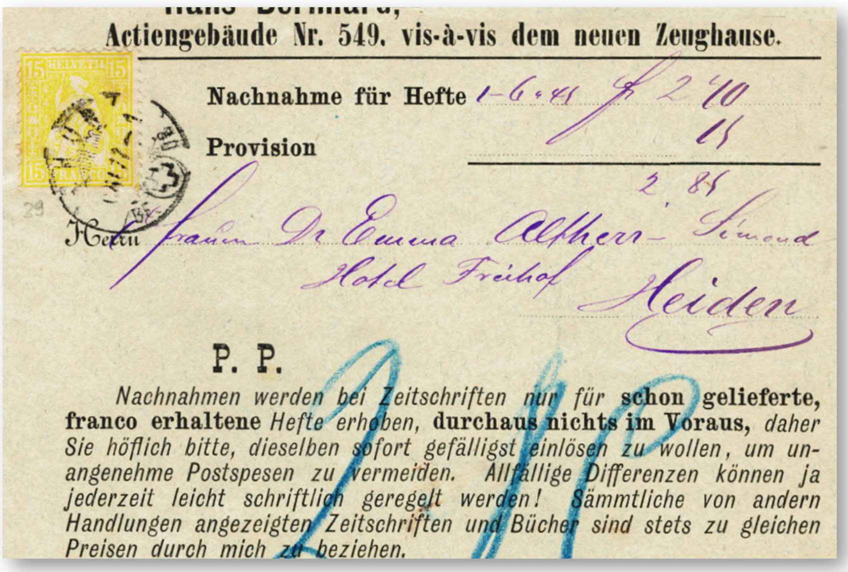


Fig. 9: Cash on delivery 1877 franked with 15 centimes stamp of the Sitting Helvetia (year of issue 1875). The cash on delivery is addressed to a person at the Hotel Freihof in Heiden, where Albrecht von Graefe also worked.

ophthalmology was literally laid in the Graefes' cradle.

From 1859 to 1869, Albrecht von Graefe regularly came to Heiden in the Appenzell region (Canton Außerrhoden) in September to recuperate and travelled through Switzerland, where he climbed high mountains. In the spa town of Heiden, he tried to alleviate his tuberculosis and combined his convalescence stays with medical eye consultations, where he operated on numerous eye patients and convalescents from all over the world in the Freihof Hotel (Fig. 9). During this time, the hotel also served as an eye clinic, which made the place famous far beyond the borders of Switzerland and made it famous as a health resort.

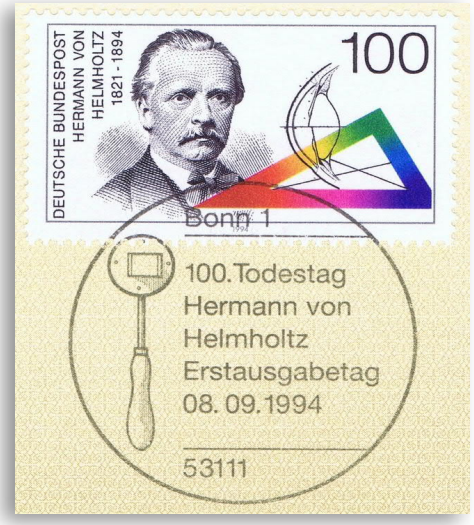


Fig. 10: Hermann von Helmholtz developed the ophthalmoscope which Albrecht von Graefe used successfully (special postmark and stamp Germany 1994)

His life and work, which lasted for almost 20 years until his early death from pulmonary tuberculosis (20 July 1870), have left their mark on ophthalmology up to the present day. This means that he is regarded as the pioneer of numerous surgical methods of treating eye diseases (glaucoma) and a special surgical technique for cataracts ("modified linear extraction method"), which generations of ophthalmologists practised successfully well into the 1960s. Because of his proximity to physicist colleagues in Germany and abroad at that time, he had knowledge of many innovations and ideas and optical apparatus. For example, he successfully applied the ophthalmoscope developed by Hermann von Helmholtz (Fig. 10) at an early stage. It is a valuable aid for reliably looking into the interior of the eye to detect changes, which has since benefited countless people with eye injuries and age-related eye diseases.

However, this is only an incomplete description of his beneficial work as an ophthalmologist, which lasted far beyond his death. Albrecht von Graefe is said to have performed more than 10,000 operations in the course of his short but powerful life as an ophthalmologist, probably 420 operations in Heiden alone. And this in a spa and recreation resort, where he wanted to recover from his daily work as an ophthalmologist, clinic director, member of the Leopoldina and lecture traveller, co-editor of famous periodicals for ophthal-mology in Berlin..

Contemporaries describe A. v. Graefe as an extremely inquisitive and socially minded doctor who treated patients without regard to their status or income. His student, Julius Hirschberg, called him an "apostle of humanity" in his obituary.

Fig. 11: First day cover (GDR 1978) with cancel and stamp of the Albrecht von Graefe monument.

The name A. von Graefe is present at least in Berlin, the place where he worked. The city authorities renamed street no. 7 in the Kreuzberg district Graefestraße in honour of him, the street in turn served as the name-giver for the neighbourhood surrounding it (Graefe-Kiez) and several monuments (Fig. 11), busts and memorial plaques in Berlin commemorate him. A school in Kreuzberg is also named after him.