Upsala Journal of Medical Sciences

ISSN: 0300-9734 (Print) 2000-1967 (Online) Journal homepage: https://www.tandfonline.com/loi/iups20

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**To cite this article:** Bo S. Lindberg (2015) Proceedings of the Upsala Medical Society: How it all started 150 years ago, Upsala Journal of Medical Sciences, 120:2, 65-71

**To link to this article:** https://doi.org/10.3109/03009734.2015.1027430

*Upsala Journal of Medical Sciences.* 2015; 120: 65–71

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healthcare

# Proceedings of the Upsala Medical Society: How it all started 150 years ago

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**Key words:** *History, journal, medicine*

*Upsala läkareförening* (The Upsala Medical Society) was founded in 1832 on the initiative of Professor Israel Hwasser, who was the chairman of the society until his death in 1860. The aims of the society were to promote medical science and create an atmosphere of friendship and collegiality among members of the faculty of medicine, medical students, and medical practitioners. An important function was the library of foreign books and journals that the society brought together. At regular meetings, a student was elected for each occasion as a vice chairman, and he would read a paper about a topic of interest, such as a case of a disease, or report on an article from the medical literature. During the first 30 years, no minutes from these lectures were kept, but during the early 1860s short records of the content of these lectures were written.

The first lecture relating to own research was given in 1864 by the young medical student Olof Hammarsten, later a famous professor of medical and physiological chemistry. The theme for his discourse was bile acids, a subject for which he was to become world famous.

As more original research was presented at the meetings, it became natural to try to disseminate the contents of the lectures to people outside the society and Uppsala. In 1865, the professor of surgery, Carl Benedict Mesterton, therefore suggested that the proceedings from the sessions of the society should be printed, and after a short deliberation the first volume of *Proceedings of The Upsala Medical Society—Upsala Läkareförenings Förhandlingar*— was published in September 1865. It was distributed to 73 private persons and book-sellers, all of whom were subscribers. Thirty-three foreign hospitals and medical associations abroad were sent free copies, and 11 other medical journals received a copy in an exchange agreement which proved to be very valuable. The first volume comprised just over 460 pages, but later the content of volumes expanded to more than 700 pages. The editor of the newly started 'journal' was Robert Fristedt (Figure 1).

## A selection of the content during the years

In the very first issue, the newly appointed professor in physiology, Frithiof Holmgren, reported a great discovery concerning the physiology of the senses: the retinal current. In the following decades, a lot of important articles about the senses were published. These are dwelt upon in a separate chapter in this supplement. Other important contributors to the journal at that time, e.g. Olof Hammarsten, Johan Anton Waldenström, and Ivar Sandström, also have their own chapters. Regular authors from the beginning were August Almén (professor of medical and physiological chemistry), Frithiof Holmgren, and Edward Clason (professor of anatomy). They contributed to the first issue with 8, 13, and 13 articles, respectively.

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*(Received 26 February 2015; accepted 28 February 2015)*

ISSN 0300-9734 print/ISSN 2000-1967 online 
DOI: 10.3109/03009734.2015.1027430


Figure 1. Robert Fristedt. Fristedt (1832–1893) was professor in pharmacology and natural history. He was the editor of *Upsala Läkareförenings Förhandlingar* from the very beginning 1865 to his death in 1893. Photo: Heinrich Osti, 1877. Uppsala Universitetsbibliotek. Kart- och bildenheten, ID 12141.

August Almén reported in 1867 on a method to detect sugar in the urine, later known as Almén's test (1). It relies on the reducing properties of glucose and other reducing sugars. The reagent is an alkaline bismuth solution. When heated in the presence of a reducing sugar, the bismuth is reduced to a black precipitate. The article was published in Swedish. Abroad, his method seems to have been unknown. In an 1883 review of test methods for sugar in the urine, George Oliver states that the Fehling test with cuprous oxide is the best available but does not even mention Almén (2). In 1907 Olof Hammarsten compared Almén's test with some other sugar tests and found it superior (3). Almén's method was used in Sweden for almost 100 years, until the test strips for glucose were introduced in 1957.

A drug that for the first time gave the practitioner an effective remedy against insomnia was chloral hydrate. It was first synthesized in 1832, but not introduced into medicine until 1869, when Mathias Liebreich discovered its effectiveness in inducing sleep. Chloral hydrate was used for short-term treatment of insomnia and as a sedative before minor surgical or dental operations. It was displaced in the late nineteenth century by bromide and in the mid-twentieth century by barbiturates. August Almén, Fredrik Björnström (later professor of psychiatry at the Karolinska institute), and Gustaf Kjellberg (the first professor of psychiatry in Uppsala) wrote in *Proceedings of Upsala Medical Society* in 1869–1870 on the new drug only a few months after Liebreich's article, *Das Chloralhydrat, ein Neues Hypnotikum*, was published in Berlin.

Almén was an analytical chemist, and he reported regularly in the journal on analyses of spring water from the many active mineral wells in Sweden. He also was very interested in the quality of pharmaceuticals, mostly vegetables, and he reported on the yearly updates of the statutes for the pharmacies in the country. This latter interest made him leave the chair as professor, and he became the general director of the Royal Medicinal Board in 1883.

As professor of medical and physiological chemistry, Almén was succeeded by Olof Hammarsten, one of the most famous scientists in Uppsala around the turn of the nineteenth century.

## Sanitary conditions and infectious diseases

In 1857–1863 Louis Pasteur had demonstrated that fermentation is caused by the growth of micro-organisms. In the following years the role of these organisms in various diseases was discussed in the whole medical world, which

was mirrored in the *Proceedings of the Upsala Medical Society*. At that time, many expeditions to remote parts of the world were undertaken. The famous Swedish–Finnish explorer, Adolf Nordenskjöld, went to Spitsbergen in 1868 on a scientific expedition on the iron steamer *Sofia*. The young physician Carl Hippolyt Nyström (father of the surgeon Gunnar Nyström) was invited to act as the ship's doctor. After a correspondence with Pasteur, he decided to investigate the fermentation and putrefaction of meat at Spitsbergen. His aim was to investigate if germs were as common in this remote and cold area of the world as in more inhabited countries. He found that, with what he said was a modern word, 'protorganisms' were present even at Spitsbergen (4).

The following year, in 1869, the Swedish chemist Henrik Gahn in Uppsala patented a preserving remedy which was called 'Aseptin'. It consisted of boric acid. Gahn was a relative of the anatomist Edward Clason and had close connections to many of the professors at the university. The professor of pathology and editor of the *Proceedings*, Per Hedenius, had suggested the brand name of Aseptin. Carl Benedict Mesterton, professor of surgery, recommended in advertisements a dilution of boric acid spiced with a decoct of clove called 'Amycos' as an excellent antiseptic agent, less toxic than carbolic acid. The professor of civil law, Viktor Nordling, was a member of the board of Henrik Gahn Aseptin-Amycos Company in Uppsala. Pure or simple Aseptin was used to preserve milk, bread, and prepared meat, and double Aseptin (two parts boric acid and one part potash alum) was used to prepare raw meat and fish. Carl Hippolyt Nyström reported in the *Proceedings* 1871–1872 on a trial with Aseptin. He concluded that Aseptin prevents the invasion of bacteria in liquids and meat and that it could put a stop to the putrefaction of meat at a concentration of 8% (5).

In 1865, Uppsala had 13,500 inhabitants. The population then increased rapidly, and in 1900 the town had 21,500 inhabitants. The sanitary conditions did not increase in parallel with the population growth. For many years a frequent issue at the meetings of the society and in its *Proceedings* was *constitutio epidemica*. Typhus, smallpox, malaria, diphtheria, and dysentery were serious infections contracted by the inhabitants of Uppsala.

In 1884 there was an epidemic of typhoid fever in Uppsala. The source of infection turned out to be a stock of cattle just outside the town, the owner of which was the professor of civil law, Viktor Nordling. The case was very awkward for him as he was also the chairman of the town council. A delegation from Upsala Medical Society with Magnus Blix as its chairman carried out an investigation and published a report in *Proceedings of The Upsala Medical Society* in 1884 (6). Nordling was prosecuted in court on the charge of having violated the sanitary regulations. He was convicted and forced to resign from all his official tasks.

The first great epidemic of cholera occurred in Sweden in 1834. The disease then recurred in nine big waves until 1872. In 1892 there was a big outbreak in Hamburg. The professor of medicine, Salomon Eberhard Henschen, gave a lecture in the society, then published with the title: 'How should we protect ourselves against cholera?' (7). He stressed the importance of quarantine and that travellers from areas with cholera should be kept isolated until they were proved not infected. With this article Henschen started a fierce dispute with August Almén, who now was general director of the Royal Medicinal Board. The Nordic directors had agreed on common rules for all Scandinavian countries with regard to quarantines. They had agreed that there was no need for medical expertise in the decisions about who must stay in quarantine and who should not. This could be decided by customs officers—an agreement Henschen said was erroneous. Customs officers without medical education did not have the competence to judge if a person was sick or not, particularly in early or abortive cases. Such rules would only lull the community into a false sense of security.

At the end of the nineteenth century, tuberculosis was one of the most common causes of death. For that reason, the public reacted euphorically to the discovery of the tuberculosis bacillus in 1882 by Robert Koch, since it aroused hopes for a cure. Until that time, the only effective remedy for an infectious disease was quinine for malaria.

At the Tenth International Medical Congress held in Berlin in 1890, Koch introduced a cure for tuberculosis, which he called tuberculin. The public trusted the famous physician and reacted enthusiastically. Tuberculin was tested in many countries, even in Sweden by, among others, Henschen in Uppsala. He reported on his trial in the 1891–1892 volume of *Proceedings of The Upsala Medical Society*, having found, as others had, that tuberculin could cause severe adverse effects such as bleedings from the kidneys (8). He strongly advised against its use as a remedy, and instead recommended isolation of the contagious patients. Once again, he came in conflict with August Almén, when he suggested it should be mandatory to register the sick persons, as was the case in Denmark and Norway. Almén thought that a register would further stigmatize the diseased, and not until 20 years later did it become mandatory to trace contagious persons and register them.

## Pharmaceutical frauds

In times when safety regulations of pharmaceutical preparations were still rudimentary, many authors warned colleagues in *Proceedings of Upsala Medical Society* about falsifications. The pharmacist Edward August Andberg

reported on falsified castoreum in 1865–1866, and Ryno Hoffstedt reported on falsified wax in 1871–1872. August Almén wrote about hops adulterated with absinth in 1874–1875, and his wife's nephew Carl Thore Mörner (later professor of medical and physiological chemistry) wrote as a young medical student in 1888–1889 about falsified *gummi resina asa foetida*. *Asa foetida*, an oleo-gum-resin, was traditionally used to treat various diseases, including asthma, gastrointestinal disorders, and intestinal parasites. In Swedish it was called '*dyvelsträck*'.

Mörner wrote in the 1898–1899 volume about some examples of misuse of chemicals. One of these was the use of Aseptin to preserve meat. The Henrik Gahn Aseptin-Amycos Company had advertised that Aseptin was quite harmless. Mörner, on the contrary, showed that it might cause serious adverse effects and that it had been prohibited in many countries, e.g. Germany (9).

Mörner collaborated with the physiologist Thorsten Thunberg, and they gave a speech on pharmaceutical fraudulence at the Upsala Medical Society's meeting of 30 October 1903 (10). Together with Fredrik Clason, medical practitioner in Uppsala and son of Edward Clason, they started 'The Office for Information on Advertisements on Drugs' in 1903. At the turn of the century, the statutes for pharmacies from 1683 were still applicable. The trade in what was called patent drugs and humbug drugs had spread into the pharmacies, and there was no general agreement on what was a genuine pharmaceutical drug. The Office published a series of booklets about fraudulent drugs. Their merciless but amusing disclosure of the contents of these drugs contributed to the new chemists shop license statute in 1913, which demanded lists of content of all pharmaceutical products. The Office relinquished its activity when it had attained its purpose.

Perhaps most amusing of all articles in the *Proceedings* is August Almén's juicy murder of 'Liebig's meat extract'. Justus von Liebig was regarded as one of the great chemists of the nineteenth century, particularly in agricultural chemistry where he had identified nitrogen as essential to plant life. He also established the first laboratory-based school of chemistry at the University of Giessen (now named Justus Liebig University Giessen). Nowadays he is considered a founder of organic chemistry, and the journal he created in 1832, *Annalen der Pharmacie* (today's *European Journal of Organic Chemistry*), is still very important in the field.

In the 1860s there was a shortage of food, particularly bread and meat, in many countries, which caused riots. In South America there was a surplus of meat, but at that time it was not possible to transport the meat to the starving populations of Europe. Liebig had devised an efficient method of producing beef extract from cattle carcasses from South America. In 1865, he founded the Liebig Extract of Meat Company, marketing the extract as a cheap, nutritious alternative to real meat. In the Swedish newspaper *Aftonbladet* from February 1867, an uncritical article about the Liebig's meat extract was published.

Almén tested Liebig's extract and found it contained very little of fats and proteins. It was just a mixture of salts, spiced water, and some nitrogen-containing substances such as creatine and creatinine, but these are without nutritive value and normally excreted via the kidneys. The nutritive value of the Liebig's extract was almost nil.

Almén condemned the company for duping consumers in its advertising, particularly the claim that 34 pounds of meat were used to make a single pound of extract. Such advertising, he argued, misled poor people into thinking they were consuming 34 pounds' worth of beef nutrients with each jar. Such a mixture of salts could be bought for 1% of the price of Liebig's extract.

Justus von Liebig responded to Almén's criticism in a letter to *The Lancet*, which Almén commented upon in *Proceedings of Upsala Medical Society*, but he concluded in his article: '*Mundus vult decipi, ergo decipiatur*', which means: 'The world wants to be deceived, so let it be deceived' (11).

## Surgery and obstetrics

On 8 December 1869, the Swiss surgeon Jacques Reverdin gave a lecture at a meeting of the Société Impériale de Chirurgie de Paris entitled *Greffe épidermique*. He had successfully transplanted small pieces of skin, of partial or full thickness, removed from a healthy area, and seeded in a granulated wound surface to be covered. He published his experiences in 1872 in a book entitled *De la greffe épidermique*, but the new method seems to have become internationally known before the book was printed. Carl Benedict Mesterton described skin transplantations in six patients in the year before. In only one case was the transplant rejected due to a purulent infection (12). His article was translated into English, published in *British Medical Journal* the same year, and mentioned in Reverdin's book.

Karl Gustaf Lennander succeeded Mesterton in 1891 as professor of surgery. The disadvantage with the Reverdin technique Mesterton had used for skin transplantation was that the small pieces of skin were often detached from the wound after a while. The German surgeon Carl Thiersch in Leipzig introduced another method at a congress in 1874 (his father-in-law was Justus von Liebig, whose meat extract Almén had criticized).

He used skin grafts consisting of thin strips or sheets of epithelium with the tops of the dermal papillae cut off with a sharp knife. Lennander started to use *thiersching*, as it has been called. In 1889, while not yet professor, he reported on his experiences. In most cases, the long-term results were good. Remarkable is that he transplanted a piece of mucous membrane from the inside of the lower lip to the conjunctiva in two patients, one of whom had a sarcoma of the conjunctiva, the other with an ulcer on the nose and the eye-lid (13).

Lennander was the first in Scandinavia to perform an appendectomy. The patient was a 28-year-old student with purulent peritonitis after appendicitis. After five months, the patient could be discharged from the hospital (14). Appendicitis then became one of Lennander's main interests. In 1892 he published the results from his first 34 patients with only one deceased (15). At that time, it was not obvious that the treatment should be surgical. Many internists argued for a conservative treatment. Because of this opposition, Lennander was keen on reporting the long-term results of the operation. His pupil and later professor in surgery in Uppsala, Gunnar Nyström, reported in his thesis the results from 460 cases of non-purulent appendicitis from 1891, when the first patient was operated upon, until the end of 1905. Only five patients had died during the hospital stay (16). In 1909, another of Lennander's pupils, Knut Harald Giertz, defended his thesis on perforated appendices with peritonitis. Of 553 patients, 20.5% died, and, because of the high mortality, he stressed the importance of early operation when appendicitis is suspected (17).

In order to facilitate the access to the appendix and other organs in the right lower part of the abdomen, Lennander introduced in 1897 a paramedian incision. Its advantage was that the iliohypogastric nerve could be spared. It is sometimes still called the Lennander incision (18).

Lennander is famous for his studies of the sensory nerves of the peritoneum. He found that there is a distinct difference in the sensitivity of the parietal and visceral peritoneum; however, he did not publish his findings in *Proceedings of the Upsala Medical Society* but in *Centralblatt für Chirugie* in 1901 (19).

He also tried to prevent deep thrombosis after abdominal surgery. He had found that a dependent position of the legs may give rise to thrombosis of the veins. In these cases, therefore, the pelvis alone must be kept low, while the legs should be raised and maintained at a higher level than the buttocks. He also recommended massage of the legs and that the patient should lift and actively move his legs regularly when lying in the bed. Infusions of solutions of sodium chloride should be given (20). At that time patients had to stay in bed for three to five weeks after an operation. The fact that early mobilization could prevent thrombosis was first proposed in Scandinavia by the Finnish gynaecologist Edvard Björkenheim at the eighth meeting of the Nordic surgery society in 1909, but his message was forgotten until the 1940s.

## Blood transfusions

During the 1870s many attempts were made to save the lives of patients by means of transfusions of blood. In the tenth volume of *Proceedings of The Upsala Medical Society* 1874–1875 several articles were published on the subject. Carl Henrik Björck reported on a case of chronic pneumonia treated with blood transfusion, and Oscar Viktor Peterson reported on a case of transfusion with blood from a lamb and a case of sudden death where blood transfusion was tried. Fredrik Belfrage wrote about five cases of carbon monoxide poisoning treated with transfusion. Johan Anton Waldenström tried in vain to get hold of a sheep when he was to give a transfusion to a 41-year-old woman who was bleeding heavily after a delivery. Instead, blood from two powerful men was used. The patient displayed all the now classical signs of strong transfusion reactions and died within a few days. It was still 25 years before blood groups were discovered and safer therapy became available.

## Proceedings of the Upsala Medical Society and the outside scientific world

*Proceedings of The Upsala Medical Society* was meant to be an organ for the Upsala Medical Society relating what was discussed at its meetings. For many years, it was a window to the surrounding scientific world. The contents of medical journals from abroad, mainly Germany, were reported. But it became evident that the communication was just one-way. As it was printed in Swedish, the *Proceedings* could not be read by more than a few. Some great scientific discoveries remained unknown abroad for many years. Not until Holmgren published an account in German of his detection of the retinal current in 1879–1880 did this pioneering work become known abroad.

What has been called the last anatomical discovery, the parathyroid glands, was published in the *Proceedings* in Swedish in 1879–1880 under the title 'Om en ny körtel hos menniskan och åtskilliga däggdjur' by Ivar Sandström. For detailed information on his remarkable achievements you are referred to Henry Johansson's chapter in this

issue (21). Its importance remained mainly unknown during his lifetime. Disappointment with the lack of acknowledgement may have contributed to his unhappy life and suicide.

Another example of late recognition is Magnus Blix's discovery of the cold-, warm-, and pressure points in 1882. They became known in the scientific world outside Sweden only when he published his findings in German in 1884. Independently of each other, Alfred Goldscheider (professor at the University of Berlin in 1884) and Henry Donaldson (at Johns Hopkins University in 1885) reported that the skin was not continuously sensitive but instead had specific loci for specific tactual senses. In many books on the history of medicine, Blix now is said to share the priority with them, but in fact he published his findings two years before them.

Disputes about priorities were common even in the nineteenth century. One example is a letter that Hermann Cohn, ophthalmologist in Breslau, wrote to the Upsala Medical Society in 1878. He complained about an article Holmgren had published on colour blindness and the distance between the pupils. Holmgren refuted Cohn's allegation and expressed his regret that the struggle for priority caused too hasty publications (22). Discoveries published in Swedish always run the risk of being overlooked.

This may have been the reason why Frithiof Holmgren founded *Skandinavisches Archiv für Physiologie* in 1889. It was meant to be an organ for all physiologists in Scandinavia. Later, several other more specialized journals were established, but *Proceedings of The Upsala Medical Society* still received many manuscripts from the members of the society. In the 1920s, when Hugo Laurell was the editor, it started to publish in English, German, and French. Later, even articles in German were not always paid attention to when Anglo-Saxon journals dominated. *Current contents*, *Index Medicus*, and similar databases were not commonly used until the 1950s. Thus, it was not easy to keep oneself always updated on the increasing flow of publications.

Concepts of the respiratory dead space were introduced during the latter part of the nineteenth century and have been continuously elaborated until the present time. A crucial stage in this development was the concept of the 'volumen inefficax' by Henrik Enghoff in 1931 (23) and his suggestion in 1938 that the $P_{CO2}$ of the *arterial blood* could be substituted for the *alveolar* $P_{CO2}$ (24). His contribution was overlooked at the time but, when rediscovered almost 10 years later, it was immediately hailed as a milestone in the understanding of respiratory function. Enghoff was the first to demonstrate through arterial blood samples that the dead space varied during different physiological conditions. Only at a later date was it realized that this essential advance had been made by Enghoff. Such appears to be the fate of so much work published in European journals. Whatever the cause, there is no reference to Enghoff in an article in *American Journal of Physiology* in 1946 by R. L. Riley, J. L. Lilienthal, D. D. Proemmel, and R. E. Franke, who in most people's eyes laid the post-war foundations of quantitative interpretation of changes in alveolar $P_{CO2}$ and $P_{O2}$. Modern clinical respiratory physiology and respirator treatment rest on Enghoff's theoretical framework on the functional dead space (25).

***Declaration of interest:*** The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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