ISSN 1061-9348, Journal of Analytical Chemistry, 2012, Vol. 67, No. 6, pp. 600–602. © Pleiades Publishing, Ltd., 2012.
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HISTORY OF ANALYTICAL CHEMISTRY

Fritz Pregl, Inventor of Quantitative Elemental Microanalysis of Organic Compounds

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Received November 16, 2011

Abstract—A sketch of the life of Nobel laureate Fritz Pregl is presented based on the materials of the Archive and Museum of Karl-Franzens University of Graz, Austria.

Keywords: quantitative microanalysis, organic compounds, microchemical balances, biochemistry, Nobel Prize.

DOI: 10.1134/S1061934812060032

When reading biographical sketches and reference books, the reader sometimes has an impression that scientists are people who are dry as dust, who trade everything for their science. Such an opinion of their life can hardly attract young people to science. We have attempted to show the life and activity of Nobel laureate Fritz Pregl in the eyes of his contemporaries using the materials of the Archive and Museum of Karl-Franzens University of Graz, where he worked [1–6].

Fritz (Frederic) Pregl was born on September 3, 1869, in the Slovenian city of Laibach (Ljubljana), at that time in Austria–Hungary. His Slovene father Raymond Pregl (in Slovenian pregl is a mattock) worked a cashier in a bank. Pregl's mother, nàé Friderika Schlaker, was German, so family members spoke two languages. In the capital of the present-day Slovenia, one can see the two-story house where Pregl was born; its wall is decorated with a bust of the scientist. After the death of his father in 1887 and finals with a gold medal of a German grammar school, Pregl and his mother moved to Graz, where he entered the university's medical faculty.

Love of science made his studies easier. Since he was a student, Pregl was made an assistant and was engaged in preparing experiments for lectures and practical works. In his student years, he published his first paper. His devotion to medicine did not exclude other interests. Pregl entered a cycling club; he played on the soccer team, which held its first official match in Graz in 1894, laying the foundation to official soccer competitions in Austria; he learned mountaineering [5]. One can consider these inadmissible time wasters, but the Dutch cultural historian Johan Hejzingi affirmed that playing is an important source of culture: homo ludens (person at play) [7].

After university, Pregl became a practicing ophthalmologist and performed complicated operations while continuing his work as an assistant of the university's Physiological Institute. In 1899, he defended his PhD thesis and was given the title of Associate Professor. Among the problems that medicine faced that time, he determined the composition of physiologically important substances of the human body, without the knowledge of which bodily functions cannot be studied comprehensively. Pregl's teacher of medical chemistry was Professor of the Chemical Institute Zdenko Skraup [7], who was engaged in the study of alkaloids. Having had foreign training, Pregl first worked at the universities of Tübingen and Heidelberg; then he studied physicochemical research methods at the Physicochemical Institute of Leipzig University under the supervision of W. Ostwald and continued training in Berlin under the supervision of organic chemist, Nobel laureate Emil Fisher. Fisher was angry at first, because, before starting his trial work on synthesis, Pregl took four days to carefully washed his workplace and instruments, and he bought new flasks for vacuum distillation [4]. Thorough preparation without haste was Pregl's style. Fisher was satisfied with the result of synthesis. With his pupil E. Abdergald, Pregl performed and published two works; they became friends for life.

Having returned to Graz, Pregl began to work as an assistant of the university's Institute of Medical Chemistry, where the young scientist conducted research into the elemental analysis of tissues and hormones. In those years, he worked a great deal in mechanical and glass-blowing shops, made an automatically adjustable furnace using a clock mechanism for the travel of the burner along the combustion tube, and developed new setups for vacuum drying and extraction. In 1910, Pregl studied the composition of

the summer bile of horned cattle. After treatment of 100 kg of bile, he could obtain 400 mg of an unknown substance, which was insufficient for elemental analysis; he could either process tons of bile or develop methods for the microanalysis of organic compounds. He started with the miniaturization of Liebig, Dumas, Carius, and Kjeldahl devices. The same year, Pregl was invited to head the Institute of Medical Chemistry at the University of Innsbruck. The Tyrolean period of his activity appeared the most productive, but his first words in the visual inspection of the institute's rooms were "a house of thieves." Pregl started with repairing the premises and putting them in order. At the University of Innsbruck, he begun to deliver lectures in chemistry; his introductory lecture was attended by an abnormal number of listeners, about 250. At Fisher's invitation, Pregl delivered a report at a meeting of the German Chemical Society, where he demonstrated the determination of elements and their molecular weights. Pregl's methods were included into the Abdergalden Manual on Biochemical Methods [9]. This year we celebrate 100 years since the publication of this manual, in which Pregl described the quantitative microchemical elemental analysis of organic compounds.

Pregl came to the conclusion that the main factor restricting the possibilities of the micromethod was the analytical balance. Balances are a great creative achievement of mankind, known already 6000 ago in ancient Babylon and Egypt. In Solomon's parables one can read: "A false balance is an abomination to the Lord." Themis, the goddess of justice, has balances in her hands, and they symbolize justice. When Ostwald visited the museum of J. Berzelius and saw there rather primitive analytical balances with which Berzelius had determined the atomic weights of elements, he said: "I uncannily understood how little it depends on the instrument and how much on the person who sits before it" [10]. Pregl had a different opinion about the role of balances in analysis. In those years the most sensitive balances were produced in Hamburg by W. Kuhlmann. They ensured weighing with an error of 0.01 mg. Pregl necessitated balances with a sensitivity ten times greater, and he suggested that Kuhlman introduce modifications in the design of the microbalance. Kuhlman personally brought his balance to Pregl and listened to his proposals on modifications. Then they went to Hamburg together and got the job done [4]. As a result, Pregl could weigh with an error of only 0.001 mg at a portion mass of up to 20 g. Then he added a lead stand, mottled board, and a temperature control. This gave the first microbalance. These can be seen not only in the university museum, but also on site at modern companies releasing microchemical balances, in particular, Shinko balances (http://www.himikatus.ru/art/tecnik_lab/0261.php). The balances exhibit virtually no distinctions. Using microchemical balances, Pregl brought the mass of the weighed portion to several milligrams, and the time of analysis was reduced to 1 h.

Methods of organic elemental macroanalysis were proposed in due time by Justus von Liebig. They consisted in the combustion of a sample in a flame, gravimetric determination of carbon concentration by an increase in the mass of sodium hydroxide reacting with carbon dioxide formed upon the combustion of carbon, and determination of hydrogen concentration by an increase in the mass of anhydrous calcium chloride absorbing water vapor [11]. The Pregl method can called microgravimetric. He reduced the sizes and masses of all instrument units and performed the catalytic combustion of a sample in a platinum crucible at a constant flow rate of oxygen. As substances sustaining combustion, Pregl proposed CuO and $PbCrO_4$ at 750°C and PbO_2 at 190°C. Water vapor he absorbed in a preliminarily weighed tube containing $Mg(ClO_4)_2$, and carbon dioxide, by sodium hydroxide on asbestos [12]. In addition, he developed a microgasometric method for determining nitrogen, enhanced the Kjeldahl method for determining nitrogen, and proposed methods for determining sulfur, halogens, and molecular weights. All the developed methods are described in [13].

The passion of a scientific researcher is indicative of his or her talent [14]. Lieb described Pregl's workday, which started in seven o'clock in the morning. Late at night, when he left work with colleagues, discussions continued in a restaurant. Once, when Pregl traveled to Italy, in Trieste during a walk, he came upon the idea of replacing the mercury gasometer with a Mariott vessel for controlling pressure in a system. He returned with haste and from the station went immediately to the laboratory [3]. At the same time, in days of successful work, Pregl could divert himself from work and play guitar for his colleagues. Sometimes he could do this in his favorite restaurant the Heinrichshoff, which still exists today.

The popularity of the method grew, and researchers from Germany, France, Sweden, Italy, Czechia, and Poland came to Pregl to study. What was the difference between the Pregl methods and present-day methods of elemental organic analysis? Today gravimetric determination in elemental analyzers is replaced by the rapid and precise method of gas chromatography [12], proposed by Martin and Synge in 1952. However, the rapidly developing fields of biochemistry and physiology could not wait so long. The Pregl method was used by many outstanding chemists, including Adolf Windaus, 1928 Nobel laureate in chemistry, who replaced Pregl at the University of Innsbruck; Henry Wieland, 1927 Nobel laureate, investigator of steroids and alkaloids; Rihard Willshtätter, 1915 Nobel laureate, determined the composition and structure of chlorophyll; Hans Fisher, 1930 Nobel laureate, studied and synthesized hemin. Characterizing Pregl's method, Windaus wrote that not only an increase in

accuracy but also the reduction of analysis time was highly important [15]. When Fisher was asked whether he could have made his discovery without the Pregl method, he answered that he would have spent two or three years more and for him, director of an institute, this could be of critical importance.

The recognition of Pregl's works came in 1923, when Pregl was awarded the Nobel Prize. The major portion of the prize Pregl donated to the modernization of his institute. The ministry, supporting his initiative, more than doubled the donated sum. In 1930, Pregl established the Foundation at the Vienna Academy of Sciences for rewarding works in biochemistry; this foundation continues its work today.

Pregl was both a severe and a kind teacher. As a director, he had an official apartment a five minute walk from the institute; he not only stayed in it after long work, but also used it for student examinations. The examinations were difficult, and at a critical moment, a laboratory assistant brought a dog, Menelaus, to soften Pregl when he examined untalented students [16].

Pregl's purchase of a Steyr car in 1930 proved fatal; he had an accident and could no longer work. He died the same year. Pregl was buried in Graz's central cemetery. Streets in Vienna, Graz, Klagenfurt, and Innsbruck were named after him.

The question arises why Pregl, a physician, became the inventor of a new chemical analysis method? Why did the botanist and biochemist Michael Tswett create chromatographic analysis? The list of such questions can easily be continued, but the answer is the same. Biology in the hierarchy of sciences occupies a higher place than chemistry, which reflects the sequence of the evolution of matter. Biologists see an integral pattern of events, and the most talented of them can extract the features that can be generalized and taken up the universal level. Fritz Pregl was undoubtedly such a scientist.

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