Marking a Century of the Department of Chemistry and Biochemistry at School of Medicine in Zagreb: Honoring Professors Tomislav Pinter and Mihovil Proštenik as Fran Bubanović’s Successors

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Abstract: In 2018 the Department of Chemistry and Biochemistry at Zagreb School of Medicine celebrated 100 years since it was established by professor Fran Bubanović. This essay is focused on his successors, outstanding teachers and scientists, professors Tomislav Pinter and Mihovil Proštenik, members of Yugoslavian (today Croatian) Academy of Sciences and Arts. Tomislav Pinter was a prominent physical chemist who had an original approach and gave novel interpretation of van der Waals and Wohl’s equations. He also served as the president of Croatian Chemical Society. Neurobiochemist Mihovil Proštenik started as an organic chemist at “Prelog’s Zagreb School of Organic Chemistry”. He collaborated with two Croatian Nobel prize winners in chemistry: his PhD thesis supervisor Vladimir Prelog and Lavoslav Ružička. He was the founder of “Zagreb School of Lipidology”, discovered a new sphingoid base C20-sphingosine, and had a major role in the establishment of Ruđer Bošković Institute. Herein we honor their contributions to Croatian science and beyond, and share so far unpublished valuable material from the Department archive.

Keywords: School of Medicine University of Zagreb, 100th anniversary, medical chemistry, medical biochemistry.

INTRODUCTION

We are approaching the 145th anniversary of continuous education in chemistry at the University of Zagreb. In addition, we just celebrated a century of founding the Department of Chemistry and Biochemistry at School of Medicine in Zagreb. School of Medicine in Zagreb was founded in 1917, and very soon after that in 1918, amongst the first Departments at the School, Department of Chemistry and Biochemistry was established. At that time, the Department bore the name Department of Applied Physician Chemistry, and during its one hundred years, the Department changed many names. Also, as one might expect, during an active century, many people, including teachers, technicians and other staff passed through the Department and left their mark not only in chemistry and biochemistry education for medical students, but also in Croatian chemical and biochemical science. In this essay we show fragments of that rich history focusing on professors Tomislav Pinter and Mihovil Proštenik, members of Yugoslavian (today Croatian) Academy of Sciences and Arts.

Even though chemistry as a science evolved during centuries, up until the 19th century there were still no stand-alone chemistry courses at European Universities. Rather, it was taught together with other natural sciences. It wasn’t until Justus Liebig (1803–1873) at the University of Giessen that chemistry was introduced as a special course. Liebig’s former students and PhD students then founded chemistry laboratories and taught classes all over Europe and USA.1–3 The first chemistry professor, from 1875 until 1887, at the University of Zagreb was Aleksandar Veljkov (1847–1878) who thought chemistry as a separate discipline at Faculty of Philosophy. Veljkov was followed by Gustav Janeček (1848–1929) in 1879 after a very brief
period during which chemistry was taught by Bohuslav Jiruš (1841–1901).[1–3] It should be noted that professor Janeček was the first professor who taught physical chemistry as a separate course in the whole Austro-Hungarian Empire.[4,5] Janeček’s students Fran Bubanović, who was Janeček’s assistant at Faculty of Philosophy, Vladimir Njegovan and Ivan Marek then established chemistry courses at other Faculties at the University of Zagreb: Bubanović at School of Medicine, Njegovan and Marek at Technical Faculty.[1]

Professor Janeček is considered as a first Croatian chemist who introduced scientific research to the chemistry education.[6] His approach to chemistry classes and laboratory work where science and teaching are intertwined was at that time absolutely modern and based on educational model of the best European Universities where professors enabled students to participate in scientific research.[6] Janeček’s successor at Faculty of Philosophy was Nikola (Nikolaj) Antonović Pušin (1875–1947).[3–5]

The founder of the Department of Chemistry and Biochemistry at School of Medicine was professor Fran Bubanović (1883–1956), a prominent Croatian teacher, scientist and science communicator (Figure 1). To date, many Croatian chemists have written numerous papers regarding his work and professional career.[4,7–17] From these papers it is obvious that his impact on chemistry and biochemistry education at Zagreb University and wider had been immeasurable, as well as bestowing a legacy in scientific research that stemmed from his collaboration and friendship with the chemistry Nobel prize winner Svante Arrhenius.[4,7–17] After School of Medicine was founded, Bubanović was sent to Vienna to the laboratory of Otto von Fürth for training after which he started his work at Chemistry Department at School of Medicine in Zagreb. Starting new, he envisaged and fulfilled his vision about a modern chemistry department fully equipped for scientific research as well as teaching. It should be noted that chemistry and biochemistry was not taught only to medical students, but also to chemistry and pharmacy students at Faculty of Philosophy and to veterinary medicine students at the Faculty of Veterinary Medicine, University of Zagreb. After Bubanović was retired, Tomislav Pinter assumed his duties as Department Head. Tomislav Pinter also continued to coordinate chemistry classes, while Mihovil Proštenik led biochemistry classes. It is also worthwhile to mention, that even though Pinter’s scientific interests were related to Nikola Pušin, and Proštenik’s scientific work with Nobel prize winner Vladimir Prelog (1906–1998), they were primarily influenced by Bubanović who let them freely pursue their scientific interests, while shaping them as excellent teachers.[1]

TOMISLAV PINTER (1899–1980)

Tomislav Pinter (Figure 2) was the Head of the Department for a quarter of a century, from 1945 until his retirement in 1970. He was born on September 13th 1899 in Zagreb where he also finished his primary, secondary and university education. He studied chemistry with physics and mathematics at Faculty of Philosophy. He was awarded a doctorate in science in 1926 with thesis “On the viscosity in the systems of binary organic liquid mixtures” (original title “O viskozitetu u sistemima binarnih organskih tekućih smjesa”) under the supervision of Nikola Pušin.[4] He started working at School of Medicine in 1924 as one of the first Bubanović’s assistants. Therefore, he was greatly influenced in his teaching style by Bubanović whom he worked closely with for years. He was the president of the Croatian Chemical Society from 1954 to 1955. An interesting fact is that the name of the journal Croatica Chemica Acta was actually Archives in Chemistry (original title Arhiv za kemiju) until Croatian Chemical Society during Pinter’s presidency in 1955 decided to change the name to its current one, formally used since 1956.[18] Professor...
Pinter was elected an extraordinary member of the Yugoslavian Academy of Sciences and Arts in 1963.[19–21]

Professor Pinter was a prominent scientist in the field of theoretical and experimental physical chemistry. He was especially interested in chemical kinetics, thermodynamics and theories and properties of liquid and gas state of matter.[19] In the field of chemical kinetics he studied the catalytic effect of mercury ions on hexacyanoferrate(II) ion decomposition in aqueous solutions.[22,23] Pinter used this research as a basis to develop a colorimetric method for determination of trace mercury ions in urine of patients treated with organo-mercury-based diuretics.[22] In addition to this translational work, he studied different equations of state of gases and liquids which resulted in an original approach and novel interpretation of van der Waals and Wohl’s equations.[5,24,25] Pinter, being a theoretical chemist, was most interested in the problems of open systems and thermodynamics of irreversible processes.[19] Being an excellent mathematician and physicist in addition to chemist, he was able to understand chemistry in a holistic manner and we can undoubtedly consider him a truly universal scientist.[20] Pinter published a total of 35 scientific papers. To get a sense of the scientist he was, a paper he published with his supervisor N. Pušin in 1929 (“Viskosität binärer System emit Guajakol als Komponente”) is still cited in scientific literature and the most recent citation dates to 2015.[27] In this work Pušin and Pinter presented the results of investigation on viscosity of binary systems containing guaiacol (Figure 3). The list of all Tomislav Pinter’s papers can be found in Refs. [19–21,23].

In addition to scientific papers, Pinter was the author of many professional papers, as well as university texts and textbooks. Amongst those, he was the sole author of “Physical chemistry for medical students” textbook (original title “Fizikalna kemija za medicinare”) which was published in three editions.[28] He was also the co-author of “Organic chemistry for first year medical students” (original title “Organska kemija za studente medicine prve godine”) with Vinka Karas-Gašparec from the Department of Chemistry and Biochemistry.[29] In addition, they co-authored the “Laboratory manual of chemistry for medical students” (original title “Praktikum kemije: za studente medicine”).[30]

Tomislav Pinter died on February 7th 1980 in Zagreb. Numerous colleagues and students fondly remember him. One of the people who passed through his laboratory was academician Drago Grdenić (1919–2018) in 1942. By his own words, he was deeply impressed by professor Pinter and they turned into life-long friends.[21,22,24,27] As academician Grdenić recollects,[22,24] his interest for
chemsitry of mercury was sparked by Tomislav Pinter thereby permanently influencing his scientific life. Academician Mihovil Proštenik also wrote about Pinter and shared his own memories.\cite{19,20} That is how we know that Pinter was an optimistic and bright person. He treated all people and especially his colleagues with the utmost respect and he was always happy to help and was delighted to see them thrive and succeed (Figure 4).

**MIHOVIL PROŠTENIK (1916–1994)**

Academician Mihovil Proštenik (Figure 5) was born on February 23rd 1916 in Zagreb. He finished primary and secondary school in Zagreb as well, where he continued towards obtaining his university degree in chemistry at Technical Faculty where he graduated in 1939. On the incentive of Nobel prize winner Vladimir Prelog, he joined his group at the Department of Organic Chemistry at what is today Faculty of Chemical Engineering and Technology, where he obtained his PhD degree under Prelog’s supervision, in 1944. His doctoral thesis was entitled “About homo-meroquinene and partial syntheses of quinotoxins and cinhotoxins” (original title “O homo-merokinenu i o parcijalnim sintezama kinotoksina i cinhotoksina”).\cite{31} Vladimir Prelog stayed in Zagreb working at Technical Faculty between 1935 and 1941 and during this period Prelog established “Prelog’s Zagreb School of Organic Chemistry” which had several generations. In addition to Mihovil Proštenik, amongst the first generation of Prelog’s collaborators were also other known Croatian...
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Proštenik collaborated with Slovenian chemist Vladimir Prelog, Nobel laureate in Chemistry in 1953, even before his doctorate in 1944. Proštenik started working at the Department of Chemistry and Biochemistry at School of Medicine. A nice memory from that period is saved in Proštenik’s eulogy given by professor Krešimir Balenović. He states that they established a laboratory set-up in 1942 at School of Medicine which was identical to Prelog’s Zagreb laboratory (at that time, Prelog already relocated to Switzerland) and that Proštenik’s laboratory was the only place in war time Croatia that ensured the continuity of scientific research in the field of organic chemistry. Therefore, Proštenik was quite respected and known even at a young age, before obtaining his doctorate.

Vladimir Prelog was not the only Nobel prize winner Proštenik worked with. In 1948 Proštenik spent 6 months at ETH (Eidgenössische Technische Hochschule) in Zürich, Switzerland in the laboratories of Croatian Nobel prize winners Lavoslav (Leopold) Ružička (1887–1976) and Vladimir Prelog. Proštenik stayed in active contact with both Prelog and Ružička as well as their families for the upcoming years, nurturing personal contacts as well as vigorous scientific exchange. At the Department of Chemistry and Biochemistry archive we still keep numerous cards and notes sent by Lavoslav Ružička and Vladimir Prelog to Mihovil Proštenik for various occasions (Figures 5 and 7). In a card sent by Prelog together with Proštenik’s photograph in 1969 (Figure 5) we can read “Dear colleague Proštenik, please find enclosed a failed photograph as an expression of my deepest gratitude for your attention and hospitality during our stay

[Figure 6. a) Cover page of a paper co-authored by Vladimir Prelog and Mihovil Proštenik published in 1943. b) The formal synthesis of quinine. c) The structure of d-quinotoxine.]

chemists: Eugen Cerkovnikov (1904–1985), Rativoj Seiwerth (1916–2000), Krešimir Balenović (1914–2003), Pavao Mildner (1918–2012) and Adolf Režek (1902–1980). Proštenik even published a paper with Prelog in 1943 entitled “Über homo-merochinen und über die partielle Synthese des Chinotoxins” (Figure 6). That paper still has an impact in scientific literature worldwide. Prelog and Proštenik, continuing the work of German chemists Paul Rabe (1869–1952) and Karl Kindler (1891–1967) from 1918 reporting a three-step conversion of d-quinotoxine into quinine, published the transformation of homomero-quinine into d-quinotoxine. In that way, they were the first to make a necessary step for the quinine synthesis pathway from a still-simpler degradation product homomero-quinine.

When American chemists Robert Burns Woodward (1917–1979) and William von Eggers Doering (1917–2011) in 1944 published the results of total synthesis of quinine, one of the key steps in that synthesis was therefore resolved by Prelog and Proštenik. In 2007, a review paper published by Jeffrey I. Seeman on that matter even reveals that the American chemist Gilbert Stork (1921–2017) suggested that the whole procedure is called Woodward-Doering/Proštenik-Prelog/Rabe-Kindler total synthesis of quinine.

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in Zagreb. All the best and kindest regards, your old Vlado Prelog”. Season’s greetings were also exchanged between Proštenik and Ružička as well as Prelog (Figure 7).

Proštenik’s stay at ETH in Zürich was not his only stay abroad. In 1952 he stayed at the University of Illinois at Urbana, USA, at the institute run by organic chemist Roger Adams (1889–1971). In the upcoming years Proštenik collaborated with numerous institutions.[37] One of his great contributions to the advancement of Croatian science was the role in founding the Ruđer Bošković Institute. Very soon after the establishment of the Institute in 1950, the biochemical group at the Institute was established by Proštenik, Krešimir Balenović, Rativoj Seiwerth and Viktor Hahn (1912–1970).[33] In 1954 Ruđer Bošković Institute undergoes a significant restructuring in which the organization of scientific research in chemistry was entrusted to Drago Grdenić and Božo Težak (1907–1980) together with the above mentioned chemists.[25] From 1955 to 1962 Proštenik served as Head of one of the four biochemical divisions.[25,37,39] In 1963 he was elected as an extraordinary member of the Yugoslavian Academy of Sciences and Arts.[38] In addition to all this, Proštenik took a more active role at his home Department of Chemistry and Biochemistry at School of Medicine and served as Department Head from 1971 to his retirement in 1986.[25] This was discontinued only for two years, from 1974 to 1976 when he stayed at Tripoli, Libya where he helped establish Department of Biochemistry at School of Medicine, University of Tripoli and where he also served as first Department Head for those two years.[25,39]

In his more than 40 active years as a scientist and teacher he, like his predecessors, didn’t teach only to medical students at School of Medicine. In the 1970s he taught biochemistry, general chemistry and organic chemistry at Faculty of Science and Faculty of Pharmacy and Biochemistry.[37] He also taught numerous lipidology courses for PhD students at the University of Zagreb.[37]

Proštenik started as a synthetic organic chemist, which gave him the basis to evolve as a brilliant biochemist. Lipid chemistry is the area Proštenik is mostly recognizable for. He was the founder of “Zagreb School of Lipidology” and is considered to have given a notable contribution to neurobiochemistry.[25,37] His world renown reputation in this field is confirmed by the fact that in 1960s all the relevant scientific literature cited or published his discovery of new sphingoid bases.[40] Proštenik published around a 100 scientific papers and the focus of a significant number of those papers was functional studies in chemistry and biochemistry of lipids, especially sphingolipids which were at that time still unknown from a structural, as well as functional point of view.[37] Proštenik investigated animal central nervous system sphingolipids, extraneural tissue sphingolipids (cerebrosides, sphingomyelins, gangliosides), yeast sphingolipids and phytosphingolipids, as well as sphingoid bases sphingine, sphinganine, dihydrosphingosine, etc.[27,37,38] One of the most notable results published is the discovery of a new sphingoid base: C20-sphingosine in equine and bovine brain.[41] The list of all Mihovil Proštenik’s papers can be found in Refs [37–39].

In 1986, around his retirement from School of Medicine, Proštenik was elected as a full member of the Yugoslavian Academy of Sciences and Arts (Figure 8). He died 8 years later, on April 26th 1994 in Zagreb. In a report to Academic Council for one of Proštenik’s promotions signed by professors Bubanović and Pinter we see that he was an excellent and respected lecturer whom students readily listened to since his lectures were interesting and easily understandable. Bubanović and Pinter also state that Proštenik, without a doubt, represents one of the best Croatian organic chemists specialized in biochemistry.[37]
CONCLUSION

It is completely clear that both Tomislav Pinter and Mihovil Proštenik were extraordinary professors and scientists known and respected not only in former Yugoslavia, but also worldwide. Through their research, which was often performed in collaboration with world famous chemists, they left a mark in (bio)chemical science and made Croatian (bio)chemistry internationally recognizable. Proštenik is still one of the most highly cited scientists from School of Medicine, and is considered as one of the School’s most influential scientists in general. Pinter and Proštenik paved two directions in scientific research which are still active at the Department of Chemistry and Biochemistry today. Their respective contribution to science, teaching and academia in general is evident from numerous accolades these two universal scientists were awarded with. We can say without any reservation that the Department of Chemistry and Biochemistry at School of Medicine in Zagreb is shaped both in science as well as teaching, starting with Fran Bubanović, continued by Tomislav Pinter and Mihovil Proštenik. We can only hope to be worthy as their successors.

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Figure 8. Mihovil Proštenik at Department library (left hand side) and lecture hall (right hand side) at a celebration in honour of his acceptance as a full member of Yugoslavian (today Croatian) Academy of Sciences and Arts on September 19th 1986. The right hand side photograph shows Proštenik and his family in the first row on the right, and academician Drago Grdenić (first in the second row on the right).
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