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MEN OF THE MOLECULES

*In memoriam of Prof. Russell Doolittle,
Prof. Eduard Lugovskoi and their friendship that outlive both of them*

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In memoriam Eduard Lugovskoi and Russell Doolittle we are referring to several episodes of their life and work. Russell Doolittle an American biochemist and his friend and colleague Ukrainian scientist Eduard Lugovskoi, both studied fibrinogen structure and functions and finally united their efforts in the revealing of the new mechanism of intramolecular interactions of fibrin molecule through coiled-coil region. The results of their common work and discussions were included to the article “The fibrin B β 125-135 site is involved in the lateral association of protofibrils”. Valuable part of the communication dedicated to the poetry of Eduard Lugovskoi that inspired both of scientists in work and life. We are providing some remembrance of their collaboration, their letters sent to each other, fragments of handwriting and common photo of Russell Doolittle and Eduard Lugovskoi.

Key words: Lugovskoi, Doolittle, fibrinogen, fibrin polymerization, coiled coil region.

The article “The fibrin B β 125-135 site is involved in the lateral association of protofibrils” published in this Issue of the Ukrainian Biochemical Journal not only presents remarkable scientific data but is also the final example of an extraordinary collaboration between two outstanding scientists. One is the leading author of this article, and the other is beyond our sight. Both passed away last year, 2019.

Professor Russell Doolittle from the University of California (San Diego, USA) was best known for his important work on the sequencing of the fibrinogen polypeptide chains [1]. He was the one who defined complementary binding sites ‘A’:‘a’ and ‘B’:‘b’ as ‘holes’ and ‘knobs’ according to their structure and the nature of their interactions [1, 2]. His works on the crystal structure of fibrinogen and its proteolytic products formed the basis of our modern knowledge about the structural peculiarities of this molecule [3].

Professor Eduard Lugovskoi dedicated his life to the Palladin Institute of Biochemistry of National Academy of Sciences (NAS) of Ukraine (Kyiv, Ukraine). Professor Eduard Lugovskoi successfully integrated Volodymyr Belitser’s research with studies initiated by Professor Serhiy Komisarenko for the investigation of the fibrinogen structure using monoclonal antibodies, and created a scientific school for hemostaseology [4]. His works using monoclonal antibodies allowed determining the extremely important polymerization site in the 12–46 fragment of the fibrinogen B β -chain (site ‘C’) [5]. Unique monoclonal antibodies to fibrinogen and its fragments allowed the development of diagnostic tests for early determination of the risk of intravascular thrombus formation [6].

During almost 30 years of their scientific careers, these two remarkable scientists were united by the bond of a warm friendship that was strengthened after several meetings and can especially be seen

in the letters they wrote to each other. Living and working on the opposite sides of the Planet, Eduard and Russell had a lot to discuss or to think about together. First of all they focused on the adorable molecule of their lives – fibrinogen – that was the object of their studies.

Some of their conversations were saved on the pages of a notebook that can be witnesses of the scientific dialogue between equal brains (Fig. 1). In Summer of 2009, Eduard Lugovskoi was a guest of Russell Doolittle and his wife Frances at their California bungalow (Fig. 2). Tom Thornton – son-in-law of Eduard Lugovskoi – remembers how two old scientists had non-stop discussions. Even in picturesque La Jolla while entering the ocean for swimming they did not stop their conversations and two heads – one grey and another half-bald – were jumping in the ocean waves still exchanging opinions about the role of the coiled-coil region of fibrinogen in self-assembly of the fibrin network.

As a result of their constant dialogue, this distinct part of the fibrinogen molecule became the object of attention of both scientists. During the visit to California, Russell Doolittle presented his friend Eduard Lugovskoi an ahead-of-print copy of his latest article that summarized his findings on the crystal structure of the fibrinogen molecule (Fig. 1). In this article he explained the flexible structure of the coiled-coil region and wrote: ***“It is not impossible that associations between coiled-coils may occur in fibrin”*** [7]. This very sentence is underlined in bold

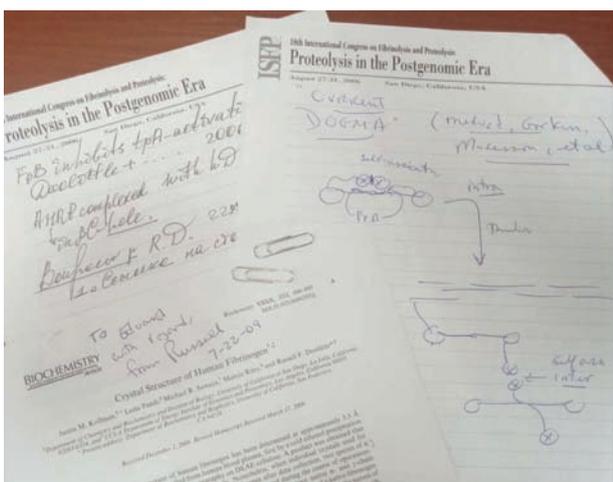


Fig. 1. Autograph of Russell Doolittle on the pre-print of his article. Pages of the notebook of E. Lugovskoi with handwriting of both professors (2009). From the personal archives of Prof. Lugovskoi

green in Eduard’s copy of the article and he knew how to experimentally prove this suggestion.

Besides the art of molecular interactions, we witnessed another remarkable bond between two scientists – the art of poetry. Eduard Lugovskoi was a talented poet whose verses were very welcome not only at the Palladin Institute of Biochemistry where he inspired people to read and write poems, but also abroad. Books of his short Japanese-style poems were disseminated among his network of scientists in many countries and Russell was one of his biggest fans. As Eduard wrote his *“rhymes did not pretend to be classical haiku [...] but were only some formulas fixating the instantaneous impression or feeling”* [8]. Very often Russell was one of the first readers of Eduard’s poems as soon as they were translated into English.

“Meanwhile, I greatly enjoyed your recent haiku, poignant as they were. I too have had to contemplate the loss of long friendships as fate takes its course. And I was a great fan of Audrey Hepburn,” – wrote Russell after reading his volume of *“Fleetingings”* by Eduard Lugovskoi [9].

Preparing his last book of poems, Eduard Lugovskoi worked on the English translations together with his eldest daughter Elena and his son-in-law Tom Thornton. However, all translations were regularly revised by his friend Russell. Once Prof Doolittle was asked to chose what version of the rhyme has to be included in the book. He answered: *“Choosing between uncut and polished diamonds is always dif-*



Fig. 2. Eduard Lugovskoi (on the left) and Russell Doolittle in the house of Prof. Doolittle in California, 2009. From the personal archives of Prof. Lugovskoi

ficult! I like both versions of the boy flying through the puddle. His eyes shine both ways. As for the green waves, I like Tom's version better. So far as I can tell, the two versions of the poem about the girl and her grandfather's cane are the same. But they're all good!" [10].

Finally, Prof. Doolittle was invited and merrily agreed to contribute the preface to Eduard's last book.

*"Scientists who are also poets are relatively uncommon. Rarely does one individual possess the talent to be outstanding in both realms. I have had the pleasure of knowing only one in my life: Eduard Lugovsky. Eduard Lugovsky and I have been friends for many years. We are both scientists studying one of Nature's most marvelous inventions: the clotting of the blood. That his poetry can be so moving to a simple **man of molecules** is testimony to its brilliance"* [11]. Apart from the brilliant preface, Russell Doolittle contributed the very first rhyme in the book, this rhyme was about him anyway: *"...in the last touching verse, perhaps a change of word order:*

*Two old men,
Friendship's fire not put out
Throughout their long lives"* [11, 12].

The illustrations to the book "Momentum," and in particular to this poem, were made by the daughter of Eduard Lugovskoi – Hanna Luhovska. Russell Doolittle enjoyed this illustration even despite the fact that both real friends looked a little bit different (Fig. 3).

Between the two men the poetry was a natural instrument for talking about complex feelings and observations, and it made their scientific communications even more fruitful. Russell Doolittle was interested in the functions of the coiled-coil region of fibrin [7, 13] and Eduard Lugovskoi used the monoclonal antibody FnI-3C and detected the new epitope in the B β 118-134 fragment of this very part of the fibrinogen molecule. Fab-fragments of this antibody specifically retarded the stage of fibrin protofibril lateral association [14].

First of all, this finding proved the idea both professors had about participation of the coiled-coil region in the lateral association of protofibrils. Much more interesting though was that the epitope of FnI-3C was hidden in the fibrinogen molecule and came atop only after cleavage of fibrinopeptide A [15].

Russell Doolittle was surprised by this fact and wrote: *"I can imagine an epitope in the seg-*



Fig. 3. Illustration to the poem "Two old men" made by Hanna Luhovska and included in E. Lugovskoi's book "Momentum" [11]

ment beta118-134 that doesn't react in fibrinogen because it may be blocked by the α C-domain until the fibrinopeptide A is released, after which the α C moves away exposing the site" [16]. Eduard Lugovskoi had his own theory about this phenomenon and planned to perform experiments with synthetic peptides mimicking this residue. Every new result was immediately shared with his friend Russell.

"You say the peptide beta 121-138 inhibits polymerization. The question is, at what relative concentration? If it is indeed a specific inhibitor, it need not be blocking an interaction between two coiled coils. I'd be careful here. Unless the beta 121-138 peptide is active at low ratios of peptide to fibrinogen (e.g., 10:1), it could be a non-specific effect. But it's an important matter, so study it well. Let me know when you hear about your paper" [16].

"The fibrin B β 125-135 site is involved in the lateral association of protofibrils" article in this Issue provides the clear answer to this question. Prof Lugovskoi with Prof Doolittle together planned studies focusing on scrambled peptide, and Prof Doolittle wrote: *"...the most critical is the matter of a control*

peptide for your B β 121-138 synthetic peptide. You definitely should synthesize a control: same length and composition, but scrambled (randomized) sequence” [17]. The data from such an experiment were also included in the final version of the manuscript and it is no surprise that Prof Doolittle was finally invited by Prof Lugovskoi to be a co-author of the article. Unfortunately, by the end of work on this fruitful endeavor, Prof Doolittle had already retired and decided to terminate the publishing of his scientific achievements. However, his name is not only listed in the acknowledgements, his style can also be recognized in the lines of the article.

Working together, Eduard and Russell defined some main principles of writing articles – somewhere on the edge of science and poetry: “*The English language is exasperating, but when it is used in scientific reports it's even worse. Think haiku. Minimum words*”. I believe that this advice can be useful for many scientists.

So too is the poetry that was part of their friendship but also a part of their scientific efforts. The last poem of Eduard Lugovskoi that was not included in the “Momentum” book appealed to his friend:

*I ate a handful of cowberry
Where once we walked together.
Luminous is men's friendship.*

Now we are reading the final article of this wonderful scientific tandem and reciting poems about their friendship. The scientists who review their research works could imagine two old scientists are walking slowly to the horizon along the ocean, and discussing the tremendously interesting theme of fibrin polymerization, that was “luminous” in their friendship, and they will be remembered as “men of the molecules”.

Ethical statement. Excerpts from letters are reprinted with the personal permission of Russell Doolittle.

ЛЮДИ ВІД МОЛЕКУЛ

В пам'ять професора Рассела Дуліттла, професора Едуарда Луговського та їхньої дружби, що пережила обох

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Пригадуючи Едуарда Луговського та Рассела Дуліттла ми наводимо декілька епізодів їхнього життя та праці. Рассел Дуліттл, американський біохімік, та його друг і колега український вчений Едуард Луговської, вивчали структуру та функції фібриногену і, нарешті, об'єднали свої зусилля у виявленні нового механізму міжмолекулярної взаємодії молекул фібрину через суперспіральні регіони. Результати їхньої спільної роботи та обговорень було викладено в статті «B β 125-135 ділянка молекули фібрину бере участь у латеральній асоціації протофібрил». Суттєва частина статті присвячена поезії Едуарда Луговського, яка надихала обох учених на працю та життя. Тут ми наводимо спогади про їхню співпрацю, їхні листи, надіслані один одному, фрагменти рукописів та спільну фотографію Рассела Дуліттла та Едуарда Луговського.

Ключові слова: Луговської, Дуліттл, фібриноген, полімеризація фібрину, суперспіральна ділянка.

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