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IN MEMORIAM OF EVGENY IOSIFOVICH SCHWARTZ

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E.I. Schwartz stood at the foundation of Russian molecular genetics: he was the first to apply the novel method of polymerase chain reaction (PCR) in this country. E.I. Schwartz graduated from the LPMI at 1967. His area of research belonged at first to the realm of the metabolic manifestations of hereditary diseases. Since 1985, he began working at the Laboratory of Molecular Genetics, Leningrad Institute of Nuclear Physics (LINP). Shortly thereafter, E.I. Schwartz began to reproduce and implement the PCR, recently proposed by K. Mullis. Coincidentally, the seemingly purely fundamental studies of thermostable polymerase, which turned out to be the key PCR enzyme, had been independently conducted in LINP and contributed to the success of E.I. Schwartz undertaking. He also initiated the development of the first Russian thermocyclers. He implemented PCR in fruitful long-term research projects on the molecular epidemiology of monogenic diseases: phenylketonuria, familial hypercholesterolemia, hereditary disorders of hemostasis, etc. E.I. Schwartz optimized the methods of isolating nucleic acids from dried blood spots and other sources, "suboptimal" for a laboratory specialist, but ideal for screening and forensic practice. Another field of his research was to elucidate the role of polymorphic alleles in multifactorial diseases. E.I. Schwartz enthusiastically propagated the new molecular approaches among clinicians and laboratory geneticists: he established close and fruitful collaborations between specialists of the vastly divergent backgrounds. In 1989 E.I. Schwartz founded the Department of Medical Genetics of LPMI, which was one of the first such departments in U.S.S.R. In 2001, he founded the Department of Molecular Genetic Technologies in I.P. Pavlov`s St. Petersburg State Medical University. In 2003, E.I. Schwartz has passed away, leaving behind him the good memory of numerous students and successors of his work.

Keywords: molecular genetics; history of science; polymerase chain reaction; gene; mutation.

ПАМЯТИ ЕВГЕНИЯ ИОСИФОВИЧА ШВАРЦА

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Е.И. Шварц стоял у истоков отечественной молекулярной генетики: под его руководством в нашей стране впервые был освоен и применен метод полимеразной цепной реакции (ПЦР). Научные интересы Е.И. Шварца, выпускника Ленинградского педиатрического медицинского института (ЛПМИ) 1967 г., первоначально состояли в изучении метаболических проявлений наследственных заболеваний. С 1985 г. он начал работать в лаборатории молекулярной генетики Ленинградского института ядерной физики (ЛИЯФ). Вскоре Е.И. Шварц приступил к воспроизведению и внедрению недавно предложенного К. Мюллисом метода ПЦР. Определенную роль в успехе его начинания сыграл тот факт, что в ЛИЯФ проводились считавшиеся фундаментальными и только исследования термостабильной полимеразы, оказавшейся ключевым ферментом ПЦР. Е.И. Шварц инициировал и разработку первых отечественных ПЦР-амплификаторов. Потенциал нового метода был успешно продемонстрирован Е.И. Шварцем в многолетних исследованиях молекулярной эпидемиологии моногенных болезней: фенилкетонурии, семейной гиперхолестеринемии, наследственных нарушений гемостаза и т. п. Уделяя большое внимание практическому внедрению ДНК-анализа, Е.И. Шварц внес вклад в оптимизацию методики выделения нуклеиновых кислот из пятен высушенной крови и иных источников, «субоптимальных» для лабораторного специалиста, но идеальных для массового применения. Еще одна область — изучение роли полиморфных аллелей в генезе частых многофакторных заболеваний. Значимость фигуры Е.И. Шварца в развитии отечественной науки

была связана еще и с тем энтузиазмом, с которым он распространял новые знания среди клиницистов и лабораторных генетиков: им было налажено тесное и плодотворное сотрудничество между самыми различными специалистами. В 1989 г. Е.И. Шварц создал и до 2001 г. возглавлял кафедру медицинской генетики ЛПМИ – одну из первых в нашей стране. В 2001 г. он организует отдел молекулярно-генетических технологий при Первом Санкт-Петербургском государственном медицинском университете им. акад. И.П. Павлова (ПСПбГМУ). В 2003 г. Е.И. Шварц скоропостижно скончался, оставив после себя добрую память многочисленных учеников и продолжателей его дела.

Ключевые слова: молекулярная генетика; история науки; полимеразная цепная реакция; ген; мутация.

This year marks the 80th year since the birth of Professor Evgeny Iosifovich Schwartz and the 17th year since this outstanding scientist has passed away. E.I. Schwartz was born just before the war broke out in Bobruisk City, Belarus. He cherished the memory of his father, a military pilot, who died in battles near Moscow in 1942. As a child, Schwartz's character was largely under the influence of his stepfather, who was the commander of reconnoiters in the partisan unit during the war period, where Schwartz and his mother were hiding from the Germans, and who worked as a director of a school in Bobruisk after the war.

In 1961, Schwartz entered the Leningrad Pediatric Medical Institute. In his student years, he became interested in biochemistry and genetics and studied enthusiastically these subjects at the Student Research Society under the leadership of Elena Aleksandrovna Savelyeva-Vasilyeva, who he remembered fondly throughout his life. Oleg Aleksandrovich Rosenberg, Viktor Glebovich Vakharlovsky, and Vyacheslav Veniaminovich Krasilnikov, who later became prominent specialists in the field of biochemical and clinical genetics, were also engaged in this Student Research Society at different times. After his graduation from the institute, Schwartz had no doubts in choosing the direction of his scientific and practical activities, and he made various efforts to enter the recently organized academic group of Evgenia Fedorovna Davidenkova, where conducted research on cytogenetics, clinical genetics, and biochemical human genetics. In 1971, Schwartz defended his PhD thesis, "Disorders of carbohydrate metabolism in muscle tissue of patients with Duchenne muscular dystrophy," [14] and his doctorate thesis, "Metabolic bases of immunological disorders in cells with trisomy on chromosome 21" in 1982 [15]. Based on the results of his study, Schwartz hypothesized that immunological disorders in Down's syndrome are caused by impaired DNA repair, which, in combination with accelerated tissue catabolism, leads to increased concentration of deoxynucleotides, inhibition of the T-system of immunity, and the development of metabolic immunosuppression.

At that time, many geneticists, including Schwartz, were focused on molecular medicine, and the academic group became insufficient for him. In 1985, he started to work in the laboratory of molecular genetics of the V.P. Konstantinov Leningrad Institute of Nuclear Physics, RAS, which was headed by Vladislav Aleksandrovich Lantsov, a student of Semyon Efimovich Bresler, who was a leading specialist in physical chemistry and biophysics and one of the founders of Russian molecular biology.

Schwartz managed to convince V.A. Lantsov to conduct molecular research not only on microorganisms, which was performed in the laboratory before Schwartz came to work there, but also on models of hereditary human diseases. To implement this idea, a working group was quickly formed by Schwartz, and in 1992, they created a separate laboratory of human molecular genetics and employed well-known researchers such as A.A. Goltsov, S.E. Khalchitsky, and A.I. Kuzmin. In 1985–1986, the group was engaged in the construction of a cDNA library of liver genes based on bacteriophage λgt10 for the analysis of genes of hereditary human diseases, in particular, phenylketonuria [12]. In this work, which was performed jointly with employees of several institutions in Moscow, a first in the country, various methods of genetic engineering were established.

Shortly after the completion of this 2-year laborious work, publications appeared on the invention of the polymerase chain reaction (PCR) method, which greatly facilitated the molecular diagnostics of mutations. Schwartz promptly made a decision to master this new technology as soon as possible [13], which required certain amount of courage. Work on the creation of a gene library has just been successfully completed, and the path to molecular diagnostics of mutations has been opened. However, a new effective diagnostic method emerged, and Schwartz, having overcome his ambitions, fostered all his efforts to its development [6, 7, 11].

Certain prerequisites were already set for this in the laboratory.

Long before the discovery of PCR in the laboratory of molecular diagnostics, studies of DNA replication under extreme conditions, such as elevated temperatures, were already conducted. To solve this problem, the topic executive O.K. Kaboev developed a method for isolation and purification of thermophilic DNA polymerase from the culture of bacteria living in the hot springs of Kuril Islands. This enzyme was necessary for PCR, and its quality was quite satisfactory. In addition, the specificity of PCR is determined by the presence in the reaction mixture of short oligonucleotides complementary to the ends of the synthesized DNA fragment, so-called primers. At that time, their production was also challenging. However, an agreement on their synthesis was achieved with Professor Yu. A. Berlin from the Moscow Institute of Bioorganic Chemistry. No devices were established for automatic PCR (amplifiers or thermal cyclers), and the work was performed manually by rearranging test tube racks in water baths in a certain temperature. Reaction conditions, temperature, and time regimens were worked out experimentally. Schwartz realized the importance of PCR for molecular diagnostics and initiated work on the creation of Russian amplifiers, which were developed on Peltier elements by a group of researchers led by Alexander Tretyakov.

Thus, under the guidance and direct participation of Schwartz, the PCR method was established for the first time in Russia and was used to diagnose mutations in the genes involved in β-thalassemia, phenylketonuria [4, 11], and later cystic fibrosis [16], as well as for genomic fingerprinting, which is now widely used in forensic medicine [26].

The discovery of PCR was a revolutionary event in the field of molecular genetics. Studies of individual genetic characteristics using genomic and cDNA library technologies required a huge amount of work, time, and costs. PCR enabled analysis extremely quickly, determination of the nucleotide sequence of the genome region of interest, ordering of primers, and obtaining information about mutations in an individual just within a few days.

One of the authors helped improve the PCR method, as it was applied to the analysis of blood stains immobilized on various carriers, such as Guthrie test strips, nylon filters, and filter paper, which greatly facilitated and accelerated the rather laborious work of collecting, storing, and transferring of biological material. This was also the undoubted priority of Schwartz's laboratory [27, 29, 30].

Schwartz was a member of the problem commission on human molecular genetics of the USSR Ministry of Health from 1987 to 1991. For many years and until the end of his life, he was an editorial board member of the international journal *Molecular Genetics and Metabolism*.

Schwartz was a staunch supporter of the need to introduce theoretical developments in the field of medical genetics into the clinical practice of doctors. In 1989, at his urgent request, a scientific and educational complex was created at the Leningrad Pediatric Institute, which, along with the training Department of Medical Genetics, included his scientific laboratory of human molecular genetics at the Leningrad Institute of Nuclear Physics (LINP). On the basis of this complex, students and teachers of clinical departments of pediatric and other medical institutions could learn practical methods of DNA diagnostics and could conduct scientific research in specific areas of molecular medicine.

The idea of creating such a complex, which was located in a clinical institution, and combining an academic laboratory and a training department was supported by the administration of the Pediatric Institute, primarily by Professor Vyacheslav Petrovich Alferov, its rector, and by Viktor Nikolaevich Fomichev, the head of the department of molecular and radiation biology of LINP, which ensured its further promotion in the Academy of Medical Sciences. It was financially supported by the USSR Ministry of Health.

Schwartz managed to strike a spark out of well-known specialists from various medical institutions of the city, who already had academic degrees and ranks, and to involve them to work at the Department of Medical Genetics of the Pediatric Institute. Although they did not have teaching experience at a medical university, in which the staff of the department was under the leadership of Schwartz, a unique system of genetic education for future doctors was developed.

The results of the scientific activity of the complex were impressive. Two main principles predetermined this success, namely, close interaction with the clinical departments of the Pediatric Academy and some other medical institutions of the city and the involvement of a large number of young specialists, both doctors and laboratory assistants, many of whom graduated from the Department of Biophysics of the Leningrad Polytechnic

Institute, which was organized by S.E. Bresler, or the Technological Institute.

The emphasis on scientific research was focused not only on the study of the molecular nature of monogenic diseases, but also on the analysis of genetic risk factors that predispose to the development of the most common socially significant multifactorial pathology. Research in this direction had not yet been conducted in Russia.

A year after its creation, the complex cooperated with the Department of Faculty Therapy of the Pediatric Academy, headed by Yuri Romanovich Kovalev, to investigate the hereditary predisposition to ischemic heart disease and arterial hypertension [9, 20, 22, 25, 31]. Since 1992, the Department of Pediatrics No. 3, headed by Igor Mikhailovich Vorontsov, has also been involved in these studies. A new scientific field was then created, which was associated with the analysis of childhood predisposition to cardiovascular diseases [5, 8]. Together with the Department of Faculty Pediatrics, headed by Albert Vazgenovich Papayan, a series of studies was carried out to investigate the pathogenetic mechanisms of the development of arterial and venous thrombosis in children with normal health status and in children with nephropathies [10, 30].

Contacts of Schwartz's laboratory with medical institutions were not limited to the Pediatric Academy. Thus, together with the laboratory of biochemical genetics of the Institute of Experimental Medicine (headed by the corresponding member of the Russian Academy of Medical Sciences Vladimir Solomonovich Gaitskhoki), the range of mutations in familial hypercholesterolemia was explored [21, 23, 26]. Since 1997, research in the field of molecular cardiology has been conducted in close cooperation with the Department of Faculty Therapy of the First Leningrad Medical Institute, headed by Vladimir Andreevich Almazov and then Evgeny Vladimirovich Shlyakhto [1, 2]. One of the most interesting areas of scientific research at this time was the study of genetic risk factors for the development of vascular complications in diabetes [28]. The studies on genetic predisposition and hereditary forms of Parkinson's disease have represented a separate scope [17–19]. At this time, over 20 theses were defended under the guidance of E.I. Schwartz.

Great practical and friendly assistance to the young workers of E.I. Schwartz's laboratory was provided by the staff of the LINP Laboratory of Molecular Genetics, headed by Professor V.A. Lantsov. This laboratory, like Schwartz's laboratory, was geographically located in the Consultative and Diagnostic Center of the Pediatric Institute.

An important result of the ongoing research was the creation of unique DNA banks of young and old patients with myocardial infarction and patients with ischemic thrombotic stroke, venous thrombosis, varicose veins, arterial hypertension, type 1 diabetes mellitus, bronchopulmonary pathology, and Parkinson's disease.

The atmosphere in the laboratory should be separately highlighted. The youth set the tone there. Every day, Schwartz discussed previous events daily with each of the employees, whether they were graduate students, residents, or laboratory assistants, and developed a plan for further actions. He took the failures and blunders of young specialists sincerely and was quite strict with them but democratic and understanding of their personal problems. As a passionate person, Schwartz could not always restrain his emotions. He absolutely did not tolerate betrayal, and sometimes, even with the slightest suspicion, which was often not always well-grounded, he could abruptly switch from love to hate. However, he was also quite demanding of himself. Such an indifferent attitude of the chief to the employees and their research evoked a reciprocal respect, sometimes turning into adoration.

A very important organizing moment in the activities of both the department and the laboratory were weekly scientific seminars held by Schwartz himself. He had comprehensive scientific knowledge, and not a single current publication on human molecular genetics remained unaddressed by him. This was also enhanced by the information support of LINP, which was excellent for that time. In the absence of the Internet, new acquisitions from the Library of the Academy of Sciences was brought to the institute on a weekly basis, and it was possible to order a photocopy of the article from any magazine and receive it promptly. However, most importantly, Schwartz spent every Saturday in the public library and was very happy to meet his employees. He was permitted to take out magazines, brought them to work in large quantities, and photocopy the necessary ones. Reports from employees on the state of affairs in the developed fields were regularly presented at seminars, as well as in reviews on the most pressing issues of modern genetics, and there was a hot dispute on whether the speaker was less informed than the head.

The joint fun feasts should be mentioned, as it also contributed to the friendly atmosphere in the

laboratory. They celebrated together official holidays, birthdays, or other pleasant events. Schwartz shone at these celebrations with his wit and great sense of humor.

In 2001, with the support of the rector, academician N.A. Yaitsky and Vice Rector for Science Professor E.E. Zvartau, Schwartz organized the Department of Molecular Genetic Technologies at the I.P. Pavlov First St. Petersburg State Medical University and went there to work with the staff of his laboratory. Along with the continuation of research on molecular cardiology and Parkinson's disease, research on hereditary forms of thrombophilia and pharmacogenetics became a priority [3, 24]. The Department of Medical Genetics still exists at the Pediatric Academy.

Schwartz's activities were not limited to the institutions of St. Petersburg. In 2000, he was an employee of Transgenomic Gaithersburg MD (USA). In 2001–2003, he actively contributed to the development of molecular genetic research at the Research Institute of Physical and Chemical Medicine and the Scientific Center for Children's Health of the Russian Academy of Medical Sciences in Moscow.

The life of E.I. Schwartz ended unexpectedly when he and his wife were stuck in a traffic jam on their way from the summer cottage. He had a heart attack, but there were no drugs to stop it. Being entirely consumed with science and handling carefully the smallest details of his research, he spent all his energy on promoting his labor of love and did not care about himself and his health at all.

Most of the young people schooled by E.I. Schwartz scattered worldwide. Only few chose to stay, namely, S.N. Pchelina, O.V. Sirotkina, S.E. Khalchitsky, and V.I. Larionova. Schwartz's students successfully continue genetic research in various Russian and international laboratories, but each of them fondly remembers his/her first teacher.

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