The School of Inge

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Abstract

These notes were written in relation to 80th anniversary of professor Sergey Inge-Vechtomov, who about 50 years is the head of laboratory of physiological genetics. Authors describe the amazing atmosphere of the scientific creativity that was cultivated by Sergey in his lab from the very beginning of its existence, recall the many people who worked there in the 60s and 70s, remember funny situations from the history of the laboratory. Sergey G. Inge-Vechtomov instilled in his students high standards of scientific research. Being a mentor is a special talent. Very few had such a strong impact on the lives and characters of his students like Sergey G. Inge-Vechtomov. Very few can be called a true Teacher.

Keywords: Inge-Vechtomov, Jubilee, Science memoirs.

Those were the days my friend
We thought they'd never end
We'd sing and dance forever and a day
We'd live the life we choose
We'd fight and never lose
For we were young and sure to have our way…

These short notes are not about the scientific and educational impact of Sergey G. Inge-Vechtomov — in other words not about his papers, monographs, ideas, talks and textbooks, but about his immeasurable role in mentoring young scientists. We are not going to talk about the quantity of the undergraduate, graduate, and doctoral theses produced under his supervision, or about their quality, we are going to describe the amazing atmosphere of scientific creativity that Inge cultivated in his lab that he built while very young, in his thirties. This atmosphere nurtured many capable researchers, quite a few of whom later started their own labs in the image of their scientific alma mater.

Inge's lab focused on yeast genetics. Readers are probably wondering why this obscure, albeit indispensable for bread and beer-making, fungus, the yeast, attracted the attention of the new research group. As we all know, the last quarter of the 20th century was the age of molecular biology. However, in the sixties the upcoming technological shift hadn't yet happened and was totally unforeseen. There was yet no genetic engineering, no protein crystallography, no fluorescence microscopy, no Northern, no Southern, no Western, no sequencing and so on. There was only formal genetics. At the same time, genetics of microorganisms was already at the forefront of modernity because in microorganisms the path from the gene to the phenotype is short, which simplifies dissection of the steps of gene expression. As opposed to prokaryotic bacteria, yeast are eukaryotes, thus just like us, but unicellular. Therefore, yeast genetics was poised to play a very important role in molecular

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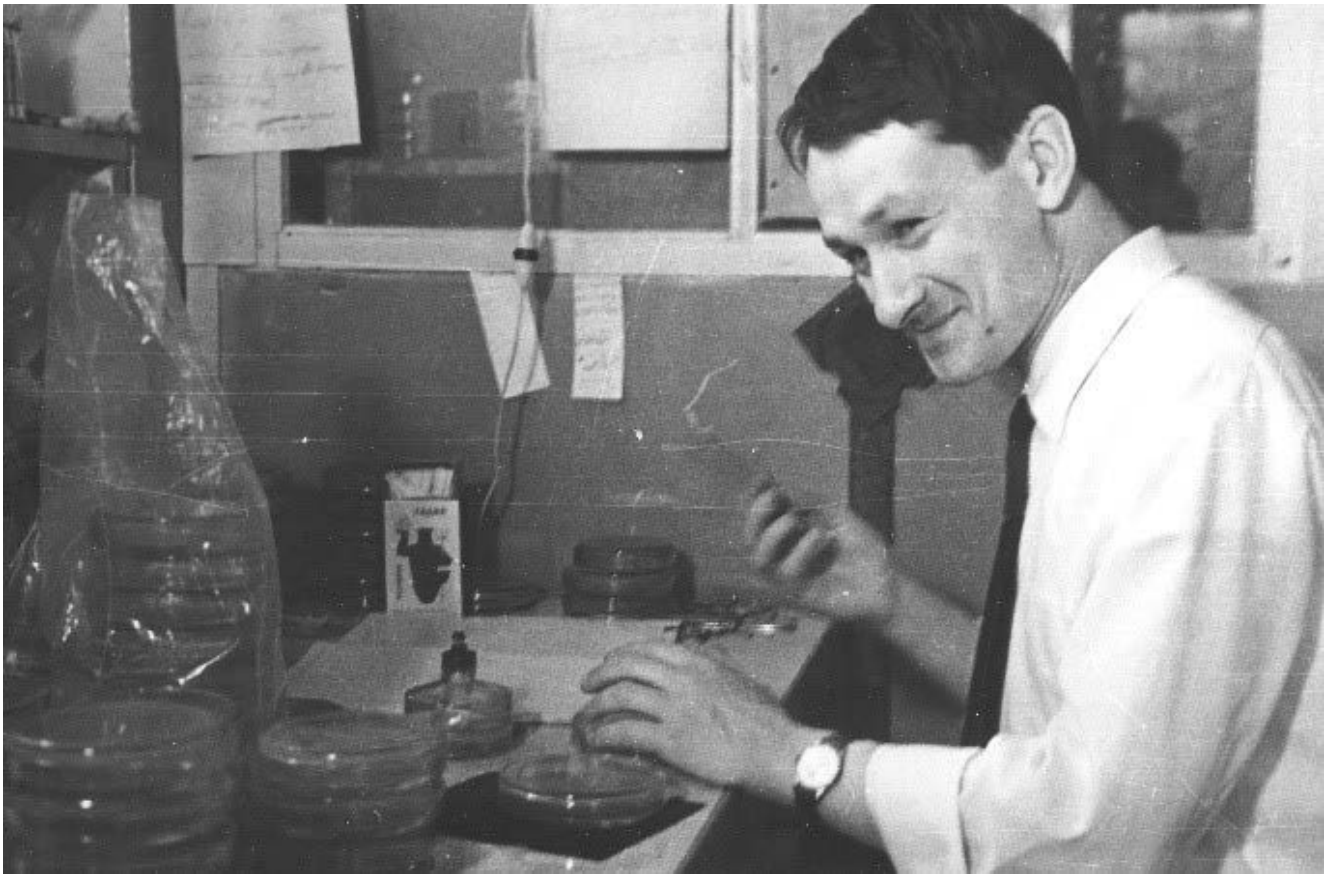

Fig. 1. Sergey Inge-Vechtomov, about 1970.

biology of the gene. However, before it happened, yeast genetics had to be developed by the few who were gifted with unusual foresight. Indeed, at that time nobody in the world paid much attention to yeast, *Saccharomyces*, as a model organism. There were very few labs working with yeast. Surprisingly, one of those early yeast research labs appeared in St. Petersburg (Leningrad).

The yeast lab emerged in St. Petersburg (Leningrad) University in the sixties, first as a research group within the lab of microbial genetics headed by K. V. Kvitko. Inge became its group leader in 1965, when the former head of the group I. A. Zakharov moved to PNPI (the former LNPI, Leningrad Nuclear Physics Institute). In 1969, the yeast group was converted into a laboratory of physiological genetics of the Biological Institute of the St. Petersburg (Leningrad) University. The initial meaning of its name is not important. Importantly, the lab focused on the physiology of the gene, in other words on gene expression. Later, many of the problems tackled at the lab bloomed into whole fields of molecular genetics. As there were very few labs working with yeast at that time, publications from Inge's lab had a significant impact on the field. We are going to describe those early years that left such a serious mark not only on yeast research but also on the lives and characters of the early members of the lab.

We, the authors of these notes, graduated from the "School of Inge-Vechtomov" with a ten-year interval. In 1966, when the first of us, LNM, joined the yeast group as a sophomore, the boss was 27, and he already held a candidate (Ph.D) degree (Fig. 1).

The core of the lab consisted of former graduates of the St. Petersburg University: Sergey A. Kozhin, Boris V. Simarov, Nikita N. Khromov-Borisov, and a graduate of the University of Tartu (Estonia), Tonu R. Soidla (Fig. 2).

Those four had not yet obtained their Ph.D; they were in their mid-twenties; however, regardless of their young age, each one led a team of staff, graduate students and undergraduates. Among those who worked in the lab in the late sixties and early seventies as staff members or students were Inessa Popova, Vera Andrianova, Vera Stepanova, Valentina Pavlenko, Larisa Ravdonikas, Valentina Golubtsova, Valentina Egorova, Vladimir Kvasha, Oxana Nitsai, Michail Ter-Avanesyan, Edda Rabinovich (Rayko), Boris Shabunov, Dmitry Gordenin, Anna Arefieva, Natalia Mikhajlova, Vera Tikhomirova, Maria Petrashen (Samsonova) and others. (Fig. 3).

The second author, TSK, joined the lab as a freshman in 1974 and thus represents a "second generation" of the lab, to which Yury Pavlov, Yury Chernoff, Tatyana Zhukova (Chernova), Anatoly Grishin, Vladimir

Fig. 2. From the left to the right, T. Soidla, S. Kozhin, B. Simarov, N. Khromov-Borisov.

Fig. 3. From the left to the right: V. Andrianova, D. Gordenin, M. Ter-Avanesyan.

Fig. 4. From the left to the right: T. Karpova. Yu. Chernov, V. Noskov, Yu. Pavlov, A. Grishin.

Noskov, Marina Repnevskaya and many others belong (Fig. 4).

At the beginning, the lab research was focused on the development of the gene model of *ADE1* and *ADE2,* encoding proteins involved in biosynthesis of adenine. Gene models play an important role in molecular biology; when the gene and its product are well studied; such models provide specific answers to specific questions. The gene model of Inge's lab was well chosen; it had significant technical advantages. Mutations in *ADE1* and ADE2 lead to the accumulation of red pigment. Changes in colony color simplify selection for mutants and observation of various genetic interactions including complementation and suppression. Soidla studied interallelic complementation for *ADE2*. Combined in a diploid cell, mutations in different regions of the gene may cancel out each other's defects (complement each other). Potentially this may be caused by the intramolecular contacts within the protein encoded by the gene. In the absence of a more direct approach, interallelic complementation

supplied preliminary information about protein folding. Simarov obtained dominant nonsense suppressors of mutations in *ADE2* and tested their effects on interallelic complementation. Kozhin and Khromov-Borisov applied the *ADE1*/*ADE2* gene model to different aspects of mutagenesis. Inge himself not only provided general leadership and integrated all the research of other groups, but also studied new and promising problems, such as recessive nonsense suppression and genetic recombination. Inge also was interested in polyploidy applied to studies of gene dosage. Notably, despite this diversity of interests, all the groups of the lab exchanged ideas freely and any method or approach developed by one of the lab members immediately spread to other groups. This free flow of ideas is an indicator of the high quality of research.

It was evident to anyone that this lab was unusual and it functioned as a tightly knit team of enthusiastic workers. Significantly, everybody worked very hard. The researchers, the support staff, graduate students, and undergraduates spent long hours in the lab well beyond the limit required by work regulations. The explanation is simple — the work was interesting; everybody understood that important research was happening, and the lab was at the forefront of science. In addition, the hard work of others served as an example, preventing any slacking. Those who preferred a more relaxed style of work left this lab soon.

According to lab mythology, Inge could work 24/7; when he got tired he just rolled under a lab bench, slept for a while and then resumed his work. However, this lab seriously lagged behind in work discipline in the general sense of the word. The lab members could stay very late finishing the experiment, but the next day they could show up a few hours later than official opening hours. In the lab there was a book in which everyone was supposed to log in the daily time of his arrival, and the first who came in would sign for a few others (we are not fools, after all…). Sometimes external forces timed our arrival, as in the mind of a bureaucrat the work of scientists does not differ from that of factory workers. Routinely, the days of such inspections were known beforehand, although even then someone managed to be late. One problem was of course that arrival was dependent on the train schedule. If you missed the train, the next would depart only in 20 minutes. TSK remembers from the seventies how after a huge snowfall everybody from the same train was walking in line along the narrow path between the snowbanks. The Director of the Biological Institute, who was trotting along in the middle of this line, joyfully called, "Whoever is behind me is late for work!"

The long work hours were possible partially because of the option to spend the night in the dormitory of the Biological Institute, which was quite close: the dormitory was in the administrative building, and the lab was in the adjacent Cavalier building (all this belonged to the former palace complex of Tsar Nicholas I's daughter). Living conditions in this dormitory were far below any standard. However, for the students the ability to stay overnight saved time for research that otherwise would be lost in commuting; the students lived and studied in St. Petersburg, but the lab was in Peterhof and could be reached only by train.

The students deserve a few extra words. Officially, only juniors were required to join the lab for training, but many freshmen or sophomores joined Inge's lab voluntarily. The greatest attraction of this training was that the students were involved in real research. Of course, at the beginning they could derail some experiments. Working in sterile conditions was a special challenge. TSK, at the beginning of her illustrious career, managed to plop a pendant into a Petri dish with a sterile suspension of yeast cells. Don't worry, the golden pendant was OK, but the suspension was spoilt. Thus, TSK had to part with pendants and with manicures, because every day she had to wash and sterilize the multi-use glass Petri dishes. Of course, at that time rubber gloves were unavailable, but what are those, anyway, against the broken glass that inflicted numerous cuts on the hands of the washer?

The further advantage of this lab was its diversity, unusual at that time. Besides Soidla, among the graduate students and postdocs of the lab there were Estonian Yaak Soom; Jacob Rajpulis from Latvia; Anna Koval, Vladimir Kvasha, Elena Rushchenko from Ukraine; Anna Rusnak from Moldova; Aivengo Shatirishvili from Georgia; Flora Tkhruni from Armenia; and Donaldas Chitavichus and Tautvile Iokantaite from Lithuania. This was also one of Inge's achievements; he made his lab a magnet for young geneticists of the whole Soviet Union. Of course, this diversity added extra excitement to the conversation and expanded the knowledge of other cultures and languages (Fig. 5).

The lab's equipment was very limited in the first years of its existence. There were two autoclaves, three micromanipulators, several thermostats and refrigerators. One thermostat was truly antique; made from beautiful hardwood, it was converted from a chicken incubator and begged to be donated to the museum of Science. Nowadays yeast cultures are stored frozen at −80 °C, but at that time we could only refrigerate them, and any refrigerator failure was a source of alarm because the precious yeast strains could die. TSK remembers the dread at the sight of the puddle of yellow fluid next to a refrigerator, but the culprit turned out to be not the refrigerator but the pet cat from the neighboring Lab of Entomology.

The main tools of the trade at that time were a microbiological inoculating loop (non-disposable) and

Fig. 5. From the left to the right: D. Chitavichus, J. Soom, A. Rusnak, A. Koval.

velveteen pads, and Petri dishes with media. There were problems with media components; something was always lacking: agar was the most difficult to procure because in a country with a centralized economy, agar was strictly allocated to the bakery factories, and the scientists formally had no right to it. Compressed cake yeast was also difficult to get: the whole country lusted for cake yeast to bake pies, and we lusted for it to make microbiological media: those contained a homemade component, the "autolyzate", or simply speaking, a soup from commercial yeast supplying the nutrients for our lab cultures. Quite often the Petri dishes, made of glass and thus breakable, became a bottleneck because officially they were distributed to medical facilities, but not to universities that had no patients and thus no business to involve themselves in work with microorganisms. As for antibiotics, we got them in the pharmacies. For that, a friend of a friend prescribed the stuff, and then all of us took turns buying it. TSK remembers how violently she was shamed in the pharmacy for buying paromomycine, and thus she learned that it was normally used for treating some despicable diseases. The velveteen pads were completely beyond the pale for official procurement and we bought them in fabric shops whenever velveteen was spotted there. Once someone bought velveteen with gold threads and it could not be used for the yeast culture replica-plating. TSK bought this velveteen out just to be friendly and made a suit from it, but the color was so ugly that she could not wear it. However, this action had unintended consequences: later TSK overheard in a conversation, "If this doesn't work out, we will sell it to TSK". Anyway, hunting for deficit items was a norm of life, and nobody was surprised by it. There were no grants available, only budget financing, and even if anything could be bought through the university purchasing system, the procurement was very slow, and staple items had to be ordered a year ahead.

To be fair, at that time the enzyme β-glucuronidase, which was very important for yeast genetics and was used to digest the asci envelope during tetrad analysis, most likely was not commercially produced even in the USA. Fortunately, it is a component of digestive juice that can be extracted from the guts of the snail *Helix pommatia* (escargot or Burgundy snail). Thus, the lab members made trips to Crimea or the Caucasus to collect the snails (and, as a bonus, to sunbathe in the balmy southern climate). Snails, called "nuts" in the shipment form to simplify the matter, were shipped to Peterhof by mail. On one occasion, the lab members were met at the post office with the unfriendly question, "And what did you ship?" — "Nuts…" — "Nuts? Ha!" The snails had woken up and they were sticking their necks through the slits of the box, which was standing on the table in the middle of the room surrounded by a dead zone. The snails had to be gutted (a chore for all the lab members) and then the yearly supply of snail juice had to be sterilized (Fig. 6). Once, the lab decided to taste the gut-free escargots; the French eat them, right? For the lack of an Escoffier cookbook, we improvised. We boiled the snails thoroughly and ate them as they were, *a la naturelle*. They tasted like rubber balls. We decided that if the French ate snails, food must be really scarce in that France.

At the beginning, the lab was located in two and a half rooms on the second floor of the Cavalier building, above the Entomology lab with their cat. "A half" means that one room wasn't a room at all but rather a short extension of the hall. It was converted into a small "box room" for sterile microbiological work. Three other box rooms belonging to Inge, Soidla, Simarov and their groups were built within one of the large rooms. The second large room served as a library, an office for Inge, a lunchroom and a room where tests could be analyzed. The box rooms were incredibly hot in summer and very stuffy, and everybody preferred to contemplate the latest experiment in this big room. In winter the box rooms were, conversely, very cold. Nobody had even heard at that time about laminar flow hoods, air conditioning and other capitalist niceties. The researchers could put on an extra sweater or work in a swimsuit, but for the yeast those temperature fluctuations were problematic, especially for the temperature-sensitive or cold-sensitive varieties. The autoclaves first stood in the hall, but later

Fig. 6. V. Egorova (left) and L. Mironova (right) preparing snails.

they were moved to another room formerly owned by the group of L. Z. Kajdanov. As the lab staff grew in numbers yearly, since anyone who came loved it and decided to stay forever, the researchers were packed into the box rooms very tightly and often worked back-to-back in a very small space. The problem was partially alleviated when a "kinder box" for the undergraduates was built on the third floor, and soon after that five more boxes for the graduate students were constructed on the veranda of the same floor. Regardless of those spartan conditions, the work in the lab was very successful, and the groundwork had been laid for the future development of the lab for many years.

The yeast lab's seminar played an important role in its function. The seminar was held on Saturdays, as Saturdays at that time were workdays, although short ones. Seminars continued indefinitely; everyone was "fighting to the last bullet" discussing the latest scientific news or results. However, the topics were not limited to science and the speakers might have no direct connection to yeast research. Priority was given to original ideas deserving consideration. Among the invited speakers were poet and philosopher Henri Volokhonsky and musician Felix Ravdonikas. The seminars were absolutely unusual for that time, not only in content but also in style: everyone was so young, and therefore there was a lot of laughing and clowning around. Thus, these seminars might produce a very wild impression on a visitor fresh from the street of the Soviet city. That epoch was so dull that even minor deviations from standard were rare and were perceived as a breath of fresh air or, alternatively, a breach of the status quo: obviously this unruly seminar met with disapproval, sometimes even at the Department of Genetics. Those times are gone, and it is hard to convey this atmosphere of the daring to the modern generation.

No lesser role in the life of the lab was played by the daily afternoon tea. First, during this tea everybody socialized; the conversational topics were exciting and mostly not about science but about books, movies and life in general. Second, everybody was hungry and wanted to eat and to wash his food down with tea. Unfor-

tunately, food was in limited supply as most scientists are not smart enough to understand that after a hearty breakfast they will be hungry again at midday. Thus, only few brought in lunch. The food had to be divided evenly between the participants (Typical: "Why are you taking so much butter, TSK? Put half of it back, there are people staying late today!"). Once, TSK, mechanically and with the best intentions, divided the cake into multiple slices one square cm each, and was awakened from her trance only by the mournful cries of the company, who, after that, immediately polished up the improvised spaghetti. The entomologists from the lab downstairs were more substantial (and older) people, thus food leftovers from their parties were highly prized by the yeast geneticists. TSK especially remembers one leftover tray that was pilfered after a private party of entomologists, with a can of sardines as a crown jewel. Inge caught us, delivered a diatribe (I don't remember whether it was about food poisoning or about the ethical issues) and cruelly threw our treasure into the trash can. After he left, we rushed to the trash can and saved the sardines.

At that time the lab felt and behaved as an extended family and the success of one translated into a victory for all. In 1967–1968 Inge spent a year in the lab of Robert Mortimer in Berkeley at the University of California in the United States. For those times it was as probable and as awe-inspiring as a flight to the moon. The lab was happy for its boss. Inge sent letters to the lab as regularly as if it was his family, and described his American impressions and adventures. The lab read those letters aloud and re-lived the details, participating in the adventure vicariously. All this was so interesting that many of those letters are remembered by the old-timers in detail, together with stories about the American labs that Inge told when he returned. It was impossible to imagine that pretty soon — although, if commensurate to the active human lifespan, not soon enough — in twenty-something years, there would be nothing superhuman in those trips abroad, and many of the former members of the lab would even move to the United States.

At that time, it was nearly impossible even to attend any conferences abroad. Publications in international scientific journals were also problematic. To submit a paper it was necessary to jump through multiple bureaucratic hoops and to specify that the paper had no novel or significant information — this was the official formula of the paperwork, in black and white. The same was required for abstracts for international conferences. However, even when those abstracts were sent and accepted, nobody was able to be physically present at the conference, although the subsequent publication in the conference book of abstracts was duly registered in the CV. Thus, when in the eighties foreign scientists started to visit the Department of Genetics, they usually left with our manuscripts in their pockets. In this way we circumvented the absurd formalities, and our foreign benefactors felt that they were fighters on the front lines of the Cold War.

Before the eighties, personal contacts with foreign scientists were scarce. Thus the arrival of any foreign geneticist was a big deal. And the biggest deal for the lab was a Soviet-American conference on yeast genetics that occurred in 1975. It was attended by Fred Sherman, Gerry Fink, Seymour Fogel, Susan Henry and other leading yeast geneticists of that time (Fig. 7). It was unforgettable, although this recollection is marred by the constant presence of the appropriate agents following our interactions with Americans and weeding out all that they considered undesirable. This surveillance was unescapable. All that was left to us was thumbing our noses behind the backs of the officials, which we all did, being of the same mind. Russians have a more colorful expression for this useful know-how — "hiding a date in the pocket".

Surely, this daily "Moveable Feast" of life depended on the extreme youth of the lab members and the lack of official rank and degrees for everybody except Inge himself, who became a Ph.D in 1965. What was surprising though was how this personal freedom coexisted with high work ethics and accountability. This stemmed from the feeling of importance of this research, cultivated primarily by Inge. He was in the know about the tiniest details of the lab research. Quite often he remembered the results better than his graduate students who did the experiments. Also, he awaited the results with the same if not greater enthusiasm than the experimenters themselves. All this inspired his disciples, made them believe in themselves, and instilled in them a sense of responsibility for the science quality. Inge also taught the skills crucial for research, such as experiment design, the necessity of proper controls, the critical evaluation of the results and, last but not least, the ability to present the data in a clear fashion. Again, it is difficult to explain to a new generation how important this was. Soviet genetics was at that time barely recovering from the crushing blow dealt to it by Lysenko and Stalin, and for many young Soviet scientists this kind of mentoring was simply not available.

Inge's mentoring was taken a notch further by his high level of culture. As an example, TSK remembers one episode that happened in the early eighties. Suddenly Inge discovered that one of the scientists working with a set of mutants did not keep the original collection names for those mutants, but changed them constantly according to his whim. Thus, the step-wise history of the research became impossible to track. What would the typical boss do in this case? What did Inge do? You will never guess. He cited the poem of Victor Hugo, in which the life of Dante Alighieri was described allegorically as transmutation from the hill, through the oak tree, then lion, to the human. Hopefully, making fun of the error by sarcastic analogy was more effective than a trivial rebuke.

Fig. 7. 1975. A Soviet-American Conference on yeast genetics. Seating are S. Fogel and N. Khromov-Borisov; standing are D. Gordenin and S. Inge-Vechtomov.

More should be said about Inge's work style. He had a gift of reaching new ideas through experiments. This is not meant in a trivial sense, as an ability to design a logical sequence of experiments, which many scientists are quite capable of, especially when it is prized and required in grant proposals as if we, the scientists, know the result from the start. This was a special intuition that allowed Inge to notice any deviations that could point to a new intriguing question, quite often cursory to the purpose of a given study. Scientists are specially trained to separate the results from the noise intrinsic to any experiment. However, nobody is trained to notice the new things among this noise, because this is impossible to train for. Nowadays several big labs routinely pursue the same goal, but who was the pathbreaker for them? Just a single person, gifted with scientific intuition. The truly new things in biology cannot be invented or imagined, they can be only recognized by lucky ones when they encounter a meaningful glitch, discarded as noise by ordinary researchers.

Those were the good times. Inge knew that and told his lab in the sixties, "Remember this time! Here and now we are happy!" However, eventually all grew up and acquired new responsibilities, some of which were formidable. Inge became Head of the Department of Genetics in 1973, and later Dean of the Biological Faculty. The other members of the first generation started their own labs. In the nineties, many lab members left for the USA. However, even before that exodus centrifugal forces started to disrupt the lab. This was sad but inevitable. Like humans, a lab passes through life stages, with one difference: the lab may resurrect itself and go through a second youth. We were lucky to witness the first youth of the lab of physiological genetics. This lab, founded by Inge, in the sixties and seventies was unique and attracted highly original talented individuals. This is a marker of the high scientific qualities of its founder. Sergey G. Inge-Vechtomov became a mentor for our generation, instilling high standards of research and expanding our horizons. Being a mentor is a special talent. Very few like Inge may be called mentors. Very few had such a strong impact on the lives and characters of his students like our Teacher Sergey G. Inge-Vechtomov.